Introduction to the Ninth Edition

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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The Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines differs substantially from the prior versions both in process and in content. In this introduction, we describe some of the differences and the rationale for the changes.

Abbreviations: ACCP = American College of Chest Physicians; AT6 = Sixth ACCP Consensus Conference on Antithrombotic Therapy; AT7 = Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines; AT8 = Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition); AT9 = Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines; GRADE = Grades of Recommendations, Assessment, Development, and Evaluation

We would like to begin by acknowledging the contributions of the visionaries whose work on past editions of these guidelines have allowed the current panel to develop this edition using the changes noted herein. First, James E. Dalen, respected clinician and researcher, while President of the American College of Chest Physicians (ACCP), had the foresight not only to propose the original consensus conference on the controversial issues of the indications for antithrombotics, antiplatelet agents, and thrombolytics for the prevention and treatment of cardiovascular disorders but also to invite Jack Hirsh, an extremely productive scientist and leader in the field of thrombosis, to join him in leading this important project. Drs Hirsh and Dalen brought a panel of leading experts together for the first antithrombotic guideline in 1986. Dr Dalen was co-editor of the first six guidelines from 1986 to 2001.

Dr Hirsh is, to an extraordinary extent, responsible not only for creating the platform that has made Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians...
Evidence-Based Clinical Practice Guidelines (AT9) possible but also for the advances from Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition) (AT8) to AT9. It was not only the creation of an expert panel—a standard feature of specialty society clinical practice guidelines from the outset—that made the antithrombotic guidelines extremely successful. Dr Hirsh, an accomplished basic science researcher and a brilliant clinical trialist, deeply understood the value of what was to become more than a decade later evidence-based medicine. He recruited one of the world leaders in the burgeoning field of clinical epidemiology, David Sackett, to play a major role in the guidelines. Drs Hirsh and Sackett developed and applied an innovative system of rating the quality of evidence and strength of recommendations that was at the time unique to specialty guidelines. The combined impact of the authoritative, carefully considered recommendations and explicit acknowledgment of the quality of evidence and strength of recommendations immediately made these guidelines the reference standard for antithrombotic therapy around the world.

Under Dr Hirsh’s leadership, the guidelines more than kept pace with advances in the science of guideline methodology and continued to improve with each iteration. Each new edition provided a model incorporating not only the latest evidence regarding antithrombotic therapy but also advances in specialty-based guidelines and therefore maintained preeminence in the field of thrombosis.

As Dr Hirsh was stepping down from the leadership of the guidelines in 2007, his insight led him to question the reliance on expert opinion that provided the basis for the first eight iterations of the antithrombotic guidelines. Reviewing his experience—and in the process giving new life to an idea suggested decades earlier but seldom applied—Dr Hirsh concluded that the conflict of interest of leading experts was highly problematic. Furthermore, the problem arose not only from their financial but equally or perhaps more important, their intellectual conflict of interest. This revelation and the changes in process that Dr Hirsh suggested as a solution to the problem had a profound impact on the leadership to whom he was passing the torch. These changes underlie all the innovations in AT9.

### The New Process in AT9—Dealing With Conflict of Interest

The solution that Dr Hirsh proposed was endorsed by the ACCP leadership and implemented in AT9. That solution is to give primary leadership and responsibility for each article not to a thrombosis expert but to a methodologist who, in almost all cases, also is a practicing physician without important conflicts of interest\(^5\) (Table 1). These editors of each article had specific training in ACCP’s approach to rating the quality of evidence and grading strength of recommendations (see “Evidence Summaries” section). Further, building on the work of prior guideline groups, the process stipulated that although conflicted thrombosis experts could engage in discussion and even draft evidence summaries, they would be excluded from the final decisions regarding quality of evidence and direction and strength of recommendations. Intellectual conflicts received the same attention as financial conflicts. Readers of the guidelines can find in the online data supplements to AT9 articles a recommendation-by-recommendation accounting of the intellectual and financial conflicts of each panel member. The most important changes in AT9 content have flowed directly from this change in process.

### Evidence Summaries

The Sixth ACCP Consensus Conference on Antithrombotic Therapy (AT6), published in 2001, adopted an approach to rating quality of evidence and strength of recommendations\(^6\) that presaged that of the Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) working group,\(^9\) itself adopted with minor modifications for AT8\(^10\) and for all ACCP guidelines.\(^11\) AT8, like AT6 and the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines (AT7), underwent thorough editing and review of the quality of evidence, including in many cases a careful assessment of single studies by topic editors and the guideline executive committee. Nevertheless, many of the topic editors did not have methodologic training or, as was the case in AT8, specific training in the ACCP-GRADE approach. The result was that in AT8, the ACCP-GRADE approach often was not applied with optimal rigor, and authors

### Table 1—Major Innovations in AT9

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
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<tbody>
<tr>
<td>1.</td>
<td>Unconflicted methodologists as topic editors. Conflicted experts did not participate in final process of making recommendations.</td>
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<tr>
<td>2.</td>
<td>Many evidence profile and summary of finding tables.</td>
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<tr>
<td>3.</td>
<td>New insights into evidence (asymptomatic thrombosis, aspirin).</td>
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<tr>
<td>4.</td>
<td>Quantitative specification of values and preferences based on systematic review of relevant evidence and formal preference rating exercise.</td>
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<tr>
<td>5.</td>
<td>Article addressing diagnosis of DVT.</td>
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produced very few of the summary tables that are the hallmark end product of the GRADE process.

There are two types of such tables: evidence profiles and summary of findings. Evidence profiles summarize the quality of a body of evidence for each relevant outcome and, when evidence comes from randomized trials, include a presentation of reviewers’ assessment of risk of bias, precision, consistency, directness, and publication bias. Readers of AT9 can find the evidence profiles in the online data supplements. The text in the main AT9 articles includes the more succinct summary of findings tables, which include the overall quality assessment as well as relative and absolute effect sizes for each outcome. We did not succeed in the lofty goal of producing a summary of findings table for each recommendation, but readers will find these for most major and potentially controversial recommendations. Readers will find >10 such tables in most articles and >20 in some articles.

Producing these tables forces a rigor of thinking achievable in few other ways. Creating a large number of evidence profiles provides deep insight into the ACCP-GRADE approach to assessing the quality of evidence and strength of recommendations. Along with recruitment of GRADE-expert topic editors, production of evidence profiles and summary of findings tables is responsible for the increased methodologic rigor of AT9.

We also tried to apply a rigorous approach to choosing the format of these tables, an issue that has generated some controversy within the GRADE working group. Per Olav Vandvik, Holger Schünemann, and Nancy Santesso led the group in a formal study in which AT9 panelists expressed their view of the optimal presentation of the tables. The results have not only guided the presentation of evidence profiles and summary of findings in AT9 but also provided one of the recommended options for the GRADE working group.

Reevaluation of Evidence

Relying on the perspective of unconflicted methodologists, rigorously applying the GRADE approach, and excluding those with financial and intellectual conflict of interests from bottom-line decisions regarding the quality of evidence and strength of recommendations led to reevaluations of previously existing evidence (Table 1). For instance, application of the ACCP-GRADE approach requires the distinction between patient-important and surrogate outcomes. The first eight editions of the antithrombotic guidelines failed to fully recognize the implications of a surrogate widely used in thrombosis prevention trials—asymptomatic, screening-detected thrombosis. Use of this surrogate creates major problems in making the trade-off between patient-important outcomes (thrombosis and serious bleeding). For instance, if one knows that an intervention increases serious bleeding by 20 events in 1,000 patients but reduces asymptomatic thrombosis by 100 in 1,000, what is the net benefit? Establishing net benefit in outcomes important to patients requires knowing the symptomatic DVT and asymptomatic pulmonary embolism reduction represented by the reduction in 100 asymptomatic events. Dr Hirsh and John Eikelboom led the prevention topic editors in developing innovative approaches to dealing with the problem of inferring the impact of thromboprophylaxis on symptomatic thrombosis from studies that relied to a considerable extent on detection of asymptomatic events. The available approaches, although representing a step forward, all have limitations and highlight the need for studies that directly measure symptomatic thrombosis without venographic or ultrasound surveillance.

As a result of a reevaluation led by Dr Eikelboom, one consequence of the recognition that measurement of patient-important events in a naturalistic clinical setting (as opposed to in the context of venographic or ultrasonographic screening for asymptomatic thrombosis) was a differing perspective on the use of aspirin in thromboprophylaxis in orthopedic surgery. The authors of AT8 had concluded that there was high-quality evidence justifying a strong recommendation against aspirin as the sole agent for thromboprophylaxis in surgical patients. Authors of AT9 focused on results from a very large trial using concealed randomization and blinding and achieving near-complete follow-up. After an exhaustive and repeated discussion involving the authors of all the prevention articles, and ultimately the entire panel, AT9 authors concluded that the trial provides moderate-quality evidence supporting the use of aspirin, which is now offered as an option for thromboprophylaxis in patients undergoing major orthopedic procedures. AT9 authors concluded that there is low-quality evidence supporting a weak recommendation of low-molecular-weight heparin over aspirin in these patients.

The GRADE approach defines quality of evidence as our level of confidence in estimates of diagnostic or treatment effect to support a particular recommendation. In general, the changing perspectives on evidence led to the conclusion that we often could not be as confident in estimates of effect as previously believed. Readers of AT9 will often find, therefore, that some of the evidence previously rated as high quality is now moderate, and evidence previously rated as moderate quality is now low.
VALUES AND PREFERENCES

Serial iterations of AT9 dating back to AT6 have gradually put increasing emphasis on patient values and preferences. For the first time, the AT7 panel made the assumptions about values and preferences explicit. The AT9 panel has accelerated that process by conducting a systematic review[17] of the relevant research of empirical investigations of values and preferences of patients regarding antithrombotic therapy. Based on that review, AT9 panelists conducted a value rating exercise that provided the basis for values and preference judgments within AT9, judgments that are summarized in the introductory section of each article.13 The judgments are more explicit and quantitative than any previous guideline. For example, we estimated that on average, patients experience the disutility of a GI bleed more or less equally to that of VTE but only one-third of the disutility of a stroke.

Among the findings of the systematic review of patient values and preferences regarding antithrombotic treatment are the heterogeneity of results between studies and the wide variability in values and preferences among patients. Because the core characteristic of a strong recommendation is the belief that across the range of values and preferences, virtually all informed patients will make the same choice, the wide variability in patient values and preferences makes strong recommendations less likely.18

IMPACT OF INNOVATIONS ON THE RECOMMENDATIONS

Readers of AT9 will find many weak recommendations replacing the strong recommendations of AT8. One major reason for this change is the more critical look at the evidence and the resulting inferences that some evidence is lower quality than previously believed. A second is the recognition of variability in values and preferences. Third, in the small number of controversial recommendations that came to a formal vote using anonymous electronic voting, we required the endorsement of >80% of panelists to make a strong recommendation. Finally, the exclusion of conflicted experts, who often hold strong opinions about optimal management approaches, from final decisions regarding quality of evidence and strength of recommendations also may have contributed.

OTHER INNOVATIONS IN AT9

For the first time, each panel included a frontline clinician not involved in thrombosis research. The goal of including these individuals was to ensure that recommendations considered the full realities of clinical practice as viewed by those outside the research environment and to support efforts to make the phrasing of recommendations more user friendly and implementable.

A limitation of AT8 was the very inconsistent approaches to assessing bleeding risk. Sam Schulman, author of the bleeding risk article in AT8,19 took responsibility for developing the AT9 approach to bleeding and ensuring that it was consistently applied across chapters.5

To address issues of economic efficiency, we included “resource use consultants” on the AT9 article panels charged with making recommendations. They developed a transparent and systematic methodology to address questions for which resource use might change the direction or strength of recommendations.5

We made an intensive effort to remove duplication between articles and to harmonize recommendations between related articles. An important strategy was to include topic editors and deputy editors as panelists from both articles when two had overlapping issues.

Finally, for the first time, the antithrombotic guidelines have addressed issues of diagnosis. Shannon Bates and Roman Jaeschke led a panel that took on the challenging task of applying the newly developed GRADE methodology for recommendations regarding the diagnosis of DVT.20

CONCLUSION

Building on the seminal work of Drs Hirsh and Dalen and their colleagues over the 20-year history of the ACCP antithrombotic guidelines, AT9 has made a number of changes in process, resulting in differences in the approach to making recommendations and their content. Past iterations of these guidelines have celebrated new high-quality evidence and the strong recommendations that such evidence warrants. The insights from AT9 include the persisting limitations in evidence quality (particularly with respect to the use of surrogate outcomes in prophylaxis trials) and the appropriateness of weak recommendations that reflect our lack of confidence in effect estimates and the variability in patient values and preferences. We believe that the objective, rigorous application of the science of guideline development will ultimately best serve our patients.

ACKNOWLEDGMENTS

Financial/nonfinancial disclosures: In summary, the authors have reported to CHEST the following conflicts of interest: Dr Crowther has served on various advisory boards, has assisted in the preparation of educational materials, and has sat on data safety and monitoring boards. His institution has received research funds from the following companies: Leo Pharma A/S, Pfizer Inc, Boehringer Ingelheim GmbH, Bayer Healthcare Pharmaceuticals,
Octapharm AG, CSL Behring, and Artisan Pharma. Personal total compensation for these activities over the last 3 years totals less than US $10,000. Dr Gutterman has had the following relationship that are entirely unrelated to the AT9 guidelines: ACCP President, GlaxoSmithKline plc grant to study vasodilation in adipose tissue, National Institutes of Health grant to study human coronary dilation, and GE Healthcare consultation on a study for ECG evaluation of chronic heart disease. Drs Guyatt and Schünemann are co-chairs of the GRADE Working Group, and Dr Akl is a member and prominent contributor to the GRADE Working Group. Dr Lewis is a full-time employee of the ACCP. The authors thank Rachel Gutterman, BA, and Joe Omelas, DC, for their assistance in managing this complex project.

**Endorsements:** This guideline is endorsed by the American Association for Clinical Chemistry, the American College of Clinical Pharmacy, the American Society of Health-System Pharmacists, the American Society of Hematology, and the International Society of Thrombosis and Hematosis.

**REFERENCES**

Executive Summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Supplemental material related to this article is available at:
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Executive Summary

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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The eighth iteration of the American College of Chest Physicians Antithrombotic Guidelines presented, in a paper version, a narrative evidence summary and rationale for the recommendations, a small number of evidence profiles summarizing bodies of evidence, and some articles with quite extensive summary tables of primary studies. In total, this represented 600 recommendations summarized in 968 pages of text. Many readers responded that the result was too voluminous for their liking or practical use.

Cognizant of this feedback, we worked hard to minimize the length of the text for the ninth iteration of the guidelines Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (AT9) without sacrificing key content. A number of topic editors found our shortening edits draconian, but we were determined to produce the leanest product possible.

There were, however, a number of obstacles. In what we believe is a key advance in AT9, we conducted a systematic review of what is known about patients’ values and preferences regarding antithrombotic therapy and included the results as an article in AT9. In another forward step, we recognized the problems with asymptomatic thrombosis as a surrogate outcome, and devised strategies to estimate reductions in symptomatic DVT and pulmonary embolism with antithrombotic prophylaxis. We felt it important to explain this innovation to users of AT9, and this meant another article.

We included, for the first time, an article on diagnosis addressing patients with symptoms and signs suggesting DVT. We increased the range of interventions we have covered, resulting in additional recommendations. Finally, we produced many summary of findings tables, which offer extremely succinct and informative presentations of best estimates of effect and the confidence associated with those estimates.

If published in the same fashion as the Antithrombotic and Thrombolytic Therapy, 8th ed: American College of Chest PhysiciansAntithrombotic Guidelines, 8th ed: American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel*
College of Chest Physicians Antithrombotic Guidelines, this would have resulted in a document with > 850 pages of paper text, an unacceptable length. Given this and with the advice of the journal, we decided to adopt a highly focused print version that includes only this executive summary and the following articles:

- An introduction describing the major innovations in AT9
- A methods article explaining how we developed the guidelines (a potential model for other guideline groups interested in optimal rigor)
- Recommendations and grading from each article embedded in the table of contents of each article

Those seeking the rationale for the recommendations, including the supporting evidence, should access the online version of the guideline (http://chestjournal.chestpubs.org/content/141/2_suppl) that includes a narrative summaries and supporting summary of findings tables. The numbering indicated beside the recommendations in this summary is aligned with the sections and tables found in the full articles. Those interested in a deeper understanding of the evidence can turn to online data supplements for each of the articles that include recommendations. There, they will find evidence profiles (expanded versions of the summary of findings tables) and some tables summarizing the methods and results, and the risk of bias, associated with the individual studies that contributed to the evidence profiles and summary of findings tables.

The world of medical information is rapidly becoming a world of electronic storage and presentation of primary studies, recommendations, and a wide variety of other information of interest to health care practitioners. Although our abbreviated paper copy presentation represents a necessary response to a challenging situation, it is also a harbinger of the increasingly electronic world of medical information into which future editions of guidelines are destined to move.

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**Summary of Recommendations**

- Note on Shaded Text: Throughout this guideline, shading is used within the summary of recommendations sections to indicate recommendations that are newly added or have been changed since the publication of Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Recommendations that remain unchanged are not shaded.

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**Evidence-Based Management of Anticoagulant Therapy**

For further details, see Holbrook et al.1

2.1 Loading Dose for Initiation of Vitamin K Antagonist (VKA) Therapy

2.1. For patients sufficiently healthy to be treated as outpatients, we suggest initiating VKA therapy with warfarin 10 mg daily for the first 2 days followed by dosing based on international normalized ratio (INR) measurements rather than starting with the estimated maintenance dose (Grade 2C).

2.2 Initial Dose Selection and Pharmacogenetic Testing

2.2. For patients initiating VKA therapy, we recommend against the routine use of pharmacogenetic testing for guiding doses of VKA (Grade 1B).

2.3 Initiation Overlap for Heparin and VKA

2.3. For patients with acute VTE, we suggest that VKA therapy be started on day 1 or 2 of low-molecular-weight heparin (LMWH) or low-dose unfractionated heparin (UFH) therapy rather than waiting for several days to start (Grade 2C).
3.1 Monitoring Frequency for VKAs

3.1. For patients taking VKA therapy with consistently stable INRs, we suggest an INR testing frequency of up to 12 weeks rather than every 4 weeks (Grade 2B).

3.2 Management of the Single Out-of-Range INR

3.2. For patients taking VKAs with previously stable therapeutic INRs who present with a single out-of-range INR of ≤ 0.5 below or above therapeutic, we suggest continuing the current dose and testing the INR within 1 to 2 weeks (Grade 2C).

3.3 Bridging for Low INRs

3.3. For patients with stable therapeutic INRs presenting with a single subtherapeutic INR value, we suggest against routinely administering bridging with heparin (Grade 2C).

3.4 Vitamin K Supplementation

3.4. For patients taking VKAs, we suggest against routine use of vitamin K supplementation (Grade 2C).

3.5 Anticoagulation Management Services for VKAs

3.5. (Best Practices Statement) We suggest that health-care providers who manage oral anticoagulation therapy should do so in a systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, follow-up, and good patient communication of results and dosing decisions.

3.6 Patient Self-Testing and Self-Management

3.6. For patients treated with VKAs who are motivated and can demonstrate competency in self-management strategies, including the self-testing equipment, we suggest patient self-management rather than usual outpatient INR monitoring (Grade 2B). For all other patients, we suggest monitoring that includes the safeguards in our best practice statement 3.5.

3.7 Dosing Decision Support

3.7. For dosing decisions during maintenance VKA therapy, we suggest using validated decision support tools (paper nomograms or computerized dosing programs) rather than no decision support (Grade 2C).

Remarks: Inexperienced prescribers may be more likely to improve prescribing with use of decision support tools than experienced prescribers.

3.8 VKA Drug Interactions to Avoid

3.8. For patients taking VKAs, we suggest avoiding concomitant treatment with nonsteroidal antiinflammatory drugs, including cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs, and certain antibiotics (see Table 8 in main article) (Grade 2C).

For patients taking VKAs, we suggest avoiding concomitant treatment with antiplatelet agents except in situations where benefit is known or is highly likely to be greater than harm from bleeding, such as patients with mechanical valves, patients with acute coronary syndrome, or patients with recent coronary stents or bypass surgery (Grade 2C).

4.1 Optimal Therapeutic INR Range

4.1. For patients treated with VKAs, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) rather than a lower (INR 2) or higher (INR 3.0-5.0) range (Grade 1B).

4.2 Therapeutic Range for High-Risk Groups

4.2. For patients with antiphospholipid syndrome with previous arterial or venous thromboembolism, we suggest VKA therapy titrated to a moderate-intensity INR range (INR 2.0-3.0) rather than higher intensity (INR 3.0-4.5) (Grade 2B).

5.0 Discontinuation of Therapy

5.0. For patients eligible to discontinue treatment with VKA, we suggest abrupt discontinuation rather than gradual tapering of the dose to discontinuation (Grade 2C).

6.1 Unfractionated Heparin (UFH) Dose Adjustment by Weight

6.1. For patients starting IV UFH, we suggest that the initial bolus and the initial rate of the continuous infusion be weight adjusted (bolus 80 units/kg followed by 18 units/kg per h for VTE; bolus 70 units/kg followed by 15 units/kg per h for cardiac or stroke patients) or use of a fixed dose (bolus 5,000 units followed by 1,000 units/h) rather than alternative regimens (Grade 2C).

6.2 Dose Management of Subcutaneous (SC) UFH

6.2. For outpatients with VTE treated with SC UFH, we suggest weight-adjusted dosing (first dose 333 units/kg, then 250 units/kg) without monitoring rather than fixed or weight-adjusted dosing with monitoring (Grade 2C).

Remarks: Inexperienced prescribers may be more likely to improve prescribing with use of decision support tools than experienced prescribers.
7.1 Therapeutic Dose of LMWH in Patients With Decreased Renal Function

7.1. For patients receiving therapeutic LMWH who have severe renal insufficiency (calculated creatinine clearance < 30 mL/min), we suggest a reduction of the dose rather than using standard doses (Grade 2C).

8.1 Fondaparinux Dose Management by Weight

8.1. For patients with VTE and body weight over 100 kg, we suggest that the treatment dose of fondaparinux be increased from the usual 7.5 mg to 10 mg daily SC (Grade 2C).

9.1 Vitamin K for Patients Taking VKAs With High INRs Without Bleeding

9.1. (a) For patients taking VKAs with INRs between 4.5 and 10 and with no evidence of bleeding, we suggest against the routine use of vitamin K (Grade 2B).

(b) For patients taking VKAs with INRs > 10.0 and with no evidence of bleeding, we suggest that oral vitamin K be administered (Grade 2C).

9.2 Clinical Prediction Rules for Bleeding While Taking VKA

9.2. For patients initiating VKA therapy, we suggest against the routine use of clinical prediction rules for bleeding as the sole criterion to withhold VKA therapy (Grade 2C).

9.3 Treatment of Anticoagulant-Related Bleeding

9.3. For patients with VKA-associated major bleeding, we suggest rapid reversal of anticoagulation with four-factor prothrombin complex concentrate rather than with plasma. (Grade 2C).

We suggest the additional use of vitamin K 5 to 10 mg administered by slow IV injection rather than reversal with coagulation factors alone (Grade 2C).

Prevention of VTE in Nonsurgical Patients

For further details, see Kahn et al.²

2.0 Hospitalized Acutely Ill Medical Patients

2.3. For acutely ill hospitalized medical patients at increased risk of thrombosis, we recommend anticoagulant thromboprophylaxis with low-molecular-weight heparin [LMWH], low-dose unfractionated heparin (LDUH) bid, LDUH tid, or fondaparinux (Grade 1B).

Remarks: In choosing the specific anticoagulant drug to be used for pharmacoprophylaxis, choices should be based on patient preference, compliance, and ease of administration (eg, daily vs bid vs tid dosing), as well as on local factors affecting acquisition costs (eg, prices of various pharmacologic agents in individual hospital formularies).

2.4. For acutely ill hospitalized medical patients at low risk of thrombosis, we recommend against the use of pharmacologic prophylaxis or mechanical prophylaxis (Grade 1B).

2.7.1. For acutely ill hospitalized medical patients who are bleeding or at high risk for bleeding, we recommend against anticoagulant thromboprophylaxis (Grade 1B).

2.7.2. For acutely ill hospitalized medical patients at increased risk of thrombosis who are bleeding or at high risk for major bleeding, we suggest the optimal use of mechanical thromboprophylaxis with graduated compression stockings (GCS) (Grade 2C) or intermittent pneumatic compression (IPC) (Grade 2C), rather than no mechanical thromboprophylaxis. When bleeding risk decreases, and if VTE risk persists, we suggest that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis (Grade 2B).

Remarks: Patients who are particularly averse to the potential for skin complications, cost, and need for clinical monitoring of GCS and IPC use are likely to decline mechanical prophylaxis.

2.8. In acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis, we suggest against extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay (Grade 2B).

3.0 Critically Ill Patients

3.2. In critically ill patients, we suggest against routine ultrasound screening for DVT (Grade 2C).

3.4.3. For critically ill patients, we suggest using LMWH or LDUH thromboprophylaxis over no prophylaxis (Grade 2C).

3.4.4. For critically ill patients who are bleeding, or are at high risk for major bleeding, we suggest mechanical thromboprophylaxis with GCS (Grade 2C) or IPC (Grade 2C) until the
bleeding risk decreases, rather than no mechanical thromboprophylaxis. When bleeding risk decreases, we suggest that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis (Grade 2C).

4.0 Patients With Cancer in the Outpatient Setting

4.2.1. In outpatients with cancer who have no additional risk factors for VTE, we suggest against routine prophylaxis with LMWH or LDUH (Grade 2B) and recommend against the prophylactic use of VKAs (Grade 1B).

Remarks: Additional risk factors for venous thrombosis in cancer outpatients include previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide.

4.2.2. In outpatients with solid tumors who have additional risk factors for VTE and who are at low risk of bleeding, we suggest prophylactic-dose LMWH or LDUH over no prophylaxis (Grade 2B).

Remarks: Additional risk factors for venous thrombosis in cancer outpatients include previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide.

4.4. In outpatients with cancer and indwelling central venous catheters, we suggest against routine prophylaxis with LMWH or LDUH (Grade 2B) and suggest against the prophylactic use of VKAs (Grade 2C).

5.0 Chronically Immobilized Patients

5.1. In chronically immobilized persons residing at home or at a nursing home, we suggest against the routine use of thromboprophylaxis (Grade 2C).

6.0 Persons Traveling Long-Distance

6.1.1. For long-distance travelers at increased risk of VTE (including previous VTE, recent surgery or trauma, active malignancy, pregnancy, estrogen use, advanced age, limited mobility, severe obesity, or known thrombophilic disorder), we suggest frequent ambulation, calf muscle exercise, or sitting in an aisle seat if feasible (Grade 2C).

6.1.2. For long-distance travelers at increased risk of VTE (including previous VTE, recent surgery or trauma, active malignancy, pregnancy, estrogen use, advanced age, limited mobility, severe obesity, or known thrombophilic disorder), we suggest use of properly fitted, below-knee GCS providing 15 to 30 mm Hg of pressure at the ankle during travel (Grade 2C). For all other long-distance travelers, we suggest against the use of GCS (Grade 2C).

6.1.3. For long-distance travelers, we suggest against the use of aspirin or anticoagulants to prevent VTE (Grade 2C).

7.0 Persons With Asymptomatic Thrombophilia

7.1. In persons with asymptomatic thrombophilia (ie, without a previous history of VTE), we recommend against the long-term daily use of mechanical or pharmacologic thromboprophylaxis to prevent VTE (Grade 1C).

Prevention of VTE in Nonorthopedic Surgical Patients

For further details, see Gould et al.3

3.6 Patients Undergoing General, GI, Urological, Gynecologic, Bariatric, Vascular, Plastic, or Reconstructive Surgery

3.6.1. For general and abdominal-pelvic surgery patients at very low risk for VTE (<0.5%; Rogers score, <7; Caprini score, 0), we recommend that no specific pharmacologic (Grade 1B) or mechanical (Grade 2C) prophylaxis be used other than early ambulation.

3.6.2. For general and abdominal-pelvic surgery patients at low risk for VTE (1.5%; Rogers score, 7-10; Caprini score, 1-2), we suggest mechanical prophylaxis, preferably with intermittent pneumatic compression (IPC), over no prophylaxis (Grade 2C).

3.6.3. For general and abdominal-pelvic surgery patients at moderate risk for VTE (3.0%; Rogers score, 10; Caprini score, 3-4) who are not at high risk for major bleeding complications, we suggest LMWH (Grade 2B), LDUH (Grade 2B), or mechanical prophylaxis, preferably with IPC (Grade 2C), over no prophylaxis.

Remarks: Three of the seven authors favored a strong (Grade 1B) recommendation in favor of LMWH or LDUH over no prophylaxis in this group.

3.6.4. For general and abdominal-pelvic surgery patients at moderate risk for VTE (3.0%; Rogers score, >10; Caprini score, 3-4) who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe, we
suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C).

3.6.5. For general and abdominal-pelvic surgery patients at high risk for VTE (~6.0%; Caprini score, ≥5) who are not at high risk for major bleeding complications, we recommend pharmacologic prophylaxis with LMWH (Grade 1B) or LDUH (Grade 1B) over no prophylaxis. We suggest that mechanical prophylaxis with elastic stockings or IPC should be added to pharmacologic prophylaxis (Grade 2C).

3.6.6. For high-VTE-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications, we recommend extended-duration pharmacologic prophylaxis (4 weeks) with LMWH over limited-duration prophylaxis (Grade 2C).

Remarks: Patients who place a high value on minimizing out-of-pocket health-care costs might prefer limited-duration over extended-duration prophylaxis in settings where the cost of extended-duration prophylaxis is borne by the patient.

3.6.7. For high-VTE-risk general and abdominal-pelvic surgery patients who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe, we suggest use of mechanical prophylaxis, preferably with IPC, over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated (Grade 2C).

3.6.8. For general and abdominal-pelvic surgery patients at high risk for VTE (6%; Caprini score, ≥5) in whom both LMWH and unfractionated heparin are contraindicated or unavailable and who are not at high risk for major bleeding complications, we suggest low-dose aspirin (Grade 2C), fondaparinux (Grade 2C), or mechanical prophylaxis, preferably with IPC (Grade 2C), over no prophylaxis.

3.6.9. For general and abdominal-pelvic surgery patients, we suggest that an inferior vena cava (IVC) filter should not be used for primary VTE prevention (Grade 2C).

3.6.10. For general and abdominal-pelvic surgery patients, we suggest that periodic surveillance with venous compression ultrasound should not be performed (Grade 2C).

4.0 Patients Undergoing Cardiac Surgery

4.4.1. For cardiac surgery patients with an uncomplicated postoperative course, we suggest the use of pharmacologic prophylaxis with low-dose aspirin (Grade 2C), unfractionated heparin (Grade 2C), or LMWH (Grade 2C).
7.4.2. For patients undergoing spinal surgery at high risk for VTE (including those with malignant disease or those undergoing surgery with a combined anterior-posterior approach), we suggest adding pharmacologic prophylaxis to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases (Grade 2C).

8.0 Patients With Major Trauma: Traumatic Brain Injury, Acute Spinal Injury, and Traumatic Spine Injury

8.4.1. For major trauma patients, we suggest use of LDUH (Grade 2C), LMWH (Grade 2C), or mechanical prophylaxis, preferably with IPC (Grade 2C), over no prophylaxis.

8.4.2. For major trauma patients at high risk for VTE (including those with acute spinal cord injury, traumatic brain injury, and spinal surgery for trauma), we suggest adding mechanical prophylaxis to pharmacologic prophylaxis (Grade 2C) when not contraindicated by lower-extremity injury.

8.4.3. For major trauma patients in whom LMWH and LDUH are contraindicated, we suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C) when not contraindicated by lower-extremity injury. We suggest adding pharmacologic prophylaxis with either LMWH or LDUH when the risk of bleeding diminishes or the contraindication to heparin resolves (Grade 2C).

8.4.4. For major trauma patients, we suggest that an IVC filter should not be used for primary VTE prevention (Grade 2C).

8.4.5. For major trauma patients, we suggest that periodic surveillance with venous compression ultrasound should not be performed (Grade 2C).

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Prevention of VTE in Orthopedic Surgery Patients

For further details, see Falck-Ytter et al.4

2.0 Patients Undergoing Major Orthopedic Surgery: Total Hip Arthroplasty (THA), Total Knee Arthroplasty (TKA), Hip Fracture Surgery (HFS)

2.1.1. In patients undergoing THA or TKA, we recommend use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis: low-molecular-weight heparin (LMWH), fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin (LDUH), adjusted-dose VKA, aspirin (all Grade 1B), or an intermittent pneumatic compression device (IPCD) (Grade 1C).

Remarks: We recommend the use of only portable, battery-powered IPCDs capable of recording and reporting proper wear time on a daily basis for inpatients and outpatients. Efforts should be made to achieve 18 h of daily compliance. One panel member believed strongly that aspirin alone should not be included as an option.

2.1.2. In patients undergoing HFS, we recommend use of one of the following rather than no antithrombotic prophylaxis for a minimum of 10 to 14 days: LMWH, fondaparinux, LDUH, adjusted-dose VKA, aspirin (all Grade 1B), or an IPCD (Grade 1C).

Remarks: We recommend the use of only portable, battery-powered IPCDs capable of recording and reporting proper wear time on a daily basis for inpatients and outpatients. Efforts should be made to achieve 18 h of daily compliance. One panel member believed strongly that aspirin alone should not be included as an option.

2.2. For patients undergoing major orthopedic surgery (THA, TKA, HFS) and receiving LMWH as thromboprophylaxis, we recommend starting either 12 h or more preoperatively or 12 h or more postoperatively rather than within 4 h or less preoperatively or 4 h or less postoperatively (Grade 1B).

2.3.1. In patients undergoing THA or TKA, irrespective of the concomitant use of an IPCD or length of treatment, we suggest the use of LMWH in preference to the other agents we have recommended as alternatives: fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH (all Grade 2B), adjusted-dose VKA, or aspirin (all Grade 2C).

Remarks: If started preoperatively, we suggest administering LMWH ≥ 12 h before surgery. Patients who place a high value on avoiding the inconvenience of daily injections with LMWH and a low value on the limitations of alternative agents are likely to choose an alternative agent. Limitations of alternative agents include the possibility of increased bleeding (which may occur with fondaparinux, rivaroxaban, and VKA), possible decreased efficacy (LDUH, VKA, aspirin, and IPCD alone), and lack of long-term safety data (apixaban, dabigatran, and rivaroxaban). Furthermore, patients who place a high value on avoiding bleeding complications and a low value on
its inconvenience are likely to choose an IPCD over the drug options.

2.3.2. In patients undergoing HFS, irrespective of the concomitant use of an IPCD or length of treatment, we suggest the use of LMWH in preference to the other agents we have recommended as alternatives: fondaparinux, LDUH (Grade 2B), adjusted-dose VKA, or aspirin (all Grade 2C).

Remarks: For patients in whom surgery is likely to be delayed, we suggest that LMWH be initiated during the time between hospital admission and surgery but suggest administering LMWH at least 12 h before surgery. Patients who place a high value on avoiding the inconvenience of daily injections with LMWH and a low value on the limitations of alternative agents are likely to choose an alternative agent. Limitations of alternative agents include the possibility of increased bleeding (which may occur with fondaparinux) or possible decreased efficacy (LDUH, VKA, aspirin, and IPCD alone). Furthermore, patients who place a high value on avoiding bleeding complications and a low value on its inconvenience are likely to choose an IPCD over the drug options.

2.4. For patients undergoing major orthopedic surgery, we suggest extending thromboprophylaxis in the outpatient period for up to 35 days from the day of surgery rather than for only 10 to 14 days (Grade 2B).

2.5. In patients undergoing major orthopedic surgery, we suggest using dual prophylaxis with an antithrombotic agent and an IPCD during the hospital stay (Grade 2C).

Remarks: We recommend the use of only portable, battery-powered IPCDs capable of recording and reporting proper wear time on a daily basis for inpatients and outpatients. Efforts should be made to achieve 18 h of daily compliance. Patients who place a high value on avoiding the undesirable consequences associated with prophylaxis with both a pharmacologic agent and an IPCD are likely to decline use of dual prophylaxis.

2.6. In patients undergoing major orthopedic surgery and increased risk of bleeding, we suggest using an IPCD or no prophylaxis rather than pharmacologic treatment (Grade 2C).

Remarks: We recommend the use of only portable, battery-powered IPCDs capable of recording and reporting proper wear time on a daily basis for inpatients and outpatients. Efforts should be made to achieve 18 h of daily compliance. Patients who place a high value on avoiding the discomfort and inconvenience of IPCD and a low value on avoiding a small absolute increase in bleeding with pharmacologic agents when only one bleeding risk factor is present (in particular the continued use of antiplatelet agents) are likely to choose pharmacologic thromboprophylaxis over IPCD.

2.7. In patients undergoing major orthopedic surgery and who decline or are uncooperative with injections or an IPCD, we recommend using apixaban or dabigatran (alternatively rivaroxaban or adjusted-dose VKA if apixaban or dabigatran are unavailable) rather than alternative forms of prophylaxis (all Grade 1B).

2.8. In patients undergoing major orthopedic surgery, we suggest against using IVC filter placement for primary prevention over no thromboprophylaxis in patients with an increased bleeding risk or contraindications to both pharmacologic and mechanical thromboprophylaxis (Grade 2C).

2.9. For asymptomatic patients following major orthopedic surgery, we recommend against Doppler (or duplex) ultrasound screening before hospital discharge (Grade 1B).

3.0 Patients With Isolated Lower-Leg Injuries Distal to the Knee

3.0. We suggest no prophylaxis rather than pharmacologic thromboprophylaxis in patients with isolated lower-leg injuries requiring leg immobilization (Grade 2C).

4.0 Patients Undergoing Knee Arthroscopy

4.0. For patients undergoing knee arthroscopy without a history of prior VTE, we suggest no thromboprophylaxis rather than prophylaxis (Grade 2B).

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Perioperative Management of Antithrombotic Therapy

For further details, see Douketis et al.5

2.1 Interruption of VKAs Before Surgery

2.1. In patients who require temporary interruption of a VKA before surgery, we recommend stopping VKAs approximately 5 days before surgery instead of stopping VKAs a shorter time before surgery (Grade 1C).

2.2 Resumption of VKAs After Surgery

2.2. In patients who require temporary interruption of a VKA before surgery, we recommend
resuming VKAs approximately 12 to 24 h after surgery (evening of or next morning) and when there is adequate hemostasis instead of later resumption of VKAs (Grade 2C).

2.4 Bridging Anticoagulation During Interruption of VKA Therapy

2.4. In patients with a mechanical heart valve, atrial fibrillation, or VTE at high risk for thromboembolism, we suggest bridging anticoagulation instead of no bridging during interruption of VKA therapy (Grade 2C).

Remarks: Patients who place a higher value on avoiding perioperative bleeding than on avoiding perioperative thromboembolism are likely to decline heparin bridging.

In patients with a mechanical heart valve, atrial fibrillation, or VTE at low risk for thromboembolism, we suggest no bridging instead of bridging anticoagulation during interruption of VKA therapy (Grade 2C).

In patients with a mechanical heart valve, atrial fibrillation, or VTE at moderate risk for thromboembolism, the bridging or no-bridging approach chosen is, as in the higher- and lower-risk patients, based on an assessment of individual patient- and surgery-related factors.

2.5 Perioperative Management of VKA-Treated Patients Who Require Minor Procedures

2.5. In patients who require a minor dental procedure, we suggest continuing VKAs with coadministration of an oral prohemostatic agent or stopping VKAs 2 to 3 days before the procedure instead of alternative strategies (Grade 2C). In patients who require minor dermatologic procedures and are receiving VKA therapy, we suggest continuing VKAs around the time of the procedure and optimizing local hemostasis instead of other strategies (Grade 2C). In patients who require cataract surgery and are receiving VKA therapy, we suggest continuing VKAs around the time of the surgery instead of other strategies (Grade 2C).

3.4. In patients who are receiving acetylsalicylic acid (ASA) for the secondary prevention of cardiovascular disease and are having minor dental or dermatologic procedures or cataract surgery, we suggest continuing ASA around the time of the procedure instead of stopping ASA 7 to 10 days before the procedure (Grade 2C).

3.5. In patients at moderate to high risk for cardiovascular events who are receiving ASA therapy and require noncardiac surgery, we suggest continuing ASA around the time of surgery instead of stopping ASA 7 to 10 days before surgery (Grade 2C). In patients at low risk for cardiovascular events who are receiving ASA therapy, we suggest stopping ASA 7 to 10 days before surgery instead of continuation of ASA (Grade 2C).

3.6 Patients Undergoing Coronary Artery Bypass Graft Surgery

3.6. In patients who are receiving ASA and require coronary artery bypass graft (CABG) surgery, we suggest continuing ASA around the time of surgery instead of stopping ASA 7 to 10 days before surgery (Grade 2C). In patients who are receiving dual antiplatelet drug therapy and require CABG surgery, we suggest continuing ASA around the time of surgery and stopping clopidogrel/prasugrel 5 days before surgery instead of continuing dual antiplatelet therapy around the time of surgery (Grade 2C).

3.7 Surgical Patients With Coronary Stents

3.7. In patients with a coronary stent who are receiving dual antiplatelet therapy and require surgery, we recommend deferring surgery for at least 6 weeks after placement of a bare-metal stent and for at least 6 months after placement of a drug-eluting stent instead of undertaking surgery within these time periods (Grade 1C). In patients who require surgery within 6 weeks of placement of a bare-metal stent or within 6 months of placement of a drug-eluting stent, we suggest continuing dual antiplatelet therapy around the time of surgery instead of stopping dual antiplatelet therapy 7 to 10 days before surgery (Grade 2C).

Remarks: Patients who are more concerned about avoiding the unknown, but potentially large increase in bleeding risk associated with the perioperative continuation of dual antiplatelet therapy than avoiding the risk for coronary stent thrombosis are unlikely to choose continuation of dual antiplatelet therapy.

4.2 Perioperative Use of IV UFH

4.2. In patients who are receiving bridging anticoagulation with therapeutic-dose IV UFH, we suggest stopping UFH 4 to 6 h before surgery instead of closers to surgery (Grade 2C).
4.3 Preoperative Interruption of Therapeutic-Dose Bridging LMWH

4.3. In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH, we suggest administering the last preoperative dose of LMWH approximately 24 h before surgery instead of 12 h before surgery (Grade 2C).

4.4 Postoperative Resumption of Therapeutic-Dose Bridging LMWH

4.4. In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH and are undergoing high-bleeding-risk surgery, we suggest resuming therapeutic-dose SC LMWH instead of resuming LMWH within 24 h after surgery (Grade 2C).

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**Diagnosis of DVT**

For further details, see Bates et al.6

3.0 Diagnosis of Suspected First Lower Extremity DVT

3.1. In patients with a suspected first lower extremity DVT, we suggest that the choice of diagnostic tests process should be guided by the clinical assessment of pretest probability rather than by performing the same diagnostic tests in all patients (Grade 2B).

Remarks: In considering this recommendation, five panelists voted for a strong recommendation and four voted for a weak recommendation (one declined to vote and two did not participate). According to predetermined criteria, this resulted in weak recommendation.

3.2. In patients with a low pretest probability of first lower extremity DVT, we recommend one of the following initial tests: (i) a moderately sensitive D-dimer, (ii) a highly sensitive D-dimer, or (iii) compression ultrasound (CUS) of the proximal veins rather than (i) no diagnostic testing (Grade 1B for all comparisons), (ii) venography (Grade 1B for all comparisons), or (iii) whole-leg ultrasound (US) (Grade 2B for all comparisons). We suggest initial use of a moderately sensitive (Grade 2C) or highly sensitive (Grade 2B) D-dimer rather than proximal CUS.

Remarks: The choice between a moderately sensitive D-dimer test, a highly sensitive D-dimer test, or proximal CUS as the initial test will depend on local availability, access to testing, costs of testing, and the probability of obtaining a negative D-dimer result if DVT is not present. Initial testing with US would be preferred if the patient has a comorbid condition associated with elevated D-dimer levels and is likely to have a positive D-dimer result, even if DVT is absent. In patients with suspected first lower extremity DVT in whom US is impractical (eg, when leg casting or excessive SC tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, we suggest CT scan venography or magnetic resonance (MR) venography, or MR direct thrombus imaging could be used as an alternative to venography.

If the D-dimer is negative, we recommend no further testing over further investigation with (i) proximal CUS, (ii) whole-leg US, or (iii) venography (Grade 1B for all comparisons). If the proximal CUS is negative, we recommend no further testing compared with (i) repeat proximal CUS after 1 week, (ii) whole-leg US, or (iii) venography (Grade 1B for all comparisons).

If the D-dimer is positive, we suggest further testing with CUS of the proximal veins rather than (i) whole-leg US (Grade 2C) or (ii) venography (Grade 1B). If CUS of the proximal veins is positive, we suggest treating for DVT and performing no further testing over performing confirmatory venography (Grade 2C).

Remarks: In circumstances when high-quality venography is available, patients who are not averse to the discomfort of venography, are less concerned about the complications of venography, and place a high value on avoiding treatment of false-positive results are likely to choose confirmatory venography if findings for DVT are less certain (eg, a segment of venous noncompressibility).

3.3. In patients with a moderate pretest probability of first lower extremity DVT, we recommend one of the following initial tests: (i) a highly sensitive D-dimer or (ii) proximal CUS, or (iii) whole-leg US rather than (i) no testing (Grade 1B for all comparisons) or (ii) venography (Grade 1B for all comparisons). We suggest initial use of a highly sensitive D-dimer rather than US (Grade 2C).

Remarks: The choice between a highly sensitive D-dimer test or US as the initial test will depend on local availability, access to testing, costs of testing, and the probability of obtaining a negative D-dimer result if DVT is not present. Initial testing with US may be preferred if the patient has a comorbid condition associated with elevated D-dimer levels and is likely to have a positive D-dimer result even if DVT is absent. Whole-leg US may be preferred in patients unable to return for serial testing and those with...
severe symptoms consistent with calf DVT. In patients with suspected first lower extremity DVT in whom US is impractical (eg, when leg casting or excessive SC tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, we suggest CT scan venography, MR venography, or MR direct thrombus imaging could be used as an alternative to venography.

If the highly sensitive D-dimer is negative, we recommend no further testing over further investigation with (i) proximal CUS, (ii) whole-leg US, or (iii) venography (Grade 1B for all comparisons). If the highly sensitive D-dimer is positive, we recommend proximal CUS or whole-leg US rather than no testing (Grade 1B for all comparisons). If proximal CUS is chosen as the initial test and is negative, we recommend (i) repeat proximal CUS in 1 week or (ii) testing with a moderate or highly sensitive D-dimer assay over no further testing (Grade 1B) or venography (Grade 2B). In patients with a negative proximal CUS but a positive D-dimer, we recommend repeat proximal CUS in 1 week over no further testing (Grade 1B) or venography (Grade 2B).

In patients with (i) negative serial proximal CUS or (ii) a negative single proximal CUS and negative moderate or highly sensitive D-dimer, we recommend no further testing rather than further testing with (i) whole-leg US or (ii) venography (Grade 1B for all comparisons).

If whole-leg US is negative, we recommend no further testing over (i) repeat US in one week, (ii) D-dimer testing, or (iii) venography (Grade 1B for all comparisons). If proximal CUS is positive, we recommend treating for DVT rather than confirmatory venography (Grade 1B). If isolated distal DVT is detected on whole-leg US, we suggest serial testing to rule out proximal extension over treatment (Grade 2C).

Remarks: Patients with abnormal isolated distal US findings on whole-leg US who place a high value on avoiding the inconvenience of repeat testing and a low value on avoiding treatment of false-positive results are likely to choose treatment over repeat US. Patients with severe symptoms and risk factors for extension as outlined in Perioperative Management of Antithrombotic Therapy. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines are more likely to benefit from treatment over repeat US.

3.4. In patients with a high pretest probability of first lower extremity DVT, we recommend either (i) proximal CUS or (ii) whole-leg US over no testing (Grade 1B for all comparisons) or venography (Grade 1B for all comparisons).

Remarks: Whole-leg US may be preferred to proximal CUS in patients unable to return for serial testing and those with severe symptoms consistent with calf DVT. In patients with extensive unexplained leg swelling, if there is no DVT on proximal CUS or whole-leg US and D-dimer testing has not been performed or is positive, the iliac veins should be imaged to exclude isolated iliac DVT. In patients with suspected first lower extremity DVT in whom US is impractical (eg, when leg casting or excessive SC tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, we suggest CT scan venography, MR venography, or MR direct thrombus imaging could be used as an alternative to venography.

If proximal CUS or whole-leg US is positive for DVT, we recommend treatment rather than confirmatory venography (Grade 1B).

In patients with a negative proximal CUS, we recommend additional testing with a highly sensitive D-dimer or whole-leg US or repeat proximal CUS in 1 week over no further testing (Grade 1B for all comparisons) or venography (Grade 2B for all comparisons). We recommend that patients with a single negative proximal CUS and positive D-dimer undergo whole-leg US or repeat proximal CUS in 1 week over no further testing (Grade 1B) or venography (Grade 2B). In patients with negative serial proximal CUS, a negative single proximal CUS and negative highly sensitive D-dimer, or a negative whole-leg US, we recommend no further testing over venography or additional US (Grade 1B for negative serial proximal CUS and for negative single proximal CUS and highly sensitive D-dimer; Grade 2B for negative whole-leg US).

We recommend that in patients with high pretest probability, moderately or highly sensitive D-dimer assays should not be used as standalone tests to rule out DVT (Grade 1B).

3.5. If risk stratification is not performed in patients with suspected first lower extremity DVT, we recommend one of the following initial tests: (i) proximal CUS or (ii) whole-leg US rather than (i) no testing (Grade 1B), (ii) venography (Grade 1B), or D-dimer testing (Grade 2B).
Remarks: Whole-leg US may be preferred to proximal CUS in patients unable to return for serial testing and those with severe symptoms consistent with calf DVT or risk factors for extension of distal DVT. In patients with suspected first lower extremity DVT in whom US is impractical (eg, when leg casting or excessive SC tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, we suggest that CT scan venography, MR venography, or MR direct thrombus imaging could be used as an alternative to venography.

We recommend that patients with a negative proximal CUS undergo testing with a moderate- or high-sensitivity D-dimer, whole-leg US, or repeat proximal CUS in 1 week over no further testing (Grade 2B) or venography (Grade 2B). In patients with a negative proximal CUS, we suggest D-dimer rather than routine serial CUS (Grade 2B) or whole-leg US (Grade 2C). We recommend that patients with a single negative proximal CUS and positive D-dimer undergo further testing with repeat proximal CUS in 1 week or whole-leg US rather than no further testing (Grade 1B for both comparisons).

We recommend that in patients with (i) negative serial proximal CUS, (ii) a negative D-dimer following a negative initial proximal CUS, or (iii) negative whole-leg US, no further testing be performed rather than venography (Grade 1B).

If proximal US is positive for DVT, we recommend treatment rather than confirmatory venography (Grade 1B). If isolated distal DVT is detected on whole-leg US, we suggest serial testing to rule out proximal extension over treatment (Grade 2C).

Remarks: Patients with abnormal isolated distal US findings on whole-leg US who place a high value on avoiding the inconvenience of repeat testing and a low value on avoiding treatment of false-positive results are likely to choose treatment over repeat US. Patients with severe symptoms and risk factors for extension as outlined in “Perioperative Management of Antithrombotic Therapy. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines” are more likely to benefit from treatment over repeat US.

3.6. In patients with suspected first lower extremity DVT, we recommend against the routine use of CT venography or MRI (Grade 1C).

4.1 Venography in Patients With Suspected Recurrent DVT

4.1. In patients suspected of having recurrent lower extremity DVT, we recommend initial evaluation with proximal CUS or a highly sensitive D-dimer over venography, CT venography, or MRI (all Grade 1B).

Remarks: Initial D-dimer testing with a high-sensitivity assay is preferable if prior US is not available for comparison.

If the highly sensitive D-dimer is positive, we recommend proximal CUS over venography, CT venography, or MRI (Grade 1B for all comparisons).

In patients with suspected recurrent lower extremity DVT in whom initial proximal CUS is negative (normal or residual diameter increase of <2 mm), we suggest at least one further proximal CUS (day 7 ± 1) or testing with a moderately or highly sensitive D-dimer (followed by repeat CUS [day 7 ± 1] if positive) rather than no further testing or venography (Grade 2B).

Remarks: In patients with an abnormal proximal CUS at presentation that does not meet the criteria for the diagnosis of recurrence, an additional proximal CUS on day 2 ± 1 in addition to that on (day 7 ± 1) may be preferred. Patients who place a high value on an accurate diagnosis and a low value on avoiding the inconvenience and potential side effects of a venography are likely to choose venography over missed diagnosis (in the case of residual diameter increase of <2 mm).

We recommend that patients with suspected recurrent lower extremity DVT and a negative highly sensitive D-dimer or negative proximal CUS and negative moderately or highly sensitive D-dimer or negative serial proximal CUS undergo no further testing for suspected recurrent DVT rather than venography (Grade 1B).

If CUS of the proximal veins is positive, we recommend treating for DVT and performing no further testing over performing confirmatory venography (Grade 1B for the finding of a new noncompressible segment in the common femoral or popliteal vein, Grade 2B for a ≥4-mm increase in venous diameter during compression compared with that in the same venous segment on a previous result).

Remarks: Patients with US abnormalities at presentation that do not include a new noncompressible segment who place a high value on an accurate diagnosis and a low value on avoiding the inconvenience
and potential side effects of a venography are likely to choose venography over treatment (in the case of ≥ 4-mm increase in venous diameter).

4.2 Compression Ultrasonography in Patients With Suspected Recurrent DVT

4.2. In patients with suspected recurrent lower extremity DVT and abnormal but nondiagnostic US results (eg, an increase in residual venous diameter of < 4 but ≥ 2 mm), we recommend further testing with venography, if available (Grade 1B); serial proximal CUS (Grade 2B) or testing with a moderately or highly sensitive D-dimer with serial proximal CUS as above if the test is positive (Grade 2B), as opposed to other testing strategies or treatment.

4.3 Pretest Probability Assessment in Patients With Suspected Recurrent DVT

4.3. In patients with suspected recurrent ipsilateral DVT and an abnormal US without a prior result for comparison, we recommend further testing with venography, if available (Grade 1B) or a highly sensitive D-dimer (Grade 2B) over serial proximal CUS. In patients with suspected recurrent ipsilateral DVT and an abnormal US without prior result for comparison and a negative highly sensitive D-dimer, we suggest no further testing over venography (Grade 2C). In patients with suspected recurrent ipsilateral DVT and an abnormal US without prior result for comparison and a positive highly sensitive D-dimer, we suggest venography if available over empirical treatment of recurrence (Grade 2C).

Remarks: Patients who place a high value on avoiding the inconvenience and potential side effects of a venography are likely to choose treatment over venography.

5.1 Venography in Pregnancy-Related DVT

5.1. In pregnant patients suspected of having lower extremity DVT, we recommend initial evaluation with proximal CUS over other initial tests, including a whole-leg US (Grade 2C), moderately sensitive D-dimer (Grade 2C), highly sensitive D-dimer (Grade 1B), or venography (Grade 1B).

5.2 Compression Ultrasonography in Pregnancy-Related DVT

5.2. In pregnant patients with suspected DVT in whom initial proximal CUS is negative, we suggest further testing with either serial proximal CUS (day 3 and day 7) (Grade 1B) or a sensitive D-dimer done at the time of presentation (Grade 2B) over no further testing for DVT. We recommend that patients with an initial negative proximal CUS and a subsequent negative sensitive D-dimer or negative serial proximal CUS undergo no further testing for DVT (Grade 1B) and that patients with positive D-dimer have an additional follow-up proximal CUS (day 3 and day 7) rather than venography (Grade 1B) or whole-leg US (Grade 2C).

5.3 Pretest Probability in Pregnancy-Related DVT

5.3. In pregnant patients with symptoms suggestive of isolated iliac vein thrombosis (swelling of the entire leg, with or without flank, buttock, or back pain) and no evidence of DVT on standard proximal CUS, we suggest further testing with either Doppler US of the iliac vein (Grade 2C), venography (Grade 2C), or direct MRI (Grade 2C), rather than standard serial CUS of the proximal deep veins.

6.1 Ultrasonography in Patients With Upper-Extremity DVT (UEDVT)

6.1. In patients suspected of having UEDVT, we suggest initial evaluation with combined modality US (compression with either Doppler or color Doppler) over other initial tests, including highly sensitive D-dimer or venography (Grade 2C).

6.2 Clinical Pretest Probability Assessment in Patients With UEDVT

6.2. In patients with suspected UEDVT in whom initial US is negative for thrombosis despite a high clinical suspicion of DVT, we suggest further testing with a moderate or highly sensitive D-dimer, serial US, or venographic-based imaging (traditional, CT scan, or MRI), rather than no further testing (Grade 2C).

In patients with suspected UEDVT and an initial negative combined-modality US and subsequent negative moderate or highly sensitive D-dimer or CT or MRI, we recommend no further testing, rather than confirmatory venography (Grade 1C). We suggest that patients with an initial combined negative modality US and positive D-dimer or those with less than complete evaluation by US undergo venography rather than no further testing, unless there is an alternative explanation for their symptoms (Grade 2B), in which case testing to evaluate for the presence an alternative diagnosis should be performed. We suggest that patients with a positive D-dimer or those with less than complete
Antithrombotic Therapy for VTE Disease

For further details, see Kearon et al.7

2.1 Initial Anticoagulation for Patients With Acute DVT of the Leg

2.1. In patients with acute DVT of the leg treated with VKA therapy, we recommend initial treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such initial treatment (Grade 1B).

2.2 Parenteral Anticoagulation Prior to Receipt of the Results of Diagnostic Work-up for VTE

2.2.1. In patients with a high clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C).

2.2.2. In patients with an intermediate clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C).

2.2.3. In patients with a low clinical suspicion of acute VTE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C).

2.3 Anticoagulation in Patients With Isolated Distal DVT

2.3.1. In patients with acute isolated distal DVT of the leg and without severe symptoms or risk factors for extension, we suggest serial imaging of the deep veins for 2 weeks over initial anticoagulation (Grade 2C).

2.3.2. In patients with acute isolated distal DVT of the leg and severe symptoms or risk factors for extension (see text), we suggest initial anticoagulation over serial imaging of the deep veins (Grade 2C).

Remarks: Patients at high risk for bleeding are more likely to benefit from serial imaging. Patients who place a high value on avoiding the inconvenience of repeat imaging and a low value on the inconvenience of treatment and on the potential for bleeding are likely to choose initial anticoagulation over serial imaging.

2.3.3. In patients with acute isolated distal DVT of the leg who are managed with initial anticoagulation, we recommend using the same approach as for patients with acute proximal DVT (Grade 1B).

2.3.4. In patients with acute isolated distal DVT of the leg who are managed with serial imaging, we recommend no anticoagulation if the thrombus does not extend (Grade 1B); we suggest anticoagulation if the thrombus extends but remains confined to the distal veins (Grade 2C); we recommend anticoagulation if the thrombus extends into the proximal veins (Grade 1B).

2.4 Timing of Initiation of VKA and Associated Duration of Parenteral Anticoagulant Therapy

2.4. In patients with acute DVT of the leg, we recommend early initiation of VKA (eg, same day as parenteral therapy is started) over delayed initiation, and continuation of parenteral anticoagulation for a minimum of 5 days and until the international normalized ratio (INR) is 2.0 or above for at least 24 h (Grade 1B).

2.5 Choice of Initial Anticoagulant Regimen in Patients With Proximal DVT

2.5.1. In patients with acute DVT of the leg, we suggest LMWH or fondaparinux over IV UFH (Grade 2C) and over SC UFH (Grade 2B for LMWH; Grade 2C for fondaparinux).

Remarks: Local considerations such as cost, availability, and familiarity of use dictate the choice between fondaparinux and LMWH. LMWH and fondaparinux are retained in patients with renal impairment, whereas this is not a concern with UFH.

2.5.2. In patients with acute DVT of the leg treated with LMWH, we suggest once- over twice-daily administration (Grade 2C).

Remarks: This recommendation only applies when the approved once-daily regimen uses the same daily dose as the twice-daily regimen (ie, the once-daily injection contains double the dose of each twice-daily injection). It also places value on avoiding an extra injection per day.
2.7 At-Home vs In-Hospital Initial Treatment of Patients With DVT

2.7. In patients with acute DVT of the leg and whose home circumstances are adequate, we recommend initial treatment at home over treatment in hospital (Grade 1B).

Remarks: The recommendation is conditional on the adequacy of home circumstances: well-maintained living conditions, strong support from family or friends, phone access, and ability to quickly return to the hospital if there is deterioration. It is also conditional on the patient feeling well enough to be treated at home (eg, does not have severe leg symptoms or comorbidity).

2.9 Catheter-Directed Thrombolysis for Patients With Acute DVT

2.9. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over catheter-directed thrombolysis (CDT) (Grade 2C).

Remarks: Patients who are most likely to benefit from CDT (see text), who attach a high value to prevention of postthrombotic syndrome (PTS), and a lower value to the initial complexity, cost, and risk of bleeding with CDT, are likely to choose CDT over anticoagulation alone.

2.10 Systemic Thrombolytic Therapy for Patients With Acute DVT

2.10. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over systemic thrombolysis (Grade 2C).

Remarks: Patients who are most likely to benefit from systemic thrombolytic therapy (see text), who do not have access to CDT, and who attach a high value to prevention of PTS, and a lower value to the initial complexity, cost, and risk of bleeding with systemic thrombolytic therapy, are likely to choose systemic thrombolytic therapy over anticoagulation alone.

2.11 Operative Venous Thrombectomy for Acute DVT

2.11. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over operative venous thrombectomy (Grade 2C).

2.12 Anticoagulation in Patients Who Have Had Any Method of Thrombus Removal Performed

2.12. In patients with acute DVT of the leg who undergo thrombosis removal, we recommend the same intensity and duration of anticoagulant therapy as in comparable patients who do not undergo thrombosis removal (Grade 1B).

2.13 Vena Cava Filters for the Initial Treatment of Patients With DVT

2.13.1. In patients with acute DVT of the leg, we recommend against the use of an IVC filter in addition to anticoagulants (Grade 1B).

2.13.2. In patients with acute proximal DVT of the leg and contraindication to anticoagulation, we recommend the use of an IVC filter (Grade 1B).

2.13.3. In patients with acute proximal DVT of the leg and an IVC filter inserted as an alternative to anticoagulation, we suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 2B).

Remarks: We do not consider that a permanent IVC filter, of itself, is an indication for extended anticoagulation.

2.14 Early Ambulation of Patients With Acute DVT

2.14. In patients with acute DVT of the leg, we suggest early ambulation over initial bed rest (Grade 2C).

Remarks: If edema and pain are severe, ambulation may need to be deferred. As per section 4.1, we suggest the use of compression therapy in these patients.

3.0 Long-term Anticoagulation in Patients With Acute DVT of the Leg

3.0. In patients with acute VTE who are treated with anticoagulant therapy, we recommend long-term therapy (see section 3.1 for recommended duration of therapy) over stopping anticoagulant therapy after about 1 week of initial therapy (Grade 1B).

3.1 Duration of Long-term Anticoagulant Therapy

3.1.1. In patients with a proximal DVT of the leg provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B), or (iii) extended therapy (Grade 1B regardless of bleeding risk).

3.1.2. In patients with a proximal DVT of the leg provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Grade 2B).
3.1.3. In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor (see remark), we suggest treatment with anticoagulation for 3 months over treatment of a shorter period (Grade 2C) and recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B) or extended therapy (Grade 1B regardless of bleeding risk).

3.1.4. In patients with an unprovoked DVT of the leg (isolated distal [see remark] or proximal), we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B). After 3 months of treatment, patients with unprovoked DVT of the leg should be evaluated for the risk-benefit ratio of extended therapy.

3.1.4.1. In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B).

3.1.4.2. In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy (Grade 1B).

3.1.4.3. In patients with a first VTE that is an unprovoked isolated distal DVT of the leg (see remark), we suggest 3 months of anticoagulant therapy over extended therapy in those with a low or moderate bleeding risk (Grade 2B) and recommend 3 months of anticoagulant treatment in those with a high bleeding risk (Grade 1B).

3.1.4.4. In patients with a second unprovoked VTE, we recommend extended anticoagulant therapy over 3 months of therapy in those who have a low bleeding risk (Grade 1B), and we suggest extended anticoagulant therapy in those with a moderate bleeding risk (Grade 2B).

3.1.4.5. In patients with a second unprovoked VTE who have a high bleeding risk, we suggest 3 months of anticoagulant therapy over extended therapy (Grade 2B).

3.1.5. In patients with DVT of the leg and active cancer, if the risk of bleeding is not high, we recommend extended anticoagulant therapy over 3 months of therapy (Grade 1B), and if there is a high bleeding risk, we suggest extended anticoagulant therapy (Grade 2B).

Remarks (3.1.3, 3.1.4, 3.1.4.3): Duration of treatment of patients with isolated distal DVT refers to patients in whom a decision has been made to treat with anticoagulant therapy; however, it is anticipated that not all patients who are diagnosed with isolated distal DVT will be given anticoagulants (see section 2.3). In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

3.2 Intensity of Anticoagulant Effect

3.2.1. In patients with DVT of the leg who are treated with VKA, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) over a lower (INR < 2) or higher (INR 3.0-5.0) range for all treatment durations (Grade 1B).

3.3 Choice of Anticoagulant Regimen for Long-term Therapy

3.3.1. In patients with DVT of the leg and no cancer, we suggest VKA therapy over LMWH for long-term therapy (Grade 2C). For patients with DVT and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy (Grade 2C).

3.3.2. In patients with DVT of the leg and cancer, we suggest LMWH over VKA therapy (Grade 2B). In patients with DVT and cancer who are not treated with LMWH, we suggest VKA over dabigatran or rivaroxaban for long-term therapy (Grade 2B).

Remarks (3.3.1-3.3.2): Choice of treatment in patients with and without cancer is sensitive to the individual patient’s tolerance for daily injections, need for laboratory monitoring, and treatment costs. LMWH, rivaroxaban, and dabigatran are retained in patients with renal impairment, whereas this is not a concern with VKA. Treatment of VTE with dabigatran or rivaroxaban, in addition to being less burdensome to patients, may prove to be associated with better clinical outcomes than VKA and LMWH therapy. When these guidelines were being prepared (October 2011), postmarketing studies of safety were not available. Given the paucity of currently available data and that new data are rapidly emerging, we give a weak recommendation in favor of VKA and LMWH therapy over dabigatran and rivaroxaban, and we have not made any recommendations in favor of one of the new agents over the other.

3.4 Choice of Anticoagulant Regimen for Extended Therapy

3.4.1. In patients with DVT of the leg who receive extended therapy, we suggest treatment with the
same anticoagulant chosen for the first 3 months (Grade 2C).

3.5 Treatment of Patients With Asymptomatic DVT of the Leg

3.5. In patients who are incidentally found to have asymptomatic DVT of the leg, we suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic DVT (Grade 2B).

4.1 Compression Stockings and Bandages to Prevent PTS

4.1. In patients with acute symptomatic DVT of the leg, we suggest the use of compression stockings (Grade 2B).

Remarks: Compression stockings should be worn for 2 years, and we suggest beyond that if patients have developed PTS and find the stockings helpful. Patients who place a low value on preventing PTS or a high value on avoiding the inconvenience and discomfort of stockings are likely to decline stockings.

4.2 Physical Treatment of Patients With PTS

4.2.1. In patients with PTS of the leg, we suggest a trial of compression stockings (Grade 2C).

4.2.2. In patients with severe PTS of the leg that is not adequately relieved by compression stockings, we suggest a trial of an intermittent compression device (Grade 2B).

4.3 Pharmacologic Treatment of Patients With PTS

4.3. In patients with PTS of the leg, we suggest that venaactive medications (eg, rutosides, defibrotide, and hidrosmin) not be used (Grade 2C).

Remarks: Patients who value the possibility of response over the risk of side effects may choose to undertake a therapeutic trial.

5.1 Initial Anticoagulation for Patients With Acute Pulmonary Embolism (PE)

5.1. In patients with acute PE, we recommend initial treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such initial treatment (Grade 1B).

5.2 Parenteral Anticoagulation Prior to Receipt of the Results of Diagnostic Work-up for PE

5.2.1. In patients with a high clinical suspicion of acute PE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C).

5.2.2. In patients with an intermediate clinical suspicion of acute PE, we suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C).

5.2.3. In patients with a low clinical suspicion of acute PE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C).

5.3 Timing of Initiation of VKA and Associated Duration of Parenteral Anticoagulant Therapy

5.3. In patients with acute PE, we recommend early initiation of VKA (eg, same day as parenteral therapy is started) over delayed initiation, and continuation of parenteral anticoagulation for a minimum of 5 days and until the INR is 2.0 or above for at least 24 h (Grade 1B).

5.4 Choice of Initial Parenteral Anticoagulant Regimen in Patients With PE

5.4.1. In patients with acute PE, we suggest LMWH or fondaparinux over IV UFH (Grade 2C for LMWH; Grade 2B for fondaparinux) and over SC UFH (Grade 2B for LMWH; Grade 2C for fondaparinux).

Remarks: Local considerations such as cost, availability, and familiarity of use dictate the choice between fondaparinux and LMWH. LMWH and fondaparinux are retained in patients with renal impairment, whereas this is not a concern with UFH. In patients with PE where there is concern about the adequacy of SC absorption or in patients in whom thrombolytic therapy is being considered or planned, initial treatment with IV UFH is preferred to use of SC therapies.

5.4.2. In patients with acute PE treated with LMWH, we suggest once- over twice-daily administration (Grade 2C).

Remarks: This recommendation only applies when the approved once-daily regimen uses the same daily dose as the twice-daily regimen (ie, the once-daily injection contains double the dose of each twice-daily injection). It also places value on avoiding an extra injection per day.

5.5 Early vs Standard Discharge of Patients With Acute PE

5.5. In patients with low-risk PE and whose home circumstances are adequate, we suggest early discharge over standard discharge (eg, after first 5 days of treatment) (Grade 2B).
Remarks: Patients who prefer the security of the hospital to the convenience and comfort of home are likely to choose hospitalization over home treatment.

5.6 Systemic Thrombolytic Therapy for Patients With PE

5.6.1.1. In patients with acute PE associated with hypotension (eg, systolic BP < 90 mm Hg) who do not have a high bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2C).

5.6.1.2. In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy (Grade 1C).

5.6.1.3. In selected patients with acute PE not associated with hypotension and with a low bleeding risk whose initial clinical presentation, or clinical course after starting anticoagulant therapy, suggests a high risk of developing hypotension, we suggest administration of thrombolytic therapy (Grade 2C).

5.6.2.1. In patients with acute PE, when a thrombolytic agent is used, we suggest short infusion times (eg, a 2-h infusion) over prolonged infusion times (eg, a 24-h infusion) (Grade 2C).

5.6.2.2. In patients with acute PE when a thrombolytic agent is used, we suggest administration through a peripheral vein over a pulmonary artery catheter (Grade 2C).

5.7 Catheter-Based Thrombus Removal for the Initial Treatment of Patients With PE

5.7. In patients with acute PE associated with hypotension and who have (i) contraindications to thrombolysis, (ii) failed thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect (eg, within hours), if appropriate expertise and resources are available, we suggest catheter-assisted thrombus removal over no such intervention (Grade 2C).

5.8 Surgical Embolectomy for the Initial Treatment of Patients With PE

5.8. In patients with acute PE associated with hypotension, we suggest surgical pulmonary embolectomy over no such intervention if they have (i) contraindications to thrombolysis, (ii) failed thrombolysis or catheter-assisted embolectomy, or (iii) shock that is likely to cause death before thrombolysis can take effect (eg, within hours), provided surgical expertise and resources are available (Grade 2C).

5.9 Vena Cava Filters for the Initial Treatment of Patients With PE

5.9.1. In patients with acute PE who are treated with anticoagulants, we recommend against the use of an IVC filter (Grade 1B).

5.9.2. In patients with acute PE and contraindication to anticoagulation, we recommend the use of an IVC filter (Grade 1B).

5.9.3. In patients with acute PE and an IVC filter inserted as an alternative to anticoagulation, we suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 2B).

Remarks: We do not consider that a permanent IVC filter, of itself, is an indication for extended anticoagulation.

6.0 Long-term Treatment of Patients With PE

6.1. In patients with PE provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B), or (iii) extended therapy (Grade 1B regardless of bleeding risk).

6.2. In patients with PE provoked by a non-surgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B), and (iii) extended therapy if there is a high bleeding risk (Grade 1B). We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Grade 2B).

6.3. In patients with an unprovoked PE, we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B). After 3 months of treatment, patients with unprovoked PE should be evaluated for the risk-benefit ratio of extended therapy.

6.3.1. In patients with a first VTE that is an unprovoked PE and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B).

6.3.2. In patients with a first VTE that is an unprovoked PE and who have a high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy (Grade 1B).
6.3.3. In patients with a second unprovoked VTE, we recommend extended anticoagulant therapy over 3 months of therapy in those who have a low bleeding risk (Grade 1B), and we suggest extended anticoagulant therapy in those with a moderate bleeding risk (Grade 2B).

6.3.4. In patients with a second unprovoked VTE who have a high bleeding risk, we suggest 3 months of therapy over extended therapy (Grade 2B).

6.4. In patients with PE and active cancer, if there is a low or moderate bleeding risk, we recommend extended anticoagulant therapy over 3 months of therapy (Grade 1B), and if there is a high bleeding risk, we suggest extended anticoagulant therapy (Grade 2B).

Remarks: In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

6.5. In patients with PE who are treated with VKA, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) over a lower (INR < 2) or higher (INR 3.0-5.0) range for all treatment durations (Grade 1B).

6.6. In patients with PE and no cancer, we suggest VKA therapy over LMWH for long-term therapy (Grade 2C). For patients with PE and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy (Grade 2C).

6.7. In patients with PE and cancer, we suggest LMWH over VKA therapy (Grade 2B). In patients with PE and cancer who are not treated with LMWH, we suggest VKA over dabigatran or rivaroxaban for long-term therapy (Grade 2C).

Remarks (6.6-6.7): Choice of treatment in patients with and without cancer is sensitive to the individual patient’s tolerance for daily injections, need for laboratory monitoring, and treatment costs. Treatment of VTE with dabigatran or rivaroxaban, in addition to being less burdensome to patients, may prove to be associated with better clinical outcomes than VKA and LMWH therapy. When these guidelines were being prepared (October 2011), postmarketing studies of safety were not available. Given the paucity of currently available data and that new data are rapidly emerging, we give a weak recommendation in favor of VKA and LMWH therapy over dabigatran and rivaroxaban, and we have not made any recommendation in favor of one of the new agents over the other.

6.8. In patients with PE who receive extended therapy, we suggest treatment with the same anticoagulant chosen for the first 3 months (Grade 2C).

6.9. In patients who are incidentally found to have asymptomatic PE, we suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic PE (Grade 2B).

7.1 Pulmonary Thromboendarterectomy, Anticoagulant Therapy, and Vena Cava Filter for the Treatment of Chronic Thromboembolic Pulmonary Hypertension (CTPH)

7.1.1. In patients with CTPH, we recommend extended anticoagulation over stopping therapy (Grade 1B).

7.1.2. In selected patients with CTPH, such as those with central disease under the care of an experienced thromboendarterectomy team, we suggest pulmonary thromboendarterectomy over no pulmonary thromboendarterectomy (Grade 2C).

8.1 Treatment of Patients With Superficial Vein Thrombosis

8.1.1. In patients with superficial vein thrombosis of the lower limb of at least 5 cm in length, we suggest the use of a prophylactic dose of fondaparinux or LMWH for 45 days over no anticoagulation (Grade 2B).

Remarks: Patients who place a high value on avoiding the inconvenience or cost of anticoagulation and a low value on avoiding infrequent symptomatic VTE are likely to decline anticoagulation.

8.1.2. In patients with superficial vein thrombosis who are treated with anticoagulation, we suggest fondaparinux 2.5 mg daily over a prophylactic dose of LMWH (Grade 2C).

9.1 Acute Anticoagulation for Patients With UEDVT

9.1.1. In patients with UEDVT that involves the axillary or more proximal veins, we recommend acute treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such acute treatment (Grade 1B).

9.1.2. In patients with acute UEDVT that involves the axillary or more proximal veins, we suggest LMWH or fondaparinux over IV UFH (Grade 2C) and over SC UFH (Grade 2B).
9.2 Thrombolytic Therapy for the Initial Treatment of Patients With UEDVT

9.2.1. In patients with acute UEDVT that involves the axillary or more proximal veins, we suggest anticoagulant therapy alone over thrombolysis (Grade 2C).

Remarks: Patients who (i) are most likely to benefit from thrombolysis (see text); (ii) have access to CDT; (iii) attach a high value to prevention of PTS; and (iv) attach a lower value to the initial complexity, cost, and risk of bleeding with thrombolytic therapy are likely to choose thrombolytic therapy over anticoagulation alone.

9.2.2. In patients with UEDVT who undergo thrombolysis, we recommend the same intensity and duration of anticoagulant therapy as in similar patients who do not undergo thrombolysis (Grade 1B).

9.3 Long-term Anticoagulation for Patients With UEDVT

9.3.1. In most patients with UEDVT that is associated with a central venous catheter, we suggest that the catheter not be removed if it is functional and there is an ongoing need for the catheter (Grade 2C).

9.3.2. In patients with UEDVT that involves the axillary or more proximal veins, we suggest a minimum duration of anticoagulation of 3 months over a shorter period (Grade 2B).

Remarks: This recommendation also applies if the UEDVT was associated with a central venous catheter that was removed shortly after diagnosis.

9.3.3. In patients who have UEDVT that is associated with a central venous catheter that is removed, we recommend 3 months of anticoagulation over a longer duration of therapy in patients with no cancer (Grade 1B), and we suggest this in patients with cancer (Grade 2C).

9.3.4. In patients who have UEDVT that is associated with a central venous catheter that is not removed, we recommend that anticoagulation is continued as long as the central venous catheter remains over stopping after 3 months of treatment in patients with cancer (Grade 1C), and we suggest this in patients with no cancer (Grade 2C).

9.3.5. In patients who have UEDVT that is not associated with a central venous catheter or with cancer, we recommend 3 months of anticoagulation over a longer duration of therapy (Grade 1B).

9.4 Prevention of PTS of the Arm

9.4. In patients with acute symptomatic UEDVT, we suggest against the use of compression sleeves or venoactive medications (Grade 2C).

9.5 Treatment of Patients With PTS of the Arm

9.5.1. In patients who have PTS of the arm, we suggest a trial of compression bandages or sleeves to reduce symptoms (Grade 2C).

9.5.2. In patients with PTS of the arm, we suggest against treatment with venoactive medications (Grade 2C).

10.0 Patients With Splanchnic Vein Thrombosis

10.1. In patients with symptomatic splanchnic vein thrombosis (portal, mesenteric, and/or splenic vein thromboses), we recommend anticoagulation over no anticoagulation (Grade 1B).

10.2. In patients with incidentally detected splanchnic vein thrombosis (portal, mesenteric, and/or splenic vein thromboses), we suggest no anticoagulation over anticoagulation (Grade 2C).

11.0 Patients With Hepatic Vein Thrombosis

11.1. In patients with symptomatic hepatic vein thrombosis, we suggest anticoagulation over no anticoagulation (Grade 2C).

11.2. In patients with incidentally detected hepatic vein thrombosis, we suggest no anticoagulation over anticoagulation (Grade 2C).

Treatment and Prevention of Heparin-Induced Thrombocytopenia

For further details, see Linkins et al.8

2.1 Platelet Count Monitoring Combined With the 4Ts Score for Patients Receiving Heparin/LMWH

2.1.1. For patients receiving heparin in whom clinicians consider the risk of heparin-induced thrombocytopenia (HIT) to be $>1\%$, we suggest that platelet count monitoring be performed every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first) (Grade 2C).

2.1.2. For patients receiving heparin in whom clinicians consider the risk of HIT to be $<1\%$, we suggest that platelet counts not be monitored (Grade 2C).
3.1 Discontinuation of Heparin or Initiation of VKAs vs Treatment With Nonheparin Anticoagulants

3.1. In patients with HIT complicated by thrombosis (HITT), we recommend the use of nonheparin anticoagulants, in particular lepirudin, argatroban, and danaparoid, over the further use of heparin or LMWH or initiation/continuation of a VKA (Grade 1C).

3.2 Choice of Nonheparin Anticoagulants in Patients With HITT

3.2.1. In patients with HITT who have normal renal function, we suggest the use of argatroban or lepirudin or danaparoid over other nonheparin anticoagulants (Grade 2C).

Remarks: Other factors not covered by our analysis, such as drug availability, cost, and ability to monitor the anticoagulant effect, may influence the choice of agent.

3.2.2. In patients with HITT and renal insufficiency, we suggest the use of argatroban over other nonheparin anticoagulants (Grade 2C).

3.3 Platelet Transfusions

3.3 In patients with HIT and severe thrombocytopenia, we suggest giving platelet transfusions only if bleeding or during the performance of an invasive procedure with a high risk of bleeding (Grade 2C).

3.4 Starting VKAs Before Platelet Recovery

3.4.1. In patients with strongly suspected or confirmed HIT, we recommend against starting VKA until platelets have substantially recovered (i.e., usually to at least 150 × 10^9/L) over starting VKA at a lower platelet count and that the VKA be initially given in low doses (maximum, 5 mg of warfarin or 6 mg phenprocoumon) over using higher doses (Grade 1C).

3.4.2. We further suggest that if a VKA has already been started when a patient is diagnosed with HIT, vitamin K should be administered (Grade 2C).

Remarks: We place a high value on the prevention of venous limb gangrene and a low value on the cost of the additional days of the parental nonheparin anticoagulant.

3.5 Discontinuation of Thrombin Inhibitor After a Minimum of 5 Days of Overlap With VKAs

3.5. In patients with confirmed HIT, we recommend that the VKA be overlapped with a nonheparin anticoagulant for a minimum of 5 days and until the INR is within the target range over shorter periods of overlap and that the INR be rechecked after the anticoagulant effect of the nonheparin anticoagulant has resolved (Grade 1C).

4.1 Discontinuation of Heparin or Initiation of VKAs vs Treatment With Nonheparin Anticoagulants

4.1. In patients with isolated HIT (HIT without thrombosis), we recommend the use of lepirudin or argatroban or danaparoid over the further use of heparin or LMWH or initiation/continuation of a VKA (Grade 1C).

4.2 Choice of Nonheparin Anticoagulants in Patients With Isolated HIT

4.2. In patients with isolated HIT (HIT without thrombosis) who have normal renal function, we suggest the use of argatroban or lepirudin or danaparoid over other nonheparin anticoagulants (Grade 2C).

Remarks: Other factors such as drug availability, cost, and ability to monitor the anticoagulant effect may influence the choice of agent. The dosing considerations are the same as for patients with HITT (see section 3.2). For a recommendation on choice of nonheparin anticoagulants in the setting of renal insufficiency, see Recommendation 3.2.2.

5.1 Patients Who Require Urgent Cardiac Surgery

5.1.1. In patients with acute HIT (thrombocytopenic, HIT antibody positive) or subacute HIT (platelets recovered but still HIT antibody positive) who require urgent cardiac surgery, we suggest the use of bivalirudin over other nonheparin anticoagulants and over heparin plus antiplatelet agents (Grade 2C).

5.1.2. In patients with acute HIT who require nonurgent cardiac surgery, we recommend delaying the surgery (if possible) until HIT has resolved and HIT antibodies are negative (see section 6.1) (Grade 2C).

Remarks: Other factors not covered by our analysis, such as drug availability, cost, and ability to monitor the anticoagulant effect may influence the choice of agent. For recommendations for patients with a past history of HIT (>3 months previous) who require cardiac surgery, see section 6.1.

5.2 Patients Who Require Urgent Percutaneous Coronary Interventions

5.2. In patients with acute HIT or subacute HIT who require percutaneous coronary interventions, we suggest the use of bivalirudin (Grade 2B)
Executive Summary

5.2 Patients Who Require Renal Replacement Therapy

5.2.1. In patients with acute or subacute HIT who require renal replacement therapy, we suggest the use of argatroban or danaparoid over other nonheparin anticoagulants (Grade 2C).

Remarks: Other factors, such as drug availability, cost, and ability to monitor the anticoagulant effect, may influence the choice of agent.

5.3 Patients Who Require Renal Replacement Therapy

5.3.1. In patients with acute or subacute HIT who require renal replacement therapy, we suggest the use of argatroban or danaparoid over other nonheparin anticoagulants (Grade 2C).

Remarks: We acknowledge that the cost of argatroban may be prohibitive at some clinical centers. We further suggest that if the prothrombotic state of HIT appears to have resolved (as seen by normalization of the platelet count), saline flushes during dialysis would be a reasonable option. This suggestion is based on the presumed pathogenesis of thrombosis in this condition and not on the results of clinical trials.

5.3.2. In patients with a past history of HIT who require ongoing renal replacement therapy or catheter locking, we suggest the use of regional citrate over the use of heparin or LMWH (Grade 2C).

5.4 Pregnant Patients

5.4. In pregnant patients with acute or subacute HIT, we suggest danaparoid over other nonheparin anticoagulants (Grade 2C). We suggest the use of lepirudin or fondaparinux only if danaparoid is not available (Grade 2C).

Remarks: Other factors, such as drug availability, cost, and ability to monitor the anticoagulant effect, may influence the choice of agent.

6.1 Patients With a History of HIT Who Require Cardiac Surgery

6.1.1. In patients with a history of HIT who require cardiac surgery, we suggest the use of heparin (short-term use only) over nonheparin anticoagulants (Grade 2C).

6.1.2. In patients with a history of HIT who require cardiac surgery, we suggest the use of nonheparin anticoagulants (see 5.1.1) over heparin or LMWH (Grade 2C).

6.2 Patients Who Require PCI

6.2. In patients with a history of HIT in whom heparin antibodies have been shown to be absent who require cardiac catheterization or percutaneous coronary interventions, the recommended treatment is the same as 5.2.

6.3 Patients Who Require Prophylaxis or Treatment of Thrombosis

6.3. In patients with a past history of HIT who have acute thrombosis (not related to HIT) and normal renal function, we suggest the use of fondaparinux at full therapeutic doses until transition to a VKA can be achieved (Grade 2C).

Antithrombotic Therapy for Atrial Fibrillation

For further details, see You et al.9

2.1 Patients With Nonrheumatic Atrial Fibrillation (AF)

2.1.8. For patients with AF, including those with paroxysmal AF, who are at low risk of stroke (eg, CHADS2 [congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack] score = 0), we suggest no therapy rather than antithrombotic therapy (Grade 2B). For patients who do choose antithrombotic therapy, we suggest aspirin (75 mg to 325 mg once daily) rather than oral anticoagulation (Grade 2B) or combination therapy with aspirin and clopidogrel (Grade 2B).

Remarks: Patients who place an exceptionally high value on stroke reduction and a low value on avoiding bleeding and the burden associated with antithrombotic therapy are likely to choose antithrombotic therapy rather than no antithrombotic therapy. Other factors that may influence the choices above are a consideration of patient-specific bleeding risk and the presence of additional risk factors for stroke, including age 65 to 74 years and female gender, which have been more consistently validated, and vascular disease, which has been less well validated (see section 2.1.12). The presence of multiple non-CHADS2 risk factors for stroke may favor oral anticoagulation therapy.

2.1.9. For patients with AF, including those with paroxysmal AF, who are at intermediate risk of stroke (eg, CHADS2 score = 1), we recommend oral anticoagulation rather than no therapy (Grade 1B). We suggest oral anticoagulation rather than aspirin (75 mg to 325 mg once daily) (Grade 2B) or combination therapy with aspirin and clopidogrel (Grade 2B). For patients
who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), we suggest combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily) (Grade 2B).

Remarks: Patients who place an exceptionally high value on stroke reduction and a low value on avoiding bleeding and the burden associated with anticoagulant therapy are likely to choose oral anticoagulation rather than antiplatelet therapy. Other factors that may influence the choice among antithrombotic therapies are a consideration of bleeding risk and the presence of additional risk factors for stroke, including age 65 to 74 years and female gender, which have been more consistently validated, and vascular disease, which has been less well validated (see section 2.1.12). The presence of multiple additional non-CHADS$_2$ risk factors for stroke may favor oral anticoagulation therapy.

2.1.10. For patients with AF, including those with paroxysmal AF, who are at high risk of stroke (eg, CHADS$_2$ score of 2 or greater) during the first month after placement of a bare-metal stent or the first 3 to 6 months after placement of a drug-eluting stent, we suggest triple therapy (eg, VKA therapy, aspirin, and clopidogrel) rather than dual antiplatelet therapy (eg, aspirin and clopidogrel) (Grade 2C). After this initial period of triple therapy, we suggest a VKA (INR 2.0-3.0) plus a single antiplatelet drug rather than VKA alone (Grade 2C). At 12 months after intracoronary stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1).

For patients with AF at high risk of stroke (eg, CHADS$_2$ score of 2 or greater) during the first month after placement of a bare-metal stent or the first 3 to 6 months after placement of a drug-eluting stent, we suggest triple therapy (eg, VKA therapy, aspirin, and clopidogrel) rather than dual antiplatelet therapy (eg, aspirin and clopidogrel) (Grade 2C). After this initial period of triple therapy, we suggest a VKA (INR 2.0-3.0) plus a single antiplatelet drug rather than VKA alone (Grade 2C). At 12 months after intracoronary stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1).

2.1.11. For patients with AF, including those with paroxysmal AF, for recommendations in favor of oral anticoagulation (including 2.1.9, 2.1.10, and excluding 2.2, 3.1, 3.2, 3.3), we suggest dabigatran 150 mg twice daily rather than adjusted-dose VKA therapy (target INR range, 2.0-3.0) (Grade 2B).

Remarks: Dabigatran is excreted primarily by the kidney. It has not been studied and is contraindicated in patients with severe renal impairment (estimated creatinine clearance of 30 mL/min or less). Clinicians should be aware that there is no antidote for dabigatran.

2.2 Patients With AF and Mitral Stenosis

2.2. For patients with AF and mitral stenosis, we recommend adjusted-dose VKA therapy (target INR range, 2.0-3.0) rather than no therapy, aspirin (75 mg to 325 mg once daily), or combination therapy with aspirin and clopidogrel (all Grade 2B). For patients with AF and mitral stenosis who are unsuitable for or choose not to take adjusted-dose VKA therapy (for reasons other than concerns about major bleeding), we recommend combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily) alone (Grade 1B).

3.1 Patients With AF and Stable Coronary Artery Disease

3.1. For patients with AF and stable coronary artery disease (eg, no acute coronary syndrome within the previous year) and who choose oral anticoagulation, we suggest adjusted-dose VKA therapy alone (target international normalized ratio [INR] range, 2.0-3.0) rather than the combination of adjusted-dose VKA therapy and aspirin (Grade 2C).

3.2 Patients With AF and Placement of an Intracoronary Stent

3.2. For patients with AF at high risk of stroke (eg, CHADS$_2$ score of 0 or 1) during the first 12 months after placement of an intracoronary stent (bare metal or drug eluting), we suggest dual antiplatelet therapy rather than triple therapy (Grade 2C). At 12 months after intracoronary stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1).
3.3 Patients With AF and ACS Who Do Not Undergo Intracoronary Stent Placement

3.3. For patients with AF at intermediate to high risk of stroke (eg, CHADS₂ score of 1 or greater) who experience an acute coronary syndrome and do not undergo intracoronary stent placement, we suggest for the first 12 months, adjusted-dose VKA therapy (INR 2.0-3.0) plus single antiplatelet therapy rather than dual antiplatelet therapy (eg, aspirin and clopidogrel) or triple therapy (eg, warfarin, aspirin, and clopidogrel) (Grade 2C). After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1).

For patients with AF at low risk of stroke (eg, CHADS₂ score of 0), we suggest dual antiplatelet therapy (eg, aspirin and clopidogrel) rather than adjusted-dose VKA therapy (INR 2.0-3.0) plus single antiplatelet therapy or triple therapy (eg, warfarin, aspirin, and clopidogrel) (Grade 2C). After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1).

Remarks: Patients who place an exceptionally high value on stroke reduction and a low value on avoiding bleeding and the burden associated with anticoagulant therapy are likely to choose adjusted-dose VKA therapy plus single antiplatelet therapy rather than dual antiplatelet therapy. Other factors that may influence this choice are a consideration of bleeding risk and the presence of additional non-CHADS₂ risk factors for stroke (see section 2.1.12).

3.4 Patients With AF Managed by a Rhythm Control Strategy

3.4. For patients with AF being managed with a rhythm control strategy (pharmacologic or catheter ablation), we suggest that antithrombotic therapy decisions follow the general risk-based recommendations for patients with AF in section 2.1, regardless of the apparent persistence of normal sinus rhythm (Grade 2C).

3.5 Patients With Atrial Flutter

3.5. For patients with atrial flutter, we suggest that antithrombotic therapy decisions follow the same risk-based recommendations as for AF.

4.1 Patients Undergoing Elective Cardioversion of AF

4.1.1. For patients with AF of greater than 48 h or unknown duration undergoing elective electrical or pharmacologic cardioversion, we recommend therapeutic anticoagulation (adjusted-dose VKA therapy, target INR range 2.0-3.0, low-molecular-weight heparin at full venous thromboembolism treatment doses, or dabigatran) for at least 3 weeks before cardioversion or a transesophageal echocardiography (TEE)-guided approach with abbreviated anticoagulation before cardioversion rather than no anticoagulation (Grade 1B). We recommend therapeutic anticoagulation for at least 4 weeks after successful cardioversion to sinus rhythm rather than no anticoagulation, regardless of the baseline risk of stroke (Grade 1B). Decisions about anticoagulation beyond 4 weeks should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy in section 2.1.

4.1.2. For patients with AF of documented duration of 48 h or less undergoing elective cardioversion (electrical or pharmacologic), we suggest starting anticoagulation at presentation (low-molecular-weight heparin or unfractionated heparin at full venous thromboembolism treatment doses) and proceeding to cardioversion rather than delaying cardioversion for 3 weeks of therapeutic anticoagulation or a TEE-guided approach (Grade 2C). After successful cardioversion to sinus rhythm, we recommend therapeutic anticoagulation for at least 4 weeks rather than no anticoagulation, regardless of baseline stroke risk (Grade 2C). Decisions about long-term anticoagulation after cardioversion should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy in section 2.1.

4.2 Patients Undergoing Urgent Cardioversion for Hemodynamically Unstable AF

4.2. For patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical or pharmacologic), we suggest that therapeutic-dose parenteral anticoagulation be started before cardioversion, if possible (Grade 2C), but that initiation of anticoagulation must not delay any emergency intervention (Grade 2C). After successful cardioversion to sinus rhythm, we suggest therapeutic anticoagulation for at least 4 weeks after successful cardioversion to sinus rhythm rather than no anticoagulation, regardless of baseline stroke risk (Grade 2C). Decisions about anticoagulation beyond 4 weeks should be made in accordance with our risk-based recommendations.
for long-term antithrombotic therapy in section 2.1.

4.3 Patients Undergoing Elective or Urgent Cardioversion for Atrial Flutter

4.3. For patients with atrial flutter undergoing elective or urgent pharmacologic or electrical cardioversion, we suggest that the same approach to thromboprophylaxis be used as for patients with atrial fibrillation undergoing cardioversion.

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**Antithrombotic and Thrombolytic Therapy for Valvular Disease**

For further details, see Whitlock et al.10

2.0 Patients With Rheumatic Mitral Valve Disease

2.0.1. In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter < 55 mm we suggest not using antiplatelet or VKA therapy (Grade 2C).

2.0.2. In patients with rheumatic mitral valve disease and normal sinus rhythm with a left atrial diameter > 55 mm, we suggest VKA therapy (target INR, 2.5; range, 2.0-3.0) over no VKA therapy or antiplatelet (Grade 2C).

2.0.3. For patients with rheumatic mitral valve disease complicated by the presence of left atrial thrombus, we recommend VKA therapy (target INR, 2.5; range, 2.0-3.0) over no VKA or antiplatelet therapy (Grade 2C).

2.0.4. For patients with rheumatic mitral valve disease complicated singly or in combination by the presence of atrial fibrillation or previous systemic embolism, we recommend VKA therapy (target INR, 2.5; range, 2.0-3.0) over no VKA therapy (Grade 1A).

2.1 Patients With Rheumatic Mitral Valve Disease Undergoing Percutaneous Mitral Balloon Valvotomy (PMBV) 5

2.1.1. For patients being considered for PMBV with preprocedural TEE showing left atrial thrombus, we recommend postponement of PMBV and that VKA therapy (target INR, 3.0; range, 2.5-3.5) be administered until thrombus resolution is documented by repeat TEE over no VKA therapy (Grade 1A).

2.1.2. For patients being considered for PMBV with preprocedural TEE showing left atrial thrombus, if the left atrial thrombus does not resolve with VKA therapy, we recommend that PMBV not be performed (Grade 1A).

6.2.1. In patients with asymptomatic patent foramen ovale (PFO) or atrial septal aneurysm, we suggest against antithrombotic therapy (Grade 2C).

6.2 Patients With PFO and Atrial Septal Aneurysm

6.2.2. In patients with cryptogenic stroke and PFO or atrial septal aneurysm, we recommend aspirin (50-100 mg/d) over no aspirin (Grade 1A).

6.2.3. In patients with cryptogenic stroke and PFO or atrial septal aneurysm, who experience recurrent events despite aspirin therapy, we suggest treatment with VKA therapy (target INR, 2.5; range, 2.0-3.0) and consideration of device closure over aspirin therapy (Grade 2C).

6.2.4. In patients with cryptogenic stroke and PFO, with evidence of DVT, we recommend VKA therapy for 3 months (target INR, 2.5; range, 2.0-3.0) and consideration of device closure over no VKA therapy or aspirin therapy (Grade 2C).

7.1 Role of Anticoagulants and Antiplatelet Agents in Patients With Native Valve Endocarditis

7.1.1. In patients with infective endocarditis (IE), we recommend against routine anticoagulant therapy, unless a separate indication exists (Grade 1C).

7.1.2. In patients with IE, we recommend against routine antiplatelet therapy, unless a separate indication exists (Grade 1B).

7.2 Role of Anticoagulants in Patients With Prosthetic Valve Endocarditis

7.2. In patients on VKA for a prosthetic valve who develop IE, we suggest VKA be discontinued at the time of initial presentation until it is clear that invasive procedures will not be required and the patient has stabilized without signs of CNS involvement. When the patient is deemed stable without contraindications or neurologic complications, we suggest reinstitution of VKA therapy (Grade 2C).

7.3 Patients With Nonbacterial Thrombotic Endocarditis

7.3. In patients with nonbacterial thrombotic endocarditis and systemic or pulmonary emboli, we suggest treatment with full-dose IV UFH or SC LMWH over no anticoagulation (Grade 2C).
8.2 Antithrombotic Therapy in the First 3 Months After Surgery

8.2.1. In patients with aortic bioprosthetic valves, who are in sinus rhythm and have no other indication for VKA therapy, we suggest aspirin (50-100 mg/d) over VKA therapy in the first 3 months (Grade 2C).

8.2.2. In patients with transcatheter aortic bioprosthetic valves, we suggest aspirin (50-100 mg/d) plus clopidogrel (75 mg/d) over VKA therapy and no antiplatelet therapy in the first 3 months (Grade 2C).

8.2.3. In patients with a bioprosthetic valve in the mitral position, we suggest VKA therapy (target INR, 2.5; range, 2.0-3.0) over no VKA therapy for the first 3 months after valve insertion (Grade 2C).

8.3 Long-term Antithrombotic Therapy for Patients With Bioprosthetic Valves

8.3. In patients with bioprosthetic valves in normal sinus rhythm, we suggest aspirin therapy over no aspirin therapy after 3 months postoperative (Grade 2C).

9.1 Early Postoperative Bridging to Intermediate/Long-term Therapy (Postoperative Day 0 to 5)

9.1. In patients with mechanical heart valves, we suggest bridging with unfractionated heparin (UFH, prophylactic dose) or LMWH (prophylactic or therapeutic dose) over IV therapeutic UFH until stable on VKA therapy (Grade 2C).

9.2 Long-term Antithrombotic Therapy for Patients With Mechanical Valves

9.2. In patients with mechanical heart valves, we recommend VKA therapy over no VKA therapy for long-term management (Grade 1B).

9.3 Intensity of VKA Therapy for Patients With Mechanical Aortic Valve Prostheses

9.3.1. In patients with a mechanical aortic valve, we suggest VKA therapy with a target of 2.5 (range, 2.0-3.0) over lower targets (Grade 2C).

9.3.2. In patients with a mechanical aortic valve, we recommend VKA therapy with a target of 2.5 (range 2.0-3.0) over higher targets (Grade 1B).

9.4 Intensity of VKA Therapy for Patients With Mechanical Mitral Valve Prostheses

9.4. In patients with a mechanical mitral valve, we suggest VKA therapy with a target of 3.0 (range, 2.5-3.5) over lower INR targets (Grade 2C).

9.5 Intensity of VKA Therapy in Patients With Double Mechanical Valve or With Additional Risk Factors

9.5. In patients with mechanical heart valves in both the aortic and mitral position, we suggest target INR 3.0 (range 2.5-3.5) over target INR 2.5 (range 2.0-3.0) (Grade 2C).

9.6 Antiplatelet Agent in Addition to VKA Therapy for Patients With Mechanical Aortic or Mitral Valve Prostheses

9.6. In patients with a mechanical mitral or aortic valve at low risk of bleeding, we suggest adding over not adding an antiplatelet agent such as low-dose aspirin (50-100 mg/d) to the VKA therapy (Grade 1B).

Remarks: Caution should be used in patients at increased bleeding risk, such as history of GI bleeding.

9.7 Antiplatelet Agent Therapy Instead of VKA Therapy

9.7. For patients with mechanical aortic or mitral valves we recommend VKA over antiplatelet agents (Grade 1B).

10.1 Antithrombotic Therapy After Mitral Valve Repair

10.1. In patients undergoing mitral valve repair with a prosthetic band in normal sinus rhythm, we suggest the use of antiplatelet therapy for the first 3 months over VKA therapy (Grade 2C).

10.2 Patients Undergoing Aortic Valve Repair

10.2. In patients undergoing aortic valve repair, we suggest aspirin at 50 to 100 mg/d over VKA therapy (Grade 2C).

11.1 Patients With Right-Sided Prosthetic Valve Thrombosis

11.1. For patients with right-sided prosthetic valve thrombosis (PVT), in the absence of contraindications we suggest administration of fibrinolytic therapy over surgical intervention (Grade 2C).

11.2 Patients With Left-Sided Prosthetic Valve Thrombosis

11.2.1. For patients with left-sided PVT and large thrombus area ($\geq 0.8$ cm$^2$), we suggest early surgery over fibrinolytic therapy (Grade 2C). If contraindications to surgery exist, we suggest the use of fibrinolytic therapy (Grade 2C).

11.2.2. For patients with left-sided PVT and small thrombus area ($<0.8$ cm$^2$), we suggest...
higher than the associated risks may choose this intervention.

2.4 Aspirin in Patients With Acute Ischemic Stroke
2.4. In patients with acute ischemic stroke or transient ischemic attack (TIA), we recommend early (within 48 h) aspirin therapy at a dose of 160 to 325 mg over no aspirin therapy (Grade 1A).

2.5 Anticoagulation in Patients With Acute Ischemic Stroke
2.5. In patients with acute ischemic stroke or TIA, we recommend early (within 48 h) aspirin therapy with an initial dose of 160 to 325 mg over therapeutic parenteral anticoagulation (Grade 1A).

3.1 VTE Prevention in Patients With Ischemic Stroke
3.1.1. In patients with acute ischemic stroke and restricted mobility, we suggest prophylactic-dose SC UFH or LMWH or intermittent pneumatic compression devices over no prophylaxis (Grade 2B).

3.1.2. In patients with acute ischemic stroke and restricted mobility, we suggest prophylactic-dose LMWH over prophylactic-dose UFH (Grade 2B).

3.1.3. In patients with acute stroke and restricted mobility, we suggest against elastic compression stockings (Grade 2B).

Remarks: Pharmacologic and mechanical prophylaxis should be initiated as early as possible and should be continued throughout the hospital stay or until the patient has regained mobility. Mechanical devices should be temporarily removed as often as needed to allow for early mobilization and screening for skin complications.

Combining pharmacologic therapy with intermittent pneumatic compression devices may yield additional benefit in prevention of VTEs compared with either method used alone.

3.2 VTE Prevention in Patients With Hemorrhagic Stroke
3.2.1. In patients with acute primary intracerebral hemorrhage and restricted mobility, we suggest prophylactic-dose SC heparin (UFH or LMWH) or intermittent pneumatic compression devices over no prophylaxis (Grade 2C).

3.2.2. In patients with acute primary intracerebral hemorrhage and restricted mobility, we suggest prophylactic-dose LMWH over prophylactic-dose UFH (Grade 2B).
3.2.3. In patients with primary intracerebral hemorrhage and restricted mobility, we suggest against elastic compression stockings (Grade 2B).

Remarks: Patients who prefer to avoid a theoretically increased risk of rebleeding with heparin would favor mechanical prophylaxis with intermittent pneumatic compression devices over pharmacologic prophylaxis.

Combining pharmacologic therapy with intermittent pneumatic compression devices may yield additional benefit in prevention of VTEs compared with either method used alone.

4.1 Antithrombotic Therapy for the Secondary Prevention of Noncardioembolic Stroke

4.1.1. In patients with a history of noncardioembolic ischemic stroke or TIA, we recommend long-term treatment with aspirin (75-100 mg once daily), clopidogrel (75 mg once daily), aspirin/extended-release dipyridamole (25 mg/200 mg bid), or cilostazol (100 mg bid) over no antiplatelet therapy (Grade 1A), oral anticoagulants (Grade 1B), the combination of clopidogrel plus aspirin (Grade 1B), or triflusal (Grade 2B).

4.1.2. Of the recommended antiplatelet regimens, we suggest clopidogrel or aspirin/extended-release dipyridamole over aspirin (Grade 2B) or cilostazol (Grade 2C).

Remarks: With long-term use (>5 y), the benefit of clopidogrel over aspirin in preventing major vascular events may be offset by a reduction in cancer-related mortality with regimens that contain aspirin.

4.2 Antithrombotic Therapy for the Secondary Prevention of Cardioembolic Stroke

4.2.1. In patients with a history of ischemic stroke or TIA and AF, including paroxysmal AF, we recommend oral anticoagulation over no antithrombotic therapy (Grade 1A), aspirin (Grade 1B), or combination therapy with aspirin and clopidogrel (Grade 1B).

4.2.2. In patients with a history of ischemic stroke or TIA and atrial fibrillation, including paroxysmal AF, we suggest oral anticoagulation with dabigatran 150 mg bid over adjusted-dose VKA therapy (target range, 2.0-3.0) (Grade 2B).

4.2.3. In patients with a history of ischemic stroke or TIA and atrial fibrillation, including paroxysmal AF, who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), we recommend combination therapy with aspirin and clopidogrel over aspirin (Grade 1B).

Remarks: Patients should be treated (ie, bridged) with aspirin until anticoagulation has reached a therapeutic level.

Oral anticoagulation should generally be initiated within 1 to 2 weeks after stroke onset. Earlier anticoagulation can be considered for patients at low risk of bleeding complications (eg, those with a small infarct burden and no evidence of hemorrhage on brain imaging). Delaying anticoagulation should be considered for patients at high risk of hemorrhagic complications (eg, those with extensive infarct burden or evidence of significant hemorrhagic transformation on brain imaging).

Dabigatran is excreted primarily by the kidney. It has not been studied and is contraindicated in patients with severe renal impairment (estimated creatinine clearance of 30 mL/min or less).

4.3 Antithrombotic Therapy for Stroke Prevention in Patients With a History of Intracerebral Hemorrhage (ICH)

4.3. In patients with a history of a symptomatic primary ICH, we suggest against the long-term use of antithrombotic therapy for the prevention of ischemic stroke (Grade 2C).

Remarks: Patients who might benefit from antithrombotic therapy are those at relatively low risk of recurrent ICH (eg, with deep hemorrhages) and relatively high risk (>7% per year) of thromboembolic events (eg, with mechanical heart valves or CHADS2 (Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, Stroke or TIA) score >4 points).

5.1 Anticoagulation for Patients With Symptomatic Cerebral Venous Sinus Thrombosis

5.1. In patients with cerebral venous sinus thrombosis, we suggest anticoagulation over no anticoagulant therapy during the acute and chronic phases (Grade 2C).

Remarks: Patients with a history of ICH who might benefit from antithrombotic therapy are those at relatively low risk of recurrent ICH (eg, with deep hemorrhages) and relatively high risk (>7% per year) of cardiac thromboembolic events (eg, with mechanical heart valves or CHADS2 score >4 points).

For further details, see Vandvik et al.12

The Primary and Secondary Prevention of Cardiovascular Disease
2.0 Primary Prevention of Cardiovascular Disease

2.1. For persons aged 50 years or older without symptomatic cardiovascular disease, we suggest low-dose aspirin 75 to 100 mg daily over no aspirin therapy (Grade 2B).

Remarks: Aspirin slightly reduces total mortality regardless of cardiovascular risk profile if taken over 10 years. In people at moderate to high risk of cardiovascular events, the reduction in myocardial infarction (MI) is closely balanced with an increase in major bleeds. Whatever their risk status, people who are averse to taking medication over a prolonged time period for very small benefits will be disinclined to use aspirin for primary prophylaxis. Individuals who value preventing an MI substantially higher than avoiding a GI bleed will be, if they are in the moderate or high cardiovascular risk group, more likely to choose aspirin.

3.1 Choice of Long-term Antithrombotic Therapy in Patients With Established Coronary Artery Disease (CAD)

3.1.1-3.1.5. For patients with established coronary artery disease (CAD), defined as patients 1-year post-acute coronary syndrome (ACS), with prior revascularization, coronary stenoses >50% by coronary angiogram, and/or evidence for cardiac ischemia on diagnostic testing, (including patients after the first year post-ACS and/or with prior coronary artery bypass graft [CABG] surgery):

- We recommend long-term single antiplatelet therapy with aspirin 75 to 100 mg daily or clopidogrel 75 mg daily over no antiplatelet therapy (Grade 1A).
- We suggest single over dual antiplatelet therapy with aspirin plus clopidogrel (Grade 2B).

3.2 Choice of Antithrombotic Therapy Following ACS

3.2.1-3.2.5. For patients in the first year after an ACS who have not undergone percutaneous coronary intervention (PCI):

- We recommend dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low-dose aspirin 75-100 mg daily or clopidogrel 75 mg daily plus low-dose aspirin 75-100 mg daily) over single antiplatelet therapy (Grade 1B).
- We suggest ticagrelor 90 mg twice daily plus low-dose aspirin over clopidogrel 75 mg daily plus low-dose aspirin (Grade 2B).

For patients in the first year after an ACS who have undergone PCI with stent placement:

- We recommend dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low-dose aspirin 75-100 mg daily, clopidogrel 75 mg daily plus low-dose aspirin, or prasugrel 10 mg daily plus low-dose aspirin over single antiplatelet therapy) (Grade 1B).

Remarks: Evidence suggests that prasugrel results in no benefit net harm in patients with a body weight of <60 kg. age >75 years, or with a previous stroke/transient ischemic attack.

- We suggest ticagrelor 90 mg twice daily plus low-dose aspirin over clopidogrel 75 mg daily plus low-dose aspirin (Grade 2B).

For patients with ACS who undergo PCI with stent placement, we refer to sections 4.3.1 to 4.3.5 for recommendations concerning minimum and prolonged duration of treatment.

3.2.6-3.2.7. For patients with anterior MI and left ventricular (LV) thrombus, or at high risk for LV thrombus (ejection fraction <40%, anteroapical wall motion abnormality), who do not undergo stenting:

- We recommend warfarin (INR 2.0-3.0) plus low-dose aspirin 75 to 100 mg daily over single antiplatelet therapy or dual antiplatelet therapy for the first 3 months (Grade 1B). Thereafter, we recommend discontinuation of warfarin and continuation of dual antiplatelet therapy for up to 12 months as per the ACS recommendations (see recommendations 3.2.1-3.2.5). After 12 months, single antiplatelet therapy is recommended as per the established CAD recommendations (see recommendations 3.1.1-3.1.5).

For patients with anterior MI and LV thrombus, or at high risk for LV thrombus (ejection fraction <40%, anteroapical wall motion abnormality), who undergo bare-metal stent (BMS) placement:

- We suggest triple therapy (warfarin [INR 2.0-3.0], low-dose aspirin, clopidogrel 75 mg daily) for 1 month over dual antiplatelet therapy (Grade 2C).
- We suggest warfarin (INR 2.0-3.0) and single antiplatelet therapy for the second and third month post-BMS over alternative regimens and alternative time frames for warfarin use (Grade 2C). Thereafter, we recommend discontinuation of warfarin and use of dual antiplatelet therapy for up to 12 months as per the ACS recommendations (see recommendations 3.2.1-3.2.5). After 12 months, antiplatelet therapy is recommended as per the established CAD recommendations (see recommendations 3.1.1-3.1.5).
For patients with anterior MI and LV thrombus, or at high risk for LV thrombus (ejection fraction < 40%, anteropapical wall motion abnormality) who undergo drug-eluting stent (DES) placement:

- We suggest triple therapy (warfarin INR 2.0-3.0, low-dose aspirin, clopidogrel 75 mg daily) for 3 to 6 months over alternative regimens and alternative durations of warfarin therapy (Grade 2C). Thereafter, we recommend discontinuation of warfarin and continuation of dual antiplatelet therapy for up to 12 months as per the ACS recommendations (see recommendations 3.2.1-3.2.5). After 12 months, antiplatelet therapy is recommended as per the established CAD recommendations (see recommendations 3.1.1-3.1.5).

5.0 Antithrombotic Therapy in Patients With Systolic LV Dysfunction

5.1-5.3. For patients with systolic LV dysfunction without established CAD and no LV thrombus, we suggest not to use antiplatelet therapy or warfarin (Grade 2C).

Remarks: Patients who place a high value on an uncertain reduction in stroke and a low value on avoiding an increased risk of GI bleeding are likely to choose to use warfarin.

For patients with systolic LV dysfunction without established CAD with identified acute LV thrombus (e.g., Takotsubo cardiomyopathy), we suggest moderate-intensity warfarin (INR 2.0-3.0) for at least 3 months (Grade 2C).

For patients with systolic LV dysfunction and established CAD, recommendations are as per the established CAD recommendations (see recommendations 3.1.1-3.1.5).

4.0 Antithrombotic Therapy Following Elective PCI

4.1.1-4.3.5. For patients who have undergone elective PCI with placement of BMS:

- For the first month, we recommend dual antiplatelet therapy with aspirin 75 to 325 mg daily and clopidogrel 75 mg daily over single antiplatelet therapy (Grade 1A).
- For the subsequent 11 months, we suggest dual antiplatelet therapy with combination of low-dose aspirin 75 to 100 mg daily and clopidogrel 75 mg daily over single antiplatelet therapy (Grade 2C).
- After 12 months, we recommend single antiplatelet therapy over continuation of dual antiplatelet therapy (Grade 1B).

For patients who have undergone elective PCI with placement of DES:

- For the first 3 to 6 months, we recommend dual antiplatelet therapy with aspirin 75 to 325 mg daily and clopidogrel 75 mg daily over single antiplatelet therapy (Grade 1A).
- After 3 to 6 months, we suggest continuation of dual antiplatelet therapy with low-dose aspirin 75 to 100 mg and clopidogrel (75 mg daily) until 12 months over single antiplatelet therapy (Grade 2C).
- After 12 months, we recommend single antiplatelet therapy over continuation of dual antiplatelet therapy (Grade 1B). Single antiplatelet therapy thereafter is recommended as per the established CAD recommendations (see recommendations 3.1.1-3.1.5).

Antithrombotic Therapy in Peripheral Artery Disease

For further details, see Alonso-Coello et al.13
2.0 Primary Prevention of Cardiovascular Events in Patients with Asymptomatic PAD

2.1. For persons with asymptomatic peripheral arterial disease (PAD), we suggest aspirin 75 to 100 mg daily over no aspirin therapy (Grade 2B).

Remarks: Aspirin slightly reduces total mortality regardless of cardiovascular risk profile if taken over 10 years. In people at moderate to high risk of cardiovascular events, the reduction in myocardial infarction (MI) is closely balanced with an increase in major bleeds. Whatever their risk status, people who are averse to taking medication over a prolonged time period for very small benefits will be disinclined to use aspirin for primary prophylaxis. Individuals who value preventing an MI substantially higher than avoiding a GI bleed, if they are in the moderate or high cardiovascular risk group, will be more likely to choose aspirin.

3.0 Secondary Prevention of Cardiovascular Events in Patients with Symptomatic PAD

3.1-3.4. For secondary prevention patients with symptomatic PAD, we recommend one of the two following antithrombotic regimens to be continued long term over no antithrombotic treatment: aspirin 75 to 100 mg daily or clopidogrel 75 mg daily (all Grade 1A). We suggest not to use dual antiplatelet therapy with aspirin plus clopidogrel (Grade 2B). We recommend not to use an antiplatelet agent with moderate-intensity warfarin (Grade 1B).

4.0 Antithrombotic Therapy for the Management of Patients with Claudication

4.1-4.4. For patients with intermittent claudication refractory to exercise therapy (and smoking cessation), we suggest the use of cilostazol in addition to previously recommended antithrombotic therapies (aspirin 75-100 mg daily or clopidogrel 75 mg daily) (Grade 2C); we suggest against the use of pentoxifylline, heparinoids, or prostanoids (Grade 2C).

5.0 Patients With Critical Limb Ischemia

5.1. For patients with symptomatic PAD and critical leg ischemia/rest pain who are not candidates for vascular intervention, we suggest the use of prostanoids in addition to previously recommended antithrombotic therapies (aspirin 75-100 mg daily or clopidogrel 75 mg daily) (Grade 2C).

Values and preferences: Patients who place a high value on an uncertain reduction in the risk of limb loss and a relatively low value on avoiding a definite increased risk of bleeding are more likely to choose aspirin. than avoidance of a high likelihood of drug-related side effects will be disinclined to take prostanoids.

6.0 Acute Limb Ischemia

6.1-6.3. In patients with acute limb ischemia due to arterial emboli or thrombosis, we suggest immediate systemic anticoagulation with unfractionated heparin over no anticoagulation (Grade 2C); we suggest reperfusion therapy (surgery or IA thrombolysis) over no reperfusion therapy (Grade 2C); we recommend surgery over IA thrombolysis (Grade 1B). In patients undergoing IA thrombolysis, we suggest recombinant tissue-type plasminogen activator (rt-PA) or urokinase over streptokinase (Grade 2C).

7.0 Endovascular Revascularization in Patients With Symptomatic PAD

7.1. For patients undergoing peripheral artery percutaneous transluminal angioplasty with or without stenting, we recommend long-term aspirin (75-100 mg/day) or clopidogrel (Grade 1A). For patients undergoing peripheral artery percutaneous transluminal angioplasty with stenting, we suggest single rather than dual antiplatelet therapy (Grade 2C).

Values and preferences: Patients who place a high value on an uncertain reduction in the risk of limb loss and a relatively low value on avoiding a definite increased risk of bleeding are more likely to choose dual antiplatelet therapy.

8.0 Antithrombotic Therapy Following Peripheral Artery Bypass Graft Surgery

8.1-8.4. We recommend one of the following antithrombotic regimens to be continued long term following peripheral artery bypass graft surgery over no antithrombotic treatment: aspirin 75 to 100 mg daily or clopidogrel 75 mg daily (all Grade 1A). We recommend single antiplatelet therapy over antiplatelet therapy and warfarin (Grade 1B). In patients undergoing below-knee bypass graft surgery with prosthetic grafts, we suggest clopidogrel 75 mg/d plus aspirin (75-100 mg/d) over aspirin alone for 1 year (Grade 2C). For all other patients, we suggest single over dual antiplatelet therapy (Grade 2B).

9.0 Patients With Carotid Artery Stenosis

9.1. For patients with asymptomatic carotid stenosis, we suggest aspirin 75 to 100 mg daily over no aspirin therapy (Grade 2B).
9.2-9.3. In patients with symptomatic carotid stenosis (including recent carotid endarterectomy), we recommend long-term antiplatelet therapy with clopidogrel (75 mg once daily) or aspirin-extended-release dipyridamole (25 mg/200 mg bid) or aspirin (75-100 mg once daily) over no antiplatelet therapy (Grade 1A). We suggest either clopidogrel (75 mg once daily) or aspirin-extended-release dipyridamole (25 mg/200 mg bid) over aspirin (75-100 mg) (Grade 2B).

Remarks: Aspirin slightly reduces total mortality regardless of cardiovascular risk profile if taken over 10 years. In people at moderate to high risk of cardiovascular events, the reduction in MI is closely balanced with an increase in major bleeds. Whatever their risk status, people who are averse to taking medication over a prolonged time period for very small benefits will be disinclined to use aspirin for primary prophylaxis.

9.4-9.5. In patients undergoing catheter-based intervention for peripheral vascular disease, we recommend antiplatelet therapy with clopidogrel (75 mg once daily) or aspirin-extended-release dipyridamole (25 mg/200 mg bid) over aspirin (75 mg once daily) (Grade 1B).

Remarks: Women who are averse to taking medication for very small benefit and those who consider self-injecting a considerable burden will be disinclined to use LMWH for extended thrombosis prophylaxis.

3.0.3. For pregnant women, we suggest limiting the use of fondaparinux and parenteral direct thrombin inhibitors to those with severe allergic reactions to heparin (eg, HIT) who cannot receive danaparoid (Grade 2C).

3.0.4. For pregnant women, we recommend avoiding the use of oral direct thrombin (eg, dabigatran) and anti-Xa (eg, rivaroxaban, apixaban) inhibitors (Grade 1C).

4.0 Use of Antithrombotic Therapy in Nursing Women

4.0.1. For lactating women using warfarin, acenocoumarol, or UFH who wish to breastfeed, we recommend continuing the use of warfarin, acenocoumarol, or UFH (Grade 1A).

4.0.2. For lactating women using LMWH, danaparoid, or r-hirudin who wish to breast-feed, we recommend continuing the use of LMWH, danaparoid, or r-hirudin (Grade 1B).

4.0.3. For breast-feeding women, we suggest alternative anticoagulants rather than fondaparinux (Grade 2C).

4.0.4. For breast-feeding women, we recommend alternative anticoagulants rather than oral direct thrombin (eg, dabigatran) and factor Xa inhibitors (eg, rivaroxaban, apixaban) (Grade 1C).

4.0.5. For lactating women using low-dose aspirin for vascular indications who wish to breastfeed, we suggest continuing this medication (Grade 2C).

5.0 VTE in Patients Using Assisted Reproductive Technology

5.1.1. For women undergoing assisted reproduction, we recommend against the use of routine thrombosis prophylaxis (Grade 1B).

5.1.2. For women undergoing assisted reproduction who develop severe ovarian hyperstimulation syndrome, we suggest thrombosis prophylaxis (prophylactic LMWH) for 3 months postresolution of clinical ovarian hyperstimulation syndrome rather than no prophylaxis (Grade 2C).

Remarks: Women who are averse to taking medication for very small benefit and those who consider self-injecting a considerable burden will be disinclined to use LMWH for extended thrombosis prophylaxis. Given that the absolute benefit decreases as time from the hyperstimulation event increases, such
women will be very disinclined to continue prophylaxis throughout the entire resultant pregnancy.

6.0 VTE Following Cesarean Section

6.2.1. For women undergoing cesarean section without additional thrombosis risk factors, we recommend against the use of thrombosis prophylaxis other than early mobilization (Grade 1B).

6.2.2. For women at increased risk of VTE after cesarean section because of the presence of one major or at least two minor risk factors, we suggest pharmacologic thromboprophylaxis (prophylactic LMWH) or mechanical prophylaxis (elastic stockings or intermittent pneumatic compression) in those with contraindications to anticoagulants while in hospital following delivery rather than no prophylaxis (Grade 2B).

Remarks: The reduced bleeding risk with mechanical prophylaxis should be weighed against the inconvenience of elastic stockings and intermittent pneumatic compression.

6.2.3. For women undergoing cesarean section who are considered to be at very high risk for VTE and who have multiple additional risk factors for thromboembolism that persist in the puerperium, we suggest that prophylactic LMWH be combined with elastic stockings and/or intermittent pneumatic compression over LMWH alone (Grade 2C).

6.2.4. For selected high-risk patients in whom significant risk factors persist following delivery, we suggest extended prophylaxis (up to 6 weeks after delivery) following discharge from the hospital (Grade 2C).

7.0 Treatment of Patients With Proven Acute VTE During Pregnancy

7.1.1. For pregnant women with acute VTE, we recommend therapy with adjusted-dose SC LMWH over adjusted-dose UFH (Grade 1B).

7.1.2. For pregnant women with acute VTE, we recommend LMWH over VKA treatment antenatally (Grade 1A).

7.1.3. For pregnant women with acute VTE, we suggest that anticoagulants should be continued for at least 6 weeks postpartum (for a minimum total duration of therapy of 3 months) in comparison with shorter durations of treatment (Grade 2C).

7.1.4. For pregnant women receiving adjusted-dose LMWH therapy and where delivery is planned, we recommend discontinuation of LMWH at least 24 h prior to induction of labor or cesarean section (or expected time of neuraxial anesthesia) rather than continuing LMWH up until the time of delivery (Grade 1B).

8.0 Prevention of Recurrent VTE in Pregnant Women

8.2.1. For all pregnant women with prior VTE, we suggest postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or VKAs targeted at INR 2.0 to 3.0 rather than no prophylaxis (Grade 2B).

8.2.2. For pregnant women at low risk of recurrent VTE (single episode of VTE associated with a transient risk factor not related to pregnancy or use of estrogen), we suggest clinical vigilance antepartum rather than antepartum prophylaxis (Grade 2C).

8.2.3. For pregnant women at moderate to high risk of recurrent VTE (single unprovoked VTE, pregnancy- or estrogen-related VTE, or multiple prior unprovoked VTE not receiving long-term anticoagulation), we suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH rather than clinical vigilance or routine care (Grade 2C).

8.2.4. For pregnant women receiving long-term VKAs, we suggest adjusted-dose LMWH or 75% of a therapeutic dose of LMWH throughout pregnancy followed by resumption of long-term anticoagulants postpartum, rather than prophylactic-dose LMWH (Grade 2C).

9.0 Prevention of VTE in Pregnant Women With Thromophilia and No Prior VTE

9.2.1. For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and have a positive family history for VTE, we suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or VKAs targeted at INR 2.0 to 3.0 rather than no prophylaxis (Grade 2B).

9.2.2. For pregnant women with all other thrombophilias and no prior VTE who have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis with prophylactic- or intermediate-dose LMWH or, in women who are not protein C or S deficient, VKAs targeted at INR 2.0 to 3.0 rather than routine care (Grade 2C).
9.2.3. For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and who do not have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or VKAs targeted at INR 2.0 to 3.0 rather than routine care (Grade 2B).

9.2.4. For pregnant women with all other thrombophilias and no prior VTE who do not have a positive family history for VTE, we suggest antepartum and postpartum clinical vigilance rather than pharmacologic prophylaxis (Grade 2C).

10.0 Prevention of Pregnancy Complications in Women With Thrombophilia

10.2.1. For women with recurrent early pregnancy loss (three or more miscarriages before 10 weeks of gestation), we recommend screening for antiphospholipid antibodies (APLAs) (Grade 1B).

10.2.2. For women with a history of pregnancy complications, we suggest not to screen for inherited thrombophilia (Grade 2C).

10.2.3. For women who fulfill the laboratory criteria for APLA syndrome and meet the clinical APLA criteria based on a history of three or more pregnancy losses, we recommend antepartum administration of prophylactic- or intermediate-dose UFH or prophylactic LMWH combined with low-dose aspirin, 75 to 100 mg/d, over no treatment (Grade 1B).

10.2.4. For women with inherited thrombophilia and a history of pregnancy complications, we suggest not to use antithrombotic prophylaxis (Grade 2C).

11.0 Prevention of Recurrent Preeclampsia or Pregnancy Loss in Women Without Known Thrombophilia

11.1.1. For women considered at risk for preeclampsia, we recommend low-dose aspirin throughout pregnancy, starting from the second trimester, over no treatment (Grade 1B).

11.2.1. For women with two or more miscarriages but without APLA or thrombophilia, we recommend against antithrombotic prophylaxis (Grade 1B).

12.0 Prevention of Thromboembolism in Pregnant Women With Mechanical Heart Valves

12.1.1. For pregnant women with mechanical heart valves, we recommend one of the following anticoagulant regimens in preference to no anticoagulation (all Grade 1A):

(a) Adjusted-dose bid LMWH throughout pregnancy. We suggest that doses be adjusted to achieve the manufacturer’s peak anti-Xa LMWH 4 h postsubcutaneous-injection or

(b) Adjusted-dose UFH throughout pregnancy administered subcutaneously every 12 h in doses adjusted to keep the mid-interval activated partial thromboplastin time at least twice control or attain an anti-Xa heparin level of 0.35 to 0.70 units/mL or

(c) UFH or LMWH (as above) until the 13th week, with substitution by VKAs until close to delivery when UFH or LMWH is resumed.

Remarks: For pregnant women with mechanical heart valves, the decision regarding the choice of anticoagulant regimen is so value and preference dependent (risk of thrombosis vs risk of fetal abnormalities) that we consider the decision to be completely individualized. Women of childbearing age and pregnant women with mechanical valves, should be counseled about potential maternal and fetal risks associated with various anticoagulant regimens, including continuation of VKAs with substitution by LMWH or UFH close to term, substitution of VKAs by LMWH or UFH until the 13th week and then close to term, and use of LMWH or UFH throughout pregnancy. Usual long-term anticoagulants should be resumed postpartum when adequate hemostasis is assured.

12.1.2. In women judged to be at very high risk of thromboembolism in whom concerns exist about the efficacy and safety of UFH or LMWH as dosed above (eg, older generation prosthesis in the mitral position or history of thromboembolism), we suggest VKAs throughout pregnancy with replacement by UFH or LMWH (as above) close to delivery rather than one of the regimens above (Grade 2C).

Remarks: Women who place a higher value on avoiding fetal risk than on avoiding maternal complications (eg, catastrophic valve thrombosis) are likely to choose LMWH or UFH over VKAs.

12.1.3. For pregnant women with prosthetic valves at high risk of thromboembolism, we suggest the addition of low-dose aspirin, 75 to 100 mg/d (Grade 2C).

ANTITHROMBOTIC THERAPY IN NEONATES AND CHILDREN

For further details, see Monagle et al.15
1.0. We suggest that where possible, pediatric hematologists with experience in thromboembolism manage pediatric patients with thromboembolism (Grade 2C). When this is not possible, we suggest a combination of a neonatologist/pediatrician and adult hematologist supported by consultation with an experienced pediatric hematologist (Grade 2C).

1.1 Heparin in Neonates and Children

1.1. We suggest that therapeutic unfractionated heparin (UFH) in children is titrated to achieve a target range of anti-Xa activity of 0.35 to 0.7 units/mL or an activated partial thromboplastin time range that correlates to this anti-Xa range or to a protamine titration range of 0.2 to 0.4 units/mL (Grade 2C). We suggest that when initiating UFH therapy, UFH boluses be no greater than 75 to 100 units/kg and that boluses be withheld or reduced if there are significant bleeding risks (Grade 2C). We suggest avoiding long-term use of therapeutic UFH in children (Grade 2C).

1.2 LMWH in Neonates and Children

1.2. We suggest, for neonates and children receiving either once- or twice-daily therapeutic LMWH that the drug be monitored to a target anti-Xa activity range of 0.5 to 1.0 units/mL in a sample taken 4 to 6 h after SC injection or 0.5 to 0.8 units/mL in a sample taken 2 to 6 h after SC injection (Grade 2C).

1.3 VKAs in Neonates and Children

1.3. We suggest, for children receiving VKAs, that the drug be monitored to a target INR of 2.5 (range, 2.0-3.0), except in the setting of prosthetic cardiac valves where we suggest adherence to the adult recommendations outlined in the article by Whitlock et al in this supplement (Grade 2C). We suggest that INR monitoring with point-of-care monitors be made available where resources make this possible (Grade 2C).

1.5 Aspirin in Children

1.5. We suggest that when aspirin is used for antiplatelet therapy in children, it is used in doses of 1 to 5 mg/kg per day (Grade 2C).

2.1 VTE in Neonates

2.1. We suggest that central venous access devices (CVADs) or umbilical venous catheters (UVCs) associated with confirmed thrombosis be removed after 3 to 5 days of therapeutic anticoagulation rather than left in situ (Grade 2C).

We suggest either initial anticoagulation or supportive care with radiologic monitoring for extension of thrombosis rather than no follow-up (Grade 2C); however, in previously untreated patients, we recommend the start of anticoagulation if extension occurs (Grade 2C). We suggest that anticoagulation should be with either (1) LMWH or (2) UFH followed by LMWH. We suggest a total duration of anticoagulation of between 6 weeks and 3 months rather than shorter or longer durations (Grade 2C). If either a CVAD or a UVC is still in place on completion of therapeutic anticoagulation, we suggest a prophylactic dose of anticoagulation until such time as the CVAD or UVC is removed (Grade 2C). We suggest against thrombolytic therapy for neonatal VTE unless major vessel occlusion is causing critical compromise of organs or limbs (Grade 2C). We suggest if thrombolysis is required, tissue plasminogen activator (tPA) is used rather than other lytic agents (Grade 2C), and we suggest plasminogen (fresh frozen plasma) administration prior to commencing therapy (Grade 2C).

2.2-2.3 Renal Vein Thrombosis in Neonates

2.2. For unilateral renal vein thrombosis (RVT) in the absence of renal impairment or extension into the inferior vena cava (IVC), we suggest either (1) supportive care with radiologic monitoring for extension of thrombosis (if extension occurs we suggest anticoagulation) or (2) anticoagulation with UFH/LMWH or LMWH in therapeutic doses rather than no therapy. If anticoagulation is used, we suggest a total duration of between 6 weeks and 3 months rather than shorter or longer durations of therapy (Grade 2C). For unilateral RVT that extends into the IVC, we suggest anticoagulation with UFH/LMWH or LMWH for a total duration of between 6 weeks and 3 months (Grade 2C).

2.3. For bilateral RVT with evidence of renal impairment, we suggest anticoagulation with UFH/LMWH or initial thrombolytic therapy with tPA followed by anticoagulation with UFH/LMWH (Grade 2C).

2.4 CVAD Prophylaxis in Neonates

2.4. For neonates with CVADs, we recommend to maintain CVAD patency with UFH continuous infusion at 0.5 units/kg per h over no prophylaxis (Grade 1A) or intermittent local thrombolysis (Grade 2C). For neonates with blocked CVADs, we suggest local thrombolysis after appropriate clinical assessment (Grade 2C).
2.6 Thromboprophylaxis for Neonates and Children With Blalock-Taussig Shunts and Modified Blalock-Taussig Shunts (MBTS)

2.6. For neonates and children having modified MBTS, we suggest intraoperative UFH therapy (Grade 2C). For neonates and children after MBTS surgery, we suggest either aspirin or no antithrombotic therapy as compared with prolonged LMWH or VKAs (Grade 2C).

2.9-2.10 Therapy for Femoral Artery Thrombosis in Neonates and Children

2.9. For neonates and children with acute femoral artery thrombosis, we recommend therapeutic doses of IV UFH as initial therapy compared with aspirin or no therapy (Grade 1B) or LMWH (Grade 2C). We suggest subsequent conversion to LMWH, or else continuation of UFH, to complete 5 to 7 days of therapeutic anticoagulation as compared with a shorter or longer duration (Grade 2C).

2.10. For neonates and children with limb-threatening or organ-threatening (via proximal extension) femoral artery thrombosis who fail to respond to initial UFH therapy and who have no known contraindications, we recommend thrombolysis (Grade 1C). For neonates and children with femoral artery thrombosis, we recommend surgical intervention compared with UFH therapy alone when there is a contraindication to thrombolytic therapy and organ or limb death is imminent (Grade 1C).

2.11 Prophylaxis for Peripheral Arterial Catheters in Neonates and Children

2.11. For neonates and children with peripheral arterial catheters in situ, we recommend UFH continuous infusion at 0.5 units/mL at 1 mL/h compared with normal saline (Grade 1A).

2.12 Therapy for Peripheral Artery Thrombosis Secondary to Peripheral Artery Catheters in Neonates and Children

2.12. For neonates and children with peripheral arterial catheter-related thromboembolism, we suggest immediate removal of the catheter (Grade 2B). For neonates and children with a symptomatic peripheral arterial catheter-related thromboembolism, we suggest UFH anticoagulation with or without thrombolysis or surgical thrombectomy and microvascular repair with subsequent heparin therapy (Grade 2C).

2.13-2.14 Prophylaxis of Umbilical Arterial Catheters in Neonates

2.13. For neonates with umbilical arterial catheters (UACs), we suggest UAC placement in a high rather than a low position (Grade 2B).

2.14. For neonates with UAC, we suggest prophylaxis with a low-dose UFH infusion via the UAC (heparin concentration of 0.25-1 unit/mL, total heparin dose of 25-200 units/kg per day) to maintain patency (Grade 2A).

2.16 Prophylaxis for Cardiac Catheterization in Neonates and Children

2.16. For neonates and children requiring cardiac catheterization via an artery, we recommend administration of IV UFH as thromboprophylaxis over no prophylaxis (Grade 1A) or aspirin (Grade 1B). For neonates and children requiring cardiac catheterization via an artery, we recommend the use of UFH doses of 100 units/kg as a bolus compared with a 50-unit/kg bolus (Grade 1B). In prolonged procedures, we suggest further doses of UFH rather than no further therapy (Grade 2B).

2.17 Cerebral Sinovenous Thrombosis in Neonates

2.17. For neonates with cerebral sinovenous thrombosis (CSVT) without significant intracranial hemorrhage, we suggest anticoagulation, initially with UFH or LMWH and subsequently with LMWH, for a total therapy duration between 6 weeks and 3 months rather than shorter or longer treatment duration (Grade 2C). For neonates with CSVT with significant hemorrhage, we suggest either (1) anticoagulation or (2) supportive care with radiologic monitoring of the thrombosis at 5 to 7 days and anticoagulation if thrombus extension is noted as compared with no therapy (Grade 2C).

2.18-2.20 Arterial Ischemic Stroke in Neonates

2.18. For neonates with a first arterial ischemic stroke (AIS), in the absence of a documented, ongoing cardioembolic source, we suggest supportive care over anticoagulation or aspirin therapy (Grade 2C).

2.19. For neonates with a first AIS and a documented cardioembolic source, we suggest anticoagulation with UFH or LMWH (Grade 2C).

2.20. For neonates with recurrent AIS, we suggest anticoagulant or aspirin therapy (Grade 2C).

2.21 Neonates With Purpura Fulminans

2.21. For neonates with clinical presentations of homozygous protein C deficiency, we recommend administration of either 10 to 20 mL/kg of
fresh frozen plasma every 12 h or protein C concentrate, when available, at 20 to 60 units/kg until the clinical lesions resolve (Grade 1A). For neonates with homozygous protein C deficiency, after initial stabilization, we recommend long-term treatment with VKA (Grade 1C), LMWH (Grade 1C), protein C replacement (Grade 1B), or liver transplantation (Grade 1C) compared with no therapy.

2.22 DVT and PE in Children

2.22.1. In children with first VTE (CVAD and non-CVAD related) we recommend acute anticoagulant therapy with either UFH or LMWH (Grade 1B). We recommend initial treatment with UFH or LMWH for at least 5 days (Grade 1B). For ongoing therapy, we recommend LMWH or UFH. For patients in whom clinicians will subsequently prescribe VKAs, we recommend beginning oral therapy as early as day 1 and discontinuing UFH/LMWH on day 6 or later than day 6 if the INR has not exceeded 2.0 compared with no therapy (Grade 1B).

2.22.2. We suggest that children with idiopathic VTE receive anticoagulant therapy for 6 to 12 months compared with no therapy (Grade 2C).

Values and preferences: Families who place a high value on avoiding the unknown risk of recurrence in the absence of an ongoing risk factor and a lower value on avoiding the inconvenience of therapy or potential impact of therapy on growth and development and bleeding risk associated with anti-thrombotic therapy are likely to choose to continue anticoagulant therapy beyond 6 to 12 months.

2.22.3. In children with secondary VTE (ie, VTE that has occurred in association with a clinical risk factor) in whom the risk factor has resolved, we suggest anticoagulant therapy be administered for 3 months (Grade 2C) as compared with no further therapy. In children who have ongoing, but potentially reversible risk factors, such as active nephrotic syndrome or ongoing aspirinase therapy, we suggest continuing anticoagulant therapy beyond 3 months in either therapeutic or prophylactic doses until the risk factor has resolved (Grade 2C).

2.22.4. In children with recurrent idiopathic VTE, we recommend indefinite treatment with VKAs (Grade 1A).

2.22.5. In children with recurrent secondary VTEs with an existing reversible risk factor for thrombosis, we suggest anticoagulation until resolution of the precipitating factor but for a minimum of 3 months as compared with no further therapy (Grade 2C).

2.22.6. In children with a CVAD in place who have a VTE, if a CVAD is no longer required or is nonfunctioning, we recommend it be removed (Grade 1B). We suggest at least 3 to 5 days of anticoagulation therapy prior to its removal rather than no anticoagulation prior to removal (Grade 2C). If CVAD access is required and the CVAD is still functioning, we suggest that the CVAD remain in situ and the patient given anticoagulants (Grade 2C). For children with a first CVAD-related VTE, we suggest initial management as for secondary VTE as previously described.

2.22.7. In children with CVAD in place who have a VTE and in whom the CVAD remains necessary, we suggest, after the initial 3 months of therapy, that prophylactic doses of VKAs (INR range, 1.5-1.9) or LMWH (anti-Xa level range, 0.1-0.3 units/mL) be given until the CVAD is removed (Grade 2C). If recurrent thrombosis occurs while the patient is receiving prophylactic therapy, we suggest continuing therapeutic doses until the CVAD is removed and for a minimum of 3 months following the VTE (Grade 2C).

2.23 Thrombolysis in Pediatric Patients With DVT

2.23. In children with VTE, we suggest that thrombolysis therapy be used only for life- or limb-threatening thrombosis (Grade 2C). If thrombolysis is used in the presence of physiologically low levels or pathologic deficiencies of plasminogen, we suggest supplementation with plasminogen (Grade 2C). In children with VTE in whom thrombolysis is used, we suggest systemic thrombolysis or catheter-directed thrombolysis, depending on institutional experience and, in the latter case, technical feasibility.

2.24 Thrombectomy and IVC Filter Use in Pediatric Patients With DVT

2.24. In children with life-threatening VTE, we suggest thrombectomy (Grade 2C). In children who have had a thrombectomy, we suggest anticoagulant therapy as per recommendation (2.22) (Grade 2C). In children > 10 kg body weight with lower-extremity VTE and a contraindication to anticoagulation, we suggest placement of a retrievable IVC filter (Grade 2C). In children who receive a filter, we suggest that the filter be removed as soon as possible if thrombosis is not
present in the basket of the filter and when contraindication to anticoagulation is resolved (Grade 2C). In children who receive an IVC filter, we recommend appropriate anticoagulation for VTE (see 1.2) as soon as the contraindication to anticoagulation is resolved (Grade 1C).

2.25 DVT in Children With Cancer

2.25. In children with cancer, we suggest that management of VTE follow the general recommendations for management of VTE in children. We suggest the use of LMWH in the treatment of VTE for a minimum of 3 months until the precipitating factor has resolved (eg, use of asparaginase) (Grade 2C).

Remarks: The presence of cancer, the need for surgery, chemotherapy, or other treatments may modify the risk-benefit ratio for treatment of VTE, and clinicians should consider these factors on an individual basis.

2.26 Children With APLAs and DVT

2.26. For children with VTE in the setting of APLAs, we suggest management as per general recommendations for VTE management in children.

2.27 Children With DVT and Positive Inherited Thrombophilia Testing

2.27. For children with VTE, independent of the presence or absence of inherited thrombophilic risk factors, we suggest that the duration and intensity of anticoagulant therapy as per 2.22.

2.28 Children With VTE and Structurally Abnormally Venous Systems

2.28. For children with first VTE secondary to structural venous abnormalities, we suggest anticoagulation as per other “spontaneous” VTE (2.22) and consideration of subsequent percutaneous or surgical interventions, depending on patient factors and institutional experience. For children with recurrent VTE secondary to structural venous abnormalities, we suggest indefinite anticoagulation unless successful percutaneous or surgical interventions can be performed (Grade 2C).

2.29 Children With Right Atrial Thrombosis

2.29. For children with right atrial thrombosis related to CVAD, we suggest removal of the CVAD with or without anticoagulation, depending on the individual risk factors, compared with leaving the CVAD in situ (Grade 2C). For children with large (>2 cm) mobile right atrial thrombosis, we suggest anticoagulation, with appropriately timed CVAD removal, and consideration of surgical intervention or thrombolysis based on individualized risk-benefit assessment compared with no anticoagulation therapy (Grade 2C).

2.30-2.34 Children With CVADs

2.30. For CVADs, we suggest flushing with normal saline or heparin or intermittent recombinant urokinase to maintain patency as compared with no therapy (Grade 2C). For blocked CVADs, we suggest tPA or recombinant urokinase to restore patency (Grade 2C). If after at least 30 min following local thrombolytic instillation CVAD patency is not restored, we suggest a second dose be administered. If the CVAD remains blocked following two doses of local thrombolytic agent, we suggest radiologic imaging to rule out a CVAD-related thrombosis (Grade 2C).

2.31. For children with short- or medium-term CVADs, we recommend against the use of routine systemic thromboprophylaxis (Grade 1B).

2.34. For children receiving long-term home total parenteral nutrition, we suggest thromboprophylaxis with VKAs (Grade 2C).

2.35 Children Undergoing Glenn Procedure or Bilateral Cavopulmonary Shunt

2.35. For children who have bilateral cavopulmonary shunt, we suggest postoperative UFH (Grade 2C).

2.36 Children Undergoing Fontan Surgery

2.36. For children after Fontan surgery, we recommend aspirin or therapeutic UFH followed by VKAs over no therapy (Grade 1C).

2.37 Insertion of Endovascular Stents in Children

2.37. For children having endovascular stents inserted, we suggest administration of UFH perioperatively (Grade 2C).

2.38 Pediatric Patients With Dilated Cardiomyopathy

2.38. For pediatric patients with cardiomyopathy, we suggest VKAs no later than their activation on a cardiac transplant waiting list (Grade 2C).

Values and preferences: Parents who place a high value on avoiding the inconvenience, discomfort, and limitations of anticoagulant monitoring and a lower value on the uncertain reduction in thrombotic complications are unlikely to choose VKA therapy for their children who are eligible for transplant.
2.39 Children With Primary Pulmonary Hypertension

2.39. For children with primary pulmonary hypertension, we suggest starting anticoagulation with VKAs at the same time as other medical therapy (Grade 2C).

2.40-2.42 Children With Biologic and Mechanical Prosthetic Heart Valves

2.40-2.42. For children with biologic or mechanical prosthetic heart valves, we recommend that clinicians follow the relevant recommendations from the adult population.

2.44 Children With Ventricular Assist Devices (VADs)

2.44. For children with VADs we suggest administration of UFH (Grade 2C). We suggest starting UFH between 8 and 48 h following implantation (Grade 2C). In addition, we suggest antiplatelet therapy (either aspirin or aspirin dipyridamole) to commence within 72 h of VAD placement (Grade 2C). For children with VAD, once clinically stable, we suggest switching from UFH to either LMWH or VKA (target INR 3.0 range, 2.5-3.5) until transplanted or weaned from VAD (Grade 2C).

2.45-2.46 Primary Prophylaxis for Venous Access Related to Hemodialysis

2.45. For patients undergoing hemodialysis via an arteriovenous fistula, we suggest routine use of VKAs or LMWH as fistula thromboprophylaxis as compared with no therapy (Grade 2C).

2.46. For patients undergoing hemodialysis via CVAD, we suggest routine use of VKAs or LMWH for thromboprophylaxis as compared with no therapy (Grade 2C).

2.47 Use of UFH or LMWH in Children Undergoing Hemodialysis

2.47. For children having hemodialysis, we suggest the use of UFH or LMWH during hemodialysis to maintain circuit patency independent of type of vascular access (Grade 2C).

2.48-2.50 Children With Kawasaki Disease

2.48. For children with Kawasaki disease, we recommend aspirin in high doses (80-100 mg/kg per day during the acute phase for up to 14 days) as an antiinflammatory agent, then in lower doses (1-5 mg/kg per day for 6 to 8 weeks) as an antiplatelet agent (Grade 1B). For children with Kawasaki disease, we recommend IV γ-globulin (2 g/kg, single dose) within 10 days of the onset of symptoms (Grade 1A).

2.49. For children with moderate or giant coronary aneurysms following Kawasaki disease, we suggest that warfarin in addition to low-dose aspirin be given as primary thromboprophylaxis (Grade 2C).

2.50. For children with Kawasaki disease who have giant aneurysms and acute coronary artery thrombosis, we suggest thrombolysis or acute surgical intervention (Grade 2C).

2.51 CSVT in Children

2.51. For children with CSVT without significant intracranial hemorrhage, we recommend anticoagulation initially with UFH or LMWH and subsequently with LMWH or VKA for a minimum of 3 months relative to no anticoagulation (Grade 1B). In children who after 3 months of therapy still experience occlusion of CSVT or ongoing symptoms, we suggest administration of a further 3 months of anticoagulation (Grade 2C). For children with CSVT with significant hemorrhage, we suggest initial anticoagulation as for children without hemorrhage or radiologic monitoring of the thrombosis at 5 to 7 days and anticoagulation if thrombus extension is noted at that time (Grade 2C). In children with CSVT and potentially recurrent risk factors (for example, nephrotic syndrome, asparaginase therapy), we suggest prophylactic anticoagulation at times of risk factor recurrence (Grade 2C). We suggest thrombolysis, thrombectomy, or surgical decompression only in children with severe CSVT in whom there is no improvement with initial UFH therapy (Grade 2C).

2.52 AIS in Children

2.52. For children with acute AIS, with or without thrombophilia, we recommend UFH or LMWH or aspirin as initial therapy until dissection and embolic causes have been excluded (Grade 1C). For children with acute AIS, we suggest, once dissection and cardioembolic causes are excluded, daily aspirin prophylaxis for a minimum of 2 years as compared with no antithrombotic therapy (Grade 2C). For children receiving aspirin who have recurrent AIS or transient ischemic attacks (TIAs), we suggest changing to clopidogrel or anticoagulant therapy with LMWH or VKA (Grade 2C). For children with AIS, we recommend against the use of thrombolysis (tPA) or mechanical thrombectomy outside of specific research protocols (Grade 1C).

2.53 Embolic Stroke in Children

2.53. For AIS secondary to cardioembolic causes, we suggest anticoagulant therapy with LMWH
or VKAs for at least 3 months (Grade 2C). For AIS secondary to cardioembolic causes in children with demonstrated right-to-left shunts (e.g., PFO), we suggest surgical closure of the shunt (Grade 2C).

2.54 Cerebral Arterial Dissection Underlying AIS

2.54. For AIS secondary to dissection, we suggest anticoagulant therapy with LMWH or VKAs for at least 6 weeks (Grade 2C). Ongoing treatment will depend on radiologic assessment of degree and extent of stenosis and evidence of recurrent ischemic events.

2.55 Children With Cerebral Vasculopathies

2.55. For children with acute AIS secondary to non-Moyamoya vasculopathy, we recommend UFH or LMWH or aspirin for 3 months as initial therapy compared with no treatment (Grade 1C). For children with AIS secondary to non-Moyamoya vasculopathy, we suggest ongoing antithrombotic therapy should be guided by repeat cerebrovascular imaging.

2.56-2.57 Children With Moyamoya Disease

2.56. For children with acute AIS secondary to Moyamoya, we suggest aspirin over no treatment as initial therapy (Grade 2C).

2.57. For children with Moyamoya, we suggest they be referred to an appropriate center for consideration of revascularization.

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Role of sponsors: The sponsors played no role in the development of these guidelines. Sponsoring organizations cannot recommend panelists or topics, nor are they allowed preparation access to the manuscripts and recommendations. Guideline panel members, including the chair, and members of the Health & Science Policy Committee are blinded to the funding sources. Further details on the Conflict of Interest Policy are available online at http://chestnet.org.

Endorsements: This guideline is endorsed by the American Association for Clinical Chemistry, the American College of Clinical Pharmacy, the American Society of Health-System Pharmacists, the American Society of Hematology, and the International Society of Thrombosis and Hemostasis.

REFERENCES


Gordon H. Guyatt, Susan L. Norris, Sam Schulman, Jack Hirsh, Mark H. Eckman, Elie A. Akl, Mark Crowther, Per Olav Vandvik, John W. Eikelboom, Marian S. McDonagh, Sandra Zelman Lewis, David D. Gutterman, Deborah J. Cook and Holger J. Schünemann

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Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Background: To develop the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: ACCP Evidence-Based Clinical Practice Guidelines (AT9), the American College of Chest Physicians (ACCP) assembled a panel of clinical experts, information scientists, decision scientists, and systematic review and guideline methodologists.

Methods: Clinical areas were designated as articles, and a methodologist without important intellectual or financial conflicts of interest led a panel for each article. Only panel members without significant conflicts of interest participated in making recommendations. Panelists specified the population, intervention and alternative, and outcomes for each clinical question and defined criteria for eligible studies. Panelists and an independent evidence-based practice center executed systematic searches for relevant studies and evaluated the evidence, and where resources and evidence permitted, they created standardized tables that present the quality of the evidence and key results in a transparent fashion.

Results: One or more recommendations relate to each specific clinical question, and each recommendation is clearly linked to the underlying body of evidence. Judgments regarding the quality of evidence and strength of recommendations were based on approaches developed by the Grades of Recommendations, Assessment, Development, and Evaluation Working Group. Panel members constructed scenarios describing relevant health states and rated the disutility associated with these states based on an additional systematic review of evidence regarding patient values and preferences for antithrombotic therapy. These ratings guided value and preference decisions underlying the recommendations. Each topic panel identified questions in which resource allocation issues were particularly important and, for these issues, experts in economic analysis provided additional searches and guidance.

Conclusions: AT9 methodology reflects the current science of evidence-based clinical practice guideline development, with reliance on high-quality systematic reviews, a standardized process for quality assessment of individual studies and the body of evidence, an explicit process for translating the evidence into recommendations, disclosure of financial as well as intellectual conflicts of interest followed by management of disclosed conflicts, and extensive peer review.

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Abbreviations: ACCP = American College of Chest Physicians; AT8 = Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition); AT9 = Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines; GDP = gross domestic product; GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; HSP = Health and Science Policy; PICO = population, intervention, comparator, and outcome; QALY = quality-adjusted life year; RCT = randomized controlled trial; WHO = World Health Organization
This article describes the methodology used for the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (AT9). This methodology incorporates current evidence-based approaches to the appraisal and synthesis of evidence and to the formulation of clinical practice recommendations. The process thus ensures explicit, transparent, evidence-based clinical practice guidelines.

The objective of AT9 is to optimize patient-important health outcomes and the processes of care for patients who have experienced or are at risk for thrombotic events. The targeted users of these guidelines are health-care providers in both primary and specialty care who assist patients in making treatment choices that optimize benefits, minimize harms and burdens, and are consistent with patient values and preferences.

Figure 1 summarizes the process for the development of the AT9 recommendations. The primary responsibility for AT9 rests with the American College of Chest Physicians (ACCP) AT9 Executive Committee. This committee includes two methodologist-clinicians from the previous iteration, Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition) (AT8), published in 20081 (Dr Guyatt, Panel Chair, and Dr Schünemann, Vice Chair of Methodology); a third methodologist-clinician (Dr Akl); a leading thrombosis expert (Dr Crowther, Vice Chair for Thrombosis); and two liaisons with the ACCP Health and Science Policy (HSP) Committee who had also served on the previous guideline Executive Committee (Dr Gutterman, Vice Chair and HSP Liaison, and Dr Lewis, Project Manager).

Articles within AT9 are defined by broad populations (eg, pediatric, obstetric) or clinical conditions (eg, prevention of VTE in medical patients or stroke prophylaxis in atrial fibrillation). In addition, AT9 includes three articles addressing the basic science of oral and parenteral anticoagulants and platelet-active drugs and an article addressing new antithrombotic and thrombolytic drugs.

1.0 Composition and Selection of Topic Panel Members

The ACCP AT9 Executive Committee selected panel members for each article. A topic editor and a deputy editor led each of the AT9 panels issuing recommendations. The topic editor was the person primarily responsible for each article and was required to be a methodologist without serious financial or intellectual conflict of interest for any of the article’s recommendations. In all but one case, the topic editor also was a clinician. The Executive Committee chose these individuals on the basis of their previous experience with guideline development and, in particular, their familiarity with methods developed by the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group.2 These topic editors and all panel members were approved by the ACCP HSP Committee after review of their conflict of interest disclosures (see section 7.0 “Disclosing and Managing Conflicts of Interest”).

Criteria for selection of the remainder of the panel members, including the deputy editor-thrombosis expert, were an established record in the relevant clinical or research area, international and gender representation, and an absence of financial conflicts of interest that were judged unacceptable. Some of the panelists had prior experience on ACCP guidelines in this area and represented the thrombosis community, but there was substantial turnover from the previous edition. After an international request for applications broadcast through multiple medical societies, the Executive Committee nominated individual topic editors and deputy editors and collaborated with them to identify and nominate other topic panel members. The ACCP HSP Committee reviewed all nominees and approved all panel members after review of their...
proven as a result of the magnitude of financial conflicts of interest. Articles associated with recommendations included from seven to 14 panel members. We did not include patients or representatives of specific stakeholder groups on topic panels.

Each topic panel also included a frontline physician working in the relevant area who was neither an expert in thrombosis nor a methodologist or clinical investigator. These individuals were chosen in consultation with the topic editors and the ACCP HSP Committee. These clinicians were charged with the following: (1) proposing important real-world clinical questions on the prevention, diagnosis, and treatment of thrombosis that were not addressed in AT8 and (2) reviewing the draft manuscripts and recommendations to assess the usability of the guidelines and the feasibility of implementation of AT9 recommendations.

To address issues of economic efficiency we included six health economist-physicians on the AT9 topic panels charged with making recommendations. These resource consultants were selected and approved through identical procedures to those for topic editors and panel members. We describe their roles more fully later in this discussion.

**2.0 Ensuring Consistency Across Articles**

We used a number of strategies to ensure consistency across articles, and one of us (M. C.) participated extensively in the formulation of clinical questions for each article. To ensure consistency of judgments regarding bleeding, one of us (S. S.) was responsible for standardizing the approach to bleeding outcomes and participated in multiple topic panels (described in more detail later in this article). Additionally, to ensure consistency in the trade-offs between thrombotic and bleeding events, all articles used the same ratings of values and preferences (also described in more detail later). Because some of the same evidence summaries were relevant to several articles, five individuals were chosen to participate in each of the articles addressing coronary artery disease, stroke, and peripheral arterial disease.

In AT9, prevention of VTE is addressed in three articles as opposed to a single article as was done in AT8. The prevention topic editors and deputy editors and those of the stroke article (which includes thromboprophylaxis recommendations) participated in multiple conference calls to develop and harmonize the approach to prevention and to ensure consistency among final recommendations. Topic editors consulted with one another when issues overlapped. For example, the decision regarding the use of a vitamin K antagonist, aspirin, and clopidogrel simultaneously in patients with atrial fibrillation, valvular disease, and intravascular stents is relevant for the atrial fibrillation,
coronary, and peripheral arterial disease articles. Topic panels deferred to the Evidence-Based Management of Anticoagulant Therapy AT9 topic panel for recommendations related to the dosing and monitoring of anticoagulation therapies.

The AT9 Executive Committee met at least once a month and regularly issued statements of clarification of methods to topic editors and deputy editors (eg, use of fixed- or random-effects models for meta-analysis), conflict of interest, preparation of tables, and issues of style and presentation. All these statements were communicated directly to the topic editors and deputy editors and made available in a central repository accessible to all AT9 panelists. The chair of the Executive Committee (G. H. G.) was available for resolving any challenging issues related to the aforementioned topics. Between September 2009 and September 2010, two members of the Executive Committee (E. A. A. and S. Z. L.) held regular (every 3 months), separate conference calls with each topic editor and deputy editor during which they addressed questions and concerns. Finally, the chair of the Executive Committee reviewed every article to ensure consistency of evidence presentation, evaluation, and writing style.

In terms of writing style, we used consistent language to describe effects that did not reach statistical significance. The approach was as follows:

1. For adverse outcomes (such as thrombosis and bleeding), “A is associated with a trend toward reduced thrombosis” if the lower boundary of the CI around a relative effect is ≤ 0.7 and the upper boundary of the CI is ≤ 1.1 or if the lower boundary of the CI is ≤ 0.8 and the upper boundary of the CI is ≤ 1.05. If the point estimate is > 1.0, the language used was, “A is associated with a trend toward increased bleeding” if the lower boundary of the CI around a relative effect is > 0.9 and the upper boundary of the CI is > 1.3 or if the lower boundary of the CI is > 0.95 and the upper boundary of the CI is > 1.2.
2. “A appears to have little or no effect on thrombosis” if the above conditions are not met, and the boundaries of the CI lie between 0.80 and 1.2.
3. For all other results that fail to exclude a relative risk of 1.0, the language was, “Results failed to demonstrate or exclude a beneficial effect or detrimental effect of A on thrombosis.” Alternative wording with regard to an association is “failed to establish or refute.”

3.0 Evidence Review

3.1 Defining the Clinical Questions—Population, Intervention, Comparator, and Outcome

The thrombosis expert on the Executive Committee (M. C.) along with the deputy editors took primary responsibility for defining the scope of the clinical questions that each article would address. For each question, the topic editor and deputy editor defined the relevant population, alternative management strategies (intervention and comparator), and the outcomes (ie, population, intervention, comparator, and outcome [PICO] format). Each clinical question provided the framework for formulating study inclusion and exclusion criteria and guided the search for relevant evidence (systematic reviews and original studies). Panels typically restricted included studies to randomized controlled trials (RCTs) for intervention questions but included observational studies when there was a paucity of RCT data addressing an intervention and for questions of risk assessment. Readers can find these PICO questions in the first table of each article. One or more recommendations could be formulated for each clinical question. The next subsections (3.2-3.5) deal with the approach to selection of outcomes.

3.2 Patient-Important and Surrogate Outcomes

The outcomes for each clinical question were chosen by the topic editors and their panel members and were generally consistent across articles. Outcomes were restricted to those of importance to patients. Panels considered the burden of anticoagulation therapy as a patient-important outcome when its consideration could tip the balance of benefits and harms. If we found no data for an outcome considered at the outset as patient-important, we nevertheless included uncertainty about the effects of the intervention on that outcome when weighing its benefits and harms.

In the absence of data on patient-important outcomes, surrogates could contribute to the estimation of the effect of an intervention on the outcomes that are important. Examples of surrogate outcomes include asymptomatic venous thrombosis detected by venographic or ultrasound surveillance and the percentage of time that an international normalized ratio was in therapeutic range (used as a surrogate for bleeding and thrombosis in the assessment of the effectiveness of centralized anticoagulation services).

The issue of asymptomatic thrombosis detected by venographic or ultrasound surveillance presented particular challenges to the articles addressing VTE prevention in orthopedic and nonorthopedic surgery populations, an article addressing nonsurgical prophylaxis, and an article addressing stroke prevention. We were explicit in considering the trade-offs between VTE and bleeding events. An article by Guyatt et al in this supplement addresses these issues in some detail.
3.3 Mortality

Options considered in summarizing mortal events were (1) all-cause mortality and (2) mortality related to antithrombotic therapy (ie, deaths from pulmonary emboli and deaths from bleeding). Advantages of the former include its being the most patient-important outcome and the difficulty of ascertaining cause of death. Difficulties ascertaining cause of death may be particularly problematic when adjudication is unblinded and therefore open to bias.

The disadvantage of all-cause mortality is that the signal from antithrombotic therapy-related deaths may be lost in noise from deaths due to other causes. The decision about which mortal outcome to use (all-cause mortality or antithrombotic therapy-related morality) was left to the authors of individual articles. Availability of data sometimes forced the choice of less satisfactory mortal outcomes (eg, death related to pulmonary embolus but not death related to bleeding was reported). When mortality was one of the selected outcomes, we avoided double-counting by documenting nonfatal events for the remaining outcomes (eg, nonfatal thrombosis, nonfatal major bleeding) rather than all such events (fatal and nonfatal).

3.4 Composite End Points

Many of the primary studies we reviewed, particularly in the cardiovascular area, presented evidence in the form of composite end points. Particularly when the patient importance of the component end points and the magnitude of effect of the intervention on the components differ, composite end points can be misleading. Therefore, we present results and base inferences on the effect of interventions on individual outcomes.

3.5 Bleeding

In view of the wide variation in how bleeding was assessed and reported in the included primary studies across chapters, one individual (S. S.) was responsible for standardizing the approach to bleeding outcomes. He worked closely with the Executive Committee and the topic editors and deputy editors to ensure the uniform application of the approaches that were developed.

We began by specifying the bleeding outcomes that we believe patients consider important. We did not consider minor bleeding as incurring a burden that was important in comparison with symptomatic thromboembolic events.

We reported fatal hemorrhage as well as fatal stroke or pulmonary embolism in treatment-related or all-cause mortality. Likewise, hemorrhagic stroke and ischemic stroke were reported as “stroke.” We specified in footnotes the events attributable to each component.

We avoided any double-counting of events; for example, a fatal hemorrhagic stroke would only be reported under mortality. We also attempted to report more specific and homogeneous bleeding outcomes than “major bleeding,” which includes events with a wide range of patient importance and which investigators have defined in different ways. For example, in Falck-Ytter et al, in this supplement, bleeding outcomes of primary interest were (1) bleeding requiring reoperation and (2) other major bleeding. Because some authors, particularly in older studies, failed to define subsets of major bleeding, we were not always able to achieve the desired specificity.

3.6 Identifying the Evidence

To identify the relevant evidence, a team of methodologists and medical librarians at the Oregon Health & Science University Evidence-based Practice Center conducted literature searches of Medline, the Cochrane Library, and the Database of Abstracts of Reviews of Effects. For each article, the team conducted a search for systematic reviews and another for original studies encompassing the main populations and interventions for that article. These searches included studies indexed from week 1, January 2005, forward because AT8 searches were carried out up to that date (search strategies are available on request). Many articles supplemented these searches with more-focused searches addressing specific clinical questions. When clinical questions had not been covered in AT8, searches commenced at a date relevant to each intervention.

Titles and abstracts retrieved from bibliographic database searches generally were screened in duplicate, and full-text articles were retrieved for further review. Consensus on whether individual studies fulfilled inclusion criteria was achieved for each study between two reviewers. If consensus could not be achieved, the topic editor and other topic panelists were brought into the discussion. Deputy editors reviewed lists of included studies from the database searches in order to identify any potentially missed studies. Additional studies identified were then retrieved for further evaluation.

Topic panels also searched the same bibliographic databases for systematic reviews addressing each PICO question. The quality of reviews was assessed using principles embodied in prior instruments addressing methodologic quality of systematic reviews and wherever possible, current high-quality systematic reviews were used as the source of summary estimates. Reviews were also used to identify additional studies to complement the database searches.
4.0 Assessing Studies and Summarizing Evidence

4.1 Evaluating Risk of Bias in Individual Studies

We developed and applied uniform criteria for evaluating the risk of bias associated with individual RCTs based on the criteria recommended by the Cochrane Collaboration1 (Table 1). Although all authors assessed risk of bias for individual studies, because of resource limitations, we summarized the results of the risk of bias (eg, Table 1) for only a minority of the recommendations. Readers can find these assessments in the online data supplements. For most recommendations for which we did not develop such tables, we developed Evidence Profiles (see Table 2) that typically provide information on the risk of bias in footnotes.

We also developed specific criteria for assessing the risk of bias of observational studies (cohort studies with concurrent controls, cohort studies with historical controls, case-control studies, or case series). Again, these were based on the evidence-based domains recommended by the Cochrane Collaboration for observational studies (eg, Table 3).

Studies without internal comparisons were termed “cohort studies without internal controls” if they met the following criteria:

1. A protocol existed before the date of commencement of data collection.
2. A definition of inclusion and exclusion criteria was available.
3. The study reported the number of excluded patients.
4. The study conducted a standardized follow-up, including description of all of the following: schedule of follow-up, investigation of suspected outcomes, and criteria used to define outcomes.
5. The study reported all losses to follow-up.

We labeled studies that did not meet these criteria as “case series.” We did not make a distinction between prospective and retrospective studies because although prospective studies may on average be of higher quality, individual prospective studies may have a significant risk of bias and specific retrospective studies may not. For questions related to risk assessment, we evaluated the risk of bias of individual studies using the following criteria: valid outcome assessment, including blinding when appropriate; adjustment for between-group differences; and minimal loss to follow-up.

4.2 Evaluating Quality of Bodies of Evidence

We assessed evidence across studies on an outcome-by-outcome basis using criteria suggested by the GRADE Working Group.19 We defined quality of evidence as our confidence in the estimate of the effect to support a recommendation.19 RCTs start as high-quality evidence and observational studies as low-quality evidence (Fig 2). Additional factors that affect this rating of quality include the risk of bias (as detailed earlier in this article); precision, consistency, and directness of results; likelihood of publication bias; and presence of very large effects.19 The ACCP adaptation of the GRADE system (Table 4) differs only in that the quality of a body of evidence can be high (A), moderate (B), or low (C) (Fig 2); GRADE also provides a category for very-low-quality evidence.

Often, we found that the quality of the evidence differed across outcomes. For example, in assessing the quality of evidence for thienopyridines vs warfarin in patients undergoing percutaneous coronary interventions, we determined the evidence to be of moderate quality for mortality, nonfatal myocardial infarction, and revascularization but of low quality for major bleeding.

We then made a rating of the quality of the entire body of evidence bearing on the effect of alternative management strategies for each clinical question. In other words, we assessed the quality across outcomes, including both benefits and harms. Quality for each recommendation was the lowest quality rating of the outcomes judged as critical (as opposed to important, but not critical).19

Table 1—[Section 4.1] Methodologic Quality of Randomized Trials: Fondaparinux vs No Fondaparinux for the Treatment of Superficial Vein Thrombosis

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Design</th>
<th>Randomization Concluded</th>
<th>Blinding</th>
<th>Analysis</th>
<th>Stopping Early for Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehoux et al12; CALISTO Study Group, 2010</td>
<td>RCT: randomization sequence generated “using a computer-generated randomization list”</td>
<td>DY: “Through a central telephone system”</td>
<td>Patients: PY; Caregivers: PY; Data collectors: PY; Adjudicators: DY; Data analysts: PN</td>
<td>ITT: DY for efficacy outcomes (as-treated analysis for safety outcomes); Data for primary efficacy assessment available for 98.7% of randomized patients</td>
<td>No</td>
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</table>

CALISTO = Comparison of ARIXTRA in Lower Limb Superficial Thrombophlebitis with placebo; DY = definitely yes; ITT = intent to treat; PN = probably no; PY = probably yes; RCT = randomized controlled trial.
Table 2—[Section 4.1] Evidence Profile: Question: Should LMWH Rather Than VKA be Used for Long-term Treatment of VTE?\textsuperscript{a,13-15}

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Study Event Rates (%)</th>
<th>Summary of Findings</th>
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<tbody>
<tr>
<td></td>
<td>With VKA</td>
<td>With LMWH</td>
</tr>
<tr>
<td>Participants (Studies), Median Follow-up</td>
<td>Risk of Bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>Overall mortality (critical outcome)</td>
<td>2,496 (7 RCTs), 6 mo</td>
<td>No serious risk of bias</td>
</tr>
<tr>
<td>Recurrent symptomatic VTE (critical outcome): DVT and PE</td>
<td>2,727 (8 RCTs), 6 mo</td>
<td>Serious risk of bias</td>
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<tr>
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<tr>
<td>Major bleeding (critical outcome)</td>
<td>2,737 (8 RCTs), 6 mo</td>
<td>No serious risk of bias</td>
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</tbody>
</table>

\textsuperscript{a} Uncertainty about outcome in two RCTs due to inadequate information. \textsuperscript{b} Anticipated absolute effects, with 95% CIs, for the difference in risk between VKA and LMWH. \textsuperscript{c} Evidence from high-quality RCTs. \textsuperscript{d} Adjusted for confounding variables. \textsuperscript{e} Adjusted for confounding variables and other factors. \textsuperscript{f} Adjusted for confounding variables and other factors.
Table 2—Continued

<table>
<thead>
<tr>
<th>Study Event Rates (%)</th>
<th>Relative Risk, RR (95% CI)</th>
<th>Anticipated Absolute Effectab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticipated Absolute Effects of VKA vs. LMWH (95% CI)</td>
<td>Risk With VKA</td>
<td>Risk Difference With LMWH</td>
</tr>
<tr>
<td>(Studies), Median Follow-up</td>
<td>Risk of Bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>100 (1 RCT), 3 mo</td>
<td>Serious</td>
<td>No serious</td>
</tr>
</tbody>
</table>

LMWH = low-molecular-weight heparin; PTS = postthrombotic syndrome; RCT = randomized control trial; RR = risk ratio; VKA = vitamin K agonist. (Kearon C, unpublished data).

aTime frame is 6 mo for all outcomes except PTS, which is 2 y.
bOne study did not report deaths: borderline decision.
cControl event rates from cohort study by Prandoni et al,\(^d\) adjusted to 6-mo time frame.
dOutcome less subjective: borderline decision.
eControl event rates from cohort studies by Prandoni et al\(^d\) and Beth et al\(^d\) adjusted to 6-mo time frame.
fControl event rate comes from observational studies in review by Kahn et al\(^d\) adjusted to 2-y time frame. All patients wore pressure stockings.
gMeta-analysis is based on RCTs as referenced in the article text. The control event rate for mortality comes from this meta-analysis.

\(a\) Limited to LMWH regimens that used ≥50% of the acute treatment dose during the extended phase of treatment.

\(b\) Limited to LMWH regimens that used ≥50% of the acute treatment dose during the extended phase of treatment.
4.3 Estimating Relative and Absolute Effects

Most patient-important outcomes in this guideline are binary or yes-no outcomes (death, stroke, VTE, myocardial infarction, bleeding). In general, relative effects are similar across subgroups of patients, including those with varying baseline risk. Thus, relative risk reduction translates into an absolute risk reduction in such subgroups. For example, in patients with atrial fibrillation, warfarin results in a 66% relative risk reduction in nonfatal stroke. This comes at a cost of inconvenience, lifestyle restrictions, and risk of bleeding. For patients with a CHADS (congestive heart failure, hypertension, age 75 years, diabetes mellitus, stroke) score of 0, the 66% reduction translates into an absolute risk reduction of only 0.5% (5 in 1,000) per year. Many patients consider this reduction not worth the undesirable consequences of warfarin use.

We calculated absolute effects by applying relative risks to estimates of control group risk. For instance, if control group risk of thrombosis is 4% and relative risk with an intervention is 50%, then the absolute difference between intervention and control is 4% of 50%, or 2%, and the number needed to treat to prevent an episode of thrombosis is 100/2 or 50. In many cases, the Summary of Findings tables present effects as events prevented (or caused) per 1,000 patients. In this hypothetical example, the effect would be 20 events per 1,000 patients. Whenever valid prognostic data were available from observational studies, they were used to estimate control group risks. When credible results from observational and prognostic studies were not available, risk estimates from control groups of RCTs were used.

Whenever we identified credible evidence that the relative effects vary across distinguishable subgroups of patients (i.e., interaction between the intervention and an apatient characteristic), we considered the relative and absolute effects separately. We then calculated the associated absolute effects.

### Table 3—[Section 4.1] Methodologic Quality of Observational Studies: Cohort Studies of the Treatment of Heparin-Induced Thrombocytopenia

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Intervention/Control</th>
<th>Study Design</th>
<th>Intervention/Control</th>
<th>Intervention/Control</th>
<th>Effectively Blinded</th>
<th>Loss to Follow-up</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lubenow et al/2005</td>
<td>Lepirudin: bolus 0.4 mg/kg; 0.15 mg/kg; Control: varied (danaparoid, n = 24; phenprocoumon, n = 21; other, n = 30)</td>
<td>Cohort with historical controls</td>
<td>Very</td>
<td>Not close</td>
<td>None</td>
<td>No</td>
<td>Cases and controls both required positive testing for HIT antibodies.</td>
</tr>
<tr>
<td>Lewis et al/2003</td>
<td>Argatroban: 2 mg/kg per min (no bolus); Control: varied (typically heparin discontinuation and oral anticoagulation)</td>
<td>Cohort with historical controls</td>
<td>Somewhat</td>
<td>Not close</td>
<td>None</td>
<td>No</td>
<td>HIT antibody data for cases were not provided.</td>
</tr>
<tr>
<td>Lewis et al/2001</td>
<td>Argatroban: 2 mg/kg per min (no bolus); Control: varied (typically discontinuation of heparin and oral anticoagulation)</td>
<td>Cohort with historical controls</td>
<td>Very</td>
<td>Not close</td>
<td>None</td>
<td>No</td>
<td>Sixty-five percent of cases and controls tested positive for HIT antibodies (remainder tested negative or were not tested).</td>
</tr>
</tbody>
</table>

APTT = activated partial thromboplastin time; HIT = heparin-induced thrombocytopenia.

aAPTT adjusted to 1.5 to 2.5 times baseline APTT (or the mean laboratory normal range if the baseline APTT was unavailable).
bAPTT adjusted to 1.5 to 3.0 times baseline APTT.

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4.4 Considering Subgroup-Specific Relative and Absolute Effects

Most patient-important outcomes in this guideline are binary or yes-no outcomes (death, stroke, VTE, myocardial infarction, bleeding). In general, relative effects are similar across subgroups of patients, including those with varying baseline risk. The evidence summaries (Evidence Profiles and Summary of Findings tables described later in this article) therefore include a presentation of relative effects (where possible as relative risks because they are easier to understand than ORs) of intervention vs control management strategies. Trading off desirable and undesirable consequences (e.g., thrombosis vs bleeding) requires, however, estimates of absolute effect. For example, in patients with a CHADS (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke) score of ≥ 3, the 66% relative risk reduction translates into an absolute risk reduction of 6.5% (65 in 1,000) per year. On the other hand, in patients with a CHADS score of 0, the 66% reduction translates into an absolute risk reduction of only 0.5% (5 in 1,000) per year. Many patients may consider this reduction not worth the undesirable consequences of warfarin use.
Even when the relative effect is the same, the absolute magnitude of treatment effects may differ in patients with varying levels of risk. For instance, although the relative risk reduction of warfarin vs aspirin in stroke prevention for patients with atrial fibrillation is likely close to 50% across risk groups, this translates into an absolute risk reduction of <1% per year in the lowest-risk groups and ~5% per year in the highest-risk groups.

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Quality of Evidence</th>
<th>Lower if</th>
<th>Higher if</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trial</td>
<td>High</td>
<td>Risk of bias</td>
<td>Large effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1 Serious</td>
<td>+1 Large</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2 Very serious</td>
<td>+2 Very large</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td>Inconsistency</td>
<td>Dose response</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1 Serious</td>
<td>+1 Evidence of a gradient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2 Very serious</td>
<td>All plausible confounding</td>
</tr>
<tr>
<td>Observational study</td>
<td>Low</td>
<td>Indirectness</td>
<td>+1 Would reduce a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1 Serious</td>
<td>demonstrated effect or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2 Very serious</td>
<td>spurious effect when</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imprecision</td>
<td>results show no effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1 Serious</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2 Very serious</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Publication bias</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1 Likely</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2 Very likely</td>
<td></td>
</tr>
</tbody>
</table>

| Figure 2. GRADE approach to rating quality of evidence. See Figure 1 legend for expansion of abbreviation. |

<table>
<thead>
<tr>
<th>Table 4—Strength of the Recommendations Grading System</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Grade of Recommendation</th>
<th>Benefit vs Risk and Burdens</th>
<th>Methodologic Strength of Supporting Evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong recommendation, high-quality evidence (1A)</td>
<td>Benefits clearly outweigh risk and burdens or vice versa.</td>
<td>Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.</td>
<td>Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Strong recommendation, moderate-quality evidence (1B)</td>
<td>Benefits clearly outweigh risk and burdens or vice versa.</td>
<td>Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies.</td>
<td>Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td>Strong recommendation, low- or very-low-quality evidence (1C)</td>
<td>Benefits clearly outweigh risk and burdens or vice versa.</td>
<td>Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence.</td>
<td>Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.</td>
</tr>
<tr>
<td>Weak recommendation, high-quality evidence (2A)</td>
<td>Benefits closely balanced with risks and burden.</td>
<td>Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.</td>
<td>The best action may differ depending on circumstances or patient or societal values. Further research is very unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Weak recommendation, moderate-quality evidence (2B)</td>
<td>Benefits closely balanced with risks and burden.</td>
<td>Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies.</td>
<td>Best action may differ depending on circumstances or patient or societal values. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td>Weak recommendation, low- or very-low-quality evidence (2C)</td>
<td>Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced.</td>
<td>Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence.</td>
<td>Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.</td>
</tr>
</tbody>
</table>
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Results
Outcomes
Control
Intervention

Fondaparinux, 2.5 mg Placebo
Primary efficacy outcome:
Primary efficacy outcome:
Patients aged " 18 years with acute symptomatic,
subcutaneous once
for 45 d
-Composite of symptomatic events up to day 47:
13/1,502 vs 88/1,500;
objectively confirmed SVT of the legs
daily for 45 d Use
death from any cause, symptomatic DVT or PE,
RR, 0.15; 95% CI,
Exclusion criteria:
of GCS encouraged
symptomatic extension to the saphenofemoral
0.08-0.26
-Symptoms . 3 wk
for all patients
junction, recurrence of SVT
-DVT or PE at presentation
Secondary efficacy outcomes:
Composite of DVT and
-SVT following sclerotherapy, IV line
-Composite of symptomatic events up to day 77
PE up to day 77: 4/1,502
-SVT within 3 cm of the saphenofemoral junction
-Each component of primary efficacy outcomes
vs 22/1,500; RR, 0.18;
-SVT within the past 3 mo, DVT or PE within the past 6 mo
-Composite of symptomatic PE or DVT
95% CI, 0.06-0.53
-Treated for cancer within the past 6 mo
-Surgery for SVT
-Antithrombotic therapy for . 48 h or NSAID for . 72 h
Safety outcomes (up to day 47 or up to day 77): All other efficacy outcomes:
for current episode of SVT
-Major bleeding
P , .05; major bleeding
-Ligation or stripping
-Nonmajor, minor, total bleeding
by day 47, one event
-Major surgery within 3 mo
-Arterial thromboembolic event
per group; RR, 1
-Bleeding risk
-Pregnant or childbearing age women not using
reliable contraception
GCS 5 graduated compression stockings; NSAID 5 nonsteroidal antiinflammatory drug; PE 5 pulmonary embolism; RR 5 risk ratio; SVT 5 superficial vein thrombosis. See Table 1 for expansion of other
abbreviation.

When resources permitted, we used a standardized
approach for summarizing the evidence and methodology of individual studies (examples in Tables 1, 2, 5).
These summaries appear in the online data supplements. Wherever possible, we report nonfatal events
(eg, nonfatal stroke) so that there is no overlap with
the number of fatal events reported.
For a large number of recommendations, we summarized the quality of the body of evidence (Fig 2)
and estimates of relative and absolute effect of alternative management strategies using the methods
of the GRADE Working Group.23 Evidence Profiles
summarize the quality of the body of evidence and
when evidence comes from randomized trials, generally include a presentation of reviewer assessment of
risk of bias, precision, consistency, directness, and
publication bias associated with each outcome (eg,
see Table 2). As specified in GRADE methodology,19

Decousus et al12;
CALISTO Study
Group/2010

4.6 Summary Tables

Patients

When pooled estimates of effects were not available from existing high-quality systematic reviews,
we performed meta-analyses if the data were sufficiently homogeneous. When pooling two studies,
we used a fixed-effects model. When three or more
studies were available for generating a pooled estimate, we used a random-effects model as the primary
analysis and a fixed-effects model as a secondary
analysis. If there were discrepancies between the
two, we considered the following reasons: If there
was substantial heterogeneity leading to wider CIs
with the random-effects model, we considered that
model more trustworthy, and if the discrepancy was
due to a single large dominant study with a result
substantially different from smaller studies, we considered the fixed-effects model more trustworthy.
We also assessed statistical heterogeneity using both
a x2 test and I2 as well as assessed possible explanations of heterogeneity considering a priori-generated
hypotheses.22

Author/Year

4.5 Conducting Meta-analyses

Table 5—[Section 4.1] Descriptive Table: Randomized Controlled Trials of Fondaparinux vs No Fondaparinux for the Treatment of Superficial Vein Thrombosis

We included control group risks and absolute
effect estimates for different groups in the summaries of effect when (and only when) two conditions
were present. First, we required validated prognostic
models or, at the very least, credible strategies for
clinicians to easily identify higher- and lower-risk
patients. Second, we identified varying risk groups
only when recommendations differed in strength or
direction between groups. Both conditions were met,
for instance, in the atrial fibrillation recommendations in which strong recommendations in favor of
anticoagulation were restricted to the higher-risk
patients.

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the overall quality of evidence represents the lowest quality of any critical outcome.

Evidence Profiles can be found in the online data supplement. The format for these tables was determined through a formal survey of panelists that evaluated the panelists’ preferences for alternative presentations and the impact of these presentations on their understanding of the evidence. The text in the printed version of the AT9 recommendations includes more succinct Summary of Findings tables (eg, see Table 624), which include the overall quality assessment as well as the relative and absolute effect sizes for each outcome. Use of an associated computer program facilitated the production of the Evidence Profiles and Summary of Findings tables.25

5.0 VALUES AND PREFERENCES

Making trade-offs between desirable and undesirable consequences of alternative management strategies—the fundamental process of making recommendations—requires making value and preference judgments. For antithrombotic therapy guidelines, this trade-off involves, in most instances, a reduction in thrombotic events compared with an increase in bleeding events. Ideally, the values and preferences applied to this decision would be the average values and preferences of the patient population. We know, however, that patient values for health outcomes vary substantially from patient to patient. Knowledge of the extent to which patient values and preferences vary is one factor in deciding on the strength of a recommendation. The greater the variability in values and preferences, the more likely a weak recommendation is appropriate.23

To inform these decisions, we conducted a systematic review of the literature bearing on patient values and preferences regarding antithrombotic therapy.26 The methodology of conducting such studies remains to be fully developed, and the area remains underinvestigated. Nevertheless, the results of the review provided guidance for the values and preferences that we adopted for these guidelines.26

As an additional strategy for achieving meaningful value and preference decisions by each topic panel and to facilitate consistency across articles, we conducted a values rating exercise. Topic editors and deputy editors constructed patient scenarios for key outcomes of thrombosis and bleeding relevant to their articles. Then informed by the systematic review of values and preferences, panelists used these scenarios to rate each outcome from 0 (death) to 100 (full health). The mean values of these ratings guided the trade-offs between thrombotic and bleeding events and, thus, the determination of strong

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**Table 6—[Section 4.6] Summary of Findings Table: Prasugrel + Aspirin vs Clopidogrel + Aspirin in Patients With a Recent ACS and PCI**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated Absolute Effect (1-y Time Frame)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular mortality</td>
<td>RR (95% CI) 0.89 (0.7-1.12) 24 deaths per 1,000a 3 fewer deaths per 1,000 (from 7 fewer to 3 more)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>RR (95% CI) 0.76 (0.67-0.85) 95 MI per 1,000a 22 fewer MI per 1,000 (from 33 fewer to 14 fewer)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>RR (95% CI) 1.02 (0.71-1.45) 10 strokes per 1,000a 0 fewer strokes per 1,000 (from 3 fewer to 5 more)</td>
</tr>
<tr>
<td>Major extracranial bleed Non-CABG-related TIMI major bleeding</td>
<td>RR (95% CI) 1.32 (1.03-1.68) 22 major bleeds per 1,000a 6 more major bleeds per 1,000 (from 12 more to 6 more)</td>
</tr>
</tbody>
</table>

Endnotes:

24 GRADE Grades of Recommendations, Assessment, Development, and Evaluation
25 ACS acute coronary syndromes
26 CABG coronary artery bypass graft
27 TIMI thrombolysis in myocardial infarction
28 PCI percutaneous coronary intervention
vs weak recommendations. The scenarios and results of the rating exercise are available in the online data supplements.

The introductory section in each chapter includes a summary, quantitative wherever possible, of the key values and preferences underlying the recommendations. Where value and preference judgments were particularly relevant or controversial, explicit statements of values and preferences accompany individual recommendations.

The literature review revealed extensive heterogeneity of results across studies of patient values and preferences—variability that often is difficult to explain. Both the variability between studies and the considerable variability in values and preferences among patients within studies, mandated circumspection in making strong recommendations. Therefore, we restricted strong recommendations to situations in which the desirable consequences of an intervention substantially and convincingly outweighed the undesirable consequences (or the reverse) and to unusual situations in which there was reason to believe that values and preferences are relatively uniform.

6.0 Resource Use Issues

In addressing resource use (cost) issues in AT9, we followed previously developed principles. In particular, we restricted economic evaluation to recommendations in which it was plausible that resource use considerations might change the direction or strength of the recommendation and in which high-quality economic evaluations were available. When this was not the case, we did not consider resource use in the recommendations.

Six clinicians with the requisite expertise in decision and economic analyses participated in the guideline development process; each article had the benefit of one of these experts as a full committee member. In the following subsections, we present key points in the process of considering resource allocation issues in the recommendations.

6.1 Overview of the Process

Panelists, in consultation with resource use consultants, determined questions for which resource use might change the direction or strength of recommendations. For those questions, we sought high-quality economic analyses. If such analyses were available, we applied the evidence regarding resource use to the relevant recommendation. If net costs or marginal cost-effectiveness ratios were very high, panelists considered rating down the quality of evidence for an intervention from high to low or possibly changing the direction of the recommendation using guides described in section 6.4 “Criteria for Resource Allocation Issues to Affect Recommendations—Thresholds for Cost-Effectiveness.”

6.2 Identifying the Literature

The Oregon Health & Science University Evidence-based Practice Center conducted thorough literature searches for economic analyses relevant to the different AT9 articles. The resource use experts supplemented these by searches focused on the specific questions of interest for each article. The searches were conducted in Medline and the Cochrane Central Register of Clinical Trials. On the basis that data from studies appreciably more than a decade old would not reflect the current situation, searches were restricted to published studies from 1999 forward. Thus, bibliographic database searches encompassed publications from January 1999 forward: The end date varied across articles and ranged between November 2009 and March 2010 when the searches were executed.

6.3 Evaluating the Evidence

A standardized data extraction form was used to ensure uniform evaluation of the quality of relevant economic analyses. Quality assessment was based on published criteria and included specification of perspective of analysis (eg, societal, health system), appropriateness of time horizon (preferably lifetime), use of high-quality evidence for probabilities and rates, use of high-quality sources for costs (eg, primary data, Medicare payments, claims data as proxies), use of appropriate methods for measurement of preferences, and performance of sensitivity analyses to explore uncertainty (both deterministic and probabilistic).

6.4 Criteria for Resource Allocation Issues To Affect Recommendations—Thresholds for Cost-Effectiveness

The results of economic analyses may either increase the strength of an otherwise weak recommendation or weaken the strength of a strong recommendation. If cost-effectiveness studies bolstered an already strong recommendation, no change to the recommendation was necessary. We chose the following thresholds for cost-effectiveness considerations affecting recommendations:

1. When the clinical evidence warrants a strong recommendation for A over B:

   a. Strong recommendation favoring A when high-quality evidence from economic evaluations shows that A costs <3 times the gross domestic
product (GDP) per capita (approximately US $150,000) per quality-adjusted life year (QALY) gained relative to \( B \).

b. Weak recommendation favoring \( A \) when high-quality evidence from economic evaluations shows that \( A \) costs 3 to 5 times the GDP per capita (~$150,000-$250,000) per QALY gained relative to \( B \).

c. Weak recommendation favoring \( B \) when high-quality evidence from economic evaluations shows that \( A \) costs >5 times the GDP per capita (~$250,000) per QALY gained relative to \( B \).

2. When the clinical evidence warrants a weak recommendation for \( A \) over \( B \):

a. Strong recommendation favoring \( A \) if \( A \) results in cost savings of >10% to 20% of the GDP per capita (~$5,000-$10,000) relative to \( B \) (Cost savings must represent all downstream costs and not just the actual cost of the intervention, and analysis must demonstrate a high level of confidence that there is a cost savings.)

b. Continued weak recommendation favoring \( A \) when \( B \) is marginally more costly than \( A \) (<10% the GDP per capita)

c. Continued weak recommendation favoring \( A \) when \( A \) costs 0 to 5 times the GDP per capita per QALY gained relative to \( B \)

d. Weak recommendation favoring \( B \) if \( A \) costs >5 times the GDP per capita (~$250,000) per QALY gained relative to \( B \).

6.5 Extension of Economic Analyses to Low- and Middle-Income Countries

Although certain interventions may be cost-effective in high-income countries (e.g., <$20,000 per QALY gained), in poor countries, $20,000 gained per QALY may be prohibitive. The choice of a threshold will vary depending on who is making resource allocation decisions. To facilitate the use of already published cost-effectiveness analyses, the World Health Organization (WHO), through its WHO-CHOICE (Choosing Interventions that are Cost Effective) program has used criteria suggested by the Commission on Macroeconomics and Health. Interventions that cost <1 times the average per-capita income for a given country or region per QALY gained are considered very cost-effective. Interventions that cost up to three times the average per-capita income per QALY gained are still considered cost-effective, whereas those that exceed this level are not considered to be cost-effective. To facilitate this process, WHO has developed tables of such threshold values for different regions and countries around the world. Thus, the thresholds discussed in the previous section have been defined in terms of GDP per capita. Although referencing thresholds for cost-effectiveness to average per-capita income in middle- and low-income countries can help to extend results of economic analyses performed in high-income countries, such analyses may be less relevant in low-income countries because of significantly different material and labor costs and, thus, may be difficult to extrapolate. Furthermore, the comparator strategies may not be feasible or customary in these locales.

7.0 Disclosing and Managing Conflicts of Interest

All panelists were required to disclose both financial conflicts of interest, such as receipt of funds for consulting with industry, and intellectual conflicts of interest, such as publication of original data bearing directly on a recommendation. Financial and intellectual conflicts of interest were classified as primary (more serious) or secondary (less serious). The operational definition of primary intellectual conflicts of interest included authorship of original studies and peer-reviewed grant funding (government, not-for-profit organizations) directly bearing on a recommendation. The operational definition of primary financial conflicts of interest included consultancies, advisory board membership, and the like from industry. Topic editors had no primary conflicts of interest, as noted. Some deputy editors, who were clinical experts in the topic of the article, had relevant primary conflicts of interest. The ACCP HSP Committee deemed some of these conflicts serious enough to require “management.” Management involved more frequent updates of disclosures than required of the approved panelists without any conflicts and recusal from activities relevant to that conflict.

Topic panel members, including the deputy editor, with primary conflicts related to a particular recommendation did not participate in the final deliberations that led to the decision regarding the direction or strength of a recommendation, nor did they vote on recommendations for which they were primarily conflicted. Panelists with primary conflicts could, however, participate in discussions and offer their opinions on interpretations of the evidence. Readers will find a record of panelist conflicts of interest on a recommendation-by-recommendation basis in the online data supplement.

8.0 Finalizing the Recommendations

8.1 Formulating Recommendations

Following approaches recommended by the GRADE Working Group, the topic editor, in some cases
8.2 Finalizing Recommendations

After completing the steps described previously, the topic panel members without primary conflicts discussed draft recommendations (Fig 1). Initial discussions generally led to a consensus at the article level on the quality of evidence and the direction and strength of recommendations. At least two members of the Executive Committee reviewed in detail drafts of articles, including recommendations. Written critiques were prepared and returned to the authors for revision. Articles were then made available to the entire AT9 panel.

Recommendations on which topic panels had difficulty coming to a consensus were discussed at a final conference in February 2011 attended by the topic editors and deputy editors and at least one other panel member from each article. Prior to the conference, all AT9 panelists updated their conflict of interest disclosures. The ACCP invited a number of clinical organizations with interest in the guideline interest disclosures. The ACCP invited a number of clinical organizations with interest in the guideline to attend the final conference as observers.

At this final conference, a representative of each article presented potentially controversial issues in their article’s recommendations. Following discussion, which included those present and those attending by videoconference, all panelists without primary conflicts of interest voted on each recommendation. The voting process used a GRADE grid and required that for a strong recommendation, ≥80% of those voting had to agree that a strong recommendation was appropriate.39

The AT9 Executive Committee members (G. H. G., M. C., E. A. A., and D. D. G.) harmonized the articles and resolved remaining disagreements among them through facilitated discussion with topic editors and deputy editors without primary conflicts. All major correspondence and decisions at the final conference were recorded in written and audio formats and are available on request to science@chestnet.org.

9.0 Review by ACCP and External Reviewers

The ACCP HSP Committee established a process for the thorough review of all ACCP evidence-based clinical practice guidelines. After final review by the AT9 Executive Committee, the guidelines underwent review by the Cardiovascular and Pulmonary NetWorks of the ACCP, the HSP Committee, and the ACCP Board of Regents. The latter two groups had the right of approval or disapproval but usually worked with the topic panelists and editors to make necessary revisions prior to final approval. Both the HSP Committee and the Board of Regents identified primary reviewers who read the full set of articles, and the remaining HSP Committee members were responsible for reviewing several articles each. The reviewers considered both content and methodology as well as whether there was balanced reporting and adherence to HSP Committee processes. All reviewers were vetted through the same conflict of interest disclosure and management process as described previously. Finally, the Editor in Chief of CHEST read and forwarded the manuscripts for independent, external peer review prior to acceptance for publication. No recommendations or assessments of the quality of the evidence could be changed without the express approval of the topic panel members, AT9 Executive Committee, HSP Committee, and ACCP Board of Regents.

10.0 Organization of Articles

In order to provide a transparent, explicit link among PICO questions, evidence, tables, and recommendations, the section numbering in each article corresponds to numbers in Table 1 in each article, which specifies the patients, interventions, and outcomes for each question. The section numbering also corresponds to the numbering of the recommendations themselves. Evidence Profiles and other tables include these corresponding numbers in brackets in the title, as is true for the online data supplement tables.

11.0 Revisions in the Process Since AT8

AT9 includes improvements from AT8 that reflect the evolution of the science of systematic reviews and clinical practice guidelines. In this supplement,40 some of these improvements include augmented provisions.
to decrease the likelihood of conflict of interest influence, more stringent application of GRADE criteria for evidence and recommendations (both facilitated by methodologists without primary conflicts taking the role of topic editor), and a systematic review of values and preferences to guide the recommendations.

12.0 Limitations of Methods

Although encouraged to use Evidence Profiles and Summary of Findings tables for all recommendations, there were some for which the authors were unable to produce such tables. However, those recommendations used an evidence-based systematic review and assessment of relevant studies. Some recommendations would have benefited from meta-analyses that would have clarified aspects of the evidence. Although panelists were instructed in completing the value and preference rating exercise to estimate patient values and preferences rather than to use their own, we cannot be assured that they succeeded in all instances.41

13.0 Plans for Updating AT9

We plan to continue the tradition of the antithrombotic guidelines to update recommendations when important new studies are published that might change the current recommendations. In March 2011, the ACCP Board of Regents approved a proposal to revise the guideline development and updating process to a “living guidelines” process, whereby the evidence-based guidelines will be periodically assessed and updated as the literature warrants. From 1 year after the publication of this ninth edition onward, all clinical questions or sets of related questions will become their own units. This process will be discussed in greater depth in future publications.

In addition to the published guidelines, ACCP has historically provided clinical resources, including a quick reference to the recommendations, patient education materials, and slide sets for presentations. These resources will continue to be based on the guidelines, but they will be accessed online through the ACCP Web site. In addition, there will be related resources, tools, and links to make the content more easily useful and searchable.

14.0 Conclusion

For AT9, we used an explicit, transparent process that seeks to produce highly relevant and unbiased recommendations for clinical practice. This process involved the a priori specification of clinical questions in the PICO format along with study inclusion and exclusion criteria, an exhaustive search for relevant literature, an evaluation of the risk of bias of included studies, and a rigorous and standardized assessment of the quality of the body of evidence and its translation into recommendations using GRADE Working Group methodologies. We incorporated specification of values and preferences and resource considerations into recommendations where particularly relevant and when such data were available. Finally, we sought to minimize bias potentially introduced by intellectual and financial conflicts of interest by comprehensive disclosure requirements and aggressive management of relevant conflicts.

Acknowledgments

Author contributions: Authors contributed to the AT9 guideline process in the roles described in the article. As Topic Editor and Chair of the guideline, Dr Guyatt oversaw the development of this article.

Dr Guyatt: produced the first draft and was responsible for the final article.

Dr Norris: undertook a major revision of a late draft of the article.

Dr Schulman: took responsibility for sections relevant to their role in AT9 and reviewed and approved the final article.

Dr Hirsh: took responsibility for sections relevant to their role in AT9 and reviewed and approved the final article.

Dr Eckman: took responsibility for sections relevant to their role in AT9 and reviewed and approved the final article.

Dr Akl: took responsibility for sections relevant to their role in AT9 and reviewed and approved the final article.

Dr Crowther: took responsibility for sections relevant to their role in AT9 and reviewed and approved the final article.

Dr Cournos: took responsibility for sections relevant to their role in AT9 and reviewed and approved the final article.

Dr Vanoulis: took responsibility for sections relevant to their role in AT9 and reviewed and approved the final article.

Dr Kuhle: took responsibility for sections relevant to their role in AT9 and reviewed and approved the final article.

Dr Cook: took responsibility for sections relevant to their role in AT9 and reviewed and approved the final article.

Dr Schünemann: took responsibility for sections relevant to their role in AT9 and reviewed and approved the final article.

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“A Patient Specific Decision Support Tool for Bariatric Surgery” (National Institute of Diabetes and Digestive and Kidney Diseases [K23 DK075399]; August 2007–June 2012; no financial support); National Heart, Lung, and Blood Institute (K23 HL085357; June 2008–March 2013; no financial support); and “Cost-Effectiveness of Screening for Chronic Hepatitis B Infection” (Gilead Sciences Inc; March 2008-August 2010; ~$56,000). He has also served as consultant for Savient Pharmaceuticals (“Cost Effectiveness Analysis of Gout Medication”; 2010; ~$300) and as editorial consultant for the ACCP (“Physicians’ Information and Education Resource [PIER]: Module on Pre-Operative Assessment for Bleeding Disorders”; 2006-present; ~$250/yr). Dr Crowther has served on various advisory boards, has assisted in the preparation of educational materials, and has sat on data safety and management boards. His institution has received research funds from the following companies: Leo Pharma A/S, Pfizer Inc, Boehringer Ingelheim GmbH, Bayer Healthcare Pharmaceuticals, Octapharm AG, CSL Behring, and Artisan Pharma. Personal total compensation for these activities over the past 5 years totals less than US $10,000. Dr Eikelboom has received consulting fees and honoraria from AstraZeneca; Boehringer-Ingelheim GmbH; Bristol-Myers Squibb; Corgenix; Daiichi-Sankyo, Inc; Eisai Co, Inc; Eli Lilly and Company; GlaxoSmithKline plc; Haemometrics Corp; McNeil Consumer Healthcare; and Sanofi-Aventis LLC and grants and in-kind support from Accumetrics, Inc; AspirinWorks; Bayer Healthcare Pharmaceuticals; Boehringer Ingelheim GmbH; Bristol-Myers Squibb; Corgenix; Dade Behring Inc; GlaxoSmithKline plc; and Sanofi-Aventis LLC. Dr Gutterman has had the following relationships that are entirely unrelated to the AT9 guidelines: ACCP President, GlaxoSmithKline plc grant to study vasodilation in adipose tissue, National Institutes of Health grant to study human coronary dilation, and G E Healthcare consultation on a study for ECG evaluation of chronic heart disease. Drs Akl and Vandvik are co-chairs of the GRADE Working Group, and Drs Ak and Vandvik are members and prominent contributors to the Grade Working Group. Dr Lewis is a full-time employee of the ACCP. Drs Norris, Schulman, Hirsh, McDonagh, and Cook have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsors played no role in the development of these guidelines. Sponsoring organizations cannot recommend panelists or topics, nor are they allowed prepublishing access to the manuscripts and recommendations. Guideline panel members, including the chair, and members of the Health & Science Policy Committee are blinded to the funding sources. Further details on the Conflict of Interest Policy are available online at http://chestnet.org. 

Endorsements: This guideline is endorsed by the American Association for Clinical Chemistry, the American College of Clinical Pharmacy, the American Society of Health-System Pharmacists, the American Society of Hematology, and the International Society of Thrombosis and Hemostasis.

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Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines


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Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Background: This article addresses the treatment of VTE disease.

Methods: We generated strong (Grade 1) and weak (Grade 2) recommendations based on high-quality (Grade A), moderate-quality (Grade B), and low-quality (Grade C) evidence.

Results: For acute DVT or pulmonary embolism (PE), we recommend initial parenteral anticoagulant therapy (Grade 1B) or anticoagulation with rivaroxaban. We suggest low-molecular-weight heparin (LMWH) or fondaparinux over IV unfractionated heparin (Grade 2C) or subcutaneous unfractionated heparin (Grade 2B). We suggest thrombolytic therapy for PE with hypotension (Grade 2C). For proximal DVT or PE, we recommend treatment of 3 months over shorter periods (Grade 1B). For a first proximal DVT or PE that is provoked by surgery or by a nonsurgical transient risk factor, we recommend 3 months of therapy (Grade 1B; Grade 2B if provoked by a nonsurgical risk factor and low or moderate bleeding risk); that is unprovoked, we suggest extended therapy if bleeding risk is low or moderate (Grade 2B) and recommend 3 months of therapy if bleeding risk is high (Grade 1B); and that is associated with active cancer, we recommend extended therapy (Grade 1B; Grade 2B if high bleeding risk) and suggest LMWH over vitamin K antagonists (Grade 2B). We suggest vitamin K antagonists or LMWH over dabigatran or rivaroxaban (Grade 2B). We suggest thrombolytic therapy for PE with hypotension (Grade 2C). For proximal DVT or PE, we recommend treatment of 3 months over shorter periods (Grade 1B). For a first proximal DVT or PE that is provoked by surgery or by a nonsurgical transient risk factor, we recommend 3 months of therapy (Grade 1B; Grade 2B if provoked by a nonsurgical risk factor and low or moderate bleeding risk); that is unprovoked, we suggest extended therapy if bleeding risk is low or moderate (Grade 2B) and recommend 3 months of therapy if bleeding risk is high (Grade 1B); and that is associated with active cancer, we recommend extended therapy (Grade 1B; Grade 2B if high bleeding risk) and suggest LMWH over vitamin K antagonists (Grade 2B). We suggest vitamin K antagonists or LMWH over dabigatran or rivaroxaban (Grade 2B). We suggest compression stockings to prevent the postthrombotic syndrome (Grade 2C). For extensive superficial vein thrombosis, we suggest prophylactic-dose fondaparinux or LMWH over no anticoagulation (Grade 2B), and suggest fondaparinux over LMWH (Grade 2C).

Conclusion: Strong recommendations apply to most patients, whereas weak recommendations are sensitive to differences among patients, including their preferences.

Abbreviations: CALISTO = Comparison of ARIXTRA in Lower Limb Superficial Thrombophlebitis With Placebo; CDT = catheter-directed thrombolysis; CTPH = chronic thromboembolic pulmonary hypertension; HR = hazard ratio; INR = international normalized ratio; IVC = inferior vena cava; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; PESI = Pulmonary Embolism Severity Index; PREPIC = Prevention du Risque d’Embolie Pulmonaire par Interruption Cave; PTS = postthrombotic (phlebitic) syndrome; RR = risk ratio; rt-PA = recombinant tissue plasminogen activator; SC = subcutaneous; SVT = superficial vein thrombosis; tPA = tissue plasminogen activator; UEDVT = upper-extremity DVT; UFH = unfractionated heparin; VKA = vitamin K antagonist

Summary of Recommendations

Note on Shaded Text: Throughout this guideline, shading is used within the summary of recommendations sections to indicate recommendations that are newly added or have been changed since the publication of Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (5th Edition). Recommendations that remain unchanged are not shaded.

2.1. In patients with acute DVT of the leg treated with vitamin K antagonist (VKA) therapy, we...
recommend initial treatment with parenteral anticoagulation (low-molecular-weight heparin [LMWH], fondaparinux, IV unfractionated heparin [UFH], or subcutaneous [SC] UFH) over no such initial treatment (Grade 1B).

2.2.1. In patients with a high clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C).

2.2.2. In patients with an intermediate clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C).

2.2.3. In patients with a low clinical suspicion of acute VTE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C).

2.3.1. In patients with acute isolated distal DVT of the leg and without severe symptoms or risk factors for extension, we suggest initial anticoagulation with UFH (Grade 2B) over delayed anticoagulation (Grade 2C).

2.3.2. In patients with acute isolated distal DVT of the leg and severe symptoms or risk factors for extension (see text), we suggest initial anticoagulation over serial imaging of the deep veins (Grade 2C).

Remarks: Patients at high risk for bleeding are more likely to benefit from serial imaging. Patients who place a high value on avoiding the inconvenience of repeat imaging and a low value on the inconvenience of treatment and on the potential for bleeding are likely to choose initial anticoagulation over serial imaging.

2.3.3. In patients with acute isolated distal DVT of the leg who are managed with initial anticoagulation, we recommend using the same approach as for patients with acute proximal DVT (Grade 1B).

2.3.4. In patients with acute isolated distal DVT of the leg who are managed with serial imaging, we recommend no anticoagulation if the thrombus does not extend (Grade 1B); we suggest anticoagulation if the thrombus extends but remains confined to the distal veins (Grade 2C); we recommend anticoagulation if the thrombus extends into the proximal veins (Grade 1B).

2.4. In patients with acute DVT of the leg, we recommend early initiation of VKA (eg, same day as parenteral therapy is started) over delayed initiation, and continuation of parenteral anticoagulation for a minimum of 5 days and until the international normalized ratio (INR) is 2.0 or above for at least 24 h (Grade 1B).

2.5.1. In patients with acute DVT of the leg, we suggest LMWH or fondaparinux over IV UFH (Grade 2C) and over SC UFH (Grade 2B for LMWH; Grade 2C for fondaparinux).

Remarks: Local considerations such as cost, availability, and familiarity of use dictate the choice between fondaparinux and LMWH.

LMWH and fondaparinux are retained in patients with renal impairment, whereas this is not a concern with UFH.
2.13.1. In patients with acute DVT of the leg, we recommend against the use of an inferior vena cava (IVC) filter in addition to anticoagulants (Grade 1B).

2.13.2. In patients with acute proximal DVT of the leg and contraindication to anticoagulation, we recommend the use of an IVC filter (Grade 1B).

2.13.3. In patients with acute proximal DVT of the leg and an IVC filter inserted as an alternative to anticoagulation, we suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 2B).

Remarks: We do not consider that a permanent IVC filter, of itself, is an indication for extended anticoagulation.

2.14. In patients with acute DVT of the leg, we suggest early ambulation over initial bed rest (Grade 2C).

Remarks: If edema and pain are severe, ambulation may need to be deferred. As per section 4.1, we suggest the use of compression therapy in these patients.

3.0. In patients with acute VTE who are treated with anticoagulant therapy, we recommend long-term therapy (see section 3.1 for recommended duration of therapy) over stopping anticoagulant therapy after about 1 week of initial therapy (Grade 1B).

3.1.1. In patients with a proximal DVT of the leg provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B), or (iii) extended therapy (Grade 1B regardless of bleeding risk).

3.1.2. In patients with a proximal DVT of the leg provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B), and (iii) extended therapy if there is a high bleeding risk (Grade 1B). We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Grade 2B).

3.1.3. In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical
transient risk factor (see remark), we suggest treatment with anticoagulation for 3 months over treatment of a shorter period (Grade 2C) and recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B) or extended therapy (Grade 1B regardless of bleeding risk).

3.1.4. In patients with an unprovoked DVT of the leg (isolated distal [see remark] or proximal), we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B). After 3 months of treatment, patients with unprovoked DVT of the leg should be evaluated for the risk-benefit ratio of extended therapy.

3.1.4.1. In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B);

3.1.4.2. In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy (Grade 1B).

3.1.4.3. In patients with a first VTE that is an unprovoked isolated distal DVT of the leg (see remark), we suggest 3 months of anticoagulant therapy over extended therapy in those with a low bleeding risk (Grade 2B) and recommend 3 months of anticoagulant treatment in those with a high bleeding risk (Grade 1B).

3.1.4.4. In patients with a second unprovoked VTE, we recommend extended anticoagulant therapy over 3 months of therapy in those who have a low bleeding risk (Grade 1B), and we suggest extended anticoagulant therapy in those with a moderate bleeding risk (Grade 2B).

3.1.4.5. In patients with a second unprovoked VTE who have a high bleeding risk, we suggest 3 months of anticoagulant therapy over extended therapy (Grade 2B).

3.1.5. In patients with DVT of the leg and active cancer, if the risk of bleeding is not high, we recommend extended anticoagulant therapy over 3 months of therapy (Grade 1B), and if there is a high bleeding risk, we suggest extended anticoagulant therapy (Grade 2B).

Remarks (3.1.3, 3.1.4, 3.1.4.3): Duration of treatment of patients with isolated distal DVT refers to patients in whom a decision has been made to treat with anticoagulant therapy; however, it is anticipated that not all patients who are diagnosed with isolated distal DVT will be prescribed anticoagulants (see section 2.3).

In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

3.2. In patients with DVT of the leg who are treated with VKA, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) over a lower (INR < 2) or higher (INR 3.0-5.0) range for all treatment durations (Grade 1B).

3.3.1. In patients with DVT of the leg and no cancer, we suggest VKA therapy over LMWH for long-term therapy (Grade 2C). For patients with DVT and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy (Grade 2C).

3.3.2. In patients with DVT of the leg and cancer, we suggest LMWH over VKA therapy (Grade 2B). In patients with DVT and cancer who are not treated with LMWH, we suggest VKA over dabigatran or rivaroxaban for long-term therapy (Grade 2B).

Remarks (3.3.1-3.3.2): Choice of treatment in patients with and without cancer is sensitive to the individual patient’s tolerance for daily injections, need for laboratory monitoring, and treatment costs.

LMWH, rivaroxaban, and dabigatran are retained in patients with renal impairment, whereas this is not a concern with VKA.

Treatment of VTE with dabigatran or rivaroxaban, in addition to being less burdensome to patients, may prove to be associated with better clinical outcomes than VKA and LMWH therapy. When these guidelines were being prepared (October 2011), postmarketing studies of safety were not available. Given the paucity of currently available data and that new data are rapidly emerging, we give a weak recommendation in favor of VKA and LMWH therapy over dabigatran and rivaroxaban, and we have not made any recommendations in favor of one of the new agents over the other.

3.4. In patients with DVT of the leg who receive extended therapy, we suggest treatment with the...
3.5. In patients who are incidentally found to have asymptomatic DVT of the leg, we suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic DVT (Grade 2B).

4.1. In patients with acute symptomatic DVT of the leg, we suggest the use of compression stockings (Grade 2B).

Remarks: Compression stockings should be worn for 2 years, and we suggest beyond that if patients have developed PTS and find the stockings helpful.

Patients who place a low value on preventing PTS or a high value on avoiding the inconvenience and discomfort of stockings are likely to decline stockings.

4.2.1. In patients with PTS of the leg, we suggest a trial of compression stockings (Grade 2C).

4.2.2. In patients with severe PTS of the leg that is not adequately relieved by compression stockings, we suggest a trial of an intermittent compression device (Grade 2B).

4.3. In patients with PTS of the leg, we suggest that vasoactive medications (eg, rutosides, defibrotide, and hidrosmim) not be used (Grade 2C).

Remarks: Patients who value the possibility of response over the risk of side effects may choose to undertake a therapeutic trial.

5.1. In patients with acute PE, we recommend initial treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such initial treatment (Grade 1B).

5.2.1. In patients with a high clinical suspicion of acute PE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C).

5.2.2. In patients with an intermediate clinical suspicion of acute PE, we suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C).

5.2.3. In patients with a low clinical suspicion of acute PE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C).

5.3. In patients with acute PE, we recommend early initiation of VKA (eg, same day as parenteral therapy is started) over delayed initiation, and continuation of parenteral anticoagulation for a minimum of 5 days and until the INR is 2.0 or above for at least 24 h (Grade 1B).

5.4.1. In patients with acute PE, we suggest LMWH or fondaparinux over IV UFH (Grade 2C for LMWH; Grade 2B for fondaparinux) and over SC UFH (Grade 2B for LMWH; Grade 2C for fondaparinux).

Remarks: Local considerations such as cost, availability, and familiarity of use dictate the choice between fondaparinux and LMWH.

LMWH and fondaparinux are retained in patients with renal impairment, whereas this is not a concern with UFH.

In patients with PE where there is concern about the adequacy of SC absorption or in patients in whom thrombolytic therapy is being considered or planned, initial treatment with IV UFH is preferred to use of SC therapies.

5.4.2. In patients with acute PE treated with LMWH, we suggest once- over twice-daily administration (Grade 2C).

Remarks: This recommendation only applies when the approved once-daily regimen uses the same daily dose as the twice-daily regimen (ie, the once-daily injection contains double the dose of each twice-daily injection). It also places value on avoiding an extra injection per day.

5.5. In patients with low-risk PE and whose home circumstances are adequate, we suggest early discharge over standard discharge (eg, after first 5 days of treatment) (Grade 2B).

Remarks: Patients who prefer the security of the hospital to the convenience and comfort of home are likely to choose hospitalization over home treatment.

5.6.1.1. In patients with acute PE associated with hypotension (eg, systolic BP <90 mm Hg) who do not have a high bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2C).

5.6.1.2. In most patients with acute PE not associated with hypotension, we recommend against...
systemically administered thrombolytic therapy (Grade 1C).

5.6.1.3. In selected patients with acute PE not associated with hypotension and with a low bleeding risk whose initial clinical presentation, or clinical course after starting anticoagulant therapy, suggests a high risk of developing hypotension, we suggest administration of thrombolytic therapy (Grade 2C).

5.6.2.1. In patients with acute PE, when a thrombolytic agent is used, we suggest short infusion times (eg, a 2-h infusion) over prolonged infusion times (eg, a 24-h infusion) (Grade 2C).

5.6.2.2. In patients with acute PE when a thrombolytic agent is used, we suggest administration through a peripheral vein over a pulmonary artery catheter (Grade 2C).

5.7. In patients with acute PE associated with hypotension and who have (i) contraindications to thrombolysis, (ii) failed thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect (eg, within hours), if appropriate expertise and resources are available, we suggest catheter-assisted thrombus removal over no such intervention (Grade 2C).

5.8. In patients with acute PE associated with hypotension, we suggest surgical pulmonary embolectomy over no such intervention if they have (i) contraindications to thrombolysis, (ii) failed thrombolysis or catheter-assisted embolectomy, or (iii) shock that is likely to cause death before thrombolysis can take effect (eg, within hours), provided surgical expertise and resources are available (Grade 2C).

5.9.1. In patients with acute PE who are treated with anticoagulants, we recommend against the use of an IVC filter (Grade 1B).

5.9.2. In patients with acute PE and contraindication to anticoagulation, we recommend the use of an IVC filter (Grade 1B).

5.9.3. In patients with acute PE and an IVC filter inserted as an alternative to anticoagulation, we suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 2B).

Remarks: We do not consider that a permanent IVC filter, of itself, is an indication for extended anticoagulation.

6.1. In patients with PE provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B), or (iii) extended therapy (Grade 1B regardless of bleeding risk).

6.2. In patients with PE provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B), and (iii) extended therapy if there is a high bleeding risk (Grade 1B). We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Grade 2B).

6.3. In patients with an unprovoked PE, we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B). After 3 months of treatment, patients with unprovoked PE should be evaluated for the risk-benefit ratio of extended therapy.

6.3.1. In patients with a first VTE that is an unprovoked PE and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B).

6.3.2. In patients with a first VTE that is an unprovoked PE and who have a high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy (Grade 1B).

6.3.3. In patients with a second unprovoked VTE, we recommend extended anticoagulant therapy over 3 months of therapy in those who have a low bleeding risk (Grade 1B), and we suggest extended anticoagulant therapy in those with a moderate bleeding risk (Grade 2B).

6.3.4. In patients with a second unprovoked VTE who have a high bleeding risk, we suggest 3 months of therapy over extended therapy (Grade 2B).

6.4. In patients with PE and active cancer, if there is a low or moderate bleeding risk, we recommend extended anticoagulant therapy over 3 months of therapy (Grade 1B), and if there is a high bleeding risk, we suggest extended anticoagulant therapy (Grade 2B).

Remarks: In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).
6.5. In patients with PE who are treated with VKA, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) over a lower (INR < 2) or higher (INR 3.0-5.0) range for all treatment durations (Grade 1B).

6.6. In patients with PE and no cancer, we suggest VKA therapy over LMWH for long-term therapy (Grade 2C). For patients with PE and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy (Grade 2C).

6.7. In patients with PE and cancer, we suggest LMWH over VKA therapy (Grade 2B). In patients with PE and cancer who are not treated with LMWH, we suggest VKA over dabigatran or rivaroxaban for long-term therapy (Grade 2C).

Remarks (6.6-6.7): Choice of treatment in patients with and without cancer is sensitive to the individual patient’s tolerance for daily injections, need for laboratory monitoring, and treatment costs.

Treatment of VTE with dabigatran or rivaroxaban, in addition to being less burdensome to patients, may prove to be associated with better clinical outcomes than VKA and LMWH therapy. When these guidelines were being prepared (October 2011), postmarketing studies of safety were not available. Given the paucity of currently available data and that new data are rapidly emerging, we suggest anticoagulant therapy alone over thrombolysis (Grade 2C).

6.8. In patients with PE who receive extended therapy, we suggest treatment with the same anticoagulant chosen for the first 3 months (Grade 2C).

6.9. In patients who are incidentally found to have asymptomatic PE, we suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic PE (Grade 2B).

7.1.1. In patients with chronic thromboembolic pulmonary hypertension (CTPH), we recommend extended anticoagulation over stopping therapy (Grade 1B).

7.1.2. In selected patients with CTPH, such as those with central disease under the care of an experienced thromboendarterectomy team, we suggest pulmonary thromboendarterectomy over no pulmonary thromboendarterectomy (Grade 2C).

8.1.1. In patients with superficial vein thrombosis (SVT) of the lower limb of at least 5 cm in length, we suggest the use of a prophylactic dose of fondaparinux or LMWH for 45 days over no anticoagulation (Grade 2B).

Remarks: Patients who place a high value on avoiding the inconvenience or cost of anticoagulation and a low value on avoiding infrequent symptomatic VTE are likely to decline anticoagulation.

8.1.2. In patients with SVT who are treated with anticoagulation, we suggest fondaparinux 2.5 mg daily over a prophylactic dose of LMWH (Grade 2C).

9.1.1. In patients with acute upper-extremity DVT (UEDVT) that involves the axillary or more proximal veins, we recommend acute treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such acute treatment (Grade 1B).

9.1.2. In patients with acute UEDVT that involves the axillary or more proximal veins, we suggest LMWH or fondaparinux over IV UFH (Grade 2C) and over SC UFH (Grade 2B).

9.2.1. In patients with acute UEDVT that involves the axillary or more proximal veins, we suggest anticoagulant therapy alone over thrombolysis (Grade 2C).

Remarks: Patients who (i) are most likely to benefit from thrombolysis (see text); (ii) have access to CDT; (iii) attach a high value to prevention of PTS; and (iv) attach a lower value to the initial complexity, cost, and risk of bleeding with thrombolytic therapy are likely to choose thrombolytic therapy over anticoagulation alone.

9.2.2. In patients with UEDVT who undergo thrombolysis, we recommend the same intensity and duration of anticoagulant therapy as in similar patients who do not undergo thrombolysis (Grade 1B).

9.3.1. In most patients with UEDVT that is associated with a central venous catheter, we suggest that the catheter not be removed if it is functional and there is an ongoing need for the catheter (Grade 2C).

9.3.2. In patients with UEDVT that involves the axillary or more proximal veins, we suggest a minimum duration of anticoagulation of 3 months over a shorter period (Grade 2B).
9.3.3. In patients who have UEDVT that is associated with a central venous catheter that is removed, we recommend 3 months of anticoagulation over a longer duration of therapy in patients with no cancer (Grade 1B), and we suggest this in patients with cancer (Grade 2C).

9.3.4. In patients who have UEDVT that is associated with a central venous catheter that is not removed, we recommend that anticoagulation is continued as long as the central venous catheter remains over stopping after 3 months of treatment in patients with cancer (Grade 1C), and we suggest this in patients with no cancer (Grade 2C).

9.3.5. In patients who have UEDVT that is not associated with a central venous catheter or with cancer, we recommend 3 months of anticoagulation over a longer duration of therapy (Grade 2C).

9.4. In patients with acute symptomatic UEDVT, we suggest against the use of compression sleeves or venoactive medications (Grade 2C).

9.5.1. In patients who have PTS of the arm, we suggest a trial of compression bandages or sleeves to reduce symptoms (Grade 2C).

9.5.2. In patients with PTS of the arm, we suggest against treatment with venoactive medications (Grade 2C).

10.1. In patients with symptomatic splenic vein thrombosis (portal, mesenteric, and/or splenic vein thromboses), we recommend anticoagulation over no anticoagulation (Grade 1B).

10.2. In patients with incidentally detected splanchic vein thrombosis (portal, mesenteric, and/or splenic vein thromboses), we suggest no anticoagulation over anticoagulation (Grade 2C).

11.1. In patients with symptomatic hepatic vein thrombosis, we suggest anticoagulation over no anticoagulation (Grade 2C).

11.2. In patients with incidentally detected hepatic vein thrombosis, we suggest no anticoagulation over anticoagulation (Grade 2C).

Remarks: This recommendation also applies if the UEDVT was associated with a central venous catheter that was removed shortly after diagnosis.

This article provides recommendations for the use of antithrombotic agents as well as the use of devices or surgical techniques in the treatment of patients with DVT and pulmonary embolism (PE), which are collectively referred to as VTE. We also provide recommendations for patients with (1) post-thrombotic syndrome (PTS), (2) chronic thromboembolic pulmonary hypertension (CTPH), (3) incidentally diagnosed (asymptomatic) DVT or PE, (4) acute upper-extremity DVT (UEDVT), (5) superficial vein thrombosis (SVT), (6) splanchic vein thrombosis, and (7) hepatic vein thrombosis.

Table 1 describes the populations, interventions, comparators, and outcomes (ie, PICO elements) for the questions addressed in this article and the design of the studies used to address them. Refer to Garcia et al, Ageno et al, and Holbrook et al in these guidelines for recommendations on the management of parenteral anticoagulation (dosing and monitoring) and oral anticoagulation (dosing and monitoring). Refer to Bates et al and Monagle et al in these guidelines for recommendations for pregnancy and neonates and children. The current article builds on previous versions of these guidelines and, most recently, the eighth edition.

1.0 Methods

1.1 Presentation as DVT or PE

In addressing DVT, we first review studies that included (1) only patients who presented with symptomatic DVT or (2) patients who presented with DVT or PE (ie, meeting the broader criterion of VTE). For the PE components, we review studies (and subgroups within studies) that required patients to have presented with symptomatic PE (who may also have had symptoms of DVT). For this reason and because more patients with VTE present with symptoms of DVT alone than with symptoms of PE (including those who also have symptoms of DVT), the DVT section deals with a larger body of evidence than the PE section.

In the evaluation of anticoagulant therapy, there are a number of justifications for inclusion of patients who present with DVT and PE in the same study, and for extrapolating evidence obtained in patients with one presentation of VTE (eg, DVT) to the other presentation (eg, PE). First, a majority of patients with symptomatic DVT also have PE (symptomatic or asymptomatic), and a majority of those with symptomatic PE also have DVT (symptomatic or asymptomatic). Second, clinical trials of anticoagulant therapy have yielded similar estimates for efficacy and safety in patients with DVT alone, in those with both DVT and PE, and in those with only PE. Third, the risk of recurrence appears to be similar after PE and after proximal DVT. Consequently, the results of all studies of VTE have been considered when formulating recommendations for short- and long-term anticoagulation of proximal DVT and PE (Fig 1), and these recommendations are essentially the same for proximal DVT or PE.

There are, however, some important differences between patients who present with PE and those who present with DVT that justify separate consideration of some aspects of the treatment of PE. First, the risk of early death (within 1 month) from VTE due to either the initial acute episode or recurrent VTE is much greater after presenting with PE than after DVT; this difference may justify more aggressive initial treatment of PE (eg, thrombolytic therapy, insertion of an inferior vena cava (IVC) filter, more intensive anticoagulant therapy) compared with DVT. Second, recurrent episodes of VTE are about three times as likely to be...
### Table 1 — Structured Clinical Questions

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<td>Anticoagulation</td>
<td>No anticoagulation</td>
<td>Mortality, bowel ischemia, major bleeding, QOL, and symptomatic relief</td>
<td>RCTs and cohort studies</td>
</tr>
<tr>
<td>Role of anticoagulation in hepatic vein thrombosis (11.1, 11.2)</td>
<td>Patients with hepatic vein thrombosis</td>
<td>Anticoagulation</td>
<td>No anticoagulation</td>
<td>Mortality, liver failure, PE, major bleeding, QOL, and symptomatic relief</td>
<td>RCTs and cohort studies</td>
</tr>
</tbody>
</table>

CTPH = chronic thromboembolic pulmonary hypertension; INR = international normalized ratio; IVC = inferior vena cava; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; PICO = population, intervention, comparator, outcome; PTS = postthrombotic syndrome; QOL = quality of life; RCT = randomized controlled trial; SVT = superficial vein thrombosis; UEDVT = upper-extremity DVT; UFH = unfractionated heparin; VKA = vitamin K antagonist.
were lacking or were of low quality. Methodologic issues specifically used data from randomized trials because observational data are most likely to reflect real-life incidence. In many cases, however, estimates of recurrent VTE and bleeding were reported separately in their own categories to avoid reporting an outcome more than once in an evidence profile. However, many original reports and published meta-analyses did not report fatal and nonfatal events separately. In this situation, we have reported the outcome categories of mortality, recurrent VTE, and major bleeding, with fatal episodes of recurrent VTE and bleeding were reported separately in their own categories.

With both ways of reporting outcomes, we tried to specifically identify deaths from recurrent VTEs and major bleeds. As part of the assessment of the benefits and harms of a therapy, we generally assume that ~5% of recurrent episodes of VTE are fatal and that ~10% of major bleeds are fatal, and if we deviated from these estimates, we noted the reasons for so doing. We did not consider surrogate outcomes (eg, vein patency) when there were adequate data addressing the corresponding outcome of importance to patients (eg, PTS).

When developing evidence profiles, we tried to obtain the baseline risk of outcomes (eg, risk of recurrent VTE or major bleeding) from observational studies because these estimates are most likely to reflect real-life incidence. In many cases, however, we used data from randomized trials because observational data were lacking or were of low quality. Methodologic issues specific to duration of anticoagulation are addressed in the section on well-validated tools for stratifying risk of bleeding in patients with different risks of bleeding, and (3) there is a lack of similar disutility to vitamin K antagonist (VKA) therapy (frequent blood testing and telephone or clinic visits, attention to changes in other medications) and long-term low-molecular-weight-heparin (LMWH) therapy (daily subcutaneous [SC] injection, injection site bruising or nodules) may have been misguided led us to request a review of this issue at the final meeting of all panelists.

Our judgment that, on average, patients would prefer VKA therapy to long-term LMWH therapy was confirmed at that meeting.

1.4 Influence of Bleeding Risk and Cost

Usually, we did not assess how an individual patient’s risk of bleeding would influence each recommendation because (1) we considered that most recommendations would be unlikely to change based on differences in risk of bleeding (eg, anticoagulation vs no anticoagulation for acute VTE, comparison of anticoagulant regimens), (2) there are few data assessing outcomes in patients with different risks of bleeding, and (3) there is a lack of well-validated tools for stratifying risk of bleeding in patients with VTE. However, for a small number of the recommendations in which the risk of bleeding is very influential (eg, use of extended-duration anticoagulation), we stratified recommendations based on this risk (Table 2). Unless otherwise stated, the cost (eg, to the patient, a third-party payer, or society) associated with different treatments did not influence our recommendations. In most situations of uncertain benefit of a treatment, particularly if it was potentially harmful, we took the position of primum non nocere (first do no harm) and made a weak recommendation against the treatment.

2.0 Treatment of Acute DVT

2.1 Initial Anticoagulation of Acute DVT of the Leg

The first and only randomized trial that compared anticoagulant therapy with no anticoagulant therapy in patients with symptomatic DVT or PE was published in 1960 by Barritt and Jordan. Trial results suggested that 1.5 days of heparin and 14 days of
Table 2—[Section 2.3, 3] Risk Factors for Bleeding With Anticoagulant Therapy and Estimated Risk of Major Bleeding in Low-, Moderate-, and High-Risk Categories

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Estimated Absolute Risk of Major Bleeding, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Risk (0 Risk Factors)</td>
</tr>
<tr>
<td>Anticoagulation 0-3 mo ≤1</td>
<td></td>
</tr>
<tr>
<td>Baseline risk (%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Increased risk (%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Total risk (%)</td>
<td>1.6</td>
</tr>
<tr>
<td>Anticoagulation after first 3 mo ≤1</td>
<td></td>
</tr>
<tr>
<td>Baseline risk (%/y)</td>
<td>0.3</td>
</tr>
<tr>
<td>Increased risk (%/y)</td>
<td>0.5</td>
</tr>
<tr>
<td>Total risk (%/y)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

See Table 1 legend for expansion of abbreviations.

The increase in bleeding associated with a risk factor will vary with (1) severity of the risk factor (eg, location and extent of metastatic disease, platelet count), (2) temporal relationships (eg, interval from surgery or previous bleeding episode), and (3) how effectively a previous cause of bleeding was corrected (eg, upper-GI bleeding).

Important for parenteral anticoagulation (eg, first 10 d) but less important for long-term or extended anticoagulation.

VKA therapy markedly reduced recurrent PE (0/16 vs 10/19) and appeared to reduce mortality (1/16 vs 5/19) in patients with acute PE. In the early 1990s, a single randomized trial established the need for an initial course of heparin in addition to VKA as compared with starting treatment with VKA therapy alone (Table 3, Table S1). (Tables that contain an “S” before the number denote supplementary tables not contained in the body of the article and available instead in an online data supplement. See the “Acknowledgments” for more information.) The need for an initial course of heparin is also supported by the observation that there are high rates of recurrent VTE during 3 months of follow-up in patients...
with acute VTE treated with suboptimal heparin therapy.\textsuperscript{13,52,53} We discuss whether isolated distal (calf) DVT should be sought and if isolated distal DVT is diagnosed, whether and how it should be treated in section 2.3.

Recommendation

2.1. In patients with acute DVT of the leg treated with VKA therapy, we recommend initial treatment with parenteral anticoagulation (LMWH, fondaparinux, IV unfractionated heparin [UFH], or SC UFH) over no such initial treatment (Grade 1B).

2.2 Whether to Treat With Parenteral Anticoagulation While Awaiting the Results of Diagnostic Work-up for VTE

We identified no trial addressing this question. The decision regarding treatment while awaiting test results requires balancing (1) minimizing thrombotic complications in patients with VTE and (2) avoiding bleeding in those without VTE. Our recommendations are based on two principles. First, the higher the clinical suspicion for VTE (use of validated prediction models for probability of having DVT\textsuperscript{54} or PE\textsuperscript{55,56} can usefully inform this assessment,\textsuperscript{57} the shorter the acceptable interval without treatment until results of diagnostic testing become available. Second, the higher the risk of bleeding, the longer the acceptable interval without treatment until results are available.

Our recommendations assume that patients do not have major risk factors for bleeding, such as recent surgery. The recommendations also take into account that starting anticoagulant therapy in patients who ultimately have DVT excluded is costly and is a burden to patients and the health-care system. Poor cardiopulmonary reserve may also encourage the use of anticoagulant therapy while awaiting diagnostic testing. If clinicians choose to administer anticoagulant therapy and diagnostic testing will be completed within 12 h, we suggest using a 12-h over a 24-h dose of LMWH. VKA therapy usually should not be started before VTE has been confirmed.

Recommendations

2.2.1. In patients with a high clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C).

2.2.2. In patients with an intermediate clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C).

2.2.3. In patients with a low clinical suspicion of acute VTE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C).

2.3 Whether and How to Prescribe Anticoagulants to Patients With Isolated Distal DVT

Whether to Look for Isolated Distal DVT and When to Prescribe Anticoagulants if Distal DVT Is Found:

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With No Parenteral Anticoagulation</th>
<th>Risk Difference With Parenteral Anticoagulation (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>120 (1 study), 6 mo</td>
<td>Moderate\textsuperscript{b,c}</td>
<td>RR 0.5 (0.05-5.37)</td>
<td>33 per 1,000</td>
<td>16 fewer per 1,000 (from 31 fewer to 144 more)</td>
</tr>
<tr>
<td>VTE symptomatic extension or recurrence</td>
<td>120 (1 study), 6 mo</td>
<td>Moderate\textsuperscript{b,c} due to imprecision</td>
<td>RR 0.33 (0.11-0.98)</td>
<td>200 per 1,000</td>
<td>134 fewer per 1,000 (from 4 fewer to 178 fewer)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>120 (1 study), 6 mo</td>
<td>Moderate\textsuperscript{b,c} due to imprecision</td>
<td>RR 0.67 (0.12-3.85)</td>
<td>50 per 1,000</td>
<td>16 fewer per 1,000 (from 44 fewer to 142 more)</td>
</tr>
</tbody>
</table>

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. GRADE = Grades of Recommendations, Assessment, Development, and Evaluation; RR = risk ratio.

\textsuperscript{a}Both groups treated with acenocoumarol.

\textsuperscript{b}Study described as double blinded; outcome adjudicators blinded. None of the study participants were lost to follow-up. Intention-to-treat analysis. Study was stopped early for benefit.

\textsuperscript{c}CI includes values suggesting no effect as well as values suggesting either appreciable benefit or appreciable harm.

\textsuperscript{d}Low number of events caused by the early stoppage of the trial.
Whether patients with isolated distal DVT (DVT of the calf [peroneal, posterior tibial, anterior tibial veins] without involvement of the popliteal or more proximal veins) are identified depends on how suspected DVT is investigated.\textsuperscript{3} If all patients with suspected DVT have ultrasound examination of the calf veins (whole-leg ultrasound), isolated distal DVT accounts for about one-half of all DVT diagnosed.\textsuperscript{3} If a diagnostic approach is used that does not include ultrasound examination of the calf veins or that only performs ultrasound examination of the calf veins in selected patients, isolated distal DVT is rarely diagnosed.\textsuperscript{39}

The primary goal of diagnostic testing for DVT is to identify patients who will benefit from anticoagulant therapy. This does not mean that all symptomatic DVT need to be identified. Isolated distal DVT do not need to be sought and treated provided that (1) there is strong evidence that the patient does not have a distal DVT that will extend into the proximal veins (ie, the patient is unlikely to have a distal DVT, and if a distal DVT is present, it is unlikely to extend); (2) if this criterion is not satisfied, a follow-up proximal ultrasound is done after 1 week to detect distal DVT that has extended into the proximal veins, in which case anticoagulant therapy is started; and (3) the patient does not have severe symptoms that would require anticoagulant therapy if the symptoms were due to a distal DVT.

Diagnostic approaches to suspected DVT that do not examine the calf veins (eg, use of a combination of clinical assessment, D-dimer testing, single and serial proximal vein ultrasound examination to manage patients) or only examine the calf veins in selected patients (eg, those who cannot have DVT excluded using the previously noted tests) have been proven safe and are presented in Bates et al\textsuperscript{37} in these guidelines. If the calf veins are imaged (usually with ultrasound) and isolated distal DVT is diagnosed, there are two management options: (1) treat patients with anticoagulant therapy or (2) do not treat patients with anticoagulant therapy unless extension of the DVT is detected on a follow-up ultrasound examination (eg, after 1 and 2 weeks or sooner if there is concern [there is no widely accepted protocol for surveillance ultrasound testing]).\textsuperscript{60} Natural history studies suggest that when left untreated, \textasciitilde15% of symptomatic distal DVT will extend into the proximal veins and that if extension does not occur within 2 weeks, it is unlikely to occur subsequently.\textsuperscript{7,60-62} The risk of extension of isolated distal DVT will vary among patients (see later discussion).

As noted in Bates et al,\textsuperscript{37} these guidelines favor diagnostic approaches to suspected DVT other than routine whole-leg ultrasound. If isolated distal DVT is diagnosed, depending on the severity of patient symptoms (the more severe the symptoms, the stronger the indication for anticoagulation) and the risk for thrombus extension (the greater the risk, the stronger the indication for anticoagulation), we suggest either (1) anticoagulation or (2) withholding of anticoagulation while performing surveillance ultrasound examinations to detect thrombus extension. We consider the following to be risk factors for extension: positive D-dimer, thrombosis that is extensive or close to the proximal veins (eg, \textasciitilde5 cm in length, involves multiple veins, \textasciitilde7 mm in maximum diameter), no reversible provoking factor for DVT, active cancer, history of VTE, and inpatient status.\textsuperscript{7,60-64} Thrombosis that is confined to the muscular veins has a lower risk of extension than true isolated distal DVT.\textsuperscript{63,65} We anticipate that isolated distal DVT detected using a selective approach to whole-leg ultrasound often will satisfy criteria for initial anticoagulation, whereas distal DVT detected by routine whole-leg ultrasound often will not. A high risk for bleeding (Table 2) favors ultrasound surveillance over initial anticoagulation, and the decision to use surveillance or initial anticoagulation is expected to be sensitive to patient preferences. The evidence supporting recommendations to prescribe anticoagulants for isolated calf DVT is low quality because it is not based on direct comparisons of the two management strategies, and the ability to predict extension of distal DVT is limited.

**How to Treat With Anticoagulants:** A single controlled trial of 51 patients with symptomatic isolated distal DVT, all of whom were initially treated with heparin, found that 3 months of VKA therapy prevented DVT extension and recurrent VTE (29% vs 0%, \textit{P} < .01).\textsuperscript{66} The evidence in support of parenteral anticoagulation and VKA therapy for isolated distal DVT, which includes indirect evidence from patients with acute proximal DVT and PE that is presented elsewhere in this article, is of moderate quality (there is high-quality evidence that anticoagulation is effective, but uncertainty that benefits outweigh risks). There have not been evaluations of alternatives to full-dose anticoagulation of symptomatic isolated distal DVT, and it is possible that less-aggressive anticoagulant strategies may be adequate. Duration of anticoagulation for isolated distal DVT is discussed in section 3.1.

**Recommendations**

2.3.1. In patients with acute isolated distal DVT of the leg and without severe symptoms or risk factors for extension (see text), we suggest serial imaging of the deep veins for 2 weeks over initial anticoagulation (Grade 2C).

2.3.2. In patients with acute isolated distal DVT of the leg and severe symptoms or risk factors
for extension (see text), we suggest initial anticoagulation over serial imaging of the deep veins (Grade 2C).

Remarks: Patients at high risk for bleeding are more likely to benefit from serial imaging. Patients who place a high value on avoiding the inconvenience of repeat imaging and a low value on the inconvenience of treatment and on the potential for bleeding are likely to choose initial anticoagulation over serial imaging.

Recommendations

2.3.3. In patients with acute isolated distal DVT of the leg who are managed with initial anticoagulation, we recommend using the same approach as for patients with acute proximal DVT (Grade 1B).

2.3.4. In patients with acute isolated distal DVT of the leg who are managed with serial imaging, we recommend no anticoagulation if the thrombus does not extend (Grade 1B); we suggest anticoagulation if the thrombus extends but remains confined to the distal veins (Grade 2C); we recommend anticoagulation if the thrombus extends into the proximal veins (Grade 1B).

2.4 Timing of Initiation of VKA and Associated Duration of Parenteral Anticoagulant Therapy

Until ~20 years ago, initiation of VKA therapy was delayed until patients had received about 5 days of heparin therapy, which resulted in patients remaining in the hospital until they had received ~10 days of heparin. Three randomized trials provided moderate-quality evidence that early initiation of VKA, with shortening of heparin therapy to ~5 days, is as effective as delayed initiation of VKA with about a 10-day course of heparin (Table 4, Table S2). Shortening the duration of initial heparin therapy from about 10 to 5 days is expected to have the added advantage of reducing the risk of heparin-induced thrombocytopenia. If the international normalized ratio (INR) exceeds the therapeutic range (ie, INR > 3.0) prematurely, it is acceptable to stop parenteral therapy before the patient has received 5 days of treatment.

Recommendation

2.4. In patients with acute DVT of the leg, we recommend early initiation of VKA (eg, same day as parenteral therapy is started) over delayed initiation, and continuation of parenteral anticoagulation for a minimum of 5 days and until the INR is 2.0 or above for at least 24 h (Grade 1B).

2.5 Choice of Initial Anticoagulant Regimen in Patients With Proximal DVT

Initial anticoagulant regimens vary according to the drug, the route of administration, and whether dose is adjusted in response to laboratory tests of coagulation. Six options are available for the initial treatment of DVT: (1) SC LMWH without monitoring, (2) IV UFH with monitoring, (3) SC UFH given based on weight initially, with monitoring, (4) SC UFH given based on weight initially, without monitoring, (5) SC fondaparinux given without monitoring, and (6) rivaroxaban given orally. We considered the SC UFH options as a single category because results were similar in studies that used SC UFH with and without laboratory monitoring (Table 5, Tables S3-S5). Rivaroxaban is used in the acute treatment of VTE without initial parenteral therapy; studies of its use for the acute treatment of VTE are reviewed under long-term treatment of DVT (section 3.1) and PE (section 6) of this article. Recommendations for dosing and monitoring of IV UFH, SC UFH, and SC LMWH are addressed in Garcia et al and Holbrook et al in these guidelines. Because LMWH, fondaparinux, and rivaroxaban have substantial renal excretion, these agents should be avoided (eg, use UFH instead) or should be used with coagulation monitoring (test selection is specific to each agent and requires expert interpretation) in patients with marked renal impairment (eg, estimated creatinine clearance < 30 mL/min [in a 70-year-old weighing 70 kg, a creatinine clearance of 30 mL/min corresponds to a serum creatinine of about 200 μmol/L (2.3 mg/dL) in a man and 175 μmol/L (2.0 mg/dL) in a woman] http://www.nephron.com/cgi-bin/CGSIdefault.cgi).

LMWH Compared With IV UFH for the Initial Treatment of DVT: A number of meta-analyses have summarized the trials addressing this question. The evidence suggests that LMWH is associated with decreased mortality, lower recurrence of VTE, and decreased incidence of major bleeding compared with IV UFH (Table 6, Table S6). However, the quality of supporting evidence is low due to a high risk of bias in the primary studies, and evidence of publication bias in favor of LMWH. LMWH has the advantage over IV UFH that it is much easier to administer (which makes outpatient treatment feasible) and that it has a lower potential for heparin-induced thrombocytopenia, but the disadvantage is that it accumulates in patients with renal failure.

SC UFH Compared With LMWH for the Initial Treatment of DVT: Four randomized trials have compared SC UFH with SC LMWH (Table 6, Tables S3-S5). This evidence suggests that SC UFH is associated with a similar frequency of
mortality, recurrent VTE, and major bleeding as LMWH. However, the quality of the evidence is moderate because of imprecision. LMWH has the disadvantage of a higher cost but is more convenient to use (LMWH can be administered once daily [see later discussion]), is more widely available for use in outpatients, has a lower potential for heparin-induced thrombocytopenia, and there is much more experience with its use than with SC UFH.

**Fondaparinux Compared With LMWH for the Initial Treatment of DVT:** The Matisse-DVT trial compared fondaparinux with LMWH for short-term treatment of DVT (Table 7, Table S7). This study suggests that fondaparinux is associated with a similar frequency of mortality, recurrent VTE, and major bleeding as LMWH. However, the quality of the evidence from this study was moderate because of imprecision. Evidence that fondaparinux is effective for the treatment of PE supports the equivalence of fondaparinux to LMWH for the treatment of acute VTE.

**Fondaparinux Compared With IV UFH for the Initial Treatment of DVT:** In the absence of direct evidence in patients with DVT, indirect evidence in patients with acute PE (section 5.4) suggests that fondaparinux is equivalent to IV UFH. As noted previously, we judge that fondaparinux and LMWH are equivalent; fondaparinux also shares the advantages that LMWH has over IV UFH and the disadvantage that it is renally excreted (section 2.5). The quality of the evidence regarding the comparison of fondaparinux and UFH is moderate as, although there is some indirectness, it is minor.

**Fondaparinux Compared With SC UFH for the Initial Treatment of DVT:** There is no direct evidence for this comparison in any patient population. Our recommendation is based on our assessment that...
The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follows: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. SC = subcutaneous. See Table 1 and 3 legends for expansion of abbreviations.

Table 5—[Section 2.5.1] Summary of Findings: LMWH vs SC UFH for Initial Anticoagulation of Acute VTE

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With SC UFH</th>
<th>Risk Difference With LMWH (95% CI)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>1,566 (3 studies), 3 mo</td>
<td>Moderate(^\uparrow) due to imprecision</td>
<td>RR 1.1 (0.68-1.76)</td>
<td>33 per 1,000(^c)</td>
<td>3 more per 1,000 (from 11 fewer to 25 more)</td>
<td>5 fewer per 1,000 (from 7 fewer to 30 more)</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>1,563 (3 studies), 3 mo</td>
<td>Moderate(^\uparrow) due to imprecision</td>
<td>RR 0.87 (0.52-1.45)</td>
<td>42 per 1,000(^c)</td>
<td>5 fewer per 1,000 (from 20 fewer to 19 more)</td>
<td>10 fewer per 1,000 (from 6 fewer to 23 fewer)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1,634 (4 studies), 3 mo</td>
<td>Moderate(^\uparrow) due to imprecision</td>
<td>RR 1.27 (0.56-2.9)</td>
<td>16 per 1,000(^c)</td>
<td>4 more per 1,000 (from 7 fewer to 30 more)</td>
<td>3 more per 1,000 (from 2 fewer to 16 fewer)</td>
</tr>
</tbody>
</table>

The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follows: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. SC = subcutaneous. See Table 1 and 3 legends for expansion of abbreviations.

Table 6—[Section 2.5.1] Summary of Findings: LMWH vs IV UFH for Initial Anticoagulation of Acute VTE

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With IV UFH</th>
<th>Risk Difference With LMWH (95% CI)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>7,908 (17 studies), 3 mo</td>
<td>Low(^\uparrow) due to risk of bias, publication bias</td>
<td>RR 0.79 (0.66-0.95)</td>
<td>46 per 1,000(^c)</td>
<td>10 fewer per 1,000 (from 2 fewer to 16 fewer)</td>
<td>5 fewer per 1,000 (from 2 fewer to 16 fewer)</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>7,976 (17 studies), 3 mo</td>
<td>Low(^\uparrow) due to risk of bias, publication bias</td>
<td>RR 0.72 (0.58-0.89)</td>
<td>55 per 1,000(^c)</td>
<td>15 fewer per 1,000 (from 6 fewer to 23 fewer)</td>
<td>10 fewer per 1,000 (from 6 fewer to 23 fewer)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>6,910 (20 studies), 3 mo</td>
<td>Low(^\uparrow) due to risk of bias, publication bias</td>
<td>RR 0.67 (0.45-1)</td>
<td>15 per 1,000(^c)</td>
<td>5 fewer per 1,000 (from 8 fewer to 0 more)</td>
<td>5 fewer per 1,000 (from 8 fewer to 0 more)</td>
</tr>
</tbody>
</table>

The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follows: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. SC = subcutaneous. See Table 1 and 3 legends for expansion of abbreviations.

Once- vs Twice-Daily Administration of LMWH for Initial Treatment of DVT: Two meta-analyses\(^{80,81}\) summarized six studies comparing once-daily and twice-daily administrations of the same LMWH.\(^{82-87}\) Table 8 and Table S8 summarize the findings of five of these studies\(^{83-87}\) that had unconfounded comparisons. This evidence suggests that LMWH once daily and twice daily are associated with similar mortality, recurrent VTE, and major bleeding. However, the quality of the evidence is low because of imprecision and inconsistency. The sixth study that used a lower total daily dose of LMWH with once-daily compared with twice-daily administration (enoxaparin 1.5 mg/kg once daily vs 1.0 mg/kg bid; enoxaparin 2 mg/kg once daily is not used) suggested that outcomes might be inferior with this once-daily regimen.\(^{85}\)

fondaparinux and LMWH are equivalent and that fondaparinux shares the advantages that LMWH has over SC UFH (section 2.5). This recommendation does not take into account difference in purchase cost between SC UFH and fondaparinux and is based on low-quality evidence.

Once- vs Twice-Daily Administration of LMWH for Initial Anticoagulation of Acute VTE
Table 7—[Section 2.5.1] Summary of Findings: Fondaparinux vs LMWH for Initial Anticoagulation of Acute DVT\(^{a,b,78}\)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With LMWH</th>
<th>Risk Difference With Fondaparinux (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>2,205 (1 study), 3 mo</td>
<td>Moderate(^d) due to imprecision</td>
<td>RR 1.25 (0.8-1.97)</td>
<td>30 per 1,000</td>
<td>7 more per 1,000 (from 6 fewer to 29 more)</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>2,205 (1 study), 3 mo</td>
<td>Moderate(^e) due to imprecision</td>
<td>RR 0.96 (0.64-1.45)</td>
<td>41 per 1,000(^f)</td>
<td>2 fewer per 1,000 (from 15 fewer to 18 more)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2,205 (1 study), 3 mo</td>
<td>Moderate(^e) due to imprecision</td>
<td>RR 0.93 (0.43-2.03)</td>
<td>12 per 1,000(^f)</td>
<td>1 fewer per 1,000 (from 7 fewer to 12 more)</td>
</tr>
</tbody>
</table>

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

\(^a\)All patients had acute symptomatic DVT.

\(^b\)Fondaparinux 7.5 mg (5.0 mg in patients weighing < 50 kg and 10.0 mg in patients weighing > 100 kg) SC once daily for at least 5 d and until VKAs induced an INR > 2.0.

\(^c\)Enoxaparin 1 mg/kg of body weight SC bid for at least 5 d and until VKAs induced an INR > 2.0.

\(^d\)Allocation was concealed. Patients, providers, data collectors, and outcome adjudicators were blinded. Analysis excluded 0.6% of randomized patients. Not stopped early for benefit.

\(^e\)CI includes values suggesting no effect and values suggesting either benefit or harm; relatively low number of events.

\(^f\)Five fatal VTE in fondaparinux group and five fatal VTE in LMWH group.

\(^g\)Twelve patients in the fondaparinux group and 13 in the LMWH group had a major bleeding event during the initial period (7 d). Of these, two in the fondaparinux group and none in the LMWH group were fatal.

Table 8—[Section 2.5.2] Summary of Findings: LMWH Once vs Twice Daily for Initial Anticoagulation of Acute VTE\(^{a,b,81}\)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With Twice Daily LMWH</th>
<th>Risk Difference With LMWH Once Daily (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>1,261 (3 studies), 3 mo</td>
<td>Low(^e) due to inconsistency and imprecision</td>
<td>RR 1.05 (0.57-1.94)</td>
<td>31 per 1,000</td>
<td>2 more per 1,000 (from 13 fewer to 29 more)</td>
</tr>
<tr>
<td>VTE recurrence</td>
<td>1,261 (3 studies), 3 mo</td>
<td>Low(^e) due to inconsistency and imprecision</td>
<td>RR 0.86 (0.52-1.42)</td>
<td>49 per 1,000</td>
<td>7 fewer per 1,000 (from 24 fewer to 21 more)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1,522 (5 studies), 10 d</td>
<td>Moderate(^e) due to imprecision</td>
<td>RR 1.13 (0.48-2.66)</td>
<td>12 per 1,000</td>
<td>2 more per 1,000 (from 6 fewer to 20 more)</td>
</tr>
</tbody>
</table>

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

\(^a\)Of the five included studies, one included patients with PE and DVT and four included only patients with DVT. All studies addressed the initial management of VTE.

\(^b\)The five included studies used four brands of LMWH (enoxaparin, tinzaparin, dalteparin, and nadroparin). In Merli et al\(^g\), enoxaparin 1 mg/kg bid was compared with 1.5 mg/kg once daily. Holmström et al\(^h\) adjusted the dose to anti-Xa levels, which resulted in different daily doses after a number of days. In the remaining studies, the dose of the once-daily administration was double the dose of the twice-daily administration (equal total daily dose).

\(^c\)All included studies concealed allocation. Two studies had a double-blind design, and two others were single blind. One study did not mention blinding. Intention to treat likely used in all studies. Participants were lost to follow-up in only two studies (0.3% and 2.2%).

\(^d\)F = 37.5%; point effect estimate in favor of twice-daily dose in Merli et al\(^g\) and in favor of once-daily dose in Charbonnier et al.\(^{83}\)

\(^e\)Imprecision judged relative to no difference.

\(^f\)P = 65%; point effect estimate in favor of twice-daily dose in Merli et al\(^g\) and in favor of once-daily dose in Charbonnier.\(^{83}\)
2.5.2. In patients with acute DVT of the leg treated with LMWH, we suggest once-over twice-daily administration (Grade 2C).

Remarks: This recommendation only applies when the approved once-daily regimen uses the same daily dose as the twice-daily regimen (ie, the once-daily injection contains double the dose of each twice-daily injection). It also places value on avoiding an extra injection per day.

2.6 Initial Treatment With Rivaroxaban vs Parenteral Therapy

One trial directly compared short- and long-term rivaroxaban (without initial parenteral anticoagulation) with parenteral anticoagulation (LMWH and VKA) in patients with acute DVT. The findings of this study and associated recommendations are presented in section 3.3.

2.7 At-Home vs In-Hospital Initial Treatment of DVT

One trial directly compared outpatient and inpatient administration of the same initial anticoagulant regimen (three LMWH preparations were used); there were few recurrent VTE and major bleeds in each group. A number of trials have compared LMWH administered at home (without hospital admission or after early discharge) in a substantial proportion of patients, with IV UFH administered in the hospital (Table 9, Table S9). This evidence suggests that home treatment is not associated with an increase in mortality, recurrent VTE, or major bleeding and may be associated with improved outcomes. However, the quality of the evidence is moderate because of indirectness (patients were not explicitly randomized to home therapy in most studies) and imprecision.

Health economic evaluations that have assessed initial treatment of DVT at home, although they have weaknesses (eg, industry funded, not derived from trials in which LMWH was used both in the hospital and at home, short time horizon (ie, ≤3 months), and limited use of sensitivity analyses), all conclude that home treatment is cost-saving (about US $500-$2,500 per patient).

Recommendation

2.7. In patients with acute DVT of the leg and whose home circumstances are adequate, we recommend initial treatment at home over treatment in hospital (Grade 1B).

Remarks: The recommendation is conditional on the patient feeling well enough to be treated at home (eg, does not have severe leg symptoms or comorbidity).

2.8 Treatment Strategies of Thrombus Removal for Acute DVT

Treatments that actively remove thrombus in patients with acute DVT have the potential to reduce acute symptoms and the risk of developing PTS. Patients with DVT that involves the iliac and common femoral veins are at highest risk for PTS and, therefore, are the subset with the greatest potential to benefit from thrombus removal strategies. Thrombus removal strategies are indicated in patients with the very rare complication of impending venous gangrene despite optimal anticoagulant therapy; such patients are not the focus of the following sections. A recent trial that randomized 183 patients with proximal DVT to percutaneous endovascular intervention or to anticoagulant therapy alone reported reduced acute symptoms, hospital stay, recurrent VTE, and PTS at 6 months in the thrombus removal group. This trial, which had a high potential for bias (randomization not described, no blinding), is not considered further because it was not possible to determine outcomes in patients treated with mechanical thrombectomy alone and in those treated with thrombolytic therapy.

2.9 Catheter-Directed Thrombolysis for Acute DVT

The rationale for catheter-directed thrombolysis (CDT) is that compared with systemic thrombolysis, it will achieve lysis of thrombus more rapidly and with lower doses of thrombolytic therapy, thereby reducing serious bleeding. The addition of mechanical thrombus fragmentation (collectively referred to as pharmacomechanical thrombolysis) with or without aspiration can further reduce the dose of thrombolytic therapy and shorten the procedure.

One randomized trial of CDT has been completed, and a second has reported short-term outcomes (but not the development of PTS). Table 10 and Table S10 present the combined findings from these studies (see also Tables S11 and S12). This evidence suggests that CDT may reduce PTS and improve quality of life without being associated with an unacceptable increase in bleeding. However, the quality of evidence is low for mortality, recurrent VTE, and major bleeding because of very serious imprecision, and is low for PTS because of indirectness (ie, use of surrogate outcome [PTS has yet to be measured directly during follow-up]).

In addition to the two randomized trials, findings of observational studies suggest that CDT improves venous patency and preserves venous valve function (Tables S11 and S12). Use of CDT, however, requires...
The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

Studies included in the systematic review should have recruited patients whose home circumstances were adequate.

All studies included patients with lower-extremity DVT and excluded patients with suspected or confirmed PE. Studies also excluded patients who were pregnant.

Four studies had partial hospital treatment of many in the home arm: Koopman et al\textsuperscript{a,b} (mean hospital stay, 2.7 d in home arm vs 8.1 d in hospital arm), Levine et al\textsuperscript{a,b} (2.1 vs 6.5 d), Boccalon et al\textsuperscript{a,b} (1 vs 9.6 d), and Rammacciotti et al\textsuperscript{a} (3 vs 7 d). In Daskalopoulos et al,\textsuperscript{a} there was no hospital stay at all in the home group. Chong et al\textsuperscript{a,b} did not report duration of hospital stay.

Only one study (Boccalon et al\textsuperscript{a,b}) used LMWH in both treatment arms. Remaining studies used UFH in the inpatient arm and LMWH in the outpatient arm.

Out of six studies, allocation was clearly concealed in three (unclear in remaining three), outcome adjudicators were blinded in the two largest studies (unclear in remaining four), loss to follow-up was significant in only one small study, intention-to-treat analysis was conducted in four (unclear in remaining two), and no study was stopped early for benefit. Overall, the judgment was that these limitations would not warrant downgrading of quality; it has already been downgraded by at least one level based on other factors.

The CI includes values suggesting benefit and harm.

Judged as precise based on the narrow CI around absolute effect.

Bäckman et al\textsuperscript{a} reported evaluation of health-related QOL using the EQ-5D. They found no differences in mean QOL scores or in the proportion of patients showing improvement in self-rated health state. Koopman et al\textsuperscript{a,b} evaluated health-related QOL using the Medical Outcome Study Short Form-20 and an adapted version of the Rotterdam Symptom Checklist. The changes over time were similar in both groups, except that the patients receiving LMWH had better scores for physical activity ($P = .002$) and social functioning ($P = .001$) at the end of the initial treatment. The authors did not report enough data to assess precision and clinical significance of results. O'Brien et al\textsuperscript{a,b} assessed changes in QOL using the Medical Outcome Study Short Form-36 in 300 patients participating in Levine et al\textsuperscript{a,b}. They found that the change in scores from baseline to day 7 was not significantly different between the treatment groups for seven of the eight domains. The one exception was the domain of social functioning, where a greater improvement was observed for the outpatient arm.

Potential inconsistency as Bäckman et al\textsuperscript{a,b} showed no effect, whereas Koopman et al\textsuperscript{a,b} and O'Brien et al\textsuperscript{a,b} showed potential benefit.

Two of the three studies had partial hospital treatment of many in the home arm: Koopman et al\textsuperscript{a,b} (mean hospital stay, 2.7 d in hospital arm vs 8.1 d in hospital arm) and Levine et al (2.1 vs 6.5 d).

Not able to evaluate, but imprecision is possible. Taken together with the potential inconsistency, we downgraded the quality of evidence by one level.

Substantial resources and expertise. Patients who are most likely to benefit from CDT have iliofemoral DVT, symptoms for $< 14$ days, good functional status, life expectancy of $\geq 1$ year, and a low risk of bleeding (Table 11). Because the balance of risks and benefits with CDT is uncertain, anticoagulant therapy alone is an acceptable alternative to CDT in all patients with acute DVT who do not have impending venous gangrene.

There is no single standardized approach to performing CDT or pharmacomechanical thrombolysis. If these interventions are performed, the technique used will vary with local resources and expertise. If CDT has been successful but there are residual lesions in the common femoral or more proximal veins, balloon angioplasty and stenting often are used to relieve obstruction. There are inadequate data to assess the benefit or risk of inserting an IVC filter in patients who have CDT performed (recommended by manufacturer with some endovascular devices and techniques, whereas not with others). Percutaneous mechanical venous thrombectomy without concomitant thrombolysis has not been evaluated in randomized trials, and its use is discouraged because small retrospective studies suggest that it often fails to remove much of the thrombus and is associated with a high risk of PE.\textsuperscript{117,118}

Recommendation

2.9. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over CDT (Grade 2C).

---

Table 9—[Section 2.7] Summary of Findings: Home Treatment vs Hospital Treatment of Acute DVT\textsuperscript{a,b,442}

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With Hospital Treatment</th>
<th>Risk Difference With Home Treatment (95% CI)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>1,708 (6 studies), 3 mo</td>
<td>Low\textsuperscript{a,b} due to indirectness and imprecision</td>
<td>RR 0.72 (0.45-1.15)</td>
<td>46 per 1,000</td>
<td>13 fewer per 1,000 (from 25 fewer to 7 more)</td>
<td>...</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>1,708 (6 studies), 3 mo</td>
<td>Moderate\textsuperscript{a} due to indirectness</td>
<td>RR 0.61 (0.42-0.9)</td>
<td>74 per 1,000</td>
<td>29 fewer per 1,000 (from 7 fewer to 43 fewer)</td>
<td>...</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1,708 (6 studies), 3 mo</td>
<td>Moderate\textsuperscript{a,c} due to indirectness</td>
<td>RR 0.67 (0.33-1.36)</td>
<td>21 per 1,000</td>
<td>7 fewer per 1,000 (from 14 fewer to 9 more)</td>
<td>...</td>
</tr>
<tr>
<td>QOL</td>
<td>0 (3 studies\textsuperscript{b}), 3 mo</td>
<td>Low\textsuperscript{a} due to indirectness and imprecision</td>
<td>Not estimable</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>


Table 10—[Section 2.9] Summary of Findings: CDT vs No CDT for Extensive Acute DVT of the Leg

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With CDT (95% CI)</th>
<th>Risk Difference With CDT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>153 (2 studies), 3 mo</td>
<td>Low due to imprecision</td>
<td>RR 0.14 (0.01-2.71)</td>
<td>39 per 1,000</td>
<td>34 fewer per 1,000 (from 39 fewer to 67 more)</td>
</tr>
<tr>
<td>Nonfatal recurrent VTE</td>
<td>153 (1 study), 3 mo</td>
<td>Low due to imprecision</td>
<td>RR 0.35 (0-8.09)</td>
<td>48 per 1,000</td>
<td>31 fewer per 1,000 (from 48 fewer to 340 more)</td>
</tr>
<tr>
<td>Nonfatal major bleeding</td>
<td>153 (2 studies), 7 d</td>
<td>Low due to imprecision</td>
<td>RR 2.00 (0.19-19.46)</td>
<td>29 per 1,000</td>
<td>29 more per 1,000 (from 23 fewer to 535 more)</td>
</tr>
<tr>
<td>PTS (complete lysis on venography [Elsharawy et al], patency on ultrasound and air plethysmography [Enden et al])</td>
<td>138 (2 studies), 2 y</td>
<td>Moderate due to indirectness</td>
<td>RR 0.46 (0-0.79)</td>
<td>588 per 1,000</td>
<td>315 fewer per 1,000 (from 123 fewer to 588 fewer)</td>
</tr>
<tr>
<td>QOL (SF-12, HUI Mark version 2/3 questionnaires)</td>
<td>98 (1 study), 16 mo</td>
<td>Low</td>
<td>See footnote</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follows: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very unlikely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. HUI = Health Utilities Index; SF-12 = Medical Outcomes Survey Short Form-12; VETO = Venous Thrombosis Outcomes. See Table 1 and 3 legends for expansion of other abbreviations.

1In selected patients with extensive acute proximal DVT (eg, iliofemoral DVT, symptoms for <14 d, good functional status, life expectancy ≥1 y) who have a low risk of bleeding.
2All patients prescribed anticoagulants per protocol, but the intervention group receives CDT in addition to anticoagulation.
3Allocation was concealed in Enden et al but unclear in Elsharawy et al. Outcome assessor blinded in both studies. Follow-up rates were 87% in Enden et al and 100% in Elsharawy et al. Neither of the studies was stopped early for benefit.
4CI includes values suggesting both benefit and harm.
5Three control patients died of cancer.
6Baseline risks for nonfatal recurrent VTE and for major bleeding derived from Douketis et al.
7Surrogate outcome: absence of patency at 6 mo in Enden et al study; absence of complete lysis at 6 mo in Elsharawy et al study.
8This estimate is based on the findings of the VETO study. This probably underestimates PTS baseline risk given that overall, 52% of patients reported the current use of compression stockings during study follow-up.
9Severe PTS: assuming the same RR of 0.46 and a baseline risk of 13.8%; the absolute reduction is 75 fewer severe PTS per 1,000 (from 29 fewer to 138 fewer) over 2 y.
10Cameroa et al.
11Participation rate was 65%.
12Recall was used to measure QOL prior to the thrombotic event; we did not consider these measurements.
13At the initial follow-up (mean, 16 mo), patients treated with CDT reported a trend toward a higher mental summary scale (P = .057) and improved HUI (P = .078). They reported better overall role physical functioning (P = .046), less stigma (P = .033), less health distress (P = .022), and fewer overall symptoms (P = .006) compared with patients who were treated with anticoagulation alone.

Remarks: Patients who are most likely to benefit from CDT (see text) and attach a high value to prevention of PTS and a lower value to the initial complexity, cost, and risk of bleeding with CDT are likely to choose CDT over anticoagulation alone.

2.10 Systemic Thrombolytic Therapy for Acute DVT

Many trials of systemic thrombolysis for the treatment of DVT assessed early lysis, often reported bleeding, but rarely reported recurrent VTE or development of PTS (Table S13 and S14). A meta-analysis summarized the findings of trials that assessed mortality, recurrent VTE, major bleeding, and PTS (Table 12, Table S15). This evidence suggests that systemic thrombolysis has the potential to reduce PTS at the expense of an increase in major bleeding. However, the overall quality of this evidence is low because of imprecision and risk of bias.

There have been no direct comparisons of different thrombolytic agents; however, prolonged infusions of streptokinase that were used predominantly in the earlier studies appear to be associated with higher bleeding rates than other regimens. No randomized trial has compared systemic thrombolysis with CDT, but a single-center, retrospective study suggested that systemic thrombolysis achieves less
systemic thrombolysis are expected to be associated with a higher risk of nonprocedure-related bleeding.

We believe that systemic thrombolysis should be considered only in patients who meet all of the following criteria: iliofemoral DVT, symptoms for < 14 days, good functional status, life expectancy of ≥1 year, and low risk of bleeding (Table 11). Based on low-quality evidence of greater effectiveness and less bleeding, if resources and expertise are available to perform CDT, we consider it the preferable approach. Because the balance of risks and benefits with systemic thrombolysis is uncertain, and particularly because of concerns about major bleeding, anticoagulant therapy alone is an acceptable alternative to systemic thrombolysis in all patients with acute DVT who do not have impending venous gangrene.

Recommendation

2.10. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over systemic thrombolysis (Grade 2C).

Remarks: Patients who are most likely to benefit from systemic thrombolytic therapy (see text), who do not have access to CDT, and who attach a high value to prevention of PTS and a lower value to the initial complexity, cost, and risk of bleeding with systemic thrombolytic therapy are likely to choose systemic thrombolytic therapy over anticoagulation alone.

2.11 Operative Venous Thrombectomy for Acute DVT

Operative venous thrombectomy, with contemporary operative techniques and more effective anticoagulant regimens, appears to achieve improved outcomes compared with earlier reports. A single small randomized trial with extended follow-up compared iliofemoral venous thrombectomy with a temporary arteriovenous fistula plus anticoagulation with anticoagulation alone. Results at 6 months, 5 years, and 10 years suggested improved iliac vein patency, less leg swelling, and fewer leg ulcers with thrombectomy (Table 13, Tables S16–S18). Evidence from this trial is of low quality because of imprecision and risk of bias.

We believe that operative venous thrombectomy should be considered only if all of the following criteria are met: iliofemoral DVT, symptoms for < 7 days (criterion used in the single randomized trial), good functional status, life expectancy of ≥1 year, and both resources and expertise are available. Based on low-quality evidence of greater effectiveness and less bleeding, we consider

### Table 11—[Section 2.9, 2.10, 5.6, 9.2] Risk Factors for Bleeding With and Contraindications to Use of Thrombolytic Therapy (Both Systemic and Locally Administered)

<table>
<thead>
<tr>
<th>Major contraindications</th>
<th>Structural intracranial disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Previous intracranial hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Ischemic stroke within 3 mo</td>
</tr>
<tr>
<td></td>
<td>Active bleeding</td>
</tr>
<tr>
<td></td>
<td>Recent brain or spinal surgery</td>
</tr>
<tr>
<td></td>
<td>Recent head trauma with fracture or brain injury</td>
</tr>
<tr>
<td></td>
<td>Bleeding diathesis</td>
</tr>
<tr>
<td>Relative contraindications</td>
<td>Systolic BP &gt; 180 mm Hg</td>
</tr>
<tr>
<td></td>
<td>Diastolic BP &gt; 110 mm Hg</td>
</tr>
<tr>
<td></td>
<td>Recent bleeding (nonintracranial)</td>
</tr>
<tr>
<td></td>
<td>Recent surgery</td>
</tr>
<tr>
<td></td>
<td>Recent invasive procedure</td>
</tr>
<tr>
<td></td>
<td>Ischemic stroke more than 3 mo previously</td>
</tr>
<tr>
<td></td>
<td>Anticoagulation (eg, VKA therapy)</td>
</tr>
<tr>
<td></td>
<td>Traumatic cardiopulmonary resuscitation</td>
</tr>
<tr>
<td></td>
<td>Pericarditis or pericardial fluid</td>
</tr>
<tr>
<td></td>
<td>Diabetic retinopathy</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td>Age ≥ 75 y</td>
</tr>
<tr>
<td></td>
<td>Low body weight (eg, &lt; 60 kg)</td>
</tr>
<tr>
<td></td>
<td>Female sex</td>
</tr>
<tr>
<td></td>
<td>Black race</td>
</tr>
</tbody>
</table>

Among 32,000 Medicare patients (≥65 y) with myocardial infarction who were treated with thrombolytic therapy, the following factors were independently associated with intracranial hemorrhage: age ≥75 y (OR, 1.6), black race (OR, 1.6), female sex (OR, 1.4), previous stroke (OR, 1.5), systolic BP ≥ 160 mm Hg (OR, 1.8), women weighing ≤ 65 kg or men weighing ≤ 80 kg (OR, 1.5), and INR > 4 (OR, 2.2). The rate of intracranial hemorrhage increased from 0.7% with none or one of these risk factors to 4.1% with five or more of these risk factors. Among 32,000 patients with myocardial infarction who were treated with thrombolytic therapy in five clinical trials, the following factors were independently associated with moderate or severe bleeding: older age (OR, 1.04 per year), black race (OR, 1.4), female sex (OR, 1.5), hypertension (OR, 1.2), and lower weight (OR, 0.99/kg). We estimated that systemic thrombolytic therapy is associated with a relative risk of major bleeding of 3.5 within 35 d (RR, ~7 for intracranial bleeding); about three-fourths of the excess of major bleeds with thrombolytic therapy occur in the first 24 h. See Table 1 legend for expansion of abbreviations.

The presence of major contraindications usually precludes use of thrombolytic therapy, and, consequently, these factors have not been well studied as risk factors for bleeding associated with thrombolytic therapy. The factors listed in this table are consistent with other recommendations for the use of thrombolytic therapy in patients with PE. Risk factors for bleeding during anticoagulant therapy noted in Table 10 that are not included in this table are also likely to be relative contraindications to thrombolytic therapy. The increase in bleeding associated with a risk factor will vary with (1) severity of the risk factor (eg, extent of trauma or recent surgery) and (2) temporal relationships (eg, interval from surgery or a previous bleeding episode believed to decrease markedly after ~2 wk). Risk factors for bleeding at critical sites (eg, intracranial, intraocular) or noncompressible sites are stronger contraindications for thrombolytic therapy.

lysis (31% vs 50%) and less preservation of valve function (13% vs 44%) (Tables S13 and S14), and the higher doses of thrombolytic agent used with
Table 12—[Section 2.10] Summary of Findings: Systemic Lysis vs No Systemic Lysis for Extensive Acute DVT of the Leg\textsuperscript{138}

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Risk With No Systemic Lysis</td>
</tr>
<tr>
<td>Mortality</td>
<td>688 (5 studies), 3 mo\textsuperscript{a}</td>
<td>Low\textsuperscript{d,e} due to imprecision</td>
<td>RR 0.86 (0.27-2.68)</td>
<td>21 per 1,000</td>
</tr>
<tr>
<td>Nonfatal recurrent VTE</td>
<td>687 (3 studies), 3 mo\textsuperscript{a}</td>
<td>Low\textsuperscript{d,e} due to imprecision</td>
<td>RR 1.28 (0.25-6.68)</td>
<td>48 per 1,000\textsuperscript{b}</td>
</tr>
<tr>
<td>Nonfatal major bleeding</td>
<td>688 (10 studies), 3 mo\textsuperscript{a}</td>
<td>Moderate\textsuperscript{d,e} due to imprecision</td>
<td>RR 1.84 (0.94-3.59)</td>
<td>29 per 1,000\textsuperscript{b}</td>
</tr>
<tr>
<td>PTS</td>
<td>678 (2 studies), 2 y\textsuperscript{c}</td>
<td>Low\textsuperscript{d,e} due to risk of bias and imprecision</td>
<td>RR 0.71 (0.49-1.04)</td>
<td>588 per 1,000\textsuperscript{b}</td>
</tr>
<tr>
<td>QOL not measured</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1, 3, and 10 legends for expansion of abbreviations.

\textsuperscript{a}Allocation was concealed in three of five studies. Follow-up inadequate in one of five studies (Common et al\textsuperscript{139}). Excluding this study from the analysis does not change the effect estimate. All studies had blinded outcome assessors. None of the studies used a placebo control.

\textsuperscript{b}The population of one study (Schulman et al\textsuperscript{136}) comprised patients with calf vein thrombosis.

\textsuperscript{c}Interventions varied across studies with regard to agent (eg, tissue plasminogen activator, streptokinase, urokinase), dose, use of the pedal vein administration, duration of treatment, and concomitant drugs (eg, steroids). However, we did not downgrade for indirectness given that there was no standard regimen and all analyses showed no heterogeneity in results.

\textsuperscript{d}CI included both no effect and a potentially significant effect.

\textsuperscript{e}Range of follow-up in included studies, 1 to 72 mo.

\textsuperscript{f}Allocation was concealed in two of three studies. Follow-up adequate in all studies. All studies had blinded outcome assessors. None of the studies used a placebo control.

\textsuperscript{g}Baseline risks for nonfatal recurrent VTE and for major bleeding derived from Douketis et al\textsuperscript{138}.

\textsuperscript{h}Allocation was concealed in seven of 10 studies. Follow-up inadequate in one of 10 studies (Common et al\textsuperscript{139}). Excluding this study from the analysis does not affect the effect estimate. All studies had blinded outcome assessors. Two studies used placebo (Turpie et al\textsuperscript{135} and Verhaeghe et al\textsuperscript{19}).

\textsuperscript{i}Only 4% of all major bleeding events were intracranial bleeds.

\textsuperscript{j}Range of follow-up in included studies, 1 to 6 y.

\textsuperscript{k}Allocation was concealed in two of two studies. Follow-up adequate in both studies. Both studies had blinded outcome assessors. Neither study used placebo control.

\textsuperscript{l}No use of a standardized validated tool reported.

\textsuperscript{m}This estimate is based on the findings of the VETO study\textsuperscript{140}. This probably underestimates PTS baseline risk, given that overall, 52% of patients reported the current use of compression stockings during study follow-up.

\textsuperscript{n}Severe PTS: Assuming the same RR of 0.71 and a baseline risk of 13.8%,\textsuperscript{139} the absolute reduction is 40 fewer severe PTS per 1,000 (from 70 fewer to 6 more) over 2 y.

CDT preferable to the operative venous thrombectomy approach.

**Recommendation**

2.11. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over operative venous thrombectomy (Grade 2C).

2.12 Anticoagulation in Patients Who Have Had Any Method of Thrombus Removal Performed

There are no randomized trials or observational studies that have compared different anticoagulant regimens or durations of therapy in patients with acute proximal DVT of the leg who have had any method of thrombus removal (including systemic thrombolysis). Mechanical components of these procedures are associated with a high early risk of early recurrent thrombosis, and thrombus removal is not known to alter the long-term risk of recurrent VTE. We used evidence from patients with DVT who did not have thrombus removal to guide anticoagulant decisions in those who had thrombus removal. This evidence is rated down to moderate quality because of its indirectness in this patient population.

**Recommendation**

2.12. In patients with acute DVT of the leg who undergo thrombosis removal, we recommend...
the same intensity and duration of anticoagulant therapy as in similar patients who do not undergo thrombosis removal (Grade 1B).

2.13 Vena Caval Filters for the Initial Treatment of DVT

No randomized trial or prospective observational study has evaluated IVC filters as sole therapy (ie, without concurrent anticoagulation) in patients with DVT. A single, large, randomized controlled trial evaluated permanent IVC filter insertion as an adjunct to anticoagulant therapy in patients with acute DVT who were considered to be at high risk for PE (Table 14, Table S19). The findings at 2 years and 8 years of follow-up, suggest that IVC filters increase the risk of recurrent DVT, reduce the risk of PE, do not alter the combined frequency of DVT and PE (ie, recurrent VTE), do not increase the risk of PTS, and do not alter mortality.

In assessing the role of an IVC filter in patients who cannot receive anticoagulant therapy (eg, actively bleeding), we assume that the relative risk of outcomes will be the same as in patients who received anticoagulant therapy in the Prevention du Risque d’Embolie Pulmonaire par Interruption Cave (PREPIC) study. However, their absolute rate of symptomatic PE and recurrent DVT will be higher compared with the PREPIC participants who were prescribed anticoagulants. A comprehensive review of mostly retrospective case series of IVC filter insertions (6,500 patients in 89 reports) suggested that venous thrombosis at the site of filter insertion occurs in ~10% of patients and that filters can be placed above the renal veins and in the superior vena cava if necessary. A prospective observational study also suggested that symptomatic VTE and asymptomatic filter thrombosis are common, and a systematic review suggested that the prevalence of PTS may be increased in patients with permanent IVC filters. A small single-center randomized trial suggested a higher complication rate with the Travenol compared with the Greenfield permanent filter.

Table 13—[Section 2.11] Summary of Findings: Surgical Thrombectomy vs No Surgical Thrombectomy for Extensive Acute DVT of the Leg

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With No Surgical Thrombectomy</th>
<th>Risk Difference With Surgical Thrombectomy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality not reported</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Nonfatal recurrent VTE</td>
<td>51 (1 study), 3 mo</td>
<td>Low due to risk of bias and imprecision</td>
<td>RR 0.37 (0.02-8.75)</td>
<td>48 per 1,000 vs 30 per 1,000 (from 47 fewer to 372 more)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal major bleeding</td>
<td>51 (1 study), 3 mo</td>
<td>Low due to risk of bias and imprecision</td>
<td>Not estimable (no events)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>PTS</td>
<td>51 (1 study), 2 y</td>
<td>Low due to risk of bias and imprecision</td>
<td>RR 0.63 (0.44-0.9)</td>
<td>588 per 1,000 vs 218 per 1,000 (from 59 fewer to 329 fewer)</td>
<td></td>
</tr>
<tr>
<td>QOL not measured</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1, 3 and 10 legends for expansion of abbreviations.

The study included patients with DVT with symptoms of leg swelling not exceeding 7 d and a proximal extension of the thrombus above the inguinal ligament but not into the vena cava.

Antithrombotic Therapy for VTE
Table 14—[Section 2.13] Summary of Findings: Vena Cava Filter vs No Vena Cava Filter for Acute Proximal DVT of the Leg Treated With Anticoagulation63,146,443

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With No vena cava Filters</th>
<th>Risk Difference With Vena cava Filters (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>400 (1 study), 8 y</td>
<td>Moderate due to imprecision</td>
<td>RR 0.95 (0.78-1.16)</td>
<td>515 per 1,000</td>
<td>26 fewer per 1,000 (from 113 fewer to 82 more)</td>
</tr>
<tr>
<td>Symptomatic PE</td>
<td>304 (1 study), 8 y</td>
<td>Moderate due to imprecision</td>
<td>RR 0.41 (0.2-0.86)</td>
<td>151 per 1,000</td>
<td>89 fewer per 1,000 (from 21 fewer to 121 fewer)</td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td>310 (1 study), 8 y</td>
<td>Moderate due to imprecision</td>
<td>RR 1.3 (0.93-1.82)</td>
<td>273 per 1,000</td>
<td>82 more per 1,000 (from 19 fewer to 224 more)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>337 (1 study), 8 y</td>
<td>Moderate due to imprecision</td>
<td>RR 0.83 (0.52-1.34)</td>
<td>155 per 1,000</td>
<td>31 fewer per 1,000 (from 89 fewer to 63 more)</td>
</tr>
<tr>
<td>PTS</td>
<td>308 (1 study), 8 y</td>
<td>Low due to risk of bias and imprecision</td>
<td>RR 0.87 (0.66-1.13)</td>
<td>609 per 1,000</td>
<td>91 fewer per 1,000 (from 238 fewer to 91 more)</td>
</tr>
<tr>
<td>Complications</td>
<td>370 (1 study), 2 y</td>
<td>Moderate due to imprecision</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>QOL not reported</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very uncertain about the estimate. PREPIC = Prevention du Risque d’Embolie Pulmonaire par Interruption Cave. See Table 1 and 3 legends for expansion of other abbreviations.

- Anticoagulation consisted of LMWH or UFH initially (according to a 2 x 2 factorial design) followed by oral anticoagulation for at least 3 mo.
- Four types of permanent vena cava filters were used: Vena Tech LGM (B. Braun Melsungen AG), titanium Greenfield (Boston Scientific Corporation), Cardial (C.R. Bard, Inc), and Bird’s Nest (Cook Group Incorporated).
- Allocation was concealed. Data collectors and outcome adjudicators were blinded. Intention-to-treat analysis. Data missing for 4% at 2 y and 1% at 8 y. Enrollment was stopped at 400 instead of targeted 800 because of slow recruitment.
- CI includes both negligible effect and appreciable benefit or appreciable harm.
- RR, 1.0 (95% CI, 0.29-3.4) at 12 d; RR, 1.08 (95% CI, 0.73-1.58) at 2 y.
- Small number of events.
- RR, 0.23 (95% CI, 0.05-1.05) at 12 d (both symptomatic and asymptomatic PE). RR, 0.54 (0.21-1.41) at 2 y (symptomatic PE).
- RR, 1.78 (95% CI, 1.09-2.94) at 2 y.
- RR, 1.5 (95% CI, 0.54-4.14) at 12 d. RR, 0.74 (95% CI, 0.41-1.36) at 2 y.
- No standardized validated tool used to measure PTS.
- No complications directly related to the filter or its insertion reported in the PREPIC trial.146 Mismetti et al443 (prospective study) reported an incidence of 3.2% (excluding filter tilting and puncture site hematoma) among 220 patients receiving a retrievable vena cava filter for secondary prevention of VTE, whereas Athanasoulis et al146 (retrospective study) reported an incidence of 0.3% for major complications among 1,731 patients receiving vena cava filters predominantly for secondary prevention of VTE.

If an IVC filter is indicated in a patient with acute DVT or PE because anticoagulant therapy is temporarily contraindicated (eg, active bleeding), there is the option of inserting a retrievable filter and removing it when it is safe to start anticoagulant therapy. However, most retrievable filters are not removed; retrievable filters that are not removed may have a higher long-term complication rate than permanent filters, and there currently is no good evidence that retrievable IVC filters improve patient outcomes.104,147,154,155

Insertion of an IVC filter does not eliminate the risk of PE and increases the risk of DVT (Table 14, Table S19). Consequently, we suggest that patients who have an IVC filter inserted should receive a conventional course of anticoagulation (eg, parenteral and long-term anticoagulation) if the contraindication to anticoagulation resolves. Such patients should be treated for the same length of time as if the same patient had not had an IVC filter inserted (see section 3.1). The duration of anticoagulation, therefore, will vary according to whether the DVT was provoked by a temporary risk factor, was unprovoked, or was associated with cancer, and may be influenced by the patient’s ongoing risk of bleeding and preferences.

Our recommendation to treat patients with an IVC filter with anticoagulants when contraindications to anticoagulation resolve is weaker than for anticoagulation of most patients with VTE because the risks of bleeding may remain elevated, and the patient’s risk of recurrence is expected to be lower if the acute episode of thrombosis occurred remotely. The evidence for IVC filter use in patients with acute proximal DVT who cannot be treated with anticoagulation is moderate because of serious imprecision and indirectness (ie, extrapolated from the PREPIC study in which...
patients were routinely treated with anticoagulants; this indirectness, however, is minor).

Recommendations

2.13.1. In patients with acute DVT of the leg, we recommend against the use of an IVC filter in addition to anticoagulants (Grade 1B).

2.13.2. In patients with acute proximal DVT of the leg and contraindication to anticoagulation, we recommend the use of an IVC filter (Grade 1B).

2.13.3. In patients with acute proximal DVT of the leg and an IVC filter inserted as an alternative to anticoagulation, we suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 2B).

Remarks: We do not consider that a permanent IVC filter, of itself, is an indication for extended anticoagulation.

Table 15—[Section 2.14] Summary of Findings: Early Ambulation vs Delayed Ambulation for Acute DVT of the Leg

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With Delayed Ambulation</th>
<th>Risk Difference With Early Ambulation (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>385 (4 studies), 3 mo</td>
<td>Low due to risk of bias, imprecision</td>
<td>RR 1.3 (0.23-7.55)</td>
<td>11 per 1,000</td>
<td>3 more per 1,000 (from 8 fewer to 70 more)</td>
</tr>
<tr>
<td>PE (symptomatic or asymptomatic)</td>
<td>385 (4 studies), 4-12 d</td>
<td>Low due to risk of bias, imprecision</td>
<td>RR 1.16 (0.66-2.05)</td>
<td>118 per 1,000</td>
<td>19 more per 1,000 (from 40 fewer to 124 more)</td>
</tr>
<tr>
<td>QOL questionnaire in chronic limb venous insufficiency (CIVIQ)</td>
<td>53 (1 study), 2 y</td>
<td>Low due to risk of bias, indirectness</td>
<td>See footnote</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTS Villalta-Prandoni scores (value, &gt; 5)</td>
<td>37 (1 study), 2 y</td>
<td>Low due to risk of bias, imprecision</td>
<td>RR 0.66 (0.42-1.03)</td>
<td>400 per 1,000</td>
<td>136 fewer per 1,000 (from 232 fewer to 12 more)</td>
</tr>
</tbody>
</table>

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follows: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. CIVIQ = Chronic Venous Insufficiency Questionnaire. See Table 1 and 3 legends for expansion of other abbreviations.

*Two of four eligible studies excluded patients with symptomatic PE; in the third study, 24% of participants had symptomatic PE at baseline. It was not clear whether the fourth study excluded patients with symptomatic PE.

*In two of four eligible trials, all patients received early compression therapy (bandages or stockings). In the two other trials, only patients randomized to early ambulation received early compression therapy.

*Three studies reporting acute-phase mortality reported no deaths.

*Concealment of allocation was reported in one of four studies; blinding of outcome assessors was reported in two of four studies; intention-to-treat analysis reported in two of four studies. Follow-up was 97% to 100%. In two of four trials, only patients randomized to early ambulation received early compression therapy (bandages or stockings). In the other two trials, all patients received early compression therapy.

*CI includes both values of clinically significant benefit and values of clinically significant harm.

*PE assessed as both symptomatic and asymptomatic PE.

*Funnel plot reported as not asymmetrical by Aissaoui et al. 856

*Concealment of allocation was not reported; outcome assessors were not blinded for this outcome. Seventy percent follow-up rate; compression stockings used on patients with early mobilization but not in patients with delayed mobilization.

*No explanation was provided.

*Psychologic and overall somatic QOL did not differ significantly between the treatment groups, whereas DVT-related items, especially those reflecting the ease of locomotion, showed significantly greater improvement with compression than with bed rest (P < .001 for bandages, P < .05 for stockings).

2.14 Early Ambulation of Patients With Acute DVT

Treatment of acute DVT with bed rest and anticoagulation (originally UFH) has given way to early mobilization with anticoagulation (often administered SC). Two meta-analyses 156,157 summarized evidence from four relevant trials (Table 15, Tables S20-S22). This evidence is of low quality because of risk of bias and imprecision. We suggest early ambulation (eg, without a period of bed rest) when feasible because of its potential to decrease PTS and improve quality of life.

Recommendation

2.14. In patients with acute DVT of the leg, we suggest early ambulation over initial bed rest (Grade 2C).

Remarks: If edema and pain are severe, ambulation may need to be deferred. As per section 4.1, we recommend the use of compression therapy in these patients.
3.0 Long-term Anticoagulation of Acute DVT of the Leg

In this review, the term long-term treatment refers to treatments (eg, VKA therapy, LMWH, dabigatran) that are continued after initial therapy (eg, parenteral anticoagulation, thrombolytic therapy) (Fig 1). In addition, we consider treatment with rivaroxaban, which is used without initial parenteral therapy. Long-term therapy has two goals: (1) to complete treatment of the acute episode of VTE and (2) to prevent new episodes of VTE that are not directly related to the acute event. During the early phase of long-term treatment (ie, first 3 months), treatment of the acute episode of VTE predominates. During the late phase of long-term treatment (ie, after the first 3 months), prevention of new episodes of VTE predominates. We use the term extended anticoagulation to refer to anticoagulation that is continued beyond 3 months without a scheduled stop date. However, regular (eg, yearly) reassessments are needed to assess whether a patient’s risk of bleeding increased or the patient’s preferences changed.

Three lines of evidence from randomized trials support the need for long-term anticoagulant treatment of DVT (ie, after 5-10 days of initial heparin therapy): (1) a randomized controlled trial of long-term anticoagulant therapy in 51 patients with symptomatic calf-vein thrombosis that documented a 25% rate of symptomatic extension of thrombosis within 3 months in the control group; (2) a randomized trial comparing long-term SC low-dose UFH (5,000 units bid) with VKA therapy in patients with proximal DVT that found that low-dose UFH was ineffective and resulted in a high rate of recurrent VTE (47% within 3 months); and (3) randomized trials in which reduced durations of treatment of 4 or 6 weeks resulted in important increases in recurrent VTE that are continued after initial therapy (eg, parenteral anticoagulation, thrombolytic therapy) (Fig 1). In patients with proximal DVT and PE, the estimated cumulative risk of recurrent VTE after stopping anticoagulant therapy of each of these categories is as follows: VTE provoked by surgery, 1% after 1 year and 3% after 5 years; VTE provoked by a nonsurgical reversible risk factor, 5% after 1 year and 15% after 5 years; and unprovoked VTE, 10% recurrence after 1 year and 30% after 5 years.

Increase in Risk of Recurrent VTE After Stopping Therapy—Current evidence suggests that the risk of recurrence after stopping therapy is largely determined by two factors: (1) whether the acute episode of VTE has been effectively treated (duration of therapy) and (2) the patient’s intrinsic risk of having a new episode of VTE (individual risk of recurrence).

Duration of therapy: The primary goal of trials that compare different time-limited durations of anticoagulation is to identify the shortest duration of therapy that results in a posttreatment risk of recurrence that is as low as can be achieved. The findings of these trials generally are not sensitive to differences in individual patient risk of bleeding.

Individual risk of recurrence: Primary factors for estimating risk of recurrence: Presence of a reversible provoking risk factor; unprovoked VTE, and presence of active cancer are the most important factors that influence risk of recurrent VTE after stopping VKA. Among patients with VTE provoked by a reversible factor, the risk of recurrence is much lower if the provoking factor was recent surgery compared with a nonsurgical trigger (eg, estrogen therapy, pregnancy, leg injury, flight of > 8 h). In patients with proximal DVT and PE, the estimated cumulative risk of recurrent VTE after stopping anticoagulant therapy of each of these categories is as follows: VTE provoked by surgery, 1% after 1 year and 3% after 5 years; VTE provoked by a nonsurgical reversible risk factor, 5% after 1 year and 15% after 5 years; and unprovoked VTE, 10% recurrence after 1 year and 30% after 5 years.

There are sparse data addressing the risk of recurrent VTE after stopping therapy in patients with cancer because treatment is rarely stopped in these patients because of a high risk for recurrence. A reasonable estimate for this risk, expressed as an annualized rate, may be 15%. However, the risk of recurrence is expected to vary according to whether the cancer is metastatic, being treated with chemotherapy, or rapidly progressing. The high mortality in patients with VTE and cancer (40% at 6 months in one large study) precludes estimating the cumulative risk of recurrence after long-term follow-up. We categorize patients with VTE according to these primary individual risk factors for recurrence when we make recommendations for duration of anticoagulant therapy.

Recommendation

3.0. In patients with acute VTE who are treated with anticoagulant therapy, we recommend long-term therapy (see section 3.1 for recommended duration of therapy) over stopping anticoagulant therapy after 1 week of initial therapy (Grade 1B).

3.1 Duration of Long-term Anticoagulant Therapy

Weighing the Benefits and Risks of Different Durations of Anticoagulant Therapy: General Considerations: Anticoagulant therapy for VTE should be continued until (1) the reduction of recurrent VTE no longer clearly outweighs the increase in bleeding or (2) it is patient preference (which may be influenced by financial burden) to stop treatment, even if the reduction in VTE would outweigh the increase in bleeding.

Increase in Risk of Recurrent VTE After Stopping Therapy—Current evidence suggests that the risk of recurrence after stopping therapy is largely determined by two factors: (1) whether the acute episode of VTE has been effectively treated (duration of therapy) and (2) the patient’s intrinsic risk of having a new episode of VTE (individual risk of recurrence).

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Individual risk of recurrence: Primary factors for estimating risk of recurrence: Presence of a reversible provoking risk factor; unprovoked VTE, and presence of active cancer are the most important factors that influence risk of recurrent VTE after stopping VKA. Among patients with VTE provoked by a reversible factor, the risk of recurrence is much lower if the provoking factor was recent surgery compared with a nonsurgical trigger (eg, estrogen therapy, pregnancy, leg injury, flight of > 8 h). In patients with proximal DVT and PE, the estimated cumulative risk of recurrent VTE after stopping anticoagulant therapy of each of these categories is as follows: VTE provoked by surgery, 1% after 1 year and 3% after 5 years; VTE provoked by a nonsurgical reversible risk factor, 5% after 1 year and 15% after 5 years; and unprovoked VTE, 10% recurrence after 1 year and 30% after 5 years.

There are sparse data addressing the risk of recurrent VTE after stopping therapy in patients with cancer because treatment is rarely stopped in these patients because of a high risk for recurrence. A reasonable estimate for this risk, expressed as an annualized rate, may be 15%. However, the risk of recurrence is expected to vary according to whether the cancer is metastatic, being treated with chemotherapy, or rapidly progressing. The high mortality in patients with VTE and cancer (40% at 6 months in one large study) precludes estimating the cumulative risk of recurrence after long-term follow-up. We categorize patients with VTE according to these primary individual risk factors for recurrence when we make recommendations for duration of anticoagulant therapy.

Secondary factors for estimating risk of recurrence: Additional factors that influence the risk of recurrence
strongly enough to modify some recommendations about duration of therapy include (1) whether DVT was confined to the distal veins (isolated distal [or calf] DVT), which is estimated to be associated with about one-half of the risk of recurrence of proximal DVT and PE,\textsuperscript{10,164,167,169,170} and (2) whether the VTE was a second or subsequent episode of VTE, which is estimated to be associated with about a 50% higher risk of recurrence compared with a first VTE.\textsuperscript{1,173,175}

Additional factors for estimating risk of recurrence: Other factors predict risk of recurrence, but not strongly or consistently enough to influence recommendations on duration of therapy once the primary and secondary factors noted previously have been considered. These factors, which have mostly been evaluated in patients with unprovoked VTE, include negative D-dimer testing 1 month after withdrawal of VKA (risk ratio [RR], \textasciitilde 0.4),\textsuperscript{48,176-181} antiphospholipid antibody (RR, \textasciitilde 2),\textsuperscript{182,185} hereditary thrombophilia (RR, \textasciitilde 1.5),\textsuperscript{162,163,174,177,180-182,185,190} male vs female sex (RR, \textasciitilde 1.6),\textsuperscript{191,192} Asian ethnicity (RR, \textasciitilde 0.8),\textsuperscript{190} and residual thrombosis in the proximal veins (RR, \textasciitilde 1.5).\textsuperscript{140,182,185,194-198} Combinations of factors have the potential to be more important predictions of recurrence risk than single factors (eg, low risk of recurrence in women with unprovoked proximal DVT or PE who have a negative D-dimer test before\textsuperscript{185} or 1 month after\textsuperscript{190,199} stopping anticoagulant therapy). PTS may be a risk factor for recurrent VTE,\textsuperscript{183,185,200} and recurrent ipsilateral DVT is a risk factor for development of PTS.\textsuperscript{201,202} Both associations may contribute to a decision to use extended therapy in a patient with established PTS.

Increase in Risk of Bleeding While Remaining on Anticoagulant Therapy—Although the decision to treat patients with different time-limited durations of anticoagulant therapy generally are insensitive to an individual’s risk of bleeding, the decision to use extended anticoagulation, particularly in patients with an unprovoked proximal DVT or PE, is sensitive to risk of bleeding. There is no validated prediction tool to stratify the risk of major bleeding during extended anticoagulant therapy specifically in patients with VTE, but this risk appears to increase with the prevalence of the factors noted in Table 2. This table also provides our estimate of the absolute risk of bleeding without anticoagulation (baseline risk), the increase with anticoagulation, and the sum of these two risks (ie, risk of bleeding on therapy).

Comparisons of Time-Limited Durations of Therapy: Randomized trials have compared either a short (eg, 4 or 6 weeks) with an intermediate (eg, 3 or 6 months) duration of therapy, or two intermediate durations of therapy (eg, 3 months vs 6 or 12 months). VKA therapy targeted to an INR of 2.5 was the anticoagulant regimen in all comparisons.

Short vs Intermediate Durations of Therapy—Five trials have evaluated shortening the duration of oral anticoagulant therapy from 3 or 6 months to 4 or 6 weeks in patients with mostly first episodes of VTE (Table 16, Tables S23-S25).\textsuperscript{156,160,167,169} This evidence, which is high quality, indicates that with the shorter duration of therapy, the absolute decrease in bleeding was small compared with the absolute increase in recurrent VTE. Patients with isolated distal DVT provoked by a major transient risk factor have a very low risk of recurrence after anticoagulant therapy is stopped (~1% per year\textsuperscript{170}). It is uncertain whether this risk is lowered by treating for 3 months compared with 4 or 6 weeks (hazard ratio [HR] for 4 or 6 weeks vs \textasciitilde 3 months at 2 years after stopping therapy, \textasciitilde 0.36; 95% CI, 0.09-1.54\textsuperscript{170}). For this reason, we make a weaker recommendation for 3 months compared with a shorter duration of therapy in patients with isolated distal DVT that was provoked by a reversible risk factor. The evidence supporting this weaker recommendation is rated down to low quality because of serious imprecision and because it is a post hoc observation.

Different Intermediate Durations of Therapy (6 or 12 months vs 3 months)—We considered trials that randomized patients with VTE to 3 months vs to 6 or 12 months of treatment to determine, when using a time-limited duration of therapy, whether there was any benefit to treating for >3 months. Five reports, which included six randomized comparisons, contributed to this analysis (Table 17, Tables S24-S26).\textsuperscript{167,194,203-205} These studies found that 6 or 12 months of therapy did not convincingly lower risk of recurrence but increased major bleeding about 2.5-fold. In a meta-analysis of individual patient data from randomized trials, during the 2 years after stopping anticoagulant therapy, treatment of 3 months compared with \textasciitilde 6 months was associated with an HR of 1.19 (95% CI, 0.86-1.65) in all patients and an HR of 1.39 (95% CI, 0.96-2.01) in patients with unprovoked DVT or PE.\textsuperscript{170} Therefore, although anticoagulants are very effective at preventing recurrence while patients are receiving therapy, when anticoagulants are stopped, there is a similar risk of recurrence whether patients have been treated for 3 months or longer.\textsuperscript{170} This evidence is of moderate quality because of serious imprecision.

As an alternative to comparing two time-limited durations of anticoagulant therapy, the AESOPUS (Ultrasound Findings to Adjust the Duration of Anticoagulation) trial compared a predefined duration of therapy with a flexible duration of therapy that depended on whether there was residual thrombosis during follow-up in patients with a first proximal
Table 16—[Section 3.1.1-3.1.4] Summary of Findings: Four or Six Weeks vs Three or Six Months as Minimum Duration of Anticoagulation for VTE

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With Control</th>
<th>Risk Difference With 4 or 6 wk vs 3 or 6 mo Months of Anticoagulation (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>2,185 (5 studies), 1-2 y&lt;sup&gt;e&lt;/sup&gt;</td>
<td>High&lt;sup&gt;e&lt;/sup&gt;</td>
<td>RR 1.83 (1.39-2.42)</td>
<td>64 per 1,000</td>
<td>53 more per 1,000 (from 25 more to 91 more)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2,185 (5 studies), 1-2 y</td>
<td>High&lt;sup&gt;e&lt;/sup&gt;</td>
<td>RR 0.54 (0.22-1.32)</td>
<td>12 per 1,000</td>
<td>5 fewer per 1,000 (from 9 fewer to 4 more)</td>
</tr>
<tr>
<td>Mortality</td>
<td>2,098 (5 studies), 1-2 y</td>
<td>High&lt;sup&gt;e&lt;/sup&gt;</td>
<td>RR 0.97 (0.68-1.38)</td>
<td>55 per 1,000</td>
<td>2 fewer per 1,000 (from 18 fewer to 21 more)</td>
</tr>
</tbody>
</table>

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

<sup>a</sup>Populations varied among studies: first provoked isolated distal DVT, proximal DVT, or PE provoked in Kearon et al<sup>169</sup>; first isolated distal DVT in Pinede et al<sup>167</sup>; first isolated distal DVT, proximal DVT, or PE in Schulman et al<sup>168</sup>; proximal DVT (21% had cancer) in Levine et al<sup>169</sup>; DVT or PE (29% not objectively confirmed) in British Thoracic Society.<sup>160</sup>

<sup>b</sup>Short vs longer duration of anticoagulation was 6 wk vs 6 mo for Schulman et al<sup>166</sup>, 6 wk vs 3 mo for Pinede et al<sup>167</sup> and 4 wk vs 3 mo for the other three studies.

<sup>e</sup>Timing of randomization relative to the start of treatment varied across studies: Pinede et al<sup>167</sup>, Schulman et al<sup>166</sup> and British Thoracic Society<sup>160</sup> randomized at diagnosis, and Kearon et al<sup>169</sup> and Levine et al<sup>169</sup> randomized to stop or to continue treatment for 2 mo more after the initial 4 wk of treatment.

<sup>f</sup>Follow-up was for ~1 y in all studied except for Schulman et al<sup>169</sup> in which it was 2 y.

<sup>g</sup>Generally, study design was strong. No study stopped early for benefit; two stopped early because of slow recruitment (Kearon et al<sup>169</sup> Pinede et al<sup>167</sup>). In one study (British Thoracic Society<sup>160</sup>), 44 randomized patients were excluded centrally as they did not satisfy eligibility criteria. Patients and caregivers were blinded in two studies (Kearon et al, Levine et al<sup>169</sup>). Adjudicators of outcomes were blinded in all but one study (British Thoracic Society). All studies appear to have used effective randomization concealment, intention-to-treat analysis, and a low unexplained drop-out frequency.

<sup>h</sup>No heterogeneity with I<sup>2</sup> = 0%.

<sup>i</sup>No imprecision for overall estimates. However, for the subgroup of patients with isolated distal DVT, who are known to have a very low risk of recurrence, there is imprecision and the possibility that the shorter duration of anticoagulation is adequate and not associated with a clinically important higher risk of recurrence.

<sup>j</sup>Differences in mortality are expected to be mediated by differences in recurrent VTE and bleeding.

The results indicate that randomization to indefinite treatment with conventional-intensity VKA (target INR 2.0-2.85, 1-2 y<sup>j</sup>) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

<sup>1</sup>Populations varied among studies: first provoked isolated distal DVT, proximal DVT, or PE provoked in Kearon et al<sup>169</sup>; first isolated distal DVT, proximal DVT, or PE in Schulman et al<sup>168</sup>; proximal DVT (21% had cancer) in Levine et al<sup>169</sup>; DVT or PE (29% not objectively confirmed) in British Thoracic Society.<sup>160</sup>

<sup>2</sup>Short vs longer duration of anticoagulation was 6 wk vs 6 mo for Schulman et al<sup>166</sup>, 6 wk vs 3 mo for Pinede et al<sup>167</sup> and 4 wk vs 3 mo for the other three studies.

<sup>3</sup>Timing of randomization relative to the start of treatment varied across studies: Pinede et al<sup>167</sup>, Schulman et al<sup>166</sup> and British Thoracic Society<sup>160</sup> randomized at diagnosis, and Kearon et al<sup>169</sup> and Levine et al<sup>169</sup> randomized to stop or to continue treatment for 2 mo more after the initial 4 wk of treatment.

<sup>4</sup>Follow-up was for ~1 y in all studied except for Schulman et al<sup>169</sup> in which it was 2 y.

<sup>5</sup>Generally, study design was strong. No study stopped early for benefit; two stopped early because of slow recruitment (Kearon et al<sup>169</sup> Pinede et al<sup>167</sup>). In one study (British Thoracic Society<sup>160</sup>), 44 randomized patients were excluded centrally as they did not satisfy eligibility criteria. Patients and caregivers were blinded in two studies (Kearon et al, Levine et al<sup>169</sup>). Adjudicators of outcomes were blinded in all but one study (British Thoracic Society). All studies appear to have used effective randomization concealment, intention-to-treat analysis, and a low unexplained drop-out frequency.

<sup>6</sup>No heterogeneity with I<sup>2</sup> = 0%.

<sup>7</sup>No imprecision for overall estimates. However, for the subgroup of patients with isolated distal DVT, who are known to have a very low risk of recurrence, there is imprecision and the possibility that the shorter duration of anticoagulation is adequate and not associated with a clinically important higher risk of recurrence.

<sup>8</sup>Differences in mortality are expected to be mediated by differences in recurrent VTE and bleeding.

DVT<sup>168</sup> (Tables S24 and S25). Its findings suggest that the latter approach may be helpful for tailoring the duration of therapy.

**Extended vs Time-Limited Anticoagulant Therapy:** Five trials compared extended anticoagulation with VKA therapy (target INR 2.0-2.85, 1-2 y<sup>j</sup>) with stopping VKA therapy at 3 or 6 months in patients who were judged to have a high risk of recurrence (Table 18, Table S24, S25, and S27). The results indicate that randomization to indefinite treatment with conventional-intensity VKA (target INR 2.5) reduces recurrent VTE by about 90% (RR for the four studies, 0.12; 95% CI, 0.05-0.25<sup>169,182,180</sup>) and randomization to low-intensity therapy (target INR 1.75) reduces VTE by 64% (95% CI for HR, 23%-81%),<sup>174</sup> with about one-half of recurrent VTE in the active treatment groups in these studies occurring in patients who had prematurely stopped VKA therapy. Extended anticoagulant therapy was associated with about a 2.6-fold increase in major bleeding. The quality of evidence for the reduction in recurrent VTE with extended therapy is high but is rated down to moderate for bleeding and mortality because of imprecision.

Weighing the Benefits and Risks of Extended VKA Therapy—The decision to extend anticoagulation therapy beyond 3 months is sensitive to both baseline risks of recurrent VTE and major bleeding. We did not identify a validated prediction tool for either outcome that takes into account all relevant risk factors. As an alternative, for patients without cancer, we chose to stratify our recommendations according to four primary risk groups for recurrent VTE (section 3.1) and three risk groups for major bleeding (section 3.1) (Table 2). This approach resulted in a total of 12 combinations of risk profiles. Table 19 shows the estimated total (and fatal) number of recurrent episodes of VTE prevented and the number of major bleeds caused by 5 years of extended therapy for each of the 12 combinations. In the absence of robust trial data for mortality for recurrent VTE and
bleeding, we assumed that 3.6% of recurrent VTE and 11.3% of major bleeds will be fatal.12

We make (1) a strong recommendation for extended therapy when it is associated with a reduction in VTE that is substantially more frequent than the increase in major bleeding and with a mortality advantage, (2) a weak recommendation for extended therapy when it is associated with a reduction in VTE that is more frequent than the increase in major bleeding but the magnitude of this difference and the suggested mortality advantage are more modest, (3) a weak recommendation against extended therapy when extended therapy is associated with a reduction in VTE that is less frequent than the increase in major bleeding and no mortality advantage exists, and (4) a strong recommendation against extended therapy when extended therapy is associated with a reduction in VTE that is less frequent than the increase in major bleeding and a mortality disadvantage may exist. We assume that on average, extended anticoagulation with VKA therapy is a modest burden to patients.15 However, this differs markedly among patients; some do not find anticoagulant therapy a burden and have an enhanced feeling of well-being because they feel protected from recurrence, whereas others find it a major burden that greatly erodes their sense of well-being.210

The presence of additional risk factors for VTE recurrence (section 3.1), the patient’s relative value for the different outcome of interest (recurrence of VTE, major bleeding, PTS), and the patient’s perceived burden of anticoagulant therapy may influence decisions about the use of extended anticoagulant therapy in patient groups for which we provide a weak recommendation but are unlikely to influence this decision in patient groups for which we provide a strong recommendation.16 Similarly, the costs of therapy and how those costs are paid (eg, patient, third party) are more likely to influence treatment decisions when there is a weak recommendation (Grade 2) in favor of extended therapy.

Patients With VTE and Cancer: As previously noted (section 3.1), because they have a high risk of recurrence, patients with active cancer (eg, treated within the past 6 months, persistent or progressive) should benefit from extended anticoagulant therapy unless they have a very high risk of bleeding. The quality of the evidence supporting this recommendation is moderate because of indirectness (the relative effects of anticoagulation are based, in part, on evidence

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Table 17—[Section 3.1.1-3.1.4] Summary of Findings: Six or Twelve Months vs Three Months as Minimum Duration of Anticoagulation for VTE

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With 3 mo</th>
<th>Risk Difference With 6 or 12 mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>2,061 (6 studies), 1-3 y</td>
<td>Moderate+ due to imprecision</td>
<td>RR 0.89 (0.69-1.14)</td>
<td>115 per 1,000</td>
<td>13 fewer per 1,000 (from 36 fewer to 16 more)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2,061 (6 studies), 1-3 y</td>
<td>Highi</td>
<td>RR 2.49 (1.2-5.16)</td>
<td>9 per 1,000</td>
<td>13 more per 1,000 (from 2 more to 37 more)</td>
</tr>
<tr>
<td>Mortality‡</td>
<td>1,331 (5 studies), 1-3 y</td>
<td>Moderate† due to imprecision</td>
<td>RR 1.3 (0.51-2.08)</td>
<td>44 per 1,000</td>
<td>13 more per 1,000 (from 8 fewer to 47 more)</td>
</tr>
</tbody>
</table>

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumption of a high risk of recurrence in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follows: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of other abbreviations.

iStudy populations varied across studies: Pinede et al202 enrolled provoked and unprovoked proximal DVT and PE; Campbell et al203 enrolled provoked and unprovoked isolated distal DVT, proximal DVT, and PE; Agnelli et al204 had separate randomizations for provoked PE (3 vs 6 mo) and unprovoked (3 vs 12 mo); and Agnelli et al205 enrolled unprovoked proximal DVT.

Timing of randomization relative to the start of treatment and length of treatment in the non-3 mo group varied across studies: Pinede et al206 and Campbell et al207 randomized at diagnosis; and Agnelli et al208,209 randomized after the initial 3 mo of treatment to stop or continue treatment. The longer duration of treatment was 6 mo in Agnelli et al209 (provoked PE) and 12 mo in Agnelli et al208 and Agnelli et al209 (unprovoked PE).

Generally, study design was strong. No study stopped early for benefit; two stopped early because of slow recruitment (Campbell et al,200 Pinede et al201) and one because of lack of benefit (Agnelli et al202). In one study (Campbell et al), 20% of VTE outcomes were not objectively confirmed. Patients and caregivers were not blinded in any study. Adjudicators of outcomes were blinded in all but one study (Campbell et al). All studies used effective randomization concealment, intention-to-treat analysis, and a low unexplained drop-out frequency.

cCIs include both values suggesting no effect and values suggesting either benefit or harm.

Low number of events and a total number of participants <2,000.

One study may have confined the assessment of bleeding to when subjects were receiving anticoagulant therapy, which could have inflated the increase in bleeding associated with the longer duration of treatment (Campbell et al203).

⪞Differences in mortality are expected to be mediated by differences in recurrent VTE and bleeding.
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With No Extended Duration Oral Anticoagulation</th>
<th>Risk Difference With Extended Duration Oral Anticoagulation (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>1,184 (4 studies), 10-36 mo</td>
<td>Moderate due to imprecision</td>
<td>RR 0.57 (0.31-1.03)</td>
<td>63 per 1,000</td>
<td>27 fewer per 1,000 (from 44 fewer to 2 more)</td>
</tr>
<tr>
<td>Recurrent VTE at 1y</td>
<td>1,184 (4 studies), 10-36 mo</td>
<td>High</td>
<td>RR 0.12 (0.09-0.38)</td>
<td>First VTE provoked by surgery(^3)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>10 fewer per 1,000 (from 6 fewer to 9 fewer)</td>
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<td></td>
<td></td>
<td>First proximal DVT or PE provoked nonsurgical/</td>
<td>44 fewer per 1,000 (from 31 fewer to 45 fewer)</td>
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<td></td>
<td>first unprovoked distal DVT(^1)</td>
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<td>50 per 1,000</td>
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<td>First unprovoked VTE(^1)</td>
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<td>100 per 1,000</td>
<td>88 fewer per 1,000 (from 62 fewer to 91 fewer)</td>
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<td>Second unprovoked VTE(^1)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>150 per 1,000</td>
<td>132 fewer per 1,000 (from 93 fewer to 137 fewer)</td>
</tr>
<tr>
<td>Major bleeding at 1y</td>
<td>1,184 (4 studies), 10-36 mo</td>
<td>Moderate due to imprecision</td>
<td>RR 2.63 (1.02-6.76)</td>
<td>Low(^4) (see Table 2)</td>
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<td></td>
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<td></td>
<td>3 more per 1,000 (from 0 more to 15 more)</td>
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<td></td>
<td></td>
<td>Moderate(^5) (see Table 2)</td>
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<td></td>
<td>6 per 1,000</td>
<td>10 more per 1,000 (from 1 more to 29 more)</td>
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<td>High(^6) (see Table 2)</td>
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<td>25 per 1,000</td>
<td>40 more per 1,000 (from 3 more to 122 more)</td>
</tr>
<tr>
<td>Recurrent VTE at 5y</td>
<td>1,184 (4 studies), 10-36 mo</td>
<td>High</td>
<td>RR 0.12 (0.09-0.38)</td>
<td>First VTE provoked by surgery(^5)</td>
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<td></td>
<td>30 per 1,000</td>
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<td></td>
<td></td>
<td>First proximal DVT or PE provoked nonsurgical/</td>
<td>26 fewer per 1,000 (from 19 fewer to 27 fewer)</td>
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<td></td>
<td>first unprovoked distal DVT(^1)</td>
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<td></td>
<td>150 per 1,000</td>
<td>132 fewer per 1,000 (from 93 fewer to 137 fewer)</td>
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<td>First unprovoked VTE(^1)</td>
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<td>300 per 1,000</td>
<td>264 fewer per 1,000 (from 186 fewer to 273 fewer)</td>
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<td></td>
<td>Second unprovoked VTE(^1)</td>
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<td></td>
<td></td>
<td>450 per 1,000</td>
<td>396 fewer per 1,000 (from 279 fewer to 409 fewer)</td>
</tr>
<tr>
<td>Major bleeding at 5y</td>
<td>1,184 (4 studies), 10-36 mo</td>
<td>Moderate due to imprecision</td>
<td>RR 2.63 (1.02-6.76)</td>
<td>Low(^4) (see Table 2)</td>
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<td>15 per 1,000</td>
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<td></td>
<td></td>
<td>Moderate(^5) (see Table 2)</td>
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<td></td>
<td>30 per 1,000</td>
<td>48 more per 1,000 (from 4 more to 146 more)</td>
</tr>
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<td></td>
<td></td>
<td>High(^6) (see Table 2)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>125 per 1,000</td>
<td>199 more per 1,000 (from 17 more to 609 more)</td>
</tr>
</tbody>
</table>

(Continued)
from patients without cancer). Presence of factors associated with a lower risk of recurrence that may support stopping anticoagulant therapy, particularly if the risk of bleeding was high, include the following: (1) VTE was associated with a superimposed reversible risk factor (eg, recent surgery, chemotherapy), (2) the cancer has responded to treatment, (3) the cancer has not metastasized, and (4) the VTE was an isolated distal DVT.

Follow-up of Patients on Extended Therapy: Patients who are treated with extended anticoagulant therapy should be reviewed regularly (eg, annually) to ensure that (1) they have not developed contraindications to extended therapy, (2) their preferences have not changed (eg, anticoagulation has become an excessive burden), (3) they can benefit from improved ways of selecting a patient for extended therapy if these have become available, and (4) they are being treated with the anticoagulant regimen that best suits them.

LMWH for Extended Therapy: We identified no direct evidence for LMWH compared with (1) VKA, (2) other anticoagulant strategies, or (3) control for the extended phase of anticoagulation in patients who were treated with a standardized initial long-term anticoagulant regimen. Based on indirect evidence from comparisons of LMWH with VKA therapy during the initial 3 or 6 months of long-term therapy, we judged LMWH to be at least as effective in terms of recurrent VTE and as safe in terms of major bleeding (Table 20, Table S28). The potential for drug-induced osteoporosis, however, may be greater with extended therapy LMWH than with VKA therapy.1

### Table 18—Continued

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Anticipated Absolute Effects</th>
<th>Risk With No Extended Duration Oral Anticoagulation</th>
<th>Risk Difference With Extended Duration Oral Anticoagulation (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burden of anticoagulation not reported</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>Warfarin: daily medication, dietary and activity restrictions, frequent blood testing/monitoring, increased hospital/clinic visits©</td>
<td>…</td>
</tr>
<tr>
<td>PTS not reported</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>*</td>
<td>…</td>
</tr>
</tbody>
</table>
Table 19—[Section 3.1.1-3.1.4] Estimated Absolute Difference in Recurrent VTE and Major Bleeding Events (Including Fatal Events) With 5 Years of vs No Extended Anticoagulation

<table>
<thead>
<tr>
<th>Outcomes After 5 y of Treatment</th>
<th>Recurrent VTE reduction per 1,000</th>
<th>Major bleeding increase per 1,000</th>
<th>Recurrent VTE reduction per 1,000</th>
<th>Major bleeding increase per 1,000</th>
<th>Recurrent VTE reduction per 1,000</th>
<th>Major bleeding increase per 1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>First VTE provoked by surgery</td>
<td>126 (19-27) (1 fatal)(^a)</td>
<td>126 (19-27) (1 fatal)(^b)</td>
<td>126 (19-27) (1 fatal)(^b)</td>
<td>126 (19-27) (1 fatal)(^b)</td>
<td>126 (19-27) (1 fatal)(^b)</td>
<td>126 (19-27) (1 fatal)(^b)</td>
</tr>
<tr>
<td>First VTE provoked by a nonsurgical factor/first unprovoked distal DVT</td>
<td>1132 (93-137) (5 fatal)(^c)</td>
<td>1132 (93-137) (5 fatal)(^c)</td>
<td>1132 (93-137) (5 fatal)(^c)</td>
<td>1132 (93-137) (5 fatal)(^c)</td>
<td>1132 (93-137) (5 fatal)(^c)</td>
<td>1132 (93-137) (5 fatal)(^c)</td>
</tr>
<tr>
<td>First unprovoked proximal DVT or PE</td>
<td>1284 (186-273) (10 fatal)(^d)</td>
<td>1284 (186-273) (10 fatal)(^d)</td>
<td>1284 (186-273) (10 fatal)(^d)</td>
<td>1284 (186-273) (10 fatal)(^d)</td>
<td>1284 (186-273) (10 fatal)(^d)</td>
<td>1284 (186-273) (10 fatal)(^d)</td>
</tr>
<tr>
<td>second unprovoked VTE</td>
<td>1396 (279-409) (14 fatal)(^e)</td>
<td>1396 (279-409) (14 fatal)(^e)</td>
<td>1396 (279-409) (14 fatal)(^e)</td>
<td>1396 (279-409) (14 fatal)(^e)</td>
<td>1396 (279-409) (14 fatal)(^e)</td>
<td>1396 (279-409) (14 fatal)(^e)</td>
</tr>
</tbody>
</table>

**Recommendations:**

- **Risk of dying in patients with a recurrent VTE or a major bleed:**
  - Case fatality rate of recurrent VTE after discontinuing oral anticoagulation therapy: 3.6% (Carrier et al\(^e\)).
  - Case fatality rate of major bleeding during initial oral anticoagulation therapy: 11.3% (Carrier et al\(^e\)) (no data available for after discontinuing oral anticoagulation therapy).

**Annual risks of recurrent VTE after discontinuation of anticoagulation:**

- First VTE provoked by surgery: 1% (Iorio et al\(^c\)); we assumed a 0.5% yearly risk thereafter (3% over 5 y).
- First episode of VTE provoked by nonsurgical factor: ~5% the first year (Iorio et al\(^c\)); we assumed a 2.5% yearly thereafter (15% over 5 y).
- First episode of unprovoked VTE: 9.3% over 1 y (Rodger et al\(^f\)); 11.6% over 1 y, 19.6% over 3 y, 29.1% over 5 y (Prandoni et al\(^g\)). We assumed a risk of 10% the first year after discontinuation and 5% yearly thereafter (30% over 5 y).
- Second episode of unprovoked VTE: we assumed that this inflicts 1.5 the risk of recurrent VTE relative to first episode of unprovoked VTE: 15% the first year after discontinuation, 7.5% yearly thereafter (45% over 5 y).

- **Relative risk reduction with extended anticoagulation therapy:**
  - 82% based on Table 18

- **Annual risks of major bleeding in patients not on anticoagulation therapy:**
  - Low risk, 0.3%/y; intermediate risk 0.6%/y; high risk, 2.4%/y (Table 2).

- **Relative risk of major bleeding with extended anticoagulation therapy:**
  - 2.6 based on Table 18

- **Criteria used to decide on direction and strengths of recommendations:**
  - Criterion for a strong recommendation against whenever the estimated number of fatal bleeding events exceeded the estimated number of fatal recurrent VTE prevented.
  - Criterion to go from a weak recommendation against to a weak recommendation against: difference between the lower boundary of increased major bleeding and upper boundary of reduction in recurrent VTE < 2% (risk over 5 y averaged per year).
  - Criterion to go from a weak recommendation against to a weak recommendation in favor of: difference between point estimate of reduction of recurrent VTE and point estimate for increase in major bleeding is > 2% (risk over 5 y averaged per year).
  - Criterion to go from a weak recommendation against to a weak recommendation in favor of: difference between the lower boundary of reduction in VTE and upper boundary of increased major bleeding > 4% (risk over 5 y averaged per year).

Another way of interpreting the direction and strength of recommendation based on the number of deaths (related to either bleeding or recurrent VTE) is as follows:

- A strong recommendation against: extended anticoagulation is estimated to be associated with an increase in deaths.
- A weak recommendation against: extended anticoagulation is estimated to be associated with from no effect on deaths to only a very small reduction in deaths (0-4/1,000 prevented over 5 y or < 0.5%/patient-y).
- A weak recommendation for: extended anticoagulation is estimated to be associated with a small reduction in deaths (5 to 9/1,000 prevented over 5 y or 0.5%-0.9%/patient-y).
- A strong recommendation for: extended anticoagulation is estimated to be associated with a large reduction in deaths (> 10/1,000 prevented over 5 y or > 1%/patient-y).

With an eightfold risk of bleeding in the high-risk group compared with the low-risk group, a strong recommendation against extended anticoagulation for a second unprovoked VTE is justified. The high-risk group, however, includes patients who have a risk of bleeding that is less than this estimate (eg, patients aged > 75 y without additional risk factors for bleeding [Table 2]) and, therefore, may benefit from extended anticoagulant therapy. For this reason, we provide a weak rather than a strong recommendation against extended anticoagulation for patients with a second unprovoked VTE in the high-bleeding-risk group.

\(^a\)Strong against
\(^b\)Weak against
\(^c\)Weak in favor
\(^d\)Strong in favor
Rivaroxaban for Extended Therapy: Use of rivaroxaban compared with initial parenteral therapy followed by VKA therapy for the short- and long-term treatment of DVT is reviewed in section 3.3 (Table 21, Table S29). In the current section, we consider rivaroxaban compared with no anticoagulation in patients with proximal DVT or PE who have completed 6 or 12 months of anticoagulant therapy, which has been evaluated in a single study (Table 22, Table S30). This study found that rivaroxaban markedly reduced recurrent VTE at the expense of a modest absolute increase in major bleeding. The evidence from this one study is of moderate quality because of serious imprecision.

Dabigatran for Extended Therapy: There are no completed studies that have compared dabigatran with no anticoagulation for extended treatment of VTE.

Choice of Anticoagulant Regimen for Extended Therapy: This question is addressed in section 3.3.

Recommendations

3.1.1. In patients with a proximal DVT of the leg provoked by surgery, we recommend treatment with anticoagulation for 3 months over: (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B), or (iii) extended therapy (Grade 1B regardless of risk of bleeding).

3.1.2. In patients with a proximal DVT of the leg provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B), and (iii) extended therapy if there is a high bleeding risk (Table 2) (Grade 1B). We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Table 2) (Grade 2B).

3.1.3. In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor (see remark), we suggest treatment with anticoagulation for 3 months over treatment of a shorter period (Grade 2C) and recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B) or extended therapy (Grade 1B regardless of bleeding risk).

3.1.4. In patients with an unprovoked DVT of the leg (isolated distal [see remark] or proximal), we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B). After 3 months of treatment, patients with unprovoked DVT of the leg should be evaluated for the risk-benefit ratio of extended therapy.

3.1.4.1. In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a low or moderate bleeding risk (Table 2), we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B).

3.1.4.2. In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a high bleeding risk (Table 2), we recommend 3 months of anticoagulant therapy over extended therapy (Grade 1B).

3.1.4.3. In patients with a first VTE that is an unprovoked isolated distal DVT of the leg (see remark), we suggest 3 months of anticoagulant therapy over extended therapy in those with a low bleeding risk (Table 2) (Grade 2B), and recommend 3 months of anticoagulant treatment in those with a moderate or high bleeding risk (Table 2) (Grade 1B).

3.1.4.4. In patients with a second unprovoked VTE, we recommend extended anticoagulant therapy over 3 months of therapy in those who have a low bleeding risk (Table 2) (Grade 1B), and we suggest extended anticoagulant therapy in those with a moderate bleeding risk (Table 2) (Grade 2B).

3.1.4.5. In patients with a second unprovoked VTE who have a high bleeding risk (Table 2), we suggest 3 months of anticoagulant therapy over extended therapy (Grade 2B).

3.1.5. In patients with DVT of the leg and active cancer, if the risk of bleeding is not high (Table 2), we recommend extended anticoagulant therapy over 3 months of therapy (Grade 1B), and if there is a high bleeding risk (Table 2), we suggest extended anticoagulant therapy (Grade 2B).

Remarks (3.1.3, 3.1.4, 3.1.4.3): Duration of treatment of patients with isolated distal DVT refers to patients in whom a decision has been made to treat with anticoagulant therapy; however, it is anticipated that not all patients who are given a diagnosis of isolated distal DVT will be prescribed anticoagulants (see section 2.3). In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).
The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

The association between leg symptoms and signs at 3 mo and long-term PTS is uncertain.

None of the studies were blinded, whereas the diagnosis of major bleeding has a subjective component and there could be a lower threshold for the diagnosis of major bleeding in patients who are already taking LMWH because there is no attractive alternative treatment option.

Risk of recurrent VTE: low corresponds to patients without cancer (3% estimate taken from recent large RCTs of acute treatment), intermediate corresponds to patients with local or recently resected cancer (based on average rate across the six studies in this analysis and appears to be consistent with Prandoni et al. [particularly if low risk is increased to 4%], and high corresponds to patients with locally advanced or distant metastatic cancer (Prandoni et al).

No study was blinded; diagnosis of major bleeding has a subjective component.

The 95% CIs for the RR for major bleeding includes a potentially clinically important increase or decrease with LMWH and may vary with the dose of LMWH used during the extended phase of therapy.

Risk of bleeding: low corresponds to patients without risk factor for bleeding (ie, age > 75 y, cancer, metastatic disease; chronic renal or hepatic failure; platelet count < 50,000; requirement for antithrombotic therapy; history of bleeding without a reversible cause) (Table 2). Based on Prandoni et al. and Beyth et al. and adjusted to a 6-mo time frame.

Hull et al. reported no significant difference in QOL but suggested greater satisfaction with LMWH over VKA (questionnaire did not directly assess the burden of injections).

Patients and investigators not blinded. Self-reported leg symptoms and signs after 3 mo of treatment.

The association between leg symptoms and signs at 3 mo and long-term PTS is uncertain.

Baseline risk assumes that patients all wear pressure stockings. Control event rate comes from observational studies in a review by Kahn et al. adjusted to a 2-y time frame.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies, Follow-up)</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With VKA</th>
<th>Risk Difference With LMWH (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2,496 (7 studies), 6 mo</td>
<td>Moderate due to imprecision</td>
<td>RR 0.96 (0.81-1.13)</td>
<td>164 per 1,000</td>
<td>7 fewer per 1,000 (from 31 fewer to 21 more)</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>2,727 (8 studies), 6 mo</td>
<td>Moderate due to risk of bias</td>
<td>RR 0.62 (0.46-0.84)</td>
<td>30 per 1,000</td>
<td>No cancer</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2,737 (8 studies), 6 mo</td>
<td>Moderate due to imprecision</td>
<td>RR 0.81 (0.55-1.2)</td>
<td>200 per 1,000</td>
<td>4 fewer per 1,000 (from 9 fewer to 4 more)</td>
</tr>
<tr>
<td>Burden of anticoagulation</td>
<td>...</td>
<td>High</td>
<td>...</td>
<td>80 per 1,000</td>
<td>15 fewer per 1,000 (from 36 fewer to 16 more)</td>
</tr>
<tr>
<td>PTS (self-reported leg symptoms and signs)</td>
<td>100 (1 study), 2 y</td>
<td>Low due to risk of bias, indirectness</td>
<td>RR 0.85 (0.77-0.94)</td>
<td>200 per 1,000</td>
<td>30 fewer per 1,000 (from 12 fewer to 46 fewer)</td>
</tr>
</tbody>
</table>
Table 21—[Section 3.3] Summary of Findings: Rivaroxaban vs LMWH and VKA Therapy for Acute and Long-term Treatment of VTE<sup>a,b</sup>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Anticipated Absolute Effects</th>
<th>Risk With LMWH and VKA Therapy</th>
<th>Risk Difference With Rivaroxaban (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>3,449 (1 study), 6-12 mo&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Moderate&lt;sup&gt;a&lt;/sup&gt; due to imprecision</td>
<td>HR 0.67 (0.44-1.02)</td>
<td>29 per 1,000</td>
<td>9 fewer per 1,000</td>
<td>(from 16 fewer to 1 more)</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>3,449 (1 study), 6-12 mo&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Moderate&lt;sup&gt;a&lt;/sup&gt; due to imprecision</td>
<td>HR 0.68 (0.44-1.04)</td>
<td>30 per 1,000&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9 fewer per 1,000</td>
<td>(from 17 fewer to 1 more)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3,429 (1 study), 6-12 mo&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Moderate&lt;sup&gt;a&lt;/sup&gt; due to imprecision</td>
<td>HR 0.68 (0.54-1.38)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>11 per 1,000&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4 fewer per 1,000</td>
<td>(from 7 fewer to 4 more)</td>
</tr>
<tr>
<td>Burden of anticoagulation</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>Warfarin: daily medication, dietary restrictions, frequent blood testing/monitoring, increased hospital/clinic visits</td>
<td>Rivaroxaban: daily medication, no dietary restrictions, no frequent blood testing/monitoring</td>
<td></td>
</tr>
</tbody>
</table>

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. HR = hazard ratio. See Table 1 and 3 legends for expansion of other abbreviations.

-<sup>a</sup>Included patients had acute, symptomatic, and objectively verified proximal DVT of the legs (unprovoked, 62%; cancer, 6%; previous, VTE 19%).
-<sup>b</sup>Rivaroxaban 15 mg bid for 3 wk and then 20 mg/d for a total of 3 (12%), 6 (63%), or 12 (25%) mo.
-<sup>c</sup>Enoxaparin 1 mg/kg bid for ~8 d and then VKA therapy targeted to an INR of 2.5 for 3, 6, or 12 mo.
-<sup>d</sup>Follow-up was prespecified to be 3 (12%), 6 (63%), or 12 (25%) mo.
-<sup>e</sup>Allocation was concealed. Patients, providers, and data collectors were not blinded, but outcome adjudicators were blinded. Intention-to-treat analysis; 1.0% were loss to follow-up. Not stopped early for benefit.
-<sup>f</sup>CI includes values suggesting benefit or no effect; relatively low number of events.
-<sup>g</sup>CI includes values suggesting benefit and harm.
-<sup>h</sup>One definite or possible fatal VTE in the rivaroxaban group and one in the LMWH/VKA group.
-<sup>i</sup>Calculated from reported data.
-<sup>j</sup>Bleeds contributing to death: one in the rivaroxaban group and five in the warfarin group.

3.2 Intensity of Anticoagulant Effect

Ageno et al<sup>a</sup> and Holbrook et al<sup>a</sup> in these guidelines present evidence for the optimal intensity of VKA therapy (ie, target INR) during the long-term (eg, first 3 months of treatment) and extended phases of treatment of VTE.

Recommendation

3.2. In patients with DVT of the leg who are treated with VKA, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) over a lower (INR < 2) or higher (INR 3.0-5.0) range for all treatment durations (Grade 1B).

3.3 Choice of Anticoagulant Regimen for Long-term Therapy

VKA therapy has been the standard method of anticoagulant therapy for VTE. Adjusted-dose SC UFH is an effective alternative to VKA therapy, but it has never been popular because it requires initial laboratory monitoring and twice-daily injection and is associated with osteoporosis.<sup>215,216</sup> SC LMWH has advantages over SC UFH in that it does not require laboratory monitoring, is less likely to cause osteoporosis,<sup>216</sup> and can be given once a day. For these reasons, LMWH has been used for the long-term treatment of VTE. The synthetic pentasaccharide, fondaparinux, has not been evaluated or widely used for long-term treatment of VTE. Idraparinux, a long-acting pentasaccharide, is effective for the long-term treatment of VTE,<sup>217</sup> but it is not being marketed because of concerns about bleeding given its prolonged duration of action (once weekly injection) and lack of reversibility. The direct antithrombin dabigatran and the direct factor Xa inhibitors apixaban and rivaroxaban have been evaluated for treatment of VTE and are now available in many countries. In this section, we compare VKA therapy (target INR 2.5), LMWH, dabigatran, and rivaroxaban for the long-term treatment of VTE (ie, first 3 months and extended therapy).
**Table 22—[Section 3.3] Summary of Findings: Rivaroxaban vs Placebo for Extended Anticoagulation of VTE**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With Placebo</th>
<th>Risk Difference With Rivaroxaban (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>1,196 (1 study), 6 or 12 mo</td>
<td>Moderate due to imprecision</td>
<td>RR 0.49 (0.04-5.4)</td>
<td>3 per 1,000</td>
<td>2 fewer per 1,000 (from 3 fewer to 15 more)</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>1,196 (1 study), 6 or 12 mo</td>
<td>High</td>
<td>HR 0.18 (0.09-0.39)</td>
<td>71 per 1,000</td>
<td>58 fewer per 1,000 (from 43 fewer to 64 fewer)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1,188 (1 study), 6 or 12 mo</td>
<td>Moderate due to imprecision</td>
<td>RR 4.9 (0.58-42)</td>
<td></td>
<td>7 more per 1,000 (from 3 more to 16 more)</td>
</tr>
</tbody>
</table>

Burden of anticoagulation not reported

| Burden of anticoagulation not reported | Rivaroxaban: daily medication |

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follows: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1, 3, and 21 legends for expansion of abbreviations.

1 Included patients had acute, symptomatic, and objectively verified proximal DVT of the legs or PE (unprovoked, 73%; cancer, 5%; previous VTE, 19%).

2 Rivaroxaban 20 mg/d for 6 or 12 mo after initial long-term therapy.

3 Follow-up was prespecified to be 6 (60%) or 12 (40%) mo.

4 Allocation was concealed. Patients, providers, data collectors, and outcome adjudicators were blinded. Intention-to-treat analysis; 0.2% were loss to follow-up. Not stopped early for benefit.

5 CI includes values suggesting benefit or no effect; relatively low number of events.

6 Calculated from reported data with addition of one event to each event rate because event rate was 0 in the control group.

7 One definite or possible fatal VTE in the rivaroxaban group and one in the LMWH/VKA group.

8 CI includes values suggesting benefit and harm.

9 Bleeds contributing to death: none in the rivaroxaban group and none in the warfarin group.

10 PTS: baseline risk over 2 y of 58.8% for PTS and 13.8% for severe PTS (Kahn et al®). There is threefold (Prandoni et al²) to 10-fold (van Dongen et al²) increase in PTS with recurrent VTE in the ipsilateral leg.

**LMWH vs VKA Therapy for the Long-Term Treatment of VTE:** Two meta-analyses compared LMWH in widely differing doses with VKAs.²¹,²² In an analysis by Iorio and colleagues,²¹ which included seven studies and a total of 1,379 patients, among study differences of mean daily dose of LMWH, little evidence of the efficacy of LMWH compared with VKA therapy was found, but the dose of LMWH appeared to influence the risk of major bleeding (OR, ~0.2 with ~4,000 International Units/d to ~0.7 with 12,000 International Units/d, relative to the VKA groups; P = .03 for dose-dependent interaction). Because prophylactic doses of LMWH are rarely used as an alternative to VKA therapy in patients with VTE, we restricted our analysis to eight studies that used ≥50% of the full therapeutic dose of LMWH for long-term treatment of VTE (Table 20, Table S28).²³,²⁴ This evidence suggests that compared with VKA therapy, LMWH is associated with a reduction of recurrent VTE and a similar frequency of major bleeding and mortality. The quality of this evidence is moderate because of potential for bias in the assessment of recurrent VTE (nonblinded outcome assessment) and serious imprecision for major bleeding and mortality.

**Cancer vs No Cancer**—There are differences between patients with and without cancer with VTE that may influence response to anticoagulant therapies. These include about a 10-fold higher risk of dying and a threefold higher risk of recurrent VTE and major bleeding during the first 3 or 6 months of treatment; different mechanisms of thrombosis that may be associated with a poor response to VKA therapy; use of cancer chemotherapy that is associated with thrombocytopenia, vomiting, and anorexia and may have other interactions with VKA therapy; and the need for invasive therapeutic interventions (eg, drainage procedures) that require reversal of anticoagulation. Many of these factors make LMWH more attractive and VKA therapy less attractive in patients with VTE and cancer and suggest that cancer may alter the response of VTE to LMWH vs VKA therapy (ie, presence of an interaction).

Among the eight studies included in Table 20 and Table S28, separate data are provided for 1,114 patients with cancer and 660 patients without cancer. Subgroup analyses suggest the possibility that the response to LMWH vs VKA therapy may differ between patients with cancer and without cancer (recurrent VTE: RR, 0.52 with cancer...
[95% CI, 0.36-0.76] vs 0.99 without cancer [95% CI, 0.46-2.13]); major bleeding: RR, 0.92 with cancer [95% CI, 0.59-1.44] vs 0.43 without cancer [95% CI, 0.16-1.17]); mortality: RR, 0.93 with cancer [95% CI, 0.79-1.09] vs 1.85 without cancer [95% CI, 0.59-5.77]). However, none of these differences is statistically significant, making it less likely that there is a true difference in response to LMWH vs VKA in the two patient populations. For this reason, we have applied the same relative effects for LMWH vs VKA in patients with and without cancer. The baseline risks of events, however, are clearly different in the two populations.

Patient Preferences—As discussed in the Methods section, the ultimate judgment of the entire Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (AT9) panel is that most patients prefer VKA therapy over LMWH therapy. The higher purchase cost of LMWH compared with VKA therapy is an additional barrier to the long-term use of LMWH.

Quality of Evidence and Strength of Recommendations—Evidence for the comparison of long-term LMWH vs VKA therapy in patients without cancer is of low quality. The subgroup effect discussed previously was not sufficiently convincing to allow us to generate an effect estimate specifically for patients without cancer, but still reduced our confidence that the overall effect estimate applies to the noncancer subgroup that contributed a minority of data. Considerations favoring use of VKA over LMWH in patients without cancer include (1) the evidence of benefit with LMWH is of low quality, (2) the estimated absolute reductions in recurrent VTE events with LMWH compared with VKA therapy is small, (3) the high cost of LMWH, and (4) our assessment that LMWH is a greater burden to patients than VKA therapy. Considerations favoring use of LMWH over warfarin in patients with cancer include (1) a large absolute reduction in recurrent VTE with LMWH over VKA therapy and (2) that LMWH is better suited to the care of patients with cancer than is VKA therapy. Among patients with VTE and cancer, the advantages of LMWH over VKA therapy are expected to be greatest in patients (1) with metastatic disease, (2) being treated with aggressive chemotherapy, (3) presenting with extensive VTE, (4) with liver dysfunction, (5) with poor or unstable nutritional status, and (6) who wish to avoid laboratory monitoring of coagulation.

**Dabigatran vs VKA Therapy for the Long-term Treatment of DVT:** One completed study has directly compared dabigatran and VKA for the first 6 months of treatment of VTE (Table 23, Table S31). Like patients treated with VKA therapy, patients treated with dabigatran initially received parenteral therapy (usually IV UFH or LMWH). This study suggests that treatment with dabigatran or VKA therapy is associated with a similar frequency of recurrent VTE, major bleeding, and death. This evidence is of moderate quality because of serious imprecision for each outcome and lack of long-term safety data for dabigatran in this patient population. Because the study included few patients with cancer, we were unable to assess whether its findings apply equally to patients with and without cancer. In the absence of evidence of such an interaction, however, we have not further rated down the quality of evidence for patients with VTE and cancer.

**Rivaroxaban vs VKA Therapy for the Long-term Treatment of DVT:** A single study has directly compared rivaroxaban (without initial parenteral anticoagulation) with parenteral anticoagulation and VKA in patients with acute DVT (Table 21, Table S29). Results suggested that treatment with rivaroxaban and VKA therapy are associated with a similar frequency of recurrent VTE, major bleeding, and death. This evidence is of moderate quality because of serious imprecision for each outcome. Because the study included few patients with cancer, we were unable to assess whether its findings apply equally to patients with and without cancer. In the absence of evidence of such an interaction, however, we have not further rated down the quality of evidence for patients with VTE and cancer.

**Comparisons Among LMWH, Dabigatran, and Rivaroxaban for the Long-term Treatment of DVT:** There are no direct comparisons of these three agents for the long-term treatment of VTE. Recommendations about the use of one of these agents over the other are based on indirect comparisons, and the evidence is low quality.

**Recommendations**

**3.3.1. In patients with DVT of the leg and no cancer, we suggest VKA therapy over LMWH for long-term therapy** (Grade 2C). For patients with DVT and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy (Grade 2C).

**3.3.2. In patients with DVT of the leg and cancer, we suggest LMWH over VKA therapy** (Grade 2B). In patients with DVT and cancer who are not treated with LMWH, we suggest VKA over dabigatran or rivaroxaban for long-term therapy (Grade 2B).
Table 23—[Section 3.3] Summary of Findings: Dabigatran vs VKA Therapy for Long-term Treatment of VTE<sup>a-c,343</sup>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Risk With Warfarin</td>
<td>Risk Difference With Dabigatran (95% CI)</td>
</tr>
<tr>
<td>Mortality</td>
<td>2,539 (1 study), 6 mo</td>
<td>Moderate&lt;sup&gt;d&lt;/sup&gt; due to imprecision</td>
<td>HR 0.98 (0.53-1.79)</td>
<td>17 per 1,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0 fewer per 1,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(from 8 fewer to 13 more)</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>2,539 (1 study), 6 mo</td>
<td>Moderate&lt;sup&gt;d&lt;/sup&gt; due to imprecision</td>
<td>HR 1.01 (0.65-1.84)</td>
<td>19 per 1,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0 more per 1,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(from 7 fewer to 16 more)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2,539 (1 study), 6 mo</td>
<td>Moderate&lt;sup&gt;d&lt;/sup&gt; due to imprecision</td>
<td>HR 0.82 (0.45-1.48)</td>
<td>19 per 1,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 fewer per 1,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(from 10 fewer to 9 more)</td>
</tr>
</tbody>
</table>

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follows: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1, 3, and 21 legends for expansion of abbreviations.

<sup>a</sup>Included patients had acute, symptomatic, and objectively verified proximal DVT of the legs or PE.
<sup>b</sup>Dabigatran 150 mg bid taken orally for 6 mo after an initial treatment with LMWH or IV UFH.
<sup>c</sup>Warfarin adjusted to achieve an INR of 2.0 to 3.0 for 6 mo after an initial treatment with LMWH or IV UFH.
<sup>d</sup>Allocation was concealed. Patients, providers, data collectors, and outcome adjudicators were blinded. Modified intention-to-treat analysis; 1.1% loss to follow-up. Not stopped early for benefit. The CI includes values suggesting no effect and values suggesting either benefit or harm; relatively low number of events.
<sup>e</sup>One fatal VTE in dabigatran group and three fatal VTE in warfarin group.

Remarks (3.3.1-3.3.2): Choice of treatment in patients with and without cancer is sensitive to individual patient’s tolerance for daily injections, need for laboratory monitoring, and treatment costs. LMWH, rivaroxaban, and dabigatran are retained in patients with renal impairment, whereas this is not a concern with VKA. Treatment of VTE with dabigatran or rivaroxaban, in addition to being less burdensome to patients, may prove to be associated with better clinical outcomes than VKA and LMWH therapy. When these guidelines were being prepared (October 2011), postmarketing studies of safety were not available. Given the paucity of currently available data and that new data are rapidly emerging, we give a weak recommendation in favor of VKA and LMWH therapy over dabigatran and rivaroxaban, and we have not made any recommendations in favor of one of the new agents over the other.

3.4 Choice of Anticoagulant Regimen for Extended Therapy

Other than a comparison of low-intensity (target INR 1.75) with conventional-intensity VKA therapy<sup>44</sup> (Table S24 and S25), there are no completed studies that have compared different anticoagulant agents or regimens for extended therapy after a standardized initial period (eg, ≥3 months) of anticoagulation in either patients without or with cancer. Because a decision about using extended therapy occurs after an initial period of anticoagulation (eg, 3 months) and because the relative efficacy and safety of anticoagulant regimens are expected to be similar during the early and extended phases of therapy, we anticipate that most patients will continue to use their initial anticoagulant regimen for extended therapy. Possible reasons for switching from LMWH to VKA therapy include the following: cancer becomes less active, chemotherapy is completed, patient tires of SC injections, development of renal impairment causes concern about accumulation of LMWH (also applies to rivaroxaban and dabigatran), and LMWH costs become prohibitive. Reasons for switching from VKA therapy to LMWH could include difficulty with INR control and need for repeated invasive procedures. New anticoagulant therapies may expand indications for extended anticoagulant therapy because they are less burdensome than VKA or LMWH therapy and because they may be associated with improved clinical outcomes (ie, more effective or safer).

Recommendation

3.4. In patients with DVT of the leg who choose extended therapy, we suggest treatment with the same anticoagulant chosen for the first 3 months (Grade 2C).
3.5 Treatment of Asymptomatic DVT of the Leg

Rather than screen postoperative patients for the presence of asymptomatic DVT, clinicians should prescribe primary prophylaxis for VTE to surgical patients.\textsuperscript{230,231} If imaging studies performed for other reasons (eg, CT scanning for staging of cancer) incidentally detect asymptomatic proximal DVT, the high frequency of false-positive results in patients without a prior suspicion of DVT dictates caution in assuming that a DVT is truly present. Reasons for a high rate of false-positive results include (1) the imaging technique may not have been optimal for the diagnosis of DVT, (2) incidentally diagnosed DVT often is seen in the pelvis where DVT is harder to image (eg, unable to be assessed with compression ultrasound), and (3) the prevalence of DVT in asymptomatic patients is much lower than in symptomatic patients. Consequently, when there is evidence of incidental DVT, additional diagnostic testing (eg, ultrasound) to confirm the presence of DVT may be necessary. Because many cases of asymptomatic VTE are detected as PE, see also section 6.9 of this article for recommendations on the management of this condition.

No randomized trials have evaluated anticoagulant therapy in patients with incidental VTE; therefore, evidence is of moderate quality because of indirectness. Moreover, benefits of anticoagulant therapy may be less than in symptomatic patients because asymptomatic DVT may be chronic or less extensive and because the prevalence of false-positive results will be higher than in patients who were suspected of having DVT.

Factors that justify a more-aggressive approach to anticoagulation in patients with incidentally diagnosed DVT include certainty of diagnosis, extensive thrombosis that appears to be acute (eg, not present on a previous imaging study), progression of thrombosis on a follow-up imaging study, ongoing risk factors for VTE (eg, cancer), and a low risk of bleeding. A less-aggressive approach to anticoagulation could include (1) withholding of anticoagulation with surveillance to detect DVT extension or (2) limiting anticoagulant therapy to 3 months in patients with continuing risk factors for VTE (eg, cancer). Many patients have left the hospital by the time incidental DVT is reported. If it would be difficult for patients to return the same day, it is often reasonable to defer further assessment and anticoagulant therapy until the next day.

Recommendation

3.5. In patients who are incidentally found to have asymptomatic DVT of the leg, we suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic DVT (Grade 2B).

4.0 PTS of the Leg

PTS is a cluster of leg symptoms and signs attributable to previous DVT. PTS occurs in about one-third of patients after acute DVT and up to two-thirds who have had an iliofemoral DVT.\textsuperscript{102,232} The initial treatment of acute DVT, particularly with the use of thrombus removal strategies, may influence the risk of developing PTS (section 2.8). The most prominent symptoms are chronic dependent swelling and pain, discomfort on walking, and skin discoloration. The severity of symptoms may vary over time, and the most severe manifestation is a venous ulcer of the lower leg. In this section, we address prevention of PTS first and then its treatment. Unlike the last edition of these guidelines,\textsuperscript{6} we do not address treatment of leg ulcers associated with venous insufficiency.

4.1 Compression Stockings and Bandages to Prevent PTS

Five randomized trials evaluated compression stockings used at various times after diagnosis of acute DVT for the prevention of PTS (Tables S32 and S33).\textsuperscript{201,202,233-235} Two of these trials\textsuperscript{163,164} randomized patients soon after diagnosis of a first episode of symptomatic proximal DVT to prolonged use of stockings (30-40 mm Hg pressure at the ankles) or no stockings and otherwise treated patients the same way (Table 24, Table S34). These trials suggest that compression stockings started within 2 weeks of DVT and continued for 2 years reduce PTS by about 50% and do not alter the frequency of recurrent VTE. Patients with proximal DVT and a previous DVT in the same leg and who have marked symptoms are expected to gain the most benefit from compression stockings.\textsuperscript{102,201,202} The evidence is of moderate quality because the assessment of PTS, which includes a large subjective component, was not blinded, and the estimate for recurrent VTE was imprecise.

Compression stockings applying an ankle pressure of 30 to 40 mm Hg and a lower pressure higher up the leg (ie, graduated pressure) should be started as soon as feasible after starting anticoagulant therapy. Bandages may be used to provide initial compressive therapy because it may not be possible to fit compression stockings immediately and if stockings can be worn, a rapid decrease in leg swelling will require them to be refitted. The findings from a randomized trial of 69 patients suggest that immediate compression bandaging improves acute symptoms but does not reduce PTS at 1 year (RR, 0.9; 95% CI, 0.4-1.8).\textsuperscript{236} Patients or their caregivers need to be able to apply and remove stockings for their use to be feasible. Alternative approaches to the use of stockings, such as routinely wearing stockings after acute DVT but stopping them if there are no symptoms of PTS after 6 months\textsuperscript{235,237} or...
only wearing stockings if there is persistent leg swelling, have not been adequately evaluated.

**Recommendation**

**4.1. In patients with asymptomatic symptomatic DVT of the leg, we suggest the use of compression stockings (Grade 2B).**

**Remarks:** Compression stockings should be worn for 2 years, and we suggest beyond that if patients have developed PTS and find the stockings helpful. Patients who place a low value on preventing PTS or have developed PTS and find the stockings helpful. Stockings should be worn only wearing stockings if there is persistent leg swelling.

**4.2 Physical Treatment of PTS**

Treatment of PTS with compression stockings has only been evaluated in two small trials (233, 235) (Table 25, Tables S35 and S37) (all patients received rutosides in one study (236)). These studies did not find compression stockings to be of benefit. However, the quality of the evidence is low because of imprecision and risk of bias. There is anecdotal evidence that compression therapy is of benefit in many patients with PTS, and the potential benefit of a trial of compression stockings in individual patients is likely to outweigh its harm and cost. We suggest below-knee stockings in most patients, but thigh-length stockings may be preferable in those with marked thigh swelling.

Two small crossover randomized trials have evaluated the treatment of severe PTS with intermittent compression devices (239, 240) (Table 26, Table S36). Both studies suggested benefit from intermittent compression therapy. The quality of the evidence, however, is moderate because of imprecision. The goal of intermittent compression therapy is to reduce PTS symptoms rather than to alter the natural history of its development. These devices can be used with or without compression stockings, depending on patient preference. Leg swelling and associated symptoms (eg, heaviness, tightness) are more likely to respond to compression stockings or intermittent compression devices than are other symptoms.

**Table 24—[Section 4.1] Summary of Findings: Elastic Compression Stockings vs No Elastic Compression Stockings to Prevent PTS of the Leg**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With No Elastic Compression Stockings</th>
<th>Risk Difference With Elastic Compression Stockings (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTS</td>
<td>421 (2 studies), 2 y</td>
<td>Moderate due to risk of bias</td>
<td>RR 0.46 (0.34-0.63)</td>
<td>479 per 1,000</td>
<td>259 fewer per 1,000 (from 177 fewer to 316 fewer)</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>374 (2 studies), 5 y</td>
<td>Moderate due to imprecision</td>
<td>RR 1.01 (0.61-1.67)</td>
<td>210 per 1,000</td>
<td>2 more per 1,000 (from 82 fewer to 141 more)</td>
</tr>
<tr>
<td>QOL not reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1, 3 and 10 legends for expansion of abbreviations.

- Prandoni et al excluded patients with recurrent ipsilateral DVT, preexisting leg ulcers, or signs of chronic venous insufficiency, bilateral thrombosis, a short life expectancy or a contraindication for use of stockings (eg, advanced-stage peripheral arterial insufficiency). Brandjes et al excluded patients with short life expectancy, paralysis of the leg, bilateral thrombosis, leg ulcers, or extensive varicosis.
- Brandjes (241) used graded elastic compression stockings (40 mm Hg of pressure at the ankle, 36 mm Hg at the lower calf, and 21 mm Hg at the upper calf); stockings were applied 2 to 3 wk after the first episode of proximal DVT. Prandoni et al (237) used flat-knitted stockings (30 to 40 mm Hg of pressure at the ankle); stockings were started at hospital discharge, an average of 1 wk after admission. In both studies, stockings were used for 2 y.
- Patients were not blinded to the treatment assignment, and outcomes were partly based on subjective report of symptoms.
- The effect estimate shown here results from a meta-analysis (Mantel-Haenszel fixed-effects model) of the two relevant trials. A fixed-effects model was chosen because of the small number of studies available.
- This estimate is based on the findings of the VETO study. This probably underestimates PTS baseline risk given that overall, 52% of patients reported the current use of compression stockings during study follow-up.
- In Prandoni et al, most events occurred during the first 6 mo. The cumulative incidence of the PTS in the control group was 40% after 6 mo, 47% after 1 y, and 49% after 2 y.
- Severe PTS, assuming the same RR of 0.46 and a baseline risk of 8.1% over 2 y, the absolute reduction is 44 fewer severe PTS per 1,000 (from 30 fewer to 53 fewer) over 2 y.
- We did not rate down the quality of evidence for recurrent VTE for the lack of blinding because this a more objective outcome than PTS.
- CI includes both negligible effect and appreciable benefit or appreciable harm.
- This estimate is the mean of two estimates derived from two studies: 12.4% probable/definite VTE (Heit et al (242)) and 29.1% confirmed VTE (Prandoni et al (237)).
Recommendations

4.2.1. In patients with PTS of the leg, we suggest a trial of compression stockings (Grade 2C).

4.2.2. In patients with severe PTS of the leg that is not adequately relieved by compression stockings, we suggest a trial of an intermittent compression device (Grade 2B).

4.3 Pharmacologic Treatment of PTS

Hydroxylutoids, a class of flavonoid drug produced from plant glycosides, may reduce capillary permeability, reduce inflammation, improve lymphatic function, and promote ulcer healing in patients with chronic venous insufficiency.\textsuperscript{6,231,232} Two studies compared treatment of PTS (without ulceration) with rutosides vs control\textsuperscript{233} (all patients wore compression stockings in one study\textsuperscript{234}, and one study compared rutosides with hidrosmin\textsuperscript{234}(Table S37). The two controlled studies suggest that rutosides do not reduce most symptoms of PTS, although they may reduce ankle swelling (Table 27). This evidence is of low quality because of inconsistency and imprecision. Furthermore, rutosides may be associated with important side effects.

Recommendation

4.3. In patients with PTS of the leg, we suggest that venoactive medications (eg, rutosides, defibrinogenide, and hidrosmin) not be used (Grade 2C).

Remarks: Patients who value the possibility of response over the risk of side effects may choose to undertake a therapeutic trial.

5.0 Initial Treatment of Acute PE

As we noted in Methods (section 1.1), recommendations for management of patients with PE, particularly those addressing anticoagulant therapy and IVC filter insertion, are based on studies that enrolled patients with only DVT, patients with both DVT and PE, and patients with only symptoms of PE. The following sections emphasize studies that enrolled only patients with symptoms of PE (who could also have symptoms of DVT), emphasize differences in

### Table 25—[Section 4.2.1] Summary of Findings: Compression Stockings vs No Compression Stockings for Patients With PTS\textsuperscript{23,233,234}

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With No Compression Stockings (95% CI)</th>
<th>Risk Difference With Compression Stockings (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic relief</td>
<td>115 (2 studies), 12 to 26 mo</td>
<td>Low\textsuperscript{d} due to risk of bias and imprecision</td>
<td>RR 0.96 (0.70-1.31)</td>
<td>579 per 1,000</td>
<td>23 fewer per 1,000 (from 174 fewer to 179 more)</td>
</tr>
<tr>
<td>QOL not reported</td>
<td>...</td>
<td>Not estimable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE not reported</td>
<td>...</td>
<td>Not estimable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulceration\textsuperscript{a} not reported</td>
<td>...</td>
<td>Not estimable\textsuperscript{b}</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk of bias in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follows: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. CLOTS1 = Clots in Legs or Stocking After Stroke. See Table 1 and 3 legends for expansion of other abbreviations.

\textsuperscript{a}Ginsberg et al\textsuperscript{22} included patients with PTS 1 y after chronic, typical proximal DVT. Frulla et al\textsuperscript{23} included patients with clinical symptoms and signs suggestive of PTS.

\textsuperscript{b}Production bias was not detected but not ruled out given that we identified only one small study partially supported by industry (provision of graduated compression stockings).

\textsuperscript{c}Ginsberg et al\textsuperscript{22} reported treatment failure (defined a priori based on any of five clinical criteria, including symptoms and ulcer development). Treatment success refers to the absence of treatment failure. Frulla et al\textsuperscript{23} used the Villalta scale.

\textsuperscript{d}Indirect evidence from the CLOTS1 trial suggests that compression stockings is associated with an RR of 4 for skin complications.
Table 26—[Section 4.2.2] Summary of Findings: Intermittent Compression Device vs No Intermittent Compression Device for Patients With Severe PTS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Anticipated Absolute Effects</th>
<th>Risk With No Intermittent Compression Device</th>
<th>Risk Difference With Intermittent Compression Device (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic relief: symptom score includes scoring of pain, swelling, and limitation of activity on a scale of 0-70</td>
<td>82 (2 studies), 8 wk</td>
<td>Moderate due to imprecision</td>
<td></td>
<td>The mean symptomatic relief in the control groups was 0.04 (95% CI: -0.01 to 0.23)</td>
<td>The mean symptomatic relief in the intervention groups was 0.03 (95% CI: -0.02 to 0.17)</td>
<td></td>
</tr>
<tr>
<td>QOL: VEINES-QOL scale of 0-100</td>
<td>0.1 (1 study), 8 wk</td>
<td>Moderate due to imprecision</td>
<td></td>
<td>The mean QOL in the control groups was 0.50 (95% CI: -0.05 to 1.05)</td>
<td>The mean QOL in the intervention groups was 0.36 (95% CI: -0.09 to 1.08)</td>
<td></td>
</tr>
<tr>
<td>Recurrence VTE*</td>
<td></td>
<td></td>
<td></td>
<td>Not estimable</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Ulceration*</td>
<td></td>
<td></td>
<td></td>
<td>Not estimable</td>
<td>Not estimable</td>
<td></td>
</tr>
</tbody>
</table>

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follows: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. VEINES = Venous Insufficiency Epidemiological and Economic Study. See Table 1, 3, and 25 legends for expansion of other abbreviations.

*Patients with previous DVT with symptoms of severe PTS.

4Intervention group: Ginsberg et al239: Extremity pump used bid for 20 min each session; 50 mm Hg (therapeutic pressure) for 1 mo. O’Donnell et al240: Venowave lower-limb venous return assist device to wear for most of the day for 8 wk.

5Control group: Ginsberg et al239: Extremity pump used bid for 20 min each session; 15 mm Hg (placebo pressure) for 1 mo. O’Donnell et al240: Venowave lower-limb venous return assist device with no connection between motor and planar sheet for 8 wk.

6Crossover RCTs.

7In both studies, sequence generation was adequate; patients were blinded, analysis adhered to intention-to-treat principle, and there were no missing outcome data. In Ginsberg et al239 (but not O’Donnell et al240), outcome assessors were not blinded, and it was not clear whether allocation was concealed.

8Replication in another study.

9Some concerns with indirectness, given relatively short follow-up (8 wk).

10Very small number of patients. CI includes both values suggesting no effect and values suggesting a beneficial effect.

11Publication bias not detected but not ruled out given that we identified only two small studies, with one (Ginsberg et al239) partially supported by industry (provision of devices).

12O’Donnell et al240: Sequence generation was adequate; patients were blinded, analysis adhered to intention-to-treat principle, and there were no missing outcome data. However, outcome assessors were not blinded, and it was not clear whether allocation was concealed.

13Publication bias was not detected but not ruled out given that we identified only a small study.

14O’Donnell et al240 indicated no cases of recurrent VTE by the end of this study but judged the follow-up period to be short.

15O’Donnell et al240 indicated that one patient in the control group developed a venous ulceration. Three other participants developed nonsignificant skin-related side effects. Indirect evidence from the CLOTS1 suggests that compression stockings are associated with an RR of 4 for skin complications. Common side effects attributed to Venowave were heat sensation, skin irritation, and increased sweating.

The management of patients who present with PE compared with DVT, and make recommendations for the management of patients with PE. We do not repeat evidence that was presented in the corresponding section that addresses treatment of DVT; instead, the reader is directed to those sections of the article and to the related tables. We do not comment in the text on the quality of the evidence that underlies treatment recommendations for PE unless the quality of this evidence differs from that for patients who present with DVT.

5.1 Initial Anticoagulation for Acute PE

See section 2.1, Table 3, and Table S1.

Recommendation

5.1. In patients with acute PE, we recommend initial treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such initial treatment (Grade 1B).

5.2 Whether to Treat With Parenteral Anticoagulation While Awaiting the Results of Diagnostic Work-up for PE

See section 2.2. For the purpose of implementing this recommendation, validated prediction rules help with estimation of clinical probability of having PE,35,36

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Table 27—[Section 4.3] Summary of Findings: Venoactive Medication vs No Venoactive Medication for Patients With PTS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With No Venoactive Medication</th>
<th>Risk Difference With Venoactive Medication (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic relief: PTS score</td>
<td>163 (2 studies)</td>
<td>Low due to inconsistency, imprecision</td>
<td>RR 1.14 (0.85-1.52) 776 per 1,000 87 more per 1,000</td>
<td>From 71 fewer to 247 more</td>
<td></td>
</tr>
</tbody>
</table>
| (Villalta scale) < 5 or decreased by 30% at 12 mo compared with baseline in Frulla et al
| Ulceration not reported         | ...                                      | Not estimable                   |                          |                                   |
| Recurrent VTE not reported      | ...                                      | Not estimable                   |                          |                                   |
| Side effects                    | 203 (2 studies)                          | Moderate due to imprecision      | RR 2.04 (0.76-5.51) 61 per 1,000 63 more per 1,000 | From 15 fewer to 275 more |

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

- Patients with PTS and history of DVT in PTS leg.
- Investigators assessed other symptoms (pain, heaviness, swelling feeling, restless legs, and cramps) but did not report a composite score. The symptom we chose to report showed the most benefit; the effect estimates for the other symptoms ranged from 0.8 to 1.4, and none were statistically significant.
- In both studies, sequence generation and allocation concealment were unclear. Both studies blinded outcome assessors and had complete follow-up. Although de Jongste et al blinded patients, the authors did not adhere to the intention-to-treat principle and did not use a validated scale to measure symptomatic relief. Although Frulla et al adhered to the intention-to-treat principle, the author did not blind patients.
- Patients blinded to treatment assignment.
- Small number of patients. CI included both values suggesting harms and values suggesting benefits.
- Publication bias was not detected but not ruled out given that we identified only two small studies, and it unclear whether they were funded by industry.
- Patients with a total of 1,951 patients with either submassive symptomatic PE or asymptomatic PE in conjunction with symptomatic DVT failed to demonstrate or

Recommendations

5.2.1. In patients with a high clinical suspicion of acute PE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C).

5.2.2. In patients with an intermediate clinical suspicion of acute PE, we suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C).

5.2.3. In patients with a low clinical suspicion of acute PE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests provided that test results are expected within 24 h (Grade 2C).

5.3 Timing of Initiation of VKA and Associated Duration of Parenteral Anticoagulant Therapy

See section 2.4, Table 4, and Table S2.

5.4 Choice of Initial Parenteral Anticoagulant Regimen in Patients With PE

See section 2.5.

LMWH Compared With IV UFH for the Initial Treatment of PE: See section 2.5 and Table 6. Consistent with findings in patients with DVT, LMWH has been found to be as effective and safe as IV UFH in studies that included both patients with PE and DVT or only in patients with PE (Table 6). A meta-analysis of 12 studies that included a total of 1,951 patients with either submassive symptomatic PE or asymptomatic PE in conjunction with symptomatic DVT failed to demonstrate or

Antithrombotic Therapy for VTE
exclude a beneficial or detrimental effect of LMWH on recurrent VTE (OR, 0.63; 95% CI, 0.33-1.18), major bleeding (OR, 0.67; 95% CI, 0.36-1.27), and all-cause mortality (OR, 1.20; 95% CI, 0.59-2.45).255

SC UFH Compared With SC LMWH for the Initial Treatment of PE: See section 2.5, Table 5, and Tables S3 through S5.

Fondaparinux Compared With IV UFH for the Initial Treatment of PE: The Matisse-PE trial compared fondaparinux with IV UFH for acute treatment of PE79 (Table 28, Table S38). This study suggested that fondaparinux is associated with a similar frequency of mortality, recurrent VTE, and major bleeding as LMWH. The quality of this evidence is moderate because of imprecision. In making recommendations, we also considered evidence that fondaparinux is equivalent to LMWH for the treatment of DVT (see section 2.5, Table 7, and Table S38) and that fondaparinux shares the advantages that LMWH has over IV UFH.

Fondaparinux Compared With LMWH for the Initial Treatment of PE: In the absence of direct evidence in patients with PE, indirect evidence in patients with acute DVT (see section 2.5, Table 7, and Table S7) suggests that fondaparinux is equivalent to LMWH.

Fondaparinux Compared With SC UFH for the Initial Treatment of PE: There is no direct evidence for this comparison. In making recommendations, we considered that fondaparinux and LMWH are equivalent and that fondaparinux shares the advantages that LMWH has over IV UFH. We did not take into account the lower purchase cost of SC UFH compared with fondaparinux.

Once- vs Twice-Daily Administration of LMWH for Initial Treatment of PE: See section 2.5, Table 8, and Table S8. Patients who presented with PE were included in only one of the five studies with an unconfounded comparison of once- and twice-daily LMWH59 and in one additional large study that compared once-daily LMWH therapy with IV UFH in patients who presented with PE252

Recommendations

5.4.1. In patients with acute PE, we suggest LMWH or fondaparinux over IV UFH (Grade 2C for LMWH; Grade 2B for fondaparinux), and over SC UFH (Grade 2B for LMWH; Grade 2C for fondaparinux).

Remarks: Local considerations such as cost, availability, and familiarity of use dictate the choice between fondaparinux and LMWH. LMWH and fondaparinux are retained in patients with renal impairment, whereas this is not a concern with UFH. In patients with PE where there is concern about the adequacy of SC absorption or in patients in whom

Table 28—[Section 5.4] Summary of Findings: Fondaparinux vs IV UFH for Initial Anticoagulation of Acute PE79,79

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>2,213 (1 study), 3 mo</td>
<td>Moderate due to imprecision</td>
<td>RR 1.20 (0.82-1.74)</td>
<td>43 per 1,000, 9 more per 1,000 (from 8 fewer to 32 more)</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>2,213 (1 study), 3 mo</td>
<td>Moderate due to imprecision</td>
<td>RR 0.75 (0.51-1.12)</td>
<td>50 per 1,000&lt;sup&gt;a&lt;/sup&gt;, 13 fewer per 1,000 (from 25 fewer to 6 more)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2,213 (1 study), 3 mo</td>
<td>Moderate due to imprecision</td>
<td>RR 0.55 (0.49-1.49)</td>
<td>23 per 1,000&lt;sup&gt;a&lt;/sup&gt;, 4 fewer per 1,000 (from 12 fewer to 11 more)</td>
</tr>
</tbody>
</table>

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follows: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

<sup>a</sup>All patients had acute, symptomatic, hemodynamically stable PE.

<sup>b</sup>Fondaparinux (5.0, 7.5, or 10.0 mg in patients weighing < 50, 50 to 100, or > 100 kg, respectively) SC once daily given for at least 5 days and until the use of VKAs resulted in an INR > 2.0.

<sup>c</sup>UFH continuous IV infusion (ratio of the activated partial thromboplastin time to a control value of 1.5-2.5) given for at least 5 days and until the use of VKAs resulted in an INR > 2.0.

<sup>d</sup>Allocation was concealed. Patients, providers, and data collectors were not blinded. Outcome adjudicators were blinded; 0.6% of randomized patients were lost to follow-up. Not stopped early for benefit.

<sup>e</sup>CI includes values suggesting no effect and values suggesting either benefit or harm; relatively low number of events.

<sup>f</sup>Sixteen fatal VTE in fondaparinux group and 15 fatal VTE in UFH group.

<sup>g</sup>Fourteen patients in the fondaparinux group and 12 patients in the LMWH group had a major bleeding event during the initial period (6-7 d). Of these, one in the fondaparinux group and one in the UFH group were fatal.

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thrombolytic therapy is being considered or planned, initial treatment with IV UFH is preferred to use of SC therapies.

5.4.2. In patients with acute PE treated with LMWH, we suggest once- over twice-daily administration (Grade 2C).

Remarks: This recommendation only applies when the approved once-daily regimen uses the same daily dose as the twice-daily regimen (ie, the once-daily injection contains double the dose of each twice-daily injection). It also places value on avoiding an extra injection per day.

5.5 Early vs Standard Discharge of Patients With Acute PE

Consistent with our discussion of outpatient treatment of acute DVT (section 2.7), LMWH has made it feasible to treat acute PE at home either without admission to the hospital (ie, discharge from the emergency department) or with admission and early discharge. However, because acute PE is associated with much higher short-term mortality than acute DVT, the safety of treating PE at home is uncertain. Consequently, PE is treated at home much less often than DVT, and the proportion of outpatients with PE that clinical centers treat at home varies from almost none to about 50%.

Two studies randomized patients with acute PE and a low risk of complications to receive LMWH either (1) in the hospital for only 3 days vs entirely in the hospital; or (2) entirely out of the hospital (discharged within 24 h) vs at least partly in hospital (Table 29, Table S39). This evidence suggests that treating appropriately selected patients with acute PE at home does not increase recurrent VTE, bleeding, or mortality.

There are a number of prediction rules for identifying patients with acute PE who have a low risk of serious complications and may be suitable for treatment at home. Of these, the PE Severity Index (PESI) is best validated and was used to select patients for home treatment in the larger of the previously noted clinical trials (Table 29, Table S39). Patients with acute PE who meet the following criteria appear to be suitable for treatment out of the hospital: (1) Clinically stable with good cardiopulmonary reserve (eg, PESI score of < 85 or simplified PESI score of 0, including none of hypoxia, systolic BP < 100, recent bleeding, severe chest pain, platelet count < 70,000/mm³, PE while on anticoagulant therapy, and severe liver or renal disease); (2) good social support with ready access to medical care, and (3) expected to be compliant with follow-up. Patients also need to feel well enough to be treated at home (eg, absence of severe symptoms or comorbidity).

Consistent with the findings of these two trials, a systematic review of 11 observational studies (seven prospective, four retrospective; 928 patients and four more recent observational studies (two retrospective with 584 patients, two prospective with 449 patients) reported a very low frequency of complications in low-risk patients with acute PE who were initially treated partially or entirely at home. About one-third to one-half of outpatients with acute PE appear to be in this low-risk group. The evidence from the randomized trials is of moderate quality (rated down for serious imprecision), with additional supportive findings from the observational studies.

Recommendation

5.5. In patients with low-risk PE and whose home circumstances are adequate, we suggest early discharge over standard discharge (eg, after the first 5 days of treatment) (Grade 2B).

Remarks: Patients who prefer the security of the hospital to the convenience and comfort of home are likely to choose hospitalization over home treatment.

5.6 Systemic Thrombolytic Therapy for PE

5.6.1 Systemic Thrombolytic Therapy vs Anticoagulation Alone for PE: Randomized trials have established that, at 24 h, thrombolytic therapy improves pulmonary artery hemodynamic measurements (eg, mean pulmonary artery pressure improvement, 4.4 mm Hg; 95% CI, −4.6−4.2 mm Hg), arteriovenous oxygen (difference of −0.3 [−0.4 to −0.2]), pulmonary perfusion (50% early improvement in perfusion scan, OR, 3.8; 95% CI, 0.9−15.7), and (4) echocardiographic assessment (OR for improved right ventricular wall movement, 3.1; 95% CI, 1.5−6.3). Thrombolytic therapy, however, does not appear to reduce the extent of residual thrombosis. It is uncertain whether the benefits of more-rapid resolution of PE outweigh the risk of increased bleeding associated with thrombolytic therapy. In patients with PE, severity of presentation is expected to depend on the extent of embolism (ie, degree of pulmonary artery obstruction) and the presence and severity of chronic cardiopulmonary impairment. Patients with the most severe presentations who have the highest risk of dying from an acute PE have the most to gain from thrombolysis.

Prognosis in Patients With Acute PE—Of patients who are diagnosed with PE and start treatment, ~5% die of the initial PE or another PE within the next 7 days. However, although the risk of dying of PE differs markedly among patients, no validated...
risk prediction tool is available. Risk of dying of PE is estimated to be \(~70\%\) if cardiopulmonary arrest occurs (\(~1\%\) of patients at presentation), 30\% if there is shock requiring inotropic support (\(~5\%\) of patients), and \(~2\%\) in patients who are not hypotensive. In the presence of normal systemic arterial pressure, prognosis can also differ, depending on (1) clinical evaluation, (2) cardiac biomarkers such as troponin or brain natriuretic peptide, and (3) assessment of right ventricular size and function.

Clinical evaluation involves assessment of general appearance, BP, heart rate, respiratory rate, temperature, pulse oximetry, and signs of right ventricular dysfunction (eg, distended jugular veins, tricuspid regurgitation, accentuated P2). Clues on the ECG include right bundle branch block, S1 Q3 T3, and T-wave inversion in leads V1 through V4. Elevation of cardiac troponins indicates right ventricular microinfarction, and echocardiography may show right ventricular hypokinesis; both are risk factors for early mortality and are associated with a worse outcome when they occur together. Right ventricular enlargement on the CT pulmonary angiogram, defined as a right ventricular diameter \(\geq 90\%\) of the left ventricular diameter may also be an independent risk factor for death and nonfatal complications.

Risk of Bleeding With Thrombolytic Therapy—We have not identified any validated risk prediction tool for bleeding with thrombolytic therapy in patients with PE. However, we assume that the assessment of bleeding risk with thrombolytic therapy is similar in patients with PE and with acute ST-segment elevation myocardial infarction. Table 11 lists risk factors for bleeding with thrombolytic therapy, categorized as major and relative contraindications.

Trials Evaluating Thrombolytic Therapy in Patients With Acute PE—The findings of 13 randomized trials that compared thrombolytic therapy to anticoagulant therapy alone in patients with acute PE are summarized in Table 30 and Tables S40 through S42. A number of meta-analyses of these studies have been performed. This evidence suggests that thrombolytic therapy may be associated with a reduction in mortality and recurrent PE and is associated with an increase in major bleeding, as has been established in patients with myocardial infarction. The quality of evidence regarding mortality and recurrent PE is low because of risk of bias, serious imprecision, and suspected publication bias. A previous meta-analysis that categorized studies as either including, or not including, patients with cardiopulmonary compromise, suggested that thrombolytic therapy reduced the composite outcome of death and recurrent PE in studies that included the sickest patients. However, we found that the data available from these studies are not sufficiently detailed to enable a subgroup analysis of the data.
analysis evaluating outcomes in patients with hemodynamic compromise or other markers of heightened risk of death (eg, right ventricular dysfunction).

Balancing Benefits and Harms of Thrombolytic Therapy—In patients who present with PE and hypotension (eg, systolic pressure BP < 90 mm Hg or a documented drop in systolic BP > 40 mm Hg with evidence of poor perfusion), especially if they have a low risk of bleeding, even modest efficacy of thrombolytic therapy is likely to reduce deaths from PE more than it would increase fatal bleeds and nonfatal intracranial bleeds (Table 30, Tables S40-S42). The ultimate judgment of the entire AT9 panel was to issue a weak recommendation for patients with PE and hypotension given the uncertainty of the benefit. In most patients with PE, given the certain risks of bleeding and less certain benefits, thrombolysis is likely to be harmful. Selected patients without hypotension may benefit from thrombolysis because their initial clinical presentation or clinical course after starting anticoagulant therapy suggest that they are at high risk of dying.

There is no explicit clinical prediction rule that identifies this subgroup of patients. We suggest that such patients are identified predominantly by clinical evidence of instability (eg, a decrease in systolic BP that still remains > 90 mm Hg, tachycardia, elevated jugular venous pressure, clinical evidence of poor tissue perfusion, hypoxemia) and failure to improve on anticoagulant therapy. As noted previously, laboratory (eg, troponin, brain natriuretic peptide, ECG, echocardiography, and CT evidence of right ventricular dysfunction or enlargement) can supplement the clinical evaluation of instability; however, they are not sufficiently predictive to serve as indications for thrombolytic therapy on their own, and we do not recommend that they are routinely measured.

Recommendations

5.6.1.1. In patients with acute PE associated with hypotension (eg, systolic BP < 90 mm Hg) who do not have a high risk of bleeding, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2C).

5.6.1.2. In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy (Grade 1C).

5.6.1.3. In selected patients with acute PE not associated with hypotension and with a low risk of bleeding whose initial clinical presentation or clinical course after starting anticoagulant therapy suggests a high risk of developing hypotension, we suggest administration of thrombolytic therapy (Grade 2C).

5.6.2 Systemic Thrombolytic Therapy Regimen for PE: Twelve randomized trials (total of 938 patients) have compared the rate of thrombus resolution achieved with various IV thrombolytic regimens.

These regimens included urokinase given over 2 h or 12 h; streptokinase given over 2 h or 12 h; and recombinant tPA (rt-PA) given over 15 min or 2 h.

An additional study compared IV with pulmonary artery catheter administration of rt-PA (50 mg over 2 h). The results of studies that compared different approaches to thrombolysis in patients with PE (noted previously) suggest that (1) prolonged infusions of thrombolytic agents (eg, > 12 h) are associated with higher rates of bleeding; (2) 2-h infusions achieve more rapid clot lysis than 12- or 24-h infusions; (3) when a high-concentration 2-h infusion of thrombolysis is administered, there is no clear difference in the efficacy or safety of rt-PA vs streptokinase; (4) bolus rt-PA regimens (eg, ~50 mg in 15 min) appears to be as effective and safe as a 2-h infusion of 100 mg of rt-PA; and (5) infusion of rt-PA directly into a pulmonary artery as opposed to a peripheral vein does not accelerate thrombolysis but does cause more frequent bleeding at the catheter insertion site (there was no attempt to infuse rt-PA directly into or to mechanically disrupt the thrombus in this study from 1988).

When a lytic agent is appropriate for PE, current evidence supports that thrombolytic therapy should be infused into a peripheral vein over ≤ 2 h. At a dose of 100 mg over 2 h, rt-PA is currently the most widely used and evaluated regimen. In patients with imminent or actual cardiac arrest, bolus infusion of thrombolytic therapy is indicated.

The quality of evidence for comparisons of systemic thrombolytic agents and regimens (eg, different doses or durations of infusion) is low based on very serious imprecision and risk of bias. In addition, there is substantial potential for publication bias. Based on this evidence, we provide only weak recommendations for all comparisons of thrombolytic agents and regimens in the short-term treatment of PE.

Recommendations

5.6.2.1. In patients with acute PE, when a thrombolytic agent is used, we suggest short infusion times (eg, a 2-h infusion) over prolonged infusion times (eg, a 24-h infusion) (Grade 2C).
In patients with acute PE, when a thrombolytic agent is used, we suggest administration through a peripheral vein over a pulmonary artery catheter (Grade 2C).

Initial Anticoagulant Therapy in Patients Treated With Thrombolytic Therapy: Trials that evaluated thrombolysis for PE used IV UFH in conjunction with thrombolytic therapy (Table 30, Tables S40-S42), and no randomized trials have compared different regimens of IV UFH in this setting. IV UFH should be given in full therapeutic doses before thrombolytic therapy is administered, and it is acceptable to either continue or suspend the UFH infusion during administration of thrombolytic therapy (these two practices have never been

5.6.3.1 Table 30—Summary of Findings: Systemic Thrombolytic Therapy vs Anticoagulation Alone in Patients With Acute PE

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Risk With No Thrombolysis</th>
<th>Risk Difference With Thrombolysis (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>847 (12 studies), 30 d</td>
<td>Low due to risk of bias and imprecision</td>
<td>RR 0.7 (0.37-1.31)</td>
<td>Low (11 per 1,000 to 3 fewer per 1,000 from 7 fewer to 3 more)</td>
</tr>
<tr>
<td>Recurrent PE</td>
<td>501 (9 studies), 30 d</td>
<td>Low due to risk of bias and imprecision</td>
<td>RR 0.7 (0.4-1.21)</td>
<td>High (89 per 1,000 to 27 fewer per 1,000 from 56 fewer to 28 more)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>847 (12 studies), 10 d</td>
<td>Moderate due to risk of bias and imprecision</td>
<td>RR 1.63 (1-2.68)</td>
<td>Low (57 per 1,000 to 17 fewer per 1,000 from 34 fewer to 12 more)</td>
</tr>
</tbody>
</table>

The basis for the assumed risk (eg, median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Working group grades of evidence are as follows: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very-low quality, we are very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

Studies included patients at low risk for bleeding.

Included studies that used different thrombolytic agents with varying doses and durations of administration; no statistical heterogeneity was noted.

Thrombolysis was included in addition to anticoagulation (most of the studies used heparin followed by warfarin; three studies used warfarin only).

Report of methodologic quality was poor in most studies. Of the 12 eligible studies, allocation was concealed in five, three were single blind (outcome assessor), six were double blind, and three were not blinded. Most studies did not report on missing outcome data. None of the studies stopped early for benefit. For the increase in bleeding with thrombolytic therapy, quality of evidence is increased from low to moderate (outcome assessor), six were double blind, and three were not blinded. Most studies did not report on missing outcome data. None of the studies noted.

The median risk of bleeding over the first 10 d reported in the eligible trials was 3.1%. In that case, the absolute number of deaths associated with thrombolytics would be 90 fewer per 1,000 (from 189 fewer to 93 more).

Indirect evidence from studies of thrombolysis for myocardial infarction and acute stroke provide more precise estimates of increase major bleeding risk stratification derived from the RIETE (Registro Informatizado de la Enfermedad Tromboembólica) cohort.

Table 30—Summary of Findings: Systemic Thrombolytic Therapy vs Anticoagulation Alone in Patients With Acute PE

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Risk With No Systemically Administered Thrombolytic Therapy</th>
<th>Risk Difference With Systemically Administered Thrombolytic Therapy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>847 (12 studies), 30 d</td>
<td>Low due to risk of bias and imprecision</td>
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</tbody>
</table>

The median risk of bleeding over the first 10 d reported in the eligible trials was 3.1%. In that case, the absolute number of deaths associated with thrombolytics would be 90 fewer per 1,000 (from 189 fewer to 93 more).
5.7 Catheter-Based Thrombus Removal for the Initial Treatment of PE

Interventional catheterization techniques for massive PE include mechanical fragmentation of thrombus with a standard pulmonary artery catheter, clot pulverization with a rotating basket catheter, percutaneous rheolytic thrombectomy, or pigtail rotational catheter embolectomy. Pharmacologic thrombolysis and mechanical interventions are usually combined unless bleeding risk is high. Catheter embolectomy does not result in extraction of intact pulmonary arterial thrombus; instead, clot fragments are suctioned through the catheter or displaced distally with modest angiographic improvement.

No randomized trials have evaluated interventional catheterization techniques for PE. Most observation studies are retrospective series of <30 patients. Consequently, evidence for the use of interventional catheter techniques in patients with acute PE is of low quality, and our recommendations are weak. Catheter selection, catheter deployment, and adjunctive thrombolytic regimen should be based on local expertise and resources.

Recommendation

5.7. In patients with acute PE associated with hypotension and who have (i) contraindications to thrombolysis, (ii) failed thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect (eg, within hours), if appropriate expertise and resources are available, we suggest catheter-assisted thrombus removal over no such intervention (Grade 2C).

5.8. In patients with acute PE associated with hypotension, we suggest surgical pulmonary embolectomy over no such intervention if they have (i) contraindications to thrombolysis, (ii) failed thrombolysis or catheter-assisted embolectomy, or (iii) shock that is likely to cause death before thrombolysis can take effect (eg, within hours), provided surgical expertise and resources are available (Grade 2C).

5.8 Surgical Embolectomy for the Initial Treatment of PE

Emergency surgical embolectomy with cardiopulmonary bypass is another management strategy for acute PE associated with hypotension. This operation is also suited for patients with acute PE who require surgical excision of a right atrial thrombus, paradoxical arterial embolism, or closure of a patent foramen ovale. Surgical embolectomy also can be performed to rescue patients in whom thrombolysis has been unsuccessful. The procedure is best performed on a warm, beating heart, without aortic cross-clamping, cardioplegia, or fibrillatory arrest.

No randomized trials or prospective observational studies have evaluated surgical embolectomy in patients with acute PE. Consequently, evidence related to surgical embolectomy in patients with acute PE is of low quality, and our recommendations are weak.

 Recommendation

5.8. In patients with acute PE associated with hypotension, we suggest surgical pulmonary embolectomy over no such intervention if they have (i) contraindications to thrombolysis, (ii) failed thrombolysis or catheter-assisted embolectomy, or (iii) shock that is likely to cause death before thrombolysis can take effect (eg, within hours), provided surgical expertise and resources are available (Grade 2C).

5.9. Vena Caval Filters for the Initial Treatment of PE

As previously noted in section 2.13, IVC filters can be used instead of initial anticoagulant therapy in patients with acute PE if there is an unacceptable risk of bleeding or as an adjunct to anticoagulation. As in DVT, no randomized trials or prospective cohort studies have evaluated IVC filters as sole therapy for acute PE (ie, without concurrent anticoagulation). As described in section 2.13, the PREPIC study, which evaluated IVC filters as an adjunct to anticoagulation in 400 high-risk patients with proximal DVT, showed that filters reduced PE, increased DVT, and did not change overall frequency of VTE (DVT and PE combined) or mortality (Table 14; Table S19).

The PREPIC study included 145 (36%) patients with symptomatic PE and 52 (13%) patients with asymptomatic PE at enrollment. If a patient has an acute PE and a short-term contraindication to anticoagulation, provided there is no proximal DVT on ultrasound, it is reasonable not to insert an IVC filter immediately; serial ultrasound examinations can be performed to ensure that the patient remains free of proximal DVT while anticoagulation is withheld.

There is uncertainty about the risk and benefits of inserting IVC filters as an adjunct to anticoagulant and thrombolytic therapy in patients with PE and hypotension. Among patients with hemodynamic compromise in the International Cooperative Pulmonary Embolism Registry, insertion of an IVC filter was associated with a reduction of early recurrent PE and death. Consequently, our recommendation
Recommendations

5.9.1. In patients with acute PE who are treated with anticoagulants, we recommend against the use of an IVC filter (Grade 1B).

5.9.2. In patients with acute PE and contraindication to anticoagulation, we recommend the use of an IVC filter (Grade 1B).

5.9.3. In patients with acute PE and an IVC filter inserted as an alternative to anticoagulation, we suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 2B).

Remarks: We do not consider that a permanent IVC filter of itself is an indication for extended anticoagulation.

6.0 Long-term Treatment of PE

In the following sections, we emphasize studies that were performed exclusively in patients with PE and patients with PE who were enrolled in other studies. For the reasons noted in section 1.1, we make the same recommendations for long-term treatment of PE as for DVT and rate the quality of the underlying evidence as the same (see corresponding sections for treatment of DVT).

VKA for the Long-term Treatment of PE: There has been only one evaluation of duration of VKA therapy exclusively in patients with PE. After 3 months of initial treatment, patients with PE provoked by a temporary risk factor were randomized to stop or to receive 3 more months of therapy, and those with unprovoked PE were randomized to stop or to receive 6 more months of therapy (WODIT PE [Warfarin Optimal Duration Italian Trial in patients with Pulmonary Embolism]) (Table S24 and S25).194 Consistent with studies that included patients who presented with DVT, extended VKA therapy was effective while treatment was being received. However, extending the duration of treatment beyond 3 months did not lower the rates of recurrence that were observed when anticoagulants were subsequently stopped.

LMWH for the Long-term Treatment of PE: Two small studies from the same investigator group have compared long-term LMWH (enoxaparin 1 mg/kg SC bid for ~14 days followed by 1.5 mg/kg SC daily) with long-term VKA exclusively in patients who presented with PE.341,342 The two studies combined found a similar frequency of recurrent VTE (enoxaparin, 4/60; VKA, 1/40) and major bleeding (enoxaparin, 1/60; VKA, 2/40) with the two treatments.341 Of the 12 other studies that compared LMWH with VKA therapy for long-term treatment of VTE (see section 3.3), only two173,227 included patients with PE. In these two studies, all patients had cancer, and 295 had PE (36% of all enrolled patients; some PE may have been asymptomatic in one study227); subgroup analyses were not reported for the patients with PE.

Dabigatran for the Long-term Treatment of PE: In the one completed study that compared dabigatran with VKA therapy after initial parenteral therapy (Table 23, Table S31), 786 (31%) patients had symptomatic PE at enrollment.343 Subgroup analysis did not suggest that patients with symptomatic PE had a different response to dabigatran vs VKA therapy in terms of either recurrent VTE or bleeding.

Rivaroxaban for the Long-term Treatment of PE: In the Einstein Extension study that compared rivaroxaban with placebo after an initial period of long-term anticoagulation (Table 22, Table S30), 454 (38%) patients had symptomatic PE at enrollment.88 Subgroup analysis did not suggest that patients with symptomatic PE had a different response to rivaroxaban vs VKA therapy in terms of either recurrent VTE or bleeding.

Recommendations

6.1. In patients with PE provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B), or (iii) extended therapy (Grade 1B regardless of bleeding risk).

6.2. In patients with PE provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B), and (iii) extended therapy if there is a high bleeding risk (Table 2) (Grade 1B). We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Table 2) (Grade 2B).

6.3. In patients with an unprovoked PE, we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter
duration (Grade 1B). After 3 months of treatment, patients with unprovoked PE should be evaluated for the risk-benefit ratio of extended therapy.

6.3.1. In patients with a first VTE that is an unprovoked PE and who have a low or moderate bleeding risk (Table 2), we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B).

6.3.2. In patients with a first VTE that is an unprovoked PE and who have a high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy (Grade 1B).

6.3.3. In patients with a second unprovoked VTE, we recommend extended anticoagulant therapy over 3 months of therapy in those who have a low bleeding risk (Table 2) (Grade 1B), and we suggest extended anticoagulant therapy in those with a moderate bleeding risk (Table 2) (Grade 2B).

6.3.4. In patients with a second unprovoked VTE who have a high bleeding risk (Table 2), we suggest 3 months of therapy over extended therapy (Grade 2B).

6.4. In patients with PE and active cancer, if the risk of bleeding is not high (Table 2), we recommend extended anticoagulant therapy over 3 months of therapy (Grade 1B), and if there is a high bleeding risk (Table 2), we suggest extended anticoagulant therapy (Grade 2B).

Remarks: In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

6.5. In patients with PE who are treated with VKA, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) over a lower (INR < 2) or higher (INR 3.0-5.0) range for all treatment durations (Grade 1B).

6.6. In patients with PE and no cancer, we suggest VKA therapy over LMWH for long-term therapy (Grade 2C). For patients with PE and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy (Grade 2C).

6.7. In patients with PE and cancer, we suggest LMWH over VKA therapy (Grade 2B). In patients with PE and cancer who are not treated with LMWH, we suggest VKA over dabigatran or rivaroxaban for long-term therapy (Grade 2C).

Remarks (6.6-6.7): Choice of treatment in patients with and without cancer is sensitive to individual patient tolerance for daily injections, need for labora-
tory monitoring, and treatment costs. Treatment of VTE with dabigatran or rivaroxaban, in addition to being less burdensome to patients, may prove to be associated with better clinical outcomes that VKA and LMWH therapy. When these guidelines were being prepared (October 2011), postmarketing studies of safety were not available. Given the paucity of currently available data and that new data are rapidly emerging, we give a weak recommendation in favor of VKA and LMWH therapy over dabigatran and rivaroxaban, and we have not made any recommend-
dations in favor of one of the new agents over the other.

6.8. In patients with PE who receive extended therapy, we suggest treatment with the same anticoagulant chosen for the first 3 months (Grade 2C).

6.9 Treatment of Asymptomatic PE

Diagnosis of asymptomatic PE occurs in ~1% of outpatients and ~4% of inpatients who have contrast-enhanced CT scans, with a majority being in patients with known malignancy. When PE is diagnosed unexpectedly in patients with cancer, in retrospect, the clinical history may reveal symptoms that were aggravated by the PE (eg, an increase in fatigue). About one-half of such incidental PE involve the lobar or more central pulmonary arteries, whereas the other one-half are more distal.

When there is evidence of an asymptomatic PE, the first priority is to review the CT scans to determine whether the findings are convincing for acute PE. Other recent CT scans may be available for comparison, or the current scan may also reveal DVT in the central deep veins (eg, subclavian vein, IVC, iliac vein). If there is any uncertainty about the presence of an acute PE, additional diagnostic testing is required (eg, ultrasonography of the deep veins, dedicated CT pulmonary angiography, D-dimer).

Consistent with recommendations for the treat-
ment of asymptomatic DVT (section 3.5) in patients in whom clinicians are convinced that an asymptomatic PE has occurred, based on moderate-quality evidence, we suggest the same initial and long-term anticoagulation as for similar patients with symp-
tomatic PE. The indication for anticoagulation is most compelling when the presence of PE is unequivocal, PE involves the lobar and more central...
pulmonary arteries, PE is a new finding on CT, ultrasound reveals proximal DVT; there are ongoing risk factors for VTE such as active cancer, and the patient is not at high risk for bleeding (Table 2). Many patients have left the hospital by the time an incidental PE is reported. If PE is less extensive and it would be difficult for patients to return the same day, it is often reasonable to defer further assessment and anticoagulant therapy until the next day.

Recommendation

6.9. In patients who are incidentally found to have asymptomatic PE, we suggest the same initial and long-term anticoagulation as for similar patients with symptomatic PE (Grade 2B).

7.0 CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Prospective studies suggest that CTPH occurs in ~3% of patients who are treated for PE. About one-third of patients have a history of VTE, whereas two-thirds have had single or recurrent episodes of PE that were not diagnosed and may have been asymptomatic. Patients with CTPH are likely to have a high risk of recurrent VTE because they have had previous VTE and have cardiopulmonary impairment. Recurrent VTE may be fatal more often in patients with severe cardiopulmonary impairment than in those without such impairment. After PE initiates CTPH, pulmonary vascular remodeling may cause severe pulmonary hypertension out of proportion with pulmonary vascular thrombosis.

7.1 Pulmonary Thromboendarterectomy, Anticoagulant Therapy, and Vena Caval Filter for the Treatment of CTPH

Primary therapy for CTPH is pulmonary thromboendarterectomy, which, if successful, can reduce or cure pulmonary hypertension and associated symptoms. The operation is lengthy and complex, requiring a median sternotomy, cardiopulmonary bypass, deep hypothermia with periods of circulatory arrest, and exploration of both pulmonary arteries. At the most experienced centers, mortality is ~5%. Management often includes insertion of a permanent IVC filter before or during pulmonary endarterectomy and indefinite anticoagulant therapy. Patients with CTPH who are not candidates for pulmonary endarterectomy because of comorbid disease or surgically inaccessible lesions may be candidates for vasodilator therapy, balloon pulmonary angioplasty, or lung transplantation and may benefit from referral to a center with expertise in pulmonary hypertension.

There are no randomized trials of CTPH therapy and, overall, evidence is low quality. There is, however, high-quality indirect evidence that anticoagulant therapy is very effective at preventing recurrent VTE in other patient populations (see section 3.1; Table 18; and Tables S24, S25, and S27). Consequently, the evidence supporting long-term anticoagulation in patients with CTPH is of moderate quality (rated down for indirectness). Features that are expected to be associated with greater benefit with pulmonary thromboendarterectomy include younger age, central disease, progressive clinical deterioration, and access to an expert multidisciplinary thromboendarterectomy team.

Recommendations

7.1.1. In patients with CTPH, we recommend extended anticoagulation over stopping therapy (Grade 1B).

7.1.2. In selected patients with CTPH, such as those with central disease under the care of an experienced thromboendarterectomy team, we suggest pulmonary thromboendarterectomy over no pulmonary thromboendarterectomy (Grade 2C).

8.0 SUPERFICIAL VEIN THROMBOSIS

SVT has been less well studied than DVT but is estimated to occur more often. It usually affects the lower limbs; often involves a varicose vein; is associated with chronic venous insufficiency, malignancy, thrombophilia, pregnancy or estrogen therapy, obesity, sclerotherapy, long-distance travel, and a history of VTE; or may be unprovoked. The long saphenous vein is involved in about two-thirds of lower-limb SVT.

Although traditionally considered a benign disease, a number of studies indicate that the consequences of SVT may be more serious. A prospective study of 844 patients with acute SVT of ≥5 cm found that at initial presentation, ~4% of patients had symptomatic PE, and routine ultrasound detected proximal DVT in 10% and distal DVT in an additional 13% of patients. In patients without VTE at presentation, despite 90% being treated with anticoagulant therapy (therapeutic doses in two-thirds, prophylactic doses in one-third, median duration of 11 days), 3.1% developed symptomatic VTE (0.5% PE, 1.2% proximal DVT, 1.4% distal DVT), 1.9% had recurrent SVT (different location), and 3.3% had an extension of SVT (same location) at 3 months. Male sex, history of VTE, cancer, and absence of varicose veins each was associated with about a doubling of the risk of VTE during follow-up.
Given the high prevalence of concomitant proximal DVT in patients with SVT and the need to treat such patients with higher doses of anticoagulant therapy (ie, therapeutic doses), patients with SVT above the knee should have ultrasonography to exclude proximal DVT. Ultrasound can also help with the diagnosis of SVT if the clinical presentation is uncertain. With greater appreciation of the seriousness of SVT, investigators have evaluated anticoagulant therapy, often in prophylactic or intermediate doses, as a way to reduce acute symptoms, extension, recurrence, and progression to VTE (Table 31, Tables S43-S45).

8.1 Treatment of SVT

Most studies that have evaluated anticoagulant therapy for SVT have been small (eg, ≤ 100 patients per treatment group), with additional methodologic weaknesses (Tables S44, S45). Although these studies suggest that prophylactic-dose LMWH, intermediate-dose UFH or LMWH, warfarin therapy, and oral nonsteroidal antiinflammatory agents are beneficial in patients with SVT, the supporting evidence is of low quality. The recently published Comparison of ARIXTRA™ in lower Limb Superficial Thrombophlebitis with placebo (CALISTO) study, which compared fondaparinux (2.5 mg/d for 45 days) with placebo in 3,000 patients with SVT (≥5 cm in length), has helped to clarify the role of anticoagulants for the treatment of SVT (Table 31, Table S43), and the natural history of this condition.

CALISTO found that fondaparinux is very effective at reducing VTE, recurrent SVT, extension of SVT, and the need for venous surgery, and is associated with little bleeding. In the placebo group, thrombotic complications occurred more often if SVT involved the greater saphenous vein (92% of patients in the control group), extended to within 10 cm from the saphenofemoral junction (9% of patients), and involved veins above the knee (46% of patients) and if VTE (7% of patients) or SVT (12% of patients) had occurred previously. Age, sex, and presence of varicose veins were not convincingly associated with the frequency of thrombotic complications, and there were too few patients with cancer in CALISTO to assess that association.

The evidence is moderate quality. We have interpreted the findings of the CALISTO study as evidence for anticoagulation in general and assume that prophylactic doses of LMWH and fondaparinux have similar antithrombotic efficacy and safety. Because it is direct and more extensive, the evidence in support of fondaparinux is higher quality than the evidence in support of LMWH. Quality of the evidence for comparison of fondaparinux with LMWH is low because there is no direct comparison in patients with SVT. Factors that favor the use of anticoagulant therapy in patients with SVT (see Recommendation 8.1.1) include: extensive SVT; involvement above the knee, particularly if close to the saphenofemoral junction; severe symptoms; involvement of the greater saphenous vein; history of VTE or SVT; active cancer; and recent surgery. An economic evaluation found that treatment of SVT with fondaparinux was not cost-effective; it cost $500,000 per quality-adjusted life year gained compared with no treatment.

Graduated compression stockings often are used in patients with SVT (eg, 83% of patients in the CALISTO study). Oral nonsteroidal antiinflammatory agents may be used to alleviate symptoms if patients are not treated with anticoagulants. Topical nonsteroidal antiinflammatory agents may reduce symptoms and can be used with anticoagulant therapy. Surgical therapy, with ligation of the saphenofemoral junction or stripping of thrombosed superficial veins appears to be associated with higher rates of VTE than treatment with anticoagulants. Anticoagulant therapy generally is not used to treat SVT that occurs in association with an IV infusion (ie, infusion thrombophlebitis).

Recommendations

8.1.1. In patients with SVT of the lower limb of at least 5 cm in length, we suggest the use of a prophylactic dose of fondaparinux or LMWH for 45 days over no anticoagulation (Grade 2B).

Remarks: Patients who place a high value on avoiding the inconvenience or cost of anticoagulation and a low value on avoiding infrequent symptomatic VTE are likely to decline anticoagulation.

8.1.2. In patients with SVT who are treated with anticoagulation, we suggest fondaparinux 2.5 mg daily over a prophylactic dose of LMWH (Grade 2C).

9.0 Acute Upper-Extremity DVT

About 5% to 10% of VTE involve the upper extremities. UEDVT includes two etiologic groups: primary (unprovoked with or without thrombophilia, effort-related and thoracic outlet syndrome) and secondary (provoked by central venous catheters, pacemakers, or cancer). Secondary UEDVT accounts for ~75% of cases. UEDVT involves the subclavian, axillary, or brachial veins and may include extension to the brachiocephalic vein, superior vena cava, or the internal...
jugular vein. Clinical manifestations include acute and chronic arm pain, swelling, discoloration, and dilated collateral veins over the arm, neck, or chest. UEDVT may lead to complications, including symptomatic PE (7%–5% of patients), recurrent UEDVT (~50% at 5 years of follow-up), and PTS of the arm (~20% of patients). Several small prospective cohort studies have reported acute anticoagulation for initial treatment of UEDVT. As with treatment of leg DVT and PE, treatment of UEDVT may be divided into acute (eg, parenteral anticoagulants, thrombolytic therapy) and long-term phases (eg, anticoagulation, treatment of upper-extremity PTS). Because no randomized trials have evaluated treatment of UEDVT, recommendations are based on indirect evidence from studies performed in patients with leg DVT, observational studies (generally small), and understanding of the natural history of UEDVT. Therefore, quality of evidence is, at best, moderate.

### 9.1 Acute Anticoagulation for UEDVT

No randomized controlled studies have evaluated acute anticoagulation for initial treatment of UEDVT. Several small prospective cohort studies have reported low rates of recurrent DVT, PE, and major bleeding when UEDVT was treated similarly to leg DVT (Tables S46 and S47). Anticoagulant therapy is used to treat UEDVT because (1) UEDVT causes acute symptoms, can cause PE (including fatal details of Table 31—[Section 8.1] Summary of Findings: Fondaparinux vs Placebo for Acute SVT

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>3,002 (1 study), 3 mo</td>
<td>Moderate due to imprecision</td>
<td>RR 1.99 (0.18-21.87)</td>
<td>4 per 1,000&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 more per 1,000 (from 3 fewer to 3 more)</td>
</tr>
<tr>
<td>VTE</td>
<td>3,002 (1 study), 3 mo</td>
<td>High</td>
<td>RR 0.18 (0.06-0.53)</td>
<td>33 per 1,000&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>27 fewer per 1,000 (from 16 fewer to 31 fewer)</td>
</tr>
<tr>
<td>SVT recurrence</td>
<td>3,002 (1 study), 3 mo</td>
<td>High</td>
<td>RR 0.31 (0.14-0.68)</td>
<td>19 per 1,000&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13 fewer per 1,000 (from 6 fewer to 16 fewer)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2,987 (1 study), 47 d</td>
<td>Moderate due to imprecision</td>
<td>RR 0.99 (0.06-15.86)</td>
<td>1 per 1,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0 fewer per 1,000 (from 1 fewer to 10 more)</td>
</tr>
</tbody>
</table>

QOL not measured

The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Working group grades of evidence are as follow: High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is very uncertain about the estimate. See Table 1 and 3 legends for expansion of abbreviations.

*Patients with infusion-related SVT were excluded from CALISTO (Comparison of ARIXTRA in lower Limb Superficial Thrombophlebitis with Placebo).

<sup>a</sup>Fondaparinux 2.5 mg for 45 d.

<sup>b</sup>Patients in the two treatment groups benefited from close clinical monitoring with adequate diagnostic procedures in the event of new or persistent symptoms.

<sup>c</sup>Allocation concealed. Outcome adjudicators, steering committee, patients, providers, and data collectors blinded. Follow-up rate was 98%. Intent-to-treatment analysis for efficacy outcomes. Not stopped early for benefit.

<sup>d</sup>CI includes values suggesting large benefit and values suggesting large harm.

<sup>e</sup>We rated down by only one level because of the low event rate and large sample size.

<sup>f</sup>Small number of events.

<sup>g</sup>Baseline risk derived from a large prospective cohort study.

<sup>h</sup>The upper limit of the CI for absolute effect (10 more bleeds) is not low enough to suggest a clear balance of benefits vs harms.
episodes), and is associated with PTS; (2) observational studies support its use; and (3) there is strong evidence for benefit in patients with leg DVT.

Uncertainty exists about the need to prescribe anticoagulants to patients with thrombosis confined to the brachial vein. Acceptable alternatives to full-dose anticoagulation in such patients include clinical or ultrasound surveillance to detect extension of UEDVT while withholding anticoagulation, or treatment with prophylactic-dose anticoagulation, or treatment with therapeutic doses of anticoagulation for <3 months. We favor anticoagulation if isolated brachial vein thrombosis is symptomatic, associated with a central venous catheter that will remain in place, or associated with cancer in the absence of a central venous catheter. A high risk of bleeding argues against full-dose anticoagulation.

Recommendations

9.1.1. In patients with acute UEDVT that involves the axillary or more proximal veins, we recommend acute treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such acute treatment (Grade 1B).

9.1.2. In patients with acute UEDVT that involves the axillary or more proximal veins, we suggest LMWH or fondaparinux over IV UFH (Grade 2C) and over SC UFH (Grade 2B).

9.2 Thrombolytic Therapy for the Initial Treatment of UEDVT

No randomized controlled studies have evaluated thrombolytic therapy compared with anticoagulation alone in patients with UEDVT. A number of retrospective and small prospective observational studies have evaluated streptokinase, urokinase, or rt-PA administered with varying doses, methods of administration (IV, catheter directed), and infusion durations. Three of these studies included nonrandomized control groups who received anticoagulation alone. In some studies, a few patients also had venous angioplasty or surgical decompression (Tables S48 and S49).

These studies suggest that thrombolysis can improve early and late venous patency but is associated with increased bleeding. However, it is not known whether thrombolytic therapy reduces PTS of the arm or recurrent VTE. PTS of the arm appears to be a less common complication of thrombosis than PTS of the leg. We believe that thrombolysis should be considered only in patients who meet all of the following criteria: severe symptoms, thrombus involving most of the subclavian vein and the axillary vein, symptoms for <14 days, good functional status, life expectancy of ≥1 year, and low risk for bleeding (Table 11). If thrombolysis is used, in order to reduce the dose of thrombolytic therapy and the associated risk of bleeding, we encourage catheter-based therapy over systemic thrombolysis. In addition, because the balance of risks and benefits with all forms of thrombolytic therapy is uncertain, anticoagulant therapy alone is acceptable initial therapy in all patients with UEDVT. There is no evidence to suggest that thrombolysis reduces the risk of recurrent VTE.

Resection of the first rib has been advocated when UEDVT is believed to have been due to entrapment of the subclavian vein as it passes between the clavicle and the first rib. Insertion of a filter in the superior vena cava has also been used in patients with acute UEDVT who cannot be given anticoagulants. Complications, however, may be more than with IVC filters. The evidence in support of these procedures is of low quality, and because there is the potential to cause harm, their use should be confined to exceptional circumstances in specialized centers.

Recommendations

9.2.1. In patients with acute UEDVT that involves the axillary or more proximal veins, we suggest anticoagulant therapy alone over thrombolysis (Grade 2C).

Remarks: Patients who (i) are most likely to benefit from thrombolysis (see text); (ii) have access to CDT; (iii) attach a high value to prevention of PTS; and (iv) attach a lower value to the initial complexity, cost, and risk of bleeding with thrombolytic therapy are likely to choose thrombolytic therapy over anticoagulation alone.

9.2.2. In patients with UEDVT who undergo thrombolysis, we recommend the same intensity and duration of anticoagulant therapy as in similar patients who do not undergo thrombolysis (Grade 1B).

9.3 Long-term Anticoagulation for UEDVT

No randomized studies have evaluated duration or intensity of long-term anticoagulation in patients with UEDVT. In prospective observational studies, patients with UEDVT generally were treated with VKA (target INR 2.5) for periods of 3 to 6 months. Rates of recurrent VTE and PTS varied (Tables S30 and S51), but as previously noted, these rates generally were lower than those observed in patients with leg DVT.
The factors that influence long-term anticoagulation in patients with leg DVT (section 3.1) are relevant to long-term treatment of UEDVT. Some differences between UEDVT and leg DVT are worthy of emphasis, especially that UEDVT often is associated with a central venous catheter that may or may not be removed (section 9.0). The most important continuing risk factors for UEDVT are (1) the presence of a central venous catheter in the same arm and (2) active cancer in patients with UEDVT not associated with a central venous catheter.

Another important distinction between UEDVT and leg DVT relates to long-term anticoagulation in patients with unprovoked thrombosis. Because the risk of recurrent VTE is substantially lower in patients with UEDVT compared with those with proximal leg DVT, we discourage extended anticoagulant therapy (ie, beyond 3 months) in patients with an unprovoked UEDVT.

No data are available for the long-term use of LMWH monotherapy or newer anticoagulants for the long-term treatment of UEDVT. We make the same recommendations for choice of initial, long-term, and extended anticoagulant regimens for UEDVT as for leg DVT (recommendations 3.1.1, 3.1.2, and 3.1.4) and note that the supporting evidence for these weak recommendations is further weakened in this population because of indirectness.

Recommendations

9.3.1. In most patients with UEDVT that is associated with a central venous catheter, we suggest that the catheter not be removed if it is functional and there is an ongoing need for the catheter (Grade 2C).

9.3.2. In patients with UEDVT that involves the axillary or more proximal veins, we suggest a minimum duration of anticoagulation of 3 months over a shorter period (Grade 2B).

Remarks: This recommendation also applies if the UEDVT is associated with a central venous catheter that was removed shortly after diagnosis.

9.3.3. In patients who have UEDVT that is associated with a central venous catheter that is removed, we recommend 3 months of anticoagulation over a longer duration of therapy in patients with no cancer (Grade 1B), and we suggest this in patients with cancer (Grade 2C).

9.3.4. In patients who have UEDVT that is associated with a central venous catheter that is not removed, we recommend that anticoagulation is continued as long as the central venous catheter remains over stopping after 3 months of treatment in patients with cancer (Grade 1C), and we suggest this in patients with no cancer (Grade 2C).

9.3.5. In patients who have UEDVT that is not associated with a central venous catheter or with cancer, we recommend 3 months of anticoagulation over a longer duration of therapy (Grade 1B).

9.4 Prevention of PTS of the Arm

PTS of the arm occurs in ~20% of patients after treatment for UEDVT and can be a disabling condition that adversely affects quality of life, particularly if the dominant arm is involved. No randomized trials have evaluated compression bandages, compression sleeves, or venoactive drugs to prevent PTS after UEDVT. We have not considered indirect evidence from the legs for use of compression therapy to prevent PTS of the arms because (1) the pathophysiology of PTS is believed to be different in the arms than in the legs (less dependent venous hypertension), (2) arm sleeves are more difficult to fit than stockings, and (3) PTS occurs less often after UEDVT than after leg DVT.

Recommendation

9.4. In patients with acute symptomatic UEDVT, we suggest against the use of compression sleeves or venoactive medications (Grade 2C).

9.5 Treatment of PTS of the Arm

Symptoms of PTS of the arm include swelling, heaviness, and limb fatigue with exertion. No randomized trials have evaluated compression bandages, compression sleeves (as are used for lymphedema), or venoactive drugs to treat PTS after UEDVT. We considered anecdotal evidence that compression therapy benefits some patients with PTS of the arm and that the benefits of a trial of compression therapy will outweigh its harms and costs. There is no evidence that venoactive drugs are of benefit in PTS of the arm.

Recommendations

9.5.1. In patients who have PTS of the arm, we suggest a trial of compression bandages or sleeves to reduce symptoms (Grade 2C).

9.5.2. In patients with PTS of the arm, we suggest against treatment with venoactive medications (Grade 2C).
10.0 Splanchnic Vein Thrombosis

Thrombosis in the portal venous system, which includes the superior mesenteric, inferior mesenteric, splenic, and portal veins, is collectively termed splanchnic vein thrombosis. Depending on the location and extent of thrombosis, how rapidly thrombosis develops, speed and extent of thrombus recannulation, presence of collateral portal venous drainage, and adequacy of arterial inflow, splanchnic vein thrombosis may result in bowel or splenic infarction and chronic portal hypertension. Acute and chronic splanchnic vein thrombosis may be symptomatic, but many episodes are detected incidentally in imaging studies performed for other indications, such as assessing response to surgical or medical therapy in patients with cancer.

Limited understanding of the natural history of both symptomatic and incidentally detected splanchnic vein thrombosis in patients who are not treated with anticoagulants (ie, frequency of bowel infarction, development of portal hypertension, recurrence), a paucity of data from prospective cohort studies, and a lack of randomized trials of standardized anticoagulant therapy for splanchnic vein thrombosis result in uncertainty about the role of anticoagulation for this condition. Increased risk of bleeding associated with esophageal varices (secondary to portal hypertension), thrombocytopenia (secondary to hypersplenism), and the presence of cirrhosis and malignancy (which predispose to splanchnic vein thrombosis) add to this uncertainty.

A number of retrospective and two prospective studies suggested that bowel ischemia is uncommon in patients with symptomatic splanchnic vein thrombosis who are treated with anticoagulants, that recurrent venous thrombosis (both involving the splanchic and nonsplanchnic veins) is common without anticoagulation or after stopping anticoagulation, and that anticoagulation is effective at preventing progression and recurrent thrombosis, although it is associated with an increased (particularly GI), but usually acceptable, frequency of bleeding. Efficacy of anticoagulant therapy in other forms of symptomatic venous thrombosis also provides indirect evidence for anticoagulation of patients with symptomatic splanchnic vein thrombosis and, supported by the previously noted observational studies, this evidence is of moderate quality. We are not aware of studies of treated or untreated asymptomatic splanchnic vein thrombosis.

Factors that may encourage anticoagulant therapy in patients with incidental splanchnic vein thrombosis include extensive thrombosis that appears to be acute (eg, not present on a previous imaging study, presence of an intraluminal filling defect, lack of cavernous transformation), progression of thrombosis on a follow-up imaging study, and ongoing cancer chemotherapy. Esophageal varices secondary to acute portal vein thrombosis are not necessarily a contraindication to anticoagulant therapy because such treatment may improve the portal hypertension. LMWH may be preferred over VKA if there is active malignancy, liver disease, or thrombocytopenia. The presence of a reversible provoking factor for splanchnic vein thrombosis, such as intraabdominal sepsis or recent surgery, supports stopping anticoagulant therapy after 3 months. Absence of a reversible risk factor (eg, "unprovoked" thrombosis or presence of a persistent risk factor, such as myeloproliferative disease) and a low risk of bleeding support extended anticoagulant therapy.

Recommendations

10.1. In patients with symptomatic splanchnic vein thrombosis (portal, mesenteric, and/or splenic vein thromboses), we recommend anticoagulation over no anticoagulation (Grade 1B).

10.2. In patients with incidentally detected splanchnic vein thrombosis (portal, mesenteric, and/or splenic vein thromboses), we suggest no anticoagulation over anticoagulation (Grade 2C).

11.0 Hepatic Vein Thrombosis

Hepatic vein thrombosis, particularly Budd-Chiari syndrome with occlusion of the main hepatic vein, can result in impairment of liver function and an associated coagulopathy. Because there is limited understanding of the natural history of this condition and a paucity of prospective studies that have evaluated anticoagulant therapy, the role of anticoagulant therapy is uncertain.

In a prospective registry of 163 patients with Budd-Chiari syndrome of variable extent, of whom 86% were treated with anticoagulation, one-half of patients did not require invasive interventions (ie, transjugular intrahepatic portosystemic shunting in 34% of all patients, surgical portosystemic shunting in 2% of patients, liver transplantation in 12% of patients), and survival was 82% after 2 years. In an earlier retrospective study of 237 patients with Budd-Chiari syndrome performed when use of surgical portosystemic shunting was common, use of anticoagulant therapy (72% of patients) had no apparent effect on survival (RR, 1.05; 95% CI, 0.62-1.76).

Factors that encourage anticoagulant therapy in patients with incidental hepatic vein thrombosis include extensive thrombosis that appears to be acute (eg, not present on a previous imaging study, presence of an intraluminal filling defect), progression...
of thrombosis on a follow-up imaging study, and ongoing cancer chemotherapy. Coagulopathy due to liver dysfunction caused by hepatic vein thrombosis is not a contraindication to anticoagulant therapy because anticoagulants may improve hepatic function. LMWH usually will be preferred to VKA therapy when there is hepatic dysfunction and if there is active malignancy. Presence of a reversible provoking factor for hepatic vein thrombosis, such as oral contraceptive therapy, encourages a time-limited course of therapy. Absence of a reversible risk factor encourages the use of extended therapy. Treatment of hepatic vein obstruction is complex and best undertaken by a multidisciplinary team.

Recommendations

11.1. In patients with symptomatic hepatic vein thrombosis, we suggest anticoagulation over no anticoagulation (Grade 2C).

11.2. In patients with incidentally detected hepatic vein thrombosis, we suggest no anticoagulation over anticoagulation (Grade 2C).

12.0 Future Research

Several questions in the treatment of VTE need to be answered. Current evidence relating to these questions is of moderate or low quality. We list the questions roughly as they arise in this article rather than in order of importance. We do not present the rationale for each question because this is addressed in the corresponding sections of the article. We have confined ourselves to the primary question (eg. Should patients with proximal DVT be treated with anticoagulant therapy alone, or should they be treated with pharmacomechanical CDT?); however, once the primary question is answered, we anticipate that secondary questions will need to be addressed (eg. Which patients with proximal DVT should, or should not, be treated with CDT?). We are pleased to note that many of the these questions are being addressed in ongoing trials.

• Should patients with an isolated distal DVT routinely be treated with anticoagulant therapy, or should they have serial testing to determine whether the DVT is extending and only be treated if extension is detected?
• Should patients with proximal DVT be treated with anticoagulant therapy alone, or should they be treated with pharmacomechanical CDT?
• Which patients with unprovoked proximal DVT or PE or cancer-associated VTE should stop anticoagulant therapy at 3 months, and which should remain on extended anticoagulant therapy?
• Which patients with unprovoked VTE or cancer-associated VTE have an unacceptable risk of bleeding if they remain on extended anticoagulant therapy?
• How should risk of recurrent VTE if anticoagulant therapy is stopped be balanced against risk of bleeding is anticoagulant therapy is continued?
• What is the preferred anticoagulant regimen for the short- and long-term treatment of VTE in patients with and without cancer?
• Should patients receiving an incidental diagnosis of asymptomatic VTE routinely be treated with anticoagulant therapy, or should they have serial testing to determine whether they have evolving DVT and only be treated if this is detected?
• Should patients with symptomatic DVT routinely wear graduated compression stockings from the time of diagnosis, or should stockings be used selectively (eg. in selected patients, in patients whose symptoms do not rapidly resolve)?
• Should patients with PE that causes right ventricular dysfunction be treated with anticoagulant therapy alone, or should they be treated with thrombolytic therapy?
• If patients have catheter-associated UEDVT and the catheter is removed, should they be treated with anticoagulant therapy or can they be treated without anticoagulant therapy?
• Can UEDVT be treated with less-intense or a shorter duration of anticoagulant therapy than leg DVT?

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Stein PD, Matta F, Janjua M, Yaeckou AB, Jawaesh F, Alrifai A. Outcome in stable patients with acute pulmonary embolism who had right ventricular enlargement and/or elevated levels of troponin I. Am J Cardiol. 2010;106(4):558-563.


418. Sanders RJ, Cooper MA. Surgical management of subclavian vein obstruction, including six cases of subclavian vein bypass. Surgery. 1995;118(5):856-863.


Antithrombotic Therapy for VTE Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Table S1—[Section 2.1] Evidence Profile: Parenteral Anticoagulation vs No Parenteral Anticoagulation in Acute VTE<sup>a</sup>

<table>
<thead>
<tr>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With No Parenteral Anticoagulation</td>
</tr>
<tr>
<td></td>
<td>Anticipation absolute effects</td>
</tr>
<tr>
<td><strong>Mortality (important outcome)</strong></td>
<td></td>
</tr>
<tr>
<td>Participants (Studies), Follow-up</td>
<td>Risk of Bias</td>
</tr>
<tr>
<td>120 (1 study), 6 mo</td>
<td>No serious risk of bias&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Recurrent VTE (critical outcome; assessed with symptomatic extension or recurrence)</strong></td>
<td></td>
</tr>
<tr>
<td>120 (1 study), 6 mo</td>
<td>No serious risk of bias&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Major bleeding (critical outcome)</strong></td>
<td></td>
</tr>
<tr>
<td>120 (1 study), 6 mo</td>
<td>No serious risk of bias&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Bibliography: Brandjes et al.<sup>1</sup> RR = risk ratio.

<sup>a</sup> Both groups treated with acenocoumarol.

<sup>b</sup> Study described as double blinded; outcome adjudicators blinded. None of the study participants were lost to follow-up. Intention-to-treat analysis. Study was stopped early for benefit.

<sup>c</sup> CI includes values suggesting no effect as well as values suggesting either appreciable benefit or appreciable harm.

<sup>d</sup> Low number of events caused by the early stoppage of the trial.
**Table S2 — [Section 2.4] Evidence Profile: Early Warfarin (and Shorter Duration Heparin) vs Delayed Warfarin (and Longer Duration Heparin) for Acute VTE**

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Study Event Rates (%)</th>
<th>Summary of Findings</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall Quality of Evidence</td>
<td>With Delayed Warfarin Initiation (and Longer Duration Heparin)</td>
<td>With Early Warfarin Initiation (and Shorter Duration Heparin)</td>
</tr>
<tr>
<td></td>
<td>Publication Bias</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Study Event Rates (%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Studies), Follow-up</td>
<td>Risk of Bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>688 (3 studies), 3 mo</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
</tr>
<tr>
<td></td>
<td>Mortality (important outcome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>688 (3 studies), 3 mo</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
</tr>
<tr>
<td></td>
<td>Recurrent VTE (critical outcome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>688 (3 studies), 3 mo</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
</tr>
<tr>
<td></td>
<td>Major bleeding (critical outcome)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bibliography: Gallus et al,2 Hull et al,3 Leroyer et al.4 Excluded Mohinddin et al5 because 34% of subjects had mural thrombus rather than VTE, in addition to major methodologic limitations. LMWH = low-molecular-weight heparin; PE = pulmonary embolism; UFH = unfractionated heparin; VKA = vitamin K antagonist. See Table S1 legend for expansion of other abbreviation.

• VKA therapy started within 1 day of starting heparin therapy (UFH in two studies and LMWH in one study).

• VKA therapy delayed for 4 to 10 d.

• Most patients had proximal DVT; some had isolated distal DVT; most DVT were symptomatic (asymptomatic DVT included in Hull et al), and few had PE (only included in Gallus et al).

• The early initiation of VKA was associated with a lower number of days of heparin therapy (4.1 vs 9.5 in Gallus et al; 5 vs 10 in Hull et al) and a lower number of days of hospital stay (9.1 vs 13.0 in Gallus; 11.7 vs 14.7 in Hull; 11.9 vs 16.0 in Leroyer et al).

• Differences in death, independently of differences in recurrent VTE and major bleeding, is unlikely.

• Outcome assessment was at hospital discharge in the study by Gallus et al (although there was also extended follow-up) and 3 mo in the studies by Hull et al and Leroyer et al.

• Patients and investigators were not blinded in two studies (Gallus et al and Leroyer et al) and were blinded in one study (Hull et al). Concealment was not clearly described but was probable in the three studies. Primary outcome appears to have been assessed after a shorter duration of follow-up in the shorter treatment arm of one study because of earlier discharge from the hospital, and 20% of subjects in this study were excluded from the final analysis postrandomization (Gallus).

• The 95% CI on relative effect includes both clinically important benefit and clinically important harm.

• Event rate corresponds to the median event rate in the included studies.

• Bleeding was assessed early (in hospital or in the first 10 d) in two studies (Gallus et al, Hull et al) and at 3 mo in one study (Leroyer et al).

• It is unclear whether bleeding was assessed at 10 d in all subjects or just while heparin was being administered, which could yield a biased estimate in favor of short-duration therapy in one study (Hull et al).

• Because the shorter duration of heparin therapy is very unlikely to increase bleeding, the wide 95% CIs around the relative effect of shorter therapy on risk of bleeding is not a major concern.
### Table S3—[Section 2.5.1] Evidence Profile: LMWH vs SC UFH for Initial Anticoagulation of Acute VTE

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Summary of Findings</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td><strong>Study Event Rates (%)</strong></td>
<td><strong>Relative Effect (95% CI)</strong></td>
</tr>
<tr>
<td>(Studies), Follow-up</td>
<td>Relative Risk With SC UFH</td>
<td>With SC UFH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mortality</strong> (important outcome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,566 (3 studies), 3 mo</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
</tr>
<tr>
<td><strong>Recurrent VTE</strong> (critical outcome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,563 (3 studies), 3 mo</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
</tr>
<tr>
<td><strong>Major bleeding</strong> (critical outcome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,634 (4 studies), 3 mo</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
</tr>
</tbody>
</table>

Bibliography: Lopaciuk et al, Faivre et al, Prandoni et al, Kearon et al. SC = subcutaneous. See Table S1 and S2 legends for expansion of other abbreviations.

<sup>a</sup> In the two largest trials (Prandoni et al and Kearon et al, 87% of patients), allocation was concealed, outcome adjudicators and data analysts were concealed, analysis was intention to treat, and there were no losses to follow-up.

<sup>b</sup> Precision judged from the perspective of whether SC heparin is noninferior to LMWH. The total number of events and the total number of participants are relatively low.

<sup>c</sup> Event rate corresponds to the median event rate in the included studies.
Table S4—[Section 2.5.1] LMWH vs SC UFH for Initial Anticoagulation of Acute VTE: Clinical Description and Results

<table>
<thead>
<tr>
<th>Author/Year (Acronym)</th>
<th>Interventions</th>
<th>Patients Analyzed</th>
<th>Recurrent DVT or PE</th>
<th>Major Bleeding</th>
<th>Total Mortality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopaciuk et al2/1992</td>
<td>UFH 5,000 units IV followed by 250 units/kg SC bid initially and adjusted to aPTT for 10 d</td>
<td>72/75</td>
<td>1/72 (1.4%)</td>
<td>1/72 (1.4%)</td>
<td>3/72 (4.2%)</td>
<td>Population: Femoral DVT in 81% and popliteal or more distal DVT in 19%. Primary outcome was repeat venography.</td>
</tr>
<tr>
<td></td>
<td>Fraxiparine 97 International Units/kg SC bid for 10 d</td>
<td>74/74</td>
<td>0/74 RR 3.1 (0.1-7.5)</td>
<td>0/74 RR 3.1 (0.1-7.5)</td>
<td>0/74 RR 7.2 (0.4-137)</td>
<td></td>
</tr>
<tr>
<td>Faivre et al22/1988</td>
<td>UFH 5,000 units IV followed by 250 units/kg SC bid and adjusted to aPTT for 10 d</td>
<td>29/35</td>
<td>1/35</td>
<td>3/35</td>
<td>1/35</td>
<td>Population: DVT (proportion of proximal and distal not reported). Primary outcome was repeat venography.</td>
</tr>
<tr>
<td></td>
<td>CY222 2,000 International Units/kg IV followed by 150 International Units/kg SC bid for 10 d</td>
<td>30/33</td>
<td>1/33 RR 0.9 (0.1-14.5)</td>
<td>0/33 RR 6.6 (0.3-123)</td>
<td>0/33 RR 2.8 (0.1-67)</td>
<td></td>
</tr>
<tr>
<td>Prandoni et al23/2004 (Galilei)</td>
<td>UFH IV (&lt;50 kg: 4,000 units; 50-70 kg: 5,000 units; &gt;70 kg: 6,000 units) followed by SC bid doses (initially &lt;50 kg: 12,500 units; 50-70 kg: 15,000 units; &gt;70 kg: 17,500 units) adjusted to aPTT for ~6.5 d</td>
<td>360/360</td>
<td>15/360 (4.2%)</td>
<td>5/360 (1.4%)</td>
<td>12/360 (3.3%)</td>
<td>Population: Proximal DVT in 65%, distal DVT in 19%, and PE in 17%.</td>
</tr>
<tr>
<td></td>
<td>Nadroparin S5 International Units/kg SC bid for ~6.5 d</td>
<td>360/360</td>
<td>14/360 (3.9%) RR 1.1 (0.5-2.2)</td>
<td>7/360 (1.9%) RR 0.7 (0.2-2.2)</td>
<td>12/360 (3.3%) RR 1.0 (0.5-2.2)</td>
<td></td>
</tr>
<tr>
<td>Kearon et al24/2006 (FIDO)</td>
<td>UFH 333 units/kg SC followed by 250 units/kg SC bid (no adjustment) for 6.3 d</td>
<td>345/355</td>
<td>13/345 (3.8%)</td>
<td>6/348 (1.7%)</td>
<td>18/348 (5.2%)</td>
<td>Population: Proximal DVT in 77%, asymptomatic or distal DVT in 4%, and PE in 19%. Seventy percent of patients were treated entirely as an outpatient (76% of DVT and 39% of PE) Postrandomization exclusions in 10 patients receiving UFH and one patient receiving LMWH.</td>
</tr>
<tr>
<td></td>
<td>Dalteparin (n = 261) or enoxaparin (n = 91) 100 International Units/kg SC bid for 7.1 d</td>
<td>352/353</td>
<td>12/352 (3.4%) RR 1.1 (0.5-2.3)</td>
<td>12/352 (3.4%) RR 0.5 (0.2-1.3)</td>
<td>22/352 (6.3%) RR 0.8 (0.4-1.5)</td>
<td></td>
</tr>
</tbody>
</table>

aPTT = activated prothrombin time; FIDO = Fixed Dose Heparin. See Table S1 and S2 legends for expansion of other abbreviations.

*Follow-up was for 3 mo except for the study by Faivre et al22 in which it was 10 d.
<table>
<thead>
<tr>
<th>Author/Year (Acronym)</th>
<th>Interventions</th>
<th>Study Design</th>
<th>Randomization</th>
<th>Blinding</th>
<th>Loss to Follow-up</th>
<th>Analysis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopaciuk et al1992</td>
<td>UFH 5,000 units IV followed by 250 units/kg SC bid initially and adjusted to aPTT for 10 d Fraxiparine 97 International units/kg SC bid for 10 d</td>
<td>RCT</td>
<td>PY</td>
<td>Patients: CN Caregivers: CN Adjudicators: CN Data Analysts: PN</td>
<td>Not described</td>
<td>ITT</td>
<td></td>
</tr>
<tr>
<td>Faivre et al1988</td>
<td>UFH 5,000 units IV followed by 250 units/kg SC bid and adjusted to aPTT for 10 d CY222 2,000 International Units IV followed by 150 International Units/kg SC bid for 10 d</td>
<td>RCT</td>
<td>PN</td>
<td>Patients: PN Caregivers: PN Adjudicators: PN Data Analysts: PN</td>
<td>Three of CY222 group and six of UFH group who did not have repeat venography are assumed to have completed clinical follow-up</td>
<td>ITT</td>
<td></td>
</tr>
<tr>
<td>Prandoni et al2004</td>
<td>UFH IV (&lt;50 kg: 4,000 units; 50-70 kg: 5,000 units; &gt;70 kg: 6,000 units) followed by SC bid doses (initially &lt;50 kg: 12,500 units; 50-70 kg: 15,000 units; &gt;70 kg: 17,500 units) adjusted to aPTT for ~6.5 d Nadroparin 85 International Units/kg SC bid for ~6.5 d</td>
<td>RCT</td>
<td>CY</td>
<td>Patients: CN Caregivers: CN Adjudicators: CY Data Analysts: PY</td>
<td>Nil</td>
<td>ITT</td>
<td></td>
</tr>
<tr>
<td>Kearon et al2006</td>
<td>UFH 333 units/kg SC followed by 250 units/kg SC bid (no adjustment) for 6.3 d Dalteparin (n = 261) or enoxaparin (n = 91) 100 International Units/kg SC bid for 7.1 d</td>
<td>RCT</td>
<td>CY</td>
<td>Patients: CN Caregivers: CN Adjudicators: CY Data Analysts: PY</td>
<td>Nil</td>
<td>ITT</td>
<td>Postrandomization exclusions from the efficacy analysis were 10 (2.8%) for the UFH and one (0.2%) for the LMWH group.</td>
</tr>
</tbody>
</table>

CN = certainly no; CY = certainly yes; ITT = intention to treat; PN = probably no; PY = probably yes; RCT = randomized controlled trial. See Table S1, S2, and S4 legends for expansion of other abbreviations.
Table S6—[Section 2.5.1] Evidence Profile: LMWH vs IV UFH for Initial Anticoagulation of Acute VTE

<table>
<thead>
<tr>
<th>Participants (Studies), Follow-up</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication Bias</th>
<th>Overall Quality of Evidence</th>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (important outcome)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7,908 (17 studies), 3 mo</td>
<td>Serious^a</td>
<td>No serious</td>
<td>No serious</td>
<td>No serious</td>
<td>Reporting bias</td>
<td>Low^b due to risk of bias, publication bias</td>
<td>232/3,789 (6.1)</td>
<td>RR 0.79 (0.66-0.95) 46 per 1,000^c (from 2 fewer to 16 fewer)</td>
</tr>
<tr>
<td>Recurrent VTE (critical outcome)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7,976 (17 studies), 3 mo</td>
<td>Serious^a</td>
<td>No serious</td>
<td>No serious</td>
<td>No serious</td>
<td>Reporting bias</td>
<td>Low^b due to risk of bias, publication bias</td>
<td>208/3,869 (5.4)</td>
<td>RR 0.72 (0.58-0.89) 55 per 1,000^c (from 6 fewer to 23 fewer)</td>
</tr>
<tr>
<td>Major bleeding (critical outcome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6,910 (20 studies), 3 mo</td>
<td>Serious^a</td>
<td>No serious</td>
<td>No serious</td>
<td>No serious</td>
<td>Reporting bias</td>
<td>Low^b,d due to risk of bias, publication bias</td>
<td>69/3,517 (2)</td>
<td>RR 0.67 (0.45-1) 15 per 1,000^c (from 8 fewer to 0 more)</td>
</tr>
</tbody>
</table>

Bibliography: van Dongen et al.6 Included studies.7,20 See Table S1 and S2 legends for expansion of abbreviations.

^a Of the 20 trials, allocation was concealed in nine and was unclear whether concealed in the remaining 11. Eighteen trials had blinded outcome assessors. Seven trials did not have any postrandomization exclusions or losses to follow-up. Ten trials reported the number of participants lost to follow-up, which ranged from 1.0% to 12.7%. One trial did not report the drop-outs.

^b Inverted funnel plot very suggestive of publication bias. Many of the included studies are of small size, and all are funded by industry.

^c Event rate corresponds to the median event rate in the included studies.

^d CI interval includes values suggesting significant benefit and no effect.
Table S7—[Section 2.5.1] Evidence Profile: Fondaparinux vs LMWH for Initial Anticoagulation of Acute DVT

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Study Event Rates (%)</td>
<td>Relative Effect (95% CI)</td>
</tr>
<tr>
<td>(Studies), Follow-up</td>
<td>With LMWH</td>
<td>With Fondaparinux</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk With LMWH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk Difference With Fondaparinux (95% CI)</td>
</tr>
<tr>
<td>Participants</td>
<td>Study Event Rates (%)</td>
<td>Relative Effect (95% CI)</td>
</tr>
<tr>
<td>(Studies), Follow-up</td>
<td>With LMWH</td>
<td>With Fondaparinux</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk With LMWH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk Difference With Fondaparinux (95% CI)</td>
</tr>
<tr>
<td>Participants</td>
<td>Study Event Rates (%)</td>
<td>Relative Effect (95% CI)</td>
</tr>
<tr>
<td>(Studies), Follow-up</td>
<td>With LMWH</td>
<td>With Fondaparinux</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk With LMWH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk Difference With Fondaparinux (95% CI)</td>
</tr>
<tr>
<td>Participants</td>
<td>Study Event Rates (%)</td>
<td>Relative Effect (95% CI)</td>
</tr>
<tr>
<td>(Studies), Follow-up</td>
<td>With LMWH</td>
<td>With Fondaparinux</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk With LMWH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk Difference With Fondaparinux (95% CI)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mortality (important outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.205 (1 study), 3 mo</td>
</tr>
<tr>
<td>No serious risk of bias</td>
</tr>
<tr>
<td>No serious inconsistency</td>
</tr>
<tr>
<td>No serious indirectness</td>
</tr>
<tr>
<td>Serious§ Undetected</td>
</tr>
<tr>
<td>Moderate§ due to imprecision</td>
</tr>
<tr>
<td>33/1,107 (3.0)</td>
</tr>
<tr>
<td>41/1,098 (3.7)</td>
</tr>
<tr>
<td>RR 1.25 (0.8-1.97)</td>
</tr>
<tr>
<td>30 per 1,000</td>
</tr>
<tr>
<td>7 more per 1,000</td>
</tr>
<tr>
<td>(from 6 fewer to 29 more)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recurrent VTE (critical outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.205 (1 study), 3 mo</td>
</tr>
<tr>
<td>No serious risk of bias</td>
</tr>
<tr>
<td>No serious inconsistency</td>
</tr>
<tr>
<td>No serious indirectness</td>
</tr>
<tr>
<td>Serious§ Undetected</td>
</tr>
<tr>
<td>Moderate§ due to imprecision</td>
</tr>
<tr>
<td>45/1,107 (4.1)</td>
</tr>
<tr>
<td>43/1,098 (3.9)</td>
</tr>
<tr>
<td>RR 0.96 (0.64-1.45)</td>
</tr>
<tr>
<td>41 per 1,000</td>
</tr>
<tr>
<td>2 fewer per 1,000</td>
</tr>
<tr>
<td>(from 15 fewer to 18 more)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major bleeding (critical outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.205 (1 study), 3 mo</td>
</tr>
<tr>
<td>No serious risk of bias</td>
</tr>
<tr>
<td>No serious inconsistency</td>
</tr>
<tr>
<td>No serious indirectness</td>
</tr>
<tr>
<td>Serious§ Undetected</td>
</tr>
<tr>
<td>Moderate§ due to imprecision</td>
</tr>
<tr>
<td>13/1,107 (1.2)</td>
</tr>
<tr>
<td>12/1,098 (1.1)</td>
</tr>
<tr>
<td>RR 0.93 (0.43-2.03)</td>
</tr>
<tr>
<td>12 per 1,000</td>
</tr>
<tr>
<td>1 fewer per 1,000</td>
</tr>
<tr>
<td>(from 7 fewer to 12 more)</td>
</tr>
</tbody>
</table>

Bibliography: Büller et al. INR = international normalized ratio. See Table S1 and S2 legends for expansion of other abbreviations.

§Fondaparinux 7.5 mg (5.0 mg in patients weighing <50 kg and 10.0 mg in patients weighing >100 kg) SC once daily for at least 5 d and until VKAs induced an INR >2.0.

Enoxaparin 1 mg/kg of body weight SC bid for at least 5 d and until VKAs induced an INR >2.0.

All patients had acute symptomatic DVT.

‡Allocation was concealed. Patients, providers, data collectors, and outcome adjudicators were blinded. Analysis excluded 0.6% of randomized patients. Not stopped early for benefit.

§CI includes values suggesting no effect and values suggesting either benefit or harm; relatively low number of events.

Five fatal VTE in fondaparinux group and five fatal VTE in LMWH group.

Twelve patients in the fondaparinux group and 13 in the LMWH group had a major bleeding during the initial period (7 d). Of these, two in the fondaparinux group and none in the LMWH group were fatal.
Table S8—[Section 2.5.2] Evidence Profile: LMWH Once vs Twice Daily for Initial Anticoagulation of Acute VTE\(^a,b\)

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Overall Quality of Evidence</td>
<td>Study with Bid</td>
</tr>
<tr>
<td>(Studies), Follow-up</td>
<td>With Bid</td>
<td>With LMWH Once</td>
</tr>
<tr>
<td>1.261 (3 studies), No serious risk of bias</td>
<td>Serious(^d)</td>
<td>Undetected</td>
</tr>
<tr>
<td>3 mo</td>
<td>No serious indirectness</td>
<td>Serious(^e)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low(^e) due to inconsistency, imprecision</td>
</tr>
<tr>
<td>Recurrent VTE (critical outcome)</td>
<td>32/647 (4.9)</td>
<td>26/614 (4.2)</td>
</tr>
<tr>
<td></td>
<td>1,261 (3 studies), No serious risk of bias</td>
<td>Serious(^d)</td>
</tr>
<tr>
<td>3 mo</td>
<td>No serious indirectness</td>
<td>Serious(^e)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low(^e) due to inconsistency, imprecision</td>
</tr>
<tr>
<td>Major bleeding (critical outcome)</td>
<td>9772 (1.2)</td>
<td>10750 (1.3)</td>
</tr>
<tr>
<td></td>
<td>1,522 (5 studies), No serious risk of bias</td>
<td>No serious indirectness</td>
</tr>
</tbody>
</table>

Bibliography: van Dongen et al.\(^{26}\) See Table S1, S2, and S5 legends for expansion of other abbreviations.

\(^a\)The five included studies used four brands of LMWH (enoxaparin, tinzaparin, dalteparin, and nadroparin). In Merli et al, enoxaparin 1 mg/kg bid was compared with 1.5 mg/kg once daily. Holmström et al adjusted the dose to anti-Xa levels, which resulted in different daily doses after a number of days. In the remaining studies, the dose of the once-daily administration was double the dose of the twice-daily administration (equal total daily dose).

\(^b\)Of the five included studies, one included patients with PE and DVT, and four included only patients with DVT. All studies addressed the initial management of VTE.

\(^c\)All included studies concealed allocation. Two studies had a double-blind design, and two others were single blind. One study did not mention blinding. ITT likely used in all studies. Participants were lost to follow-up in only two studies (0.3% and 2.2%).

\(^d\)P = 37%: point effect estimate in favor of bid dose in Merli et al\(^{25}\) and in favor of once-daily dose in Charbonnier et al.\(^{26}\)

\(^e\)Imprecision judged relative to no difference.

\(^f\)P = 65%: point effect estimate in favor of bid dose in Merli et al\(^{25}\) and in favor of once-daily dose in Charbonnier et al.\(^{26}\)
# Table S9 — [Section 2.7] Evidence Profile: Home Treatment vs Hospital Treatment of Acute DVT

## Quality Assessment

<table>
<thead>
<tr>
<th>Participants (Studies), Follow-up</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication Bias</th>
<th>Overall Quality of Evidence</th>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mortality (important outcome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,708 (6 studies), 3 mo</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
<td>Serious&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Undetected</td>
<td>Low&lt;sup&gt;a,b&lt;/sup&gt; due to indirectness, imprecision</td>
<td>39/851 (4.6)</td>
<td>28/857 (3.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE (critical outcome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,708 (6 studies), 3 mo</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
<td>Serious&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>No serious imprecision</td>
<td>Undetected</td>
<td>Moderate&lt;sup&gt;a,b&lt;/sup&gt; due to indirectness</td>
<td>63/851 (7.4)</td>
<td>39/857 (4.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding (critical outcome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,708 (6 studies), 3 mo</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
<td>Serious&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Undetected</td>
<td>Moderate&lt;sup&gt;a,b&lt;/sup&gt; due to indirectness</td>
<td>18/851 (2.1)</td>
<td>12/857 (1.4)</td>
</tr>
<tr>
<td>Quality of life (important outcome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (3 studies&lt;sup&gt;a&lt;/sup&gt;) , 3 mo</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;k&lt;/sup&gt;</td>
<td>Undetected</td>
<td>Low&lt;sup&gt;k&lt;/sup&gt; due to indirectness, imprecision</td>
<td>…</td>
<td>…</td>
</tr>
</tbody>
</table>

Bibliography: Othieno et al<sup>34</sup> included studies<sup>34,35</sup> Quality of life. See Table S1 and S2 for expansion of abbreviations.

<sup>a</sup> Four studies had partial hospital treatment of many in the home arm: Koopman et al (mean hospital stay 2.7 in home arm vs 8.1 d in hospital arm), Levine et al (2.1 vs 6.5 d), Boccalon et al (1 vs 9.6 d), and Ramacciotti et al (3 vs 7 d). In Daskalopoulos et al, there was no hospital stay at all in the home group. Chong et al did not report duration of hospital stay.

<sup>b</sup> Only one study (Boccalon et al) used LMWH in both treatment arms. Remaining studies used UFH in the inpatient arm and LMWH in the outpatient arm.

<sup>c</sup> Studies included in the systematic review should have recruited patients whose home circumstances were adequate.

<sup>d</sup> All studies included patients with lower-extremity DVT and excluded patients with suspected or confirmed PE. Studies also excluded patients who were pregnant.

<sup>e</sup> Out of six studies, allocation was clearly concealed in three (unclear in remaining three). Outcome adjudicators were blinded in the two largest studies (unclear in remaining). Four reported loss to follow-up (was significant in only a small study). ITT analysis was conducted in four (unclear in remaining two). No study was stopped early for benefit. Overall, the judgment was that these limitations would not warrant downgrading of quality because it has already been downgraded by at least one level based on other factors.

The CI includes both values suggesting benefit and harm.

<sup>f</sup> Judged as precise based on the narrow CI around absolute effect.

<sup>g</sup> Bäckman et al<sup>36</sup> reported evaluation of health-related quality of life using the EQ-5D. They found no differences in mean quality-of-life scores or in the proportion of patients showing improvement in self-rated health state. Koopman et al evaluated health-related quality of life using the Medical Outcome Study Short Form-20 and an adapted version of the Rotterdam Symptom Checklist. The changes over time were similar in both groups except that the patients receiving LMWH had better scores for physical activity (P = .002) and social functioning (P = .001) at the end of the initial treatment. The authors did not report enough data to assess precision and clinical significance of results. O’Brien et al<sup>36</sup> assessed changes in quality of life using the Medical Outcome Study Short Form-36 in 300 patients participating in Levine et al.<sup>14</sup> They found that, the change in scores from baseline to day 7 was not significantly different between the treatment groups for seven of the eight domains. The one exception was the domain of social functioning, where a greater improvement was observed for the outpatient group.

<sup>h</sup> Potential inconsistency as Bäckman et al<sup>36</sup> showed no effect, whereas Koopman et al<sup>36</sup> and O’Brien et al<sup>36</sup> showed potential benefit.

<sup>i</sup> Two of the three studies had partial hospital treatment of many in the home arm: Koopman et al<sup>36</sup> (mean hospital stay 2.7 in home arm vs 8.1 d in hospital arm) and Levine et al (2.1 vs 6.5 d).

<sup>j</sup> Not able to evaluate but imprecision is possible. Taken together with the potential inconsistency, we downgraded the quality of evidence by one level.
Table S10—[Section 2.9] Evidence Profile: Catheter-Directed Thrombolysis vs No Catheter-Directed Thrombolysis for Extensive Acute DVT of the Leg

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With No Catheter-Directed Thrombolysis</td>
<td>With Catheter-Directed Thrombolysis</td>
</tr>
<tr>
<td>Participants (Studies), Follow-up</td>
<td>Risk of Bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>Mortality (important outcome)</td>
<td>153 (2 studies), 3 mo</td>
<td>No serious risk of bias</td>
</tr>
<tr>
<td>Nonfatal recurrent VTE (critical outcome)</td>
<td>153 (1 study), 3 mo</td>
<td>No serious risk of bias</td>
</tr>
<tr>
<td>Nonfatal major bleeding (critical outcome)</td>
<td>153 (2 studies), 7 d</td>
<td>No serious risk of bias</td>
</tr>
<tr>
<td>Postthrombotic syndrome (critical outcome; assessed with: complete lysis on venography (Elsharawy et al); patency on ultrasound and air plethysmography (Enden et al))</td>
<td>138 (2 studies), 2 y</td>
<td>No serious risk of bias</td>
</tr>
</tbody>
</table>

(Continued)
### Table S10—Continued

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study Event Rates (%)</td>
</tr>
<tr>
<td>Participants (Studies), Follow-up</td>
<td>Risk of Bias</td>
</tr>
<tr>
<td>Quality of life (important outcome; measured with the Medical Outcome Survey Short Form-12, Health Utilities Index MARK version 2/3 questionnaires; better indicated by lower values)</td>
<td>98 (1 study), 16 mo</td>
</tr>
</tbody>
</table>

Bibliography: Elsharawy et al. Enden et al. Comerota et al. CDT = catheter-directed thrombolysis; PTS = postthrombotic syndrome. See Table S1 legend for expansion of other abbreviations.

*All patients were anticoagulated per protocol, but the intervention group received CDT in addition to anticoagulation.

*In selected patients with extensive acute proximal DVT (eg, iliofemoral DVT, symptoms for < 14 d, good functional status, life expectancy ≥ 1 y) who have a low risk of bleeding.

*Allocation was concealed in Enden et al and unclear in Elsharawy et al. Outcome assessor blinded in both studies. Follow-up rates were 87% in Enden et al and 100% in Elsharawy et al. None of the studies was stopped early for benefit.

*CI includes values suggesting both benefit and harm.

*Three control patients died of cancer.

*Baseline risks for nonfatal recurrent VTE and for major bleeding derived from Douketis et al.

*In the Enden et al study, one patient had "durable and partial impairment of sensibility of the foot" immediately after receiving CDT, and nine patients had minor bleeding complications.

*Most of bleeding events occur during the first 7 d.

*Surrogate outcome: absence of patency at 6 mo in Enden et al study; absence of complete lysis at 6 mo in Elsharawy et al study.

*This estimate is based on the findings of the VETO (Venous Thrombosis Outcomes) study. This probably underestimates PTS baseline risk given that overall, 52% of patients reported the current use of compression stockings during study follow-up.

*Severe PTS: assuming the same RR of 0.46 and a baseline risk of 13.8%, the absolute reduction is 75 fewer severe PTS per 1,000 (from 29 fewer to 138 fewer) over 2 y.

*Comerota et al.

*Recall was used to measure quality of life prior to the thrombotic event; we did not consider these measurements.

*At the initial follow-up (mean, 16 mo), patients treated with CDT reported a trend toward a higher mental summary scale (P = .087) and improved Health Utilities Index (P = .078). They reported better overall role physical functioning (P = .046), less stigma (P = .033), less health distress (P = .022), and fewer overall symptoms (P = .006) compared with patients who were treated with anticoagulation alone.
Table S11—[Section 2.9] CDT vs No CDT for Extensive Acute DVT of the Leg: Clinical Description and Results (All Randomized Trials and Prospective Observational Studies of at Least 20 Patients)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Publication</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semba et al 1994</td>
<td>Prospective registry</td>
<td>21 patients (27 limbs) with iliofemoral DVT ≤ 14 d (20) or &gt; 14 d (7) duration</td>
<td>4.9 million units urokinase (mean) infused over 30 h (mean), followed by heparin and then warfarin for 8-12 wk</td>
<td>Clot lysis, complications</td>
<td>3 mo</td>
<td>Significant lysis: 18/25 (72%); Partial lysis: 5/25 (20%); No lysis: 2/25 (8%); Complications: 1 small hematoma at puncture site, no intervention/ transfusion</td>
</tr>
<tr>
<td>Semba et al 1994</td>
<td>Prospective registry</td>
<td>21 patients (27 limbs) with iliofemoral DVT ≤ 14 d (20) or &gt; 14 d (7) duration</td>
<td>4.9 million units urokinase (mean) infused over 30 h (mean), followed by heparin and then warfarin for 8-12 wk</td>
<td>Clot lysis, complications</td>
<td>3 mo</td>
<td>Significant lysis: 18/25 (72%); Partial lysis: 5/25 (20%); No lysis: 2/25 (8%); Complications: 1 small hematoma at puncture site, no intervention/ transfusion</td>
</tr>
<tr>
<td>Verhaeghe et al 1997</td>
<td>Prospective study</td>
<td>24 patients with iliofemoral DVT ≤ 14 d (16) or &gt; 14 d (8) duration</td>
<td>3 mg/h rt-PA (mean 86 mg) infused with 1,000 U/h IV heparin, followed by heparin, adjusted to APTT</td>
<td>Clot lysis, bleeding</td>
<td>13 mo (mean)</td>
<td>Significant lysis: 19/24 (79%); Partial lysis: 5/24 (21%); Bleeding: 6/24 (25%); Patency: 3 mo: 84%; 1 y: 78%</td>
</tr>
<tr>
<td>Bjarnason et al 1997</td>
<td>Prospective registry</td>
<td>77 patients (87 limbs) with iliofemoral DVT ≤ 14 d (60) or &gt; 14 d (18) duration</td>
<td>2,000-2,500 units/kg per h urokinase infused for 75 h (mean) with 5,000 International Units bolus heparin plus infusion adjusted to aPTT</td>
<td>Clot lysis, PE, bleeding</td>
<td>1 y</td>
<td>Early results: Significant lysis: 69/87 (79%); Iliac (63%); Femoral (40%); No lysis: 18/87 (21%); PE: 1 (1%); Bleeding: major, 5/77 (6%); minor, 11/77 (14%); Patency at 1 y: Iliac: 63%; Femoral: 40%</td>
</tr>
</tbody>
</table>

(Continued)
Table S11—Continued

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Publication</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mewissen et al 1999 (National Multicenter Registry)</td>
<td>Prospective multicenter registry</td>
<td>287 patients (312 infusions) with lower limb DVT ≤ 10 d (188) or &gt; 10 d (99) duration</td>
<td>7.8 million units urokinase (mean) infused for 53.4 h (mean) in 297 limbs. In 6 limbs, only systemic infusion (no CDT). Adjunctive therapy: stents (104), systemic infusion (54)</td>
<td>Clot lysis, PE, bleeding, death</td>
<td>1 y</td>
<td>Early results: 50%-100% lysis: 258/312 (83%) &lt; 50% lysis: 54/312 (17%) PE: 6/473 (1%) Bleeding: 54/473 (11%) Death: 2/473 (&lt;1%) Patency at 1 y: Iliac: 64% Femoral: 47%</td>
</tr>
<tr>
<td>AbuRahma et al 2001</td>
<td>Prospective study</td>
<td>51 patients (51 limbs) with iliofemoral DVT given choice between conventional therapy (heparin + warfarin) or lysis + angio/stent (if needed). Lysis offered only to patients with DVT ≤ 14 d duration and no contraindications</td>
<td>Anticoagulation: 33 patients given 1,000-2000 units/h heparin infusion for 5-7 d.</td>
<td>Clot lysis, PE, bleeding</td>
<td>Anticoag: 6 mo</td>
<td>Anticoagulation: 30-d significant lysis: 1/33 (3%) 6-mo patency: 8/33 (24%) Bleeding: 2/33 (6%) PE: 2/33 (6%)</td>
</tr>
<tr>
<td></td>
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<td>CDT: 18 patients given loading dose 4,500 units urokinase followed by 4,500 units/kg per h for 24-48 h or 4-8-mg bolus of rt-PA followed by 2-4-mg/h infusion. Adjunctive therapy: patients with residual stenosis &gt; 50% received stents (10)</td>
<td></td>
<td></td>
<td>CDT: 6 mo²</td>
</tr>
<tr>
<td>Elharawy et al 2002</td>
<td>RCT, single center</td>
<td>35 patients with DVT &lt; 10 d duration randomized to CDT or anticoagulation alone</td>
<td>CDT: 18 patients received ~1 million units SK pulse-spray for 1 h, followed by 100,000 units/h SK infusion until complete lysis, no change in 12 h, or complication. Adjunctive therapy: angioplasty/stent (1)</td>
<td>Clot lysis, PE, bleeding</td>
<td>1 wk and 6 mo</td>
<td>CDT: 1 wk Complete lysis: 11/18 (61%) No lysis: 0 (0%) PE: 0 Bleeding: 0 Anticoagulation, 1 wk: Complete lysis: 0/17 (0%) No lysis: 17/17 (100%) PE: 1/17 (6%) Bleeding: 0</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Publication</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enden et al. 2009 (CaVenT)</td>
<td>RCT, multicenter</td>
<td>Iliofemoral DVT &lt; 21 d duration</td>
<td>CDT: tPA 0.01 mg/kg per h, maximum of 20 mg/24 h for 4 d. Treated in four referral centers</td>
<td>Clot lysis, PE, PE bleeding (PTS at 24 mo pending)</td>
<td>1 wk and 6 mo</td>
<td>CDT, 1 wk: ≥ 50% lysis: 44/50 (68%) PE: 0 Major bleeding: 1/50 Anticoagulation, 1 wk: Lysis not assessed PE: 0 Major bleeding: 0 (puncture site nerve damage: 0) CDT, 6 mo: Iliofemoral patency: 32/50 (64%) Anticoagulation, 6 mo: Iliofemoral patency: 19/53 (36%)</td>
</tr>
</tbody>
</table>

**Interventions**
- Anticoagulation: 17 patients received 5,000 units heparin bolus, followed by heparin adjusted to aPTT
- CDT: tPA 0.01 mg/kg per h, maximum of 20 mg/24 h for 4 d. Treated in four referral centers
- Anticoagulation alone: usual practice, administered locally

**Outcomes**
- Clot lysis, PE, PE bleeding (PTS at 24 mo pending)

**Follow-up**
- 1 wk and 6 mo

**Results**
- Complete lysis: 13/18 (72%)
- No lysis: 0 (0%)
- Anticoagulation, 6 mo
  - Significant lysis: 2/17 (12%)
  - No lysis: 7/17 (41%)

**Additional Information**
- Early prospective observational studies with < 20 patients and retrospective studies are described in Table 3 of the eighth edition of these guidelines.
- AVF = arteriovenous fistula; CaVenT = Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis; rt-PA = recombinant tissue plasminogen activator; SK = streptokinase. See Table S2, S4, S5, and S10 legends for expansion of other abbreviations.
- Twenty-five of 27 limbs treated with CDT; two could not be crossed with the guidewire.
- Calculated from total number of patients in Venous Registry.
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Randomization</th>
<th>Allocation Concealment</th>
<th>Blinding</th>
<th>Loss to follow-up</th>
</tr>
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<tbody>
<tr>
<td>Semba et al^4/1994</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Verhaeghe et al^4/1997</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Bjarnason et al^4/1997</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Mewissen et al^4/1999</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>AbuRahma et al^5/2001</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Elsharawy et al^5/2002</td>
<td>Computer-designated cards</td>
<td>PN</td>
<td>N for patients, caregivers, and probably data analysts. Y for vascular imaging</td>
<td>0</td>
</tr>
<tr>
<td>Enden et al^5/2009</td>
<td>Computer-designated cards</td>
<td>Y</td>
<td>No for patients and caregivers. Yes for vascular imaging.</td>
<td>One loss to follow-up (CDT), five withdrawals, five postrandomization exclusions</td>
</tr>
</tbody>
</table>

N = no; N/A = not applicable; Y = yes. See Table S10 legend for expansion of other abbreviation.
Table S13—[Section 2.10] Systemic Lysis vs No Systemic Lysis for Extensive Acute DVT of the Leg: Clinical Description and Results (Randomized Trials That Compared Systemic Thrombolytic Therapy With No Thrombolytic Therapy)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Publication</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Browse et al 1968</td>
<td>RCT, single center</td>
<td>10 patients with lower-extremity DVT confirmed by phlebography</td>
<td>Lysis: 600,000 units SK plus 100 mg hydrocortisone for first hour, then continued every 6 h for 3 d (5 patients) Anticoagulation: 4-6 hourly doses of heparin 5,000 units for 48 h followed by warfarin (5 patients)</td>
<td>Clot lysis, PE, bleeding</td>
<td>7-10 d</td>
<td>Thrombolysis: Complete clot lysis: 3/5 (60%) Partial lysis: 1/5 (20%) No lysis: 1 (20%) PE: 0 Bleeding: 0</td>
</tr>
<tr>
<td>Robertson et al 1968</td>
<td>RCT, single center</td>
<td>16 patients with DVT</td>
<td>Thrombolysis: SK 200,000 units over 90 min, then 100,000 units as maintenance dose for 22.5 h; heparin 500 mg given during 24 h, plus prednisone (8 patients) Anticoagulation: Heparin plus prednisone (8 patients)</td>
<td>Clot lysis, bleeding</td>
<td>7 d</td>
<td>Thrombolysis: Significant lysis: 5/8 (63%) Partial lysis: 2/8 (25%) No lysis: 1/8 (12%) Bleeding: Major: 2/8 (25%) Minor: 2/8 (25%) Anticoagulation: Significant lysis: 1/8 (12%) Partial lysis: 2/8 (25%) No lysis: 5/8 (63%) Bleeding: Major: 1/8 (12%) Minor: 1/8 (12%)</td>
</tr>
<tr>
<td>Kakkar et al 1969</td>
<td>RCT, single center</td>
<td>30 patients with DVT of &lt; 4 d</td>
<td>Thrombolysis: SK 500,000 units IV over 30 min; 900,000 units every 6 h × 5 d (10 patients)</td>
<td>Clot lysis, PE, bleeding, death</td>
<td>6-12 mo</td>
<td>Thrombolysis: Complete clot lysis: 6/9 (67%) Partial lysis: 1/9 (11%) No lysis: 2/9 (22%) PE: 0 Bleeding: 4/10 (40%) Death: 2/9 (22%) Note: (1 patient excluded from treatment)</td>
</tr>
<tr>
<td>Author/Year</td>
<td>Type of Publication</td>
<td>Participants</td>
<td>Interventions</td>
<td>Outcomes</td>
<td>Follow-up</td>
<td>Results</td>
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<tr>
<td>Arvin: Arvin loading dose</td>
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<td></td>
<td>80 units IV over 6 h; 80 units over 15 min; 40-80 units every 6 h × 5 d (10 patients)</td>
<td></td>
<td></td>
<td>Arvin: Complete lysis: 1/10 (10%); Partial lysis: 3/10 (30%); No lysis: 6/10 (60%); PE: 0; Bleeding: 0; Death: 0</td>
</tr>
<tr>
<td>Anticoagulation: Heparin</td>
<td></td>
<td></td>
<td>10,000 units IV over 5 min, then 10,000-15,000 units every 6 h × 5 d (10 patients)</td>
<td></td>
<td></td>
<td>Anticoagulation: Complete clot lysis: 2/9 (22%); Partial lysis: 2/9 (22%); No lysis: 5/9 (55%); PE: 1/10; Death: 2/9 (22%); Bleeding: 2/9 (22%) Note: (1 patient excluded from treatment)</td>
</tr>
<tr>
<td>Arvin: Arvin loading dose</td>
<td></td>
<td></td>
<td>80 units IV over 6 h; 80 units over 15 min; 40-80 units every 6 h × 5 d (10 patients)</td>
<td></td>
<td></td>
<td>Arvin: Complete lysis: 1/10 (10%); Partial lysis: 3/10 (30%); No lysis: 6/10 (60%); PE: 0; Bleeding: 0; Death: 0</td>
</tr>
<tr>
<td>Anticoagulation: Heparin</td>
<td></td>
<td></td>
<td>10,000 units IV over 5 min, then 10,000-15,000 units every 6 h × 5 d (10 patients)</td>
<td></td>
<td></td>
<td>Anticoagulation: Complete clot lysis: 2/9 (22%); Partial lysis: 2/9 (22%); No lysis: 5/9 (55%); PE: 1/10; Death: 2/9 (22%); Bleeding: 2/9 (22%) Note: (1 patient excluded from treatment)</td>
</tr>
<tr>
<td>Tsapogas et al 1973</td>
<td>RCT, single center</td>
<td>34 patients with DVT of &lt; 5 d</td>
<td>Thrombolysis: titrated initial dose of SK IV, then SK 100,000 units/h maintained and adjusted up to 72 h IV heparin for 1 wk 6-12 h post SK (19 patients)</td>
<td>Clot lysis, PE, bleeding</td>
<td>7 d</td>
<td>Thrombolysis: Complete/partial lysis: 10/19 (53%); No lysis: 9/19 (47%); PE: 0; Minor bleeding: 3 (16%); Anticoagulation: Complete/partial lysis: 1/15 (7%); No lysis: 14/15 (93%); PE: 1/15 (7%); Bleeding: 0</td>
</tr>
<tr>
<td>Duckert et al 1975</td>
<td>Prospective study</td>
<td>134 patients with acute or subacute DVT</td>
<td>Thrombolysis: initial dose SK calculated according to tolerance injected over 15-30 min; maintenance dose at 30 mL/h was two-thirds of first dose (92 patients)</td>
<td>Clot lysis, PE, bleeding</td>
<td>~7 d</td>
<td>Thrombolysis: Significant lysis: 39/92 (42%); Partial lysis: 23/92 (25%); No lysis: 30/92 (33%); PE: 7 (8%); Major bleeding: 58 (62%); Minor bleeding: 24 (26%); Anticoagulation: Significant lysis: 0/42 (0%); Partial lysis: 4/42 (10%); No lysis: 38/42 (90%); PE: 5/42 (12%); Major bleeding: 2/42 (5%); Minor bleeding: 4/42 (10%)</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Publication</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porter et al 1975</td>
<td>RCT, single center</td>
<td>50 patients with DVT &lt; 14 d duration</td>
<td>Thrombolysis: SK 250,000 units IV over 30 min, then 100,000 units/h titrated for 72 h followed by IV heparin titrated over 7 d (23 patients) Anticoagulation: IV heparin 150 units/kg loading dose then titrated for 10 d (26 patients)</td>
<td>Clot lysis, PE, bleeding, death due to treatment</td>
<td>10 d</td>
<td>Thrombolysis: Complete lysis: 6/23 (26%) Partial lysis: 15/23 (65%) No lysis: 2/23 (9%) PE: 0 Bleeding: 4/23 (17%) Death: 1 (4%) Anticoagulation: Complete lysis: 1/26 (4%) Partial lysis: 20/26 (77%) No lysis: 5/26 (19%) PE: 0 Bleeding: 1/26 (4%) Death: 0</td>
</tr>
<tr>
<td>Marder et al 1977</td>
<td>RCT, single center</td>
<td>24 patients with DVT</td>
<td>Thrombolysis: initial dose of 250,000 units SK for 20 min, followed by 100,000 units/h for 72 h (12 patients) Anticoagulation: initial dose heparin 150 units/kg IV, followed by titrated infusion for 72 h Cotreatment: 100 mg bolus hydrocortisone prior to treatment</td>
<td>Clot lysis, death due to treatment</td>
<td>5 d</td>
<td>Thrombolysis: Significant lysis: 5/12 (42%) Partial lysis: 2/12 (16%) No lysis: 5/12 (42%) Death: 1/12 (8%) Anticoagulation: Significant lysis: 0/12 (0%) Partial lysis: 3/12 (25%) No lysis: 9/12 (75%) Death: 0</td>
</tr>
<tr>
<td>Arnesen et al 1978</td>
<td>RCT, single center</td>
<td>42 patients with proximal DVT of &lt; 5 d.</td>
<td>Thrombolysis: loading dose of SK 250,000 units IV, then 100,000 International Units/h IV for 72-96 h (21 patients) Anticoagulation: heparin 15,000 International Units IV bolus, then total of 30,000 International Units IV infusion for 72-90 h (21 patients)</td>
<td>Clot lysis, PE, bleeding</td>
<td>21 d-6 y</td>
<td>Thrombolysis: Significant lysis: 15/21 (71%) No lysis: 6/21 (29%) PE: 1/21 (5%) Bleeding: 2/21 (9%) Anticoagulation: Significant lysis: 5/21 (24%) No lysis: 16/21 (76%) PE: 0 Bleeding: 2/21 (9%)</td>
</tr>
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</table>

(Continued)
### Table S13—Continued

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<tr>
<th>Author/Year</th>
<th>Type of Publication</th>
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<th>Interventions</th>
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<th>Follow-up</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Elliot et al 1979</td>
<td>RCT, single center</td>
<td>51 patients with clinical history of DVT of &lt; 8 d</td>
<td>Thrombolysis: loading dose of SK 600,000 units infused over 30 min, followed by 100,000 units/h for 3 d; heparin for 4 d following SK (26 patients) Anticoagulation: heparin 10,000 units IV initially; followed by 10,000 units IV daily for a 6-h infusion to maintain clotting time of 2.5-3 times normal for 7 d (25 patients)</td>
<td>Immediate: clot lysis, PE, bleeding Long term: symptom free</td>
<td>Immediate: 5 d Long term: 19 mo (mean)</td>
<td>Immediate: Thrombolysis: Significant lysis: 17/26 (65%) Partial lysis: 1/26 (4%) No lysis: 8/26 (31%) PE: 0 Bleeding: 2 (8%) Anticoagulation: Significant lysis: 0/25 (0%) Partial lysis: 0/25 (0%) No lysis: 25/25 (100%) PE: 0 Bleeding: 2/21 (9%) Long term: Thrombolysis: Symptom-free: 12/20 (60%) Treatment 2 Symptom-free: 2/21 (9%)</td>
</tr>
<tr>
<td>Watz et al 1979</td>
<td>Prospective study</td>
<td>35 patients with DVT</td>
<td>Thrombolysis: initial dose of SK 250,000 units in 30 min, followed by maintenance 100,000 units/h (18 patients) Anticoagulation: heparin 45,000 units daily with warfarin (17)</td>
<td>Clot lysis, PE, bleeding</td>
<td>1-2 mo</td>
<td>Thrombolysis: Significant lysis: 8/18 (44%) Partial lysis: 4/18 (22%) No lysis: 6/18 (34%) PE: 1/18 (5%) Minor bleeding: 3/18 (12%) Anticoagulation: Significant lysis: 1/17 (6%) Partial lysis: 5/17 (29%) No lysis: 11/17 (65%) PE: 1/17 (6%) Minor bleeding: 2/17 (12%)</td>
</tr>
<tr>
<td>Author/Year</td>
<td>Type of Publication</td>
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<td>Outcomes</td>
<td>Follow-up</td>
<td>Results</td>
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</tr>
<tr>
<td>Kiil et al/1981</td>
<td>RCT, single center</td>
<td>20 patients with DVT of &lt;7 h</td>
<td>Thrombolysis: streptokinase 200,000 units IV for 24 h; after 18 h, heparin loading dose of 15,000 units, then 40,000 units/d for 5 d (11 patients). Anticoagulation: heparin 40,000 units/day 4 for 6 d (9 patients).</td>
<td>Clot lysis, PE, bleeding</td>
<td>2 wk</td>
<td>Thrombolysis: Partial lysis: 1/11 (9%) No lysis: 10/11 (91%) PE: 0 Bleeding: 3/11 (27%) Anticoagulation: Partial lysis: 1/8 (12%) No lysis: 7/8 (88%) PE: 0 Bleeding: 3/9 (33%) Note: 1 patient excluded from group</td>
</tr>
<tr>
<td>Arnesen et al/1982</td>
<td>Follow-up to RCT of Arnesen (1978)</td>
<td>35/42 patients from RCT</td>
<td>Phlebography and clinical examination by blinded evaluators</td>
<td>Normal legs, PTS symptoms</td>
<td>6.5 y</td>
<td>Thrombolysis: Normal legs: 13/17 (77%) PTS symptoms (moderate): 4/17 (24%) Anticoagulation: Normal legs: 6/18 (33%) PTS symptoms (moderate): 9/18 (50%)</td>
</tr>
<tr>
<td>Schulman et al/1986</td>
<td>RCT, single center</td>
<td>36 patients with calf DVT of &lt;7 d</td>
<td>Thrombolysis: SK 50,000 International Units IV over 15 min, then 100,000 International Units over 12 h for up to 7 d, titrated; given with heparin 5,000 International Units IV over 12 h (17 patients). Anticoagulation: heparin 5,000 International Units IV for 15 min then 30,000 International Units/d, titrated over 7 d (19 patients).</td>
<td>Clot lysis, bleeding, PE</td>
<td>5 y</td>
<td>Thrombolysis: Complete lysis: 7/17 (41%) Bleeding: 3/17 (18%) PE: 0 Anticoagulation: Complete lysis: 2/19 (10%) Bleeding: 1/19 (5%) PE: 0</td>
</tr>
<tr>
<td>Verhaeghe et al/1989</td>
<td>Prospective cohort study (A) and multicenter RTC (B)</td>
<td>32 patients with DVT of &lt;10 d</td>
<td>Study A: open-label study with rt-PA 100 mg over IV 8 h (day 1), 50 mg rt-PA over 8 h (day 2); 10% dose as bolus (11 patients).</td>
<td>Clot lysis, bleeding</td>
<td>72 h</td>
<td>Note: Authors assigned veins a relative value reflecting degree of thrombosis (maximum, 40 units: complete thrombosis). The unit scores reflect the reduction in thrombosis postlysis.</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Study A</th>
<th>Study B</th>
<th>Placebo</th>
<th>Co-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in unit score:</td>
<td>rt-PA 100 mg:</td>
<td>Change in unit score:</td>
<td>rt-PA 50 mg:</td>
</tr>
<tr>
<td>-3.2</td>
<td>Change in unit score:</td>
<td>rt-PA 100 mg:</td>
<td>rt-PA 50 mg:</td>
</tr>
<tr>
<td>Bleeding: 6</td>
<td>Change in unit score:</td>
<td>24.3</td>
<td>Change in unit score:</td>
</tr>
<tr>
<td>Bleeding: 0</td>
<td>Bleeding: 3</td>
<td>Bleeding: 0</td>
<td>Bleeding: 0</td>
</tr>
<tr>
<td>rt-PA: rt-PA 0.05 mg/kg per h</td>
<td>rt-PA: rt-PA 0.05 mg/kg per h</td>
<td>rt-PA: rt-PA 0.05 mg/kg per h</td>
<td>rt-PA + heparin:</td>
</tr>
<tr>
<td>IV for 24 h, then heparin 100 units/kg bolus, then 1,000 units/h, adjusted</td>
<td>rt-PA 0.05 mg/kg per h</td>
<td>rt-PA 0.05 mg/kg per h</td>
<td>Complete lysis:</td>
</tr>
<tr>
<td>(36 patients)</td>
<td>IV for 24 h, then heparin 100 units/kg bolus, then 1,000 units/h, adjusted (36 patients)</td>
<td>IV for 24 h, then heparin 100 units/kg bolus, then 1,000 units/h, adjusted (36 patients)</td>
<td>Partial lysis: 18/32 (57%)</td>
</tr>
<tr>
<td>rt-PA + heparin: rt-PA as in group 1 plus heparin concurrently (17 patients)</td>
<td>rt-PA + heparin: rt-PA as in group 1 plus heparin concurrently (17 patients)</td>
<td>rt-PA + heparin: rt-PA as in group 1 plus heparin concurrently (17 patients)</td>
<td>No lysis: 12/32 (38%)</td>
</tr>
<tr>
<td>Anticoagulation: heparin</td>
<td>Anticoagulation: heparin</td>
<td>Anticoagulation: heparin</td>
<td>Bleeding: 1/32 (3%)</td>
</tr>
<tr>
<td>100 units/kg bolus, then 1,000 units/h (12 patients)</td>
<td>100 units/kg bolus, then 1,000 units/h (12 patients)</td>
<td>100 units/kg bolus, then 1,000 units/h (12 patients)</td>
<td>rt-PA + heparin:</td>
</tr>
<tr>
<td>Clot lysis, bleeding</td>
<td>Clot lysis, bleeding</td>
<td>Clot lysis, bleeding</td>
<td>Complete lysis:</td>
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<tr>
<td>36 h</td>
<td>36 h</td>
<td>36 h</td>
<td>Partial lysis:</td>
</tr>
<tr>
<td>rt-PA:</td>
<td>rt-PA:</td>
<td>rt-PA:</td>
<td>rt-PA:</td>
</tr>
<tr>
<td>Complete lysis: 2/32 (6%)</td>
<td>Complete lysis: 1/17 (6%)</td>
<td>Complete lysis: 1/17 (6%)</td>
<td>Complete lysis:</td>
</tr>
<tr>
<td>Partial lysis: 18/32 (57%)</td>
<td>Partial lysis: 8/17 (48%)</td>
<td>Partial lysis: 8/17 (48%)</td>
<td>Partial lysis:</td>
</tr>
<tr>
<td>No lysis: 12/32 (38%)</td>
<td>No lysis: 8/17 (48%)</td>
<td>No lysis: 8/17 (48%)</td>
<td>No lysis:</td>
</tr>
<tr>
<td>Bleeding: 1/32 (3%)</td>
<td>Bleeding: 0</td>
<td>Bleeding: 0</td>
<td>Bleeding:</td>
</tr>
<tr>
<td>rt-PA + heparin:</td>
<td>rt-PA + heparin:</td>
<td>rt-PA + heparin:</td>
<td>rt-PA + heparin:</td>
</tr>
<tr>
<td>Complete lysis:</td>
<td>Complete lysis:</td>
<td>Complete lysis:</td>
<td>Complete lysis:</td>
</tr>
<tr>
<td>Partial lysis: 18/32 (57%)</td>
<td>Partial lysis: 8/17 (48%)</td>
<td>Partial lysis: 8/17 (48%)</td>
<td>Partial lysis:</td>
</tr>
<tr>
<td>No lysis: 12/32 (38%)</td>
<td>No lysis: 8/17 (48%)</td>
<td>No lysis: 8/17 (48%)</td>
<td>No lysis:</td>
</tr>
<tr>
<td>Bleeding: 1/32 (3%)</td>
<td>Bleeding: 0</td>
<td>Bleeding: 0</td>
<td>Bleeding:</td>
</tr>
<tr>
<td>Note: 5/65 venograms not analyzed</td>
<td>Note: 5/65 venograms not analyzed</td>
<td>Note: 5/65 venograms not analyzed</td>
<td>Note: 5/65 venograms not analyzed</td>
</tr>
<tr>
<td>Author/Year</td>
<td>Type of Publication</td>
<td>Participants</td>
<td>Interventions</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------</td>
<td>--------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Turpie et al/1990</td>
<td>RCT, multicenter</td>
<td>83 patients with DVT of &lt;7 d</td>
<td>Phase 1: Lysis + heparin: two-chain rt-PA 0.5 mg/kg IV for 4 h (12 patients)</td>
</tr>
<tr>
<td></td>
<td>Placebo + heparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phase 2: Lysis + heparin: one-chain rt-PA 0.5 mg/kg IV for 8 h and repeated in 24 h (29 patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo + heparin (30 pts)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cotreatment: heparin</td>
<td>5,000-unit IV bolus then 30,000 units/24 h, adjusted for 7-10 d</td>
</tr>
<tr>
<td>Schweizer et al/1998</td>
<td>RCT, single center</td>
<td>69 patients with DVT of &lt;7 d</td>
<td>rt-PA 20 mg IV into pedal vein 4 h/d for 7 d; heparin IV given concomitantly; warfarin day 7-12 mo; Urokinase 100,000 International Units/hr IV into pedal vein continuously 7 d; heparin IV 7 d; plasminogen monitored; warfarin day 7-12 mo</td>
</tr>
<tr>
<td>Author/Year</td>
<td>Type of Publication</td>
<td>Participants</td>
<td>Interventions</td>
</tr>
<tr>
<td>-------------</td>
<td>---------------------</td>
<td>--------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Schweizer et al 2000</td>
<td>RCT, multicenter</td>
<td>250 patients with DVT of &lt; 9 d</td>
<td>rt-PA: locoregional rt-PA 20 mg/day for 4 h through pedal vein for 4–7 d; IV heparin given simultaneously at 1,000 International Units/h, adjusted</td>
</tr>
</tbody>
</table>

See Table S1, S2, and S11 legends for expansion of abbreviations.

* Four deaths, other causes, two lost to follow-up.
* Four deaths, two PEs, two other causes.
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Randomization</th>
<th>Allocation concealment</th>
<th>Blinding</th>
<th>Loss to follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Browse et al 1968</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0</td>
</tr>
<tr>
<td>Robertson et al 1968</td>
<td>Patients given consecutive code numbers and divided into equal groups of 2—not truly randomized</td>
<td>Labels on SK and heparin coded</td>
<td>Y, data assessors, unclear for patients, caregivers, analysts</td>
<td>0</td>
</tr>
<tr>
<td>Kakkar et al 1969</td>
<td>Sequential sealed envelope</td>
<td>Adequate</td>
<td>Y, patients No, caregivers, assessors, analysts</td>
<td>0</td>
</tr>
<tr>
<td>Tsapogas et al 1973</td>
<td>Sealed envelope</td>
<td>Adequate</td>
<td>Not blinded</td>
<td>0</td>
</tr>
<tr>
<td>Duckert et al 1975</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Porter et al 1975</td>
<td>Assigned at random to one of two groups</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Marder et al 1977</td>
<td>Assigned at random to one of two groups. Five-day follow-up venograms were not performed in 3 of the SK patients, so an additional 3 patients were added to SK group in nonrandomized fashion.</td>
<td>Unclear</td>
<td>Not blinded</td>
<td>23</td>
</tr>
<tr>
<td>Arnesen et al 1978</td>
<td>Assigned at random to either group by sealed envelope</td>
<td>Adequate</td>
<td>Y, radiologic assessors No, patients, caregivers, analysts</td>
<td>0</td>
</tr>
<tr>
<td>Elliot et al 1979</td>
<td>Assigned at random to one of two groups</td>
<td>Unclear</td>
<td>Y, assessors N, patients, caregivers, analysts</td>
<td>N/A</td>
</tr>
<tr>
<td>Watz et al 1979</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Kiil et al 1981</td>
<td>Assigned at random to either group</td>
<td>Unclear</td>
<td>Y, assessors N, patients, caregivers</td>
<td>0</td>
</tr>
<tr>
<td>Arnesen et al 1982</td>
<td>N/A</td>
<td>N/A</td>
<td>Evaluator blinded</td>
<td>7</td>
</tr>
<tr>
<td>Schulman et al 1986</td>
<td>Assigned at random to either group by sealed envelope</td>
<td>Adequate</td>
<td>Single blind</td>
<td>0</td>
</tr>
<tr>
<td>Verhaeghe et al 1989</td>
<td>Assigned at random to one of three groups</td>
<td>Unclear</td>
<td>Y, patients, assessors N, caregivers, analysts</td>
<td>0</td>
</tr>
<tr>
<td>Goldhaber et al 1990</td>
<td>Assigned at random to one of three groups through sealed envelope</td>
<td>2:2:1 allocation scheme</td>
<td>Not blinded</td>
<td>0</td>
</tr>
<tr>
<td>Turpie et al 1990</td>
<td>Assigned at random to one of two groups in each phase of study</td>
<td>Unclear</td>
<td>Y, patients, assessors N, caregivers, analysts</td>
<td>37</td>
</tr>
<tr>
<td>Schweizer et al 1998</td>
<td>Assigned at random to one of three groups</td>
<td>Adequate</td>
<td>Y, assessors N, patients, caregivers, analysts</td>
<td>1</td>
</tr>
<tr>
<td>Schweizer et al 2000</td>
<td>Assigned at random to one of five groups</td>
<td>Unclear</td>
<td>Single blind—not sure who</td>
<td>12</td>
</tr>
</tbody>
</table>

Y = yes. See Table S5 and S12 legends for expansion of other abbreviations.
Table S15—[Section 2.10] Evidence Profile: Systemic Lysis vs No Systemic Lysis for Extensive Acute DVT of the Leg

<table>
<thead>
<tr>
<th>Study Event Rates (%)</th>
<th>Quality Assessment</th>
<th>Summary of Findings</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Participants</td>
<td>With No Systemic Lysis</td>
<td>With Systemic Lysis</td>
</tr>
<tr>
<td>Risk of Bias Inconsistency Indirectness Imprecision Publication Bias Overall Quality of Evidence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality (important outcome)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>688 (5 studies), 3 mo&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No serious risk of bias&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No serious inconsistency</td>
<td>No serious indirectness&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nonfatal recurrent VTE (critical outcome)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>687 (3 studies), 3 mo&lt;sup&gt;f&lt;/sup&gt;</td>
<td>No serious risk of bias&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No serious inconsistency</td>
<td>No serious indirectness&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nonfatal major bleeding (critical outcome)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>688 (10 studies), 3 mo&lt;sup&gt;f&lt;/sup&gt;</td>
<td>No serious risk of bias&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No serious inconsistency</td>
<td>No serious indirectness&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Participants (Studies), Follow-up</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication Bias</th>
<th>Overall Quality of Evidence</th>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>With No Systemic Lysis</td>
<td>With Systemic Lysis</td>
<td>Relative Effect (95% CI)</td>
<td>Risk With No Systemic Lysis</td>
<td>Risk Difference</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postthrombotic syndrome (critical outcome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 y&lt;sup&gt;k&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;m&lt;/sup&gt;</td>
<td>No serious inconsistency</td>
<td>No serious indirectness&lt;sup&gt;l&lt;/sup&gt;</td>
<td>Undetected Low&lt;sup&gt;e&lt;/sup&gt;-&lt;sup&gt;l&lt;/sup&gt;-&lt;sup&gt;1&lt;/sup&gt;-&lt;sup&gt;m&lt;/sup&gt;-&lt;sup&gt;1&lt;/sup&gt;-&lt;sup&gt;n&lt;/sup&gt;-&lt;sup&lt;k&gt; due to risk of bias, imprecision</td>
<td>24/230 (10.4)</td>
<td>27/448 (6)</td>
<td>RR 0.71 (0.49-1.04)</td>
<td>588 per 1,000= 171 fewer per 1,000 (from 300 fewer to 24 more)&lt;sup&gt;j&lt;/sup&gt;</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of life not measured</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bibliography: Watson et al.<sup>47</sup> We excluded Elsharawy et al.<sup>36</sup> from the analysis because it used catheter directed thrombolysis.<sup>5</sup> We identified no studies published since the search date of the systematic review. See Table S1, S10, and S11 legends for expansion of abbreviations.

<sup>a</sup>Range of follow-up in included studies, 1 to 72 mo.
<sup>b</sup>Allocation concealed in three of five studies. Follow-up inadequate in one of five (Common et al.<sup>50</sup>). Excluding this study from the analysis does not change the effect estimate. All studies had blinded outcome assessors. None of the studies used a placebo control.
<sup>c</sup>The population of one study (Schulman et al.<sup>49</sup>) consisted of patients with calf vein thrombosis.
<sup>d</sup>Interventions varied across studies with regard to agent (eg, tPA, SK, urokinase), dose, use of the pedal vein administration, duration of treatment, and concomitant drugs (eg, steroids). However, we did not downgrade for indirectness given that there is no standard regimen, and all analyses showed no heterogeneity in results.
<sup>e</sup>CI included both no effect and a potentially significant effect.
<sup>f</sup>Range of follow-up in included studies, 1 to 30 d.
<sup>g</sup>Allocation concealed in two of three studies. Follow-up adequate in all studies. All studies had blinded outcome assessors. None of the studies used a placebo control.
<sup>h</sup>Baseline risks for nonfatal recurrent VTE and for major bleeding derived from Douketis et al.<sup>39</sup>. Allocation concealed in seven of 10 studies. Follow-up inadequate in one 10 studies (Common et al.<sup>50</sup>). Excluding this study from the analysis does not affect the effect estimate. All studies had blinded outcome assessors. Two studies used placebo (Turpie et al.; Verhaeghe et al.<sup>51</sup>).
<sup>i</sup>Only 4% of all major bleeding events were intracranial bleeds.
<sup>j</sup>Range of follow-up in included studies: 1 to 6 y.
<sup>k</sup>Allocation concealed in two of two studies. Follow-up adequate in all studies. All studies had blinded outcome assessors. None of the studies used placebo control.
<sup>l</sup>No use of a standardized validated tool reported.
<sup>m</sup>Only 4% of all major bleeding events were intracranial bleeds.
<sup>n</sup>This estimate is based on the findings of the VETO (Venous Thrombosis Outcomes) study. This probably underestimates PTS baseline risk given that overall, 52% of patients reported the current use of compression stockings during study follow-up.
<sup>o</sup>Severe PTS: assuming the same RR of 0.71 and a baseline risk of 13.8%, the absolute reduction is 40 fewer severe PTS per 1,000 (from 70 fewer to 6 more) over 2 y.
Table S16—Evidence Profile: Surgical Thrombectomy Vs No Surgical Thrombectomy for Extensive Acute DVT of the Leg

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Summary of Findings</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Event Rates (%)</td>
<td>With No Surgical Thrombectomy</td>
<td>With Surgical Thrombectomy</td>
</tr>
<tr>
<td>Participants (Studies), Follow-up</td>
<td>Risk of Bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Mortality not reported</td>
<td>…</td>
<td>…</td>
</tr>
</tbody>
</table>

Nonfatal recurrent VTE (critical outcome)

| 51 (1 study), 3 mo | Serious<sup>b</sup> | No serious inconsistency | No serious indirectness | Very serious<sup>c</sup> | Undetected | Low<sup>c</sup> due to risk of bias, imprecision | 1/27 (3.7)<sup>f</sup> | 0/24 (0) | RR 0.37 (0.02-8.73) | 48 per 1,000<sup>c</sup> | 30 fewer per 1,000 (from 47 fewer to 372 more) | … |

Nonfatal major bleeding (critical outcome)

| 51 (1 study), 3 mo | Serious<sup>b</sup> | No serious inconsistency | No serious indirectness | Very serious<sup>c</sup> | Undetected | See comment | 0/27 (0) | 0/24 (0)<sup>f</sup> | Not estimable | See comment | … |

PTS (critical outcome)

| 51 (1 study), 2 y | Serious<sup>c</sup> | No serious inconsistency | No serious indirectness | Serious<sup>b</sup> | Undetected | Low<sup>c</sup> due to risk of bias, imprecision | 25/27 (92.6) | 14/24 (58.3) | RR 0.63 (0.44-0.9) | 588 per 1,000<sup>c</sup> | 218 fewer per 1,000 (from 59 fewer to 329 fewer)<sup>b</sup> | … |

Quality of life not measured

| … | … | … | … | … | … | … | … | … | … |

Bibliography: Plate et al.<sup>67</sup> See Table S1, S5, and S10 legends for expansion of abbreviations.

<sup>a</sup>The study included patients with DVT with symptoms of leg swelling not exceeding 7 d and a proximal extension of the thrombus above the inguinal ligament, but not into the vena cava.

<sup>b</sup>Not clear whether allocation was concealed. No blinding reported. Not clear whether analysis was ITT. Follow-up rate 88% at 6 mo. Study not stopped early for benefit.

<sup>c</sup>CI includes values suggesting either harm or benefit.

<sup>d</sup>One event, which was a symptomatic PE.

<sup>e</sup>Baseline risks for nonfatal recurrent VTE derived from Douketis et al.<sup>39</sup>

<sup>f</sup>No severe bleeding complications were recorded in either group. Three patients in thrombectomy group developed local wound hematoma.

<sup>g</sup>In addition to other study limitations, this outcome was assessed by those who did the surgery and anticoagulation. No standardized tool was used. One surgical patient had an amputation secondary to venous gangrene and was not counted in the PTS assessment.

<sup>h</sup>Few number of events. This warrants rating down the quality of evidence by a second level when considered along with study limitations.

<sup>i</sup>The RR is based on the 6-mo data.

<sup>j</sup>This estimate is based on the findings of the VETO (Venous Thrombosis Outcomes study.<sup>40</sup> This probably underestimates PTS baseline risk given that overall, 52% of patients reported the current use of compression stockings during study follow-up.

<sup>k</sup>Severe PTS: assuming the same RR of 0.63 and a baseline risk of 13.8% over 2 y,<sup>40</sup> the absolute reduction is 51 fewer severe PTS per 1,000 (from 14 fewer to 77 fewer) over 2 y.
Table S17  —  [Section 2.11] Surgical Thrombectomy vs No Surgical Thrombectomy for Extensive Acute DVT of the Leg: Clinical Description and Results
(All Randomized Trials and Prospective Observational Studies of at Least 20 Patients)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Publication</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plate et al® 1984</td>
<td>RCT, multicenter</td>
<td>58 patients with acute iliofemoral venous thrombosis</td>
<td>Medical: 5,000-unit bolus heparin followed by 500 units/kg per 24 h adjusted to aPTT, and oral anticoagulation (31 patients)</td>
<td>PTS sequelae: iliofemoral patency, valve competence</td>
<td>6 mo</td>
<td>Medical: PTS sequelae: 25/27 (93%) Iliofemoral patency: 9/26 (35%) Valve competence: 7/27 (26%) (PE in 1 patient) Surgical: PTS sequelae: 14/24 (58%, P &lt; .005) Iliofemoral patency: 16/21 (76%, P &lt; .025) Valve competence: 13/23, (52% P &lt; .05) (venous gangrene in 1 patient)</td>
</tr>
<tr>
<td>Einarsson et al® 1986</td>
<td>Prospective registry</td>
<td>70 patients (71 legs) with iliofemoral DVT (age of clot mean, 3 d)</td>
<td>Iliofemoral venous thrombectomy with temporary AVF closed at 6-8 wk, heparin preoperatively and postoperatively plus warfarin postoperatively</td>
<td>Venous patency, hematoma, AVF patency, PE, wound infection</td>
<td>56 d (mean)</td>
<td>Patent iliac vein: 88% Hematoma: 11% AVF patency: 86% PE: 4% Wound infection: 26%</td>
</tr>
<tr>
<td>Einarsson et al® 1986</td>
<td>Prospective registry</td>
<td>57 patients (58 limbs) with prior operative venous thrombectomy and AVF closed at 6-8 wk for iliofemoral DVT</td>
<td>Clinical PTS, venography, venous pressure, venous plethysmography, foot volumetry</td>
<td>Venous insufficiency: Good, fair, poor</td>
<td>9-10 mo</td>
<td>Venous insufficiency: Good: 75% Fair: 20% Poor: 5%</td>
</tr>
<tr>
<td>Venography (vein segment): Normal, postthrombotic, occluded</td>
<td>Venography (iliofemoral): Normal: 61% Postthrombotic: 23% Occluded: 39%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous pressure: Normal, abnormal</td>
<td>IV pressure: Normal: 82% Abnormal: 18%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plethysmography: Normal, abnormal</td>
<td>Plethysmography: Normal: 29% Abnormal: 71%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foot volumetry: Normal, abnormal</td>
<td>Foot volumetry: Normal: 29% Abnormal: 71%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plate et al® 1990</td>
<td>Five-year follow-up to RCT (Plate, 1984®)</td>
<td>41/58 patients (22 medical, 19 surgical) available for evaluation at 5 y</td>
<td>Prior treatment: Medical: anticoagulation alone vs Surgical: operative venous thrombectomy plus anticoagulation</td>
<td>PTS sequelae, iliac patency, venous pressure</td>
<td>5 y</td>
<td>Medical: PTS sequelae: 6/22 (27%) Iliac patency: 11/22 (50%) Venous pressure: 60 mm Hg (mean)</td>
</tr>
<tr>
<td>Author/Year</td>
<td>Type of Publication</td>
<td>Participants</td>
<td>Interventions</td>
<td>Outcomes</td>
<td>Follow-up</td>
<td>Results</td>
</tr>
<tr>
<td>-------------</td>
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<td>---------</td>
</tr>
<tr>
<td>Neglén et al/1991</td>
<td>Prospective registry</td>
<td>48 patients with iliofemoral DVT of 1-14 d</td>
<td>Operative venous thrombectomy with temporary AVF (closed 6-12 wk postoperative)</td>
<td>Patency, PE, clinical symptoms, normal photoplethysmography, successful AVF closure</td>
<td>24 mo (mean)</td>
<td>Surgical: PTS sequelae: 2/19 (11%) Iliac patency: 15/19 (78%) Venous pressure: 43 mm Hg (mean, ( P &lt; .05 ))</td>
</tr>
<tr>
<td>Plate et al/1997</td>
<td>Ten-year follow-up to RCT (Plate, 1984 [10] and 1990 [20])</td>
<td>30/38 patients (17 from medical arm, 13 from surgical arm) available for evaluation</td>
<td>Prior treatment Medical: anticoagulation alone vs Surgical: operative venous thrombectomy plus anticoagulation</td>
<td>PTS sequelae, iliac patency, venous pressure</td>
<td>10 y</td>
<td>Medical: PTS sequelae: 15/17 (88%) Iliac patency: 7/17 (41%) Venous pressure: 63 mm Hg (mean) Surgical: PTS sequelae: 7/13 (54%) Iliac patency: 10/12 (83%) Venous pressure: 55 mm Hg (mean)</td>
</tr>
</tbody>
</table>

Early prospective observational studies with <20 patients and retrospective studies are described in Table 5 of the eighth edition of these guidelines. See Table S1, S2, S4, S10, and S11 legends for expansion of abbreviations.
### Table S18—[Section 2.11] Surgical Thrombectomy vs No Surgical Thrombectomy for Extensive Acute DVT of the Leg: Methodologic Quality

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Randomization</th>
<th>Allocation Concealment</th>
<th>Blinding</th>
<th>Loss to Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plate et al/1984</td>
<td>ND</td>
<td>PN</td>
<td>N, patients, caregivers, assessors, and data analysts</td>
<td>7</td>
</tr>
<tr>
<td>Einarsson et al/1986</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Einarsson et al/1986</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Plate et al/1990</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>17</td>
</tr>
<tr>
<td>Neglén et al/1991</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Plate et al/1997</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>28</td>
</tr>
</tbody>
</table>

See Table S5 and S12 legends for expansion of abbreviations.
### Table S19 — [Section 2.13] Evidence Profile: Vena Cava Filter vs No Vena Cava Filter for Acute Proximal DVT of the Leg Treated With Anticoagulation

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With No Vena Cava Filters</td>
<td>With Vena Cava Filters</td>
</tr>
<tr>
<td>Participants (Studies), Follow-up</td>
<td>Risk of Bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td><strong>Mortality</strong> (important outcome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 (1 study), 8 y</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
</tr>
<tr>
<td><strong>Symptomatic PE</strong> (critical outcome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>304 (1 study), 8 y</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
</tr>
<tr>
<td><strong>Recurrent DVT</strong> (important outcome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>310 (1 study), 8 y</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
</tr>
<tr>
<td><strong>Major bleeding</strong> (important outcome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>337 (1 study), 8 y</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
</tr>
</tbody>
</table>

(Continued)
### Table 19—Continued

<table>
<thead>
<tr>
<th>Participants (Studies), Follow-up</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication Bias</th>
<th>Overall Quality of Evidence</th>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>With No Vena Cava Filters</td>
<td>With Vena Cava Filters</td>
<td>Relative Risk</td>
<td>Risk With No Vena Cava Filters</td>
<td>Risk Difference (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTS (important outcome)</td>
<td>308 (1 study), 8 y</td>
<td>Serious</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious</td>
<td>Undetected Low-d due to risk of bias, imprecision</td>
<td>107/153 (69.9)</td>
<td>109/155 (70.3)</td>
</tr>
<tr>
<td>Complications (important outcome)</td>
<td>379 (1 study), 2 y</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious</td>
<td>Undetected Moderate-e due to imprecision</td>
<td>0/186 (0)</td>
<td>0/193 (0)</td>
</tr>
</tbody>
</table>

**Bibliography:**
Decousus et al, The PREPIC Investigators. See Table S1, S2, S5, and S10 legends for expansion of abbreviations.

| Four types of permanent vena cava filters were used: Vena Tech LGM (B. Braun Melsungen AG), titanium Greenfield (Boston Scientific Corporation), Cardial (C.R. Bard, Inc), and Bird’s Nest (Cook Group Incorporated).
| Anticoagulation consisted of LMWH or UFH initially (according to a 2 × 2 factorial design) followed by oral anticoagulation for at least 3 mo.
| Allocation concealed. Data collectors and outcome adjudicators blinded. ITT analysis. Data missing for 4% at 2 y and 1% at 8 y. Enrollment was stopped at 400 instead of targeted 800 due to slow recruitment.
| CI includes both negligible effect and appreciable benefit or appreciable harm.
| RR, 1.0 (95% CI, 0.29-3.4) at 12 d; RR, 1.08 (95% CI, 0.73-1.58) at 2 y.
| Small number of events.
| RR, 0.23 (95% CI, 0.05-1.05) at 12 d (both symptomatic and asymptomatic PE). RR, 0.54 (95% CI, 0.21-1.41) at 2 y (symptomatic PE)
| RR, 1.78 (95% CI, 1.09-2.94) at 2 y.
| RR, 1.5 (95% CI, 0.54-4.14) at 12 d. RR, 0.74 (95% CI, 0.41-1.36) at 2 y.
| No standardized validated tool used to measure PTS.
| No complications directly related to the filter or its insertion reported in the PREPIC (Prevention du Risque d’Embolie Pulmonaire par Interruption Cave) trial. Mismetti et al (prospective study) reported an incidence of 3.2% (excluding filter tilting and puncture site hematoma) among 220 patients receiving retrievable vena cava filter for secondary prevention of VTE, whereas while Athanasoulis et al (retrospective study) reported an incidence of 0.3% for major complications among 1,731 patients receiving vena cava filters predominantly for secondary prevention of VTE.
Table S20—[Section 2.14] Evidence Profile: Early Ambulation vs Delayed Ambulation for Acute DVT of the Leg\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Participants (Studies), Follow-up</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Publication Bias</th>
<th>Overall Quality of Evidence</th>
<th>Study Event Rates (%)</th>
<th>Summary of Findings</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (important outcome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>385 (4 studies), 3 mo\textsuperscript{c}</td>
<td>Serious\textsuperscript{d}</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Very serious\textsuperscript{e}</td>
<td>Undetected</td>
<td>Low\textsuperscript{f} due to risk of bias, imprecision</td>
<td>2/186 (1.1)</td>
<td>3/199 (1.5)</td>
</tr>
<tr>
<td>PE (critical outcome; assessed with symptomatic or asymptomatic PE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>385 (4 studies), 4-12 d</td>
<td>Serious\textsuperscript{d}</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious\textsuperscript{e}</td>
<td>Undetected</td>
<td>Low\textsuperscript{f} due to risk of bias, imprecision</td>
<td>22/186 (11.8)</td>
<td>27/199 (13.6)</td>
</tr>
<tr>
<td>Quality of life (important outcome; measured with quality of life questionnaire in chronic limb venous insufficiency [CIVIQ]; better indicated by lower values)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>53 (1 study), 2 y</td>
<td>Serious\textsuperscript{d}</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Undetected</td>
<td>Low\textsuperscript{f} due to risk of bias, indirectness</td>
<td>17</td>
<td>36</td>
<td>-</td>
</tr>
<tr>
<td>PTS (important outcome; assessed with Villata-Prandoni score [value &gt;5])</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37 (1 study) 2 y</td>
<td>Serious\textsuperscript{d}</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious\textsuperscript{e}</td>
<td>Undetected</td>
<td>Low\textsuperscript{f} due to risk of bias, imprecision</td>
<td>9/11 (81.8)</td>
<td>14/26 (53.8)</td>
</tr>
</tbody>
</table>

Bibliography: Kahn et al,\textsuperscript{76} Aissaoui et al.\textsuperscript{77} Included studies.\textsuperscript{78-82} See Table S1, S2, S5, and S10 legend expansion of other abbreviations.

\textsuperscript{a}In two of four eligible trials, all patients received early compression therapy (bandages or stockings). In the two other trials, only patients randomized to early ambulation received early compression therapy.

\textsuperscript{b}Two of four eligible studies excluded patients with symptomatic PE; in the third study, 24% of participants had symptomatic PE at baseline. It was not clear whether the fourth study excluded patients with symptomatic PE.

\textsuperscript{c}Three studies reporting acute phase mortality reported no deaths.

\textsuperscript{d}Concealment of allocation reported in one of four studies; blinding of outcome assessors reported in two of four studies; ITT analysis reported in two of four studies. Follow-up 97%-100%. In two of four trials, only patients randomized to early ambulation received early compression therapy (bandages or stockings). In the two other trials, all patients received early compression therapy.

\textsuperscript{e}CI includes both values of clinically significant benefit and values of clinically significant harms.

\textsuperscript{f}PE assessed as both symptomatic and asymptomatic PE.

\textsuperscript{g}Funnel plot reported as not asymmetrical by Aissaoui et al.\textsuperscript{77}

\textsuperscript{h}Concealment of allocation not reported, outcome assessors not blinded for this outcome; 70% follow-up rate; compression stockings used on patients with early mobilization but in patients with delayed mobilization.

\textsuperscript{i}No explanation was provided.

\textsuperscript{j}Psychologic and overall somatic quality of life did not differ significantly between the treatment groups, whereas DVT-related items, especially those reflecting the ease of locomotion, showed significantly greater improvement with compression than with bed rest (P < .001 for bandages, P < .05 for stockings).
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Publication</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schellong et al 1999</td>
<td>RCT, single center</td>
<td>126 patients with acute proximal DVT</td>
<td>Ambulation: leg elevation until day 2, then ambulation and compression (64 patients)</td>
<td>PE by V/Q scan</td>
<td>10 d</td>
<td>Ambulation: PE: 10/59 (17%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bed rest for 8 d with leg elevation and compression (62 patients)</td>
<td></td>
<td></td>
<td>Bed Rest: PE: 14/63 (22%)</td>
</tr>
<tr>
<td>Partsch et al 2000</td>
<td>RCT, multicenter</td>
<td>45 patients with proximal DVT &lt; 14 d duration</td>
<td>Ambulation + bandages: inelastic Unna boot bandages plus walking exercises (15 patients)</td>
<td>Walking distance, pain levels, leg circumference, clinical scores, PE, side effects</td>
<td>9 d</td>
<td>Summary results between groups: Walking distance, pain, leg circumference and clinical scores significantly improved in groups A and B compared with group C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ambulation + stockings: elastic compression stockings plus walking exercises (15 patients)</td>
<td></td>
<td></td>
<td>PE, group A: 2/15 (13%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bed rest, no compression, LMWH (15 patients)</td>
<td></td>
<td></td>
<td>PE, group B: 1/15 (7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PE, group C: 1/15 (7%)</td>
</tr>
<tr>
<td>Aschwanden et al 2001</td>
<td>RCT, single center</td>
<td>129 patients with acute DVT</td>
<td>Ambulation ≥ 4 h/d for 4 d under supervision, LMWH (69 patients) Bed rest for 4 d (60 patients)</td>
<td>New PE between baseline and day 4 by V/Q scan</td>
<td>3 mo</td>
<td>Ambulation: PE: 10/69 (14%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bed rest: PE: 6/60 (10%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Note: new PEs were asymptomatic; 12/16 patients had baseline PEs</td>
</tr>
<tr>
<td>Partsch et al 2001</td>
<td>Prospective study</td>
<td>1,289 patients with acute DVT</td>
<td>All treated with LMWH, compression, and immediate ambulation</td>
<td>PE on V/Q scan at admission and after 10 d of treatment,</td>
<td>10 d</td>
<td>PE at admission: 629/1,270 (50%) PE at 10 d: 77/1,256 (61%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Note: initial lung scans were performed in 1,270/1,289 patients; follow-up scans were performed in 1,256/1,289 patients</td>
</tr>
<tr>
<td>Blättler et al 2003</td>
<td>RCT</td>
<td>53 patients with proximal DVT</td>
<td>Ambulation + bandages: firm inelastic bandages, ambulation (18 patients) Ambulation + stockings: elastic compression stockings, ambulation (18 patients)</td>
<td>Walking distance, well-being, and DVT-related quality of life, leg pain by visual analog scale, edema, clinical scores, thrombus progression</td>
<td>9 d</td>
<td>Well-being/quality of life: Improved with stockings (P &lt; .05), bandages (P &lt; .01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Leg pain: Decreased faster during first 4 d w/ bandages and stockings vs bed rest (P &lt; .01); near absence of pain at 9 d achieved with bandages only</td>
</tr>
</tbody>
</table>

(Continued)
Table S21—Continued

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Publication</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partsch et al/2004</td>
<td>2-y follow-up to RCT (77)</td>
<td>37 patients followed up 2 y post-RCT</td>
<td>Anticoagulation and bed rest vs anticoagulation and ambulation with compression bandages or stockings</td>
<td>PTS assessment (Villalta-Prandoni scale)</td>
<td>2 y</td>
<td>PTS scores: Ambulatory group (mean score, 5.1) had improved outcome vs bed rest group (mean score, 8.2; P &lt; .01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pain assessment by visual analog scale and modified Lowenberg test</td>
<td></td>
<td>Pain: Lower pain levels in mobile group vs bed rest (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thrombus regression</td>
<td></td>
<td>Thrombus extension: No difference in thrombus regression of thrombus remnants between groups</td>
</tr>
<tr>
<td>Trujillo-Santos et al/2005</td>
<td>Prospective study</td>
<td>2,650 patients with acute DVT (2,038 [77%]) or PE (612 [23%])</td>
<td>DVT group, bed rest or ambulation: 1,050 (52%) patients received bed rest, and 988 (48%) ambulated. All received LMWH. PE group, bed rest or ambulation: 385 (63%) patients received bed rest, and 227 (37%) ambulated. All received LMWH.</td>
<td>Symptomatic, confirmed PE during first 15 d of therapy</td>
<td>3 mo</td>
<td>DVT group, bed rest: PE: 7/1050 (0.7%) DVT group, ambulate: PE: 4/988 (0.4%) PE group, bed rest: PE: 2/385 (0.5%) PE group, ambulate: PE: 2/227 (0.9%)</td>
</tr>
<tr>
<td>Jünger et al/2006</td>
<td>RCT, multicenter open design stratified by age</td>
<td>103 patients with proximal DVT</td>
<td>Bed rest: 50 patients received 5 d of strict bed rest, LMWH, compression bandages. Ambulation: 52 patients ambulated for 5 d, LMWH, compression bandages</td>
<td>PE, progression of or new thrombosis, infection or serious adverse event</td>
<td>5 d</td>
<td>New PE bed rest: 8/50 (16%) ambulation: 2/52 (4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Primary target variable: Bed rest: 14/50 (28%) Ambulation: 7/52 (13%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ns = not significant; V/Q = ventilation/perfusion. See Table S2, S5, and S10 legends for expansion of other abbreviations.
### Table S22—[Section 2.14] Early Ambulation vs Delayed Ambulation for Acute DVT of the Leg: Methodologic Quality

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Randomization</th>
<th>Allocation Concealment</th>
<th>Blinding</th>
<th>Loss to Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schellong et al¹⁹/¹⁹⁹⁹</td>
<td>Patients randomized to 1 of 2 study groups</td>
<td>Unclear</td>
<td>Y, assessors N, patients, caregivers, analysts</td>
<td>4</td>
</tr>
<tr>
<td>Partsch et al¹³/²⁰⁰⁰</td>
<td>Patients randomized to 1 of 3 study groups by sealed envelope</td>
<td>Unclear</td>
<td>Y, assessors N, patients, caregivers, analysts</td>
<td>0</td>
</tr>
<tr>
<td>Aschwanden et al¹⁰/²⁰⁰¹</td>
<td>Patients randomized to 1 of 2 study groups</td>
<td>Sealed envelope</td>
<td>Not blinded</td>
<td>5</td>
</tr>
<tr>
<td>Partsch et al¹³/²⁰⁰⁰</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Blättler et al¹⁰/²⁰⁰³</td>
<td>Patients randomized to 1 of 3 study groups by sealed envelope</td>
<td>Not specified</td>
<td>Y, assessors N, patients, caregivers, analysts</td>
<td>0</td>
</tr>
<tr>
<td>Partsch et al¹³/²⁰⁰⁴</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>21</td>
</tr>
<tr>
<td>Trujillo-Santos et al¹⁰/²⁰⁰⁵</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Jünger et al¹⁰/²⁰⁰⁶</td>
<td>Patients randomized to 1 of 2 study groups by sealed envelope</td>
<td>Unclear</td>
<td>Y, analysts N, patients, caregivers, assessors</td>
<td></td>
</tr>
</tbody>
</table>

See Table S5 and S12 legends for expansion of abbreviations.
Table S23—[Sections 3.1.1-3.1.4] Evidence Profile: Four or Six Weeks vs Three or Six Months as Minimum Duration of Anticoagulation for VTEa,b

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Study Event Rates (%)</th>
<th>Summary of Findings</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Overall quality of Evidence</td>
<td>With 4 or 6 wk</td>
</tr>
<tr>
<td>Participants (Studies), Follow up</td>
<td>Risk of Bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>Recurrent VTE (critical outcome)</td>
<td>2,185 (5 studies), 1-2 y</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
</tr>
<tr>
<td>Major bleeding (critical outcome)</td>
<td>2,185 (5 studies), 1-2 y</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
</tr>
<tr>
<td>Mortality (important outcome)</td>
<td>2,098 (5 studies), 1-2 y</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
</tr>
</tbody>
</table>

Bibliography: Kearon et al,86 Pinede et al,87 Schulman et al,88 Levine et al,89 British Thoracic Society.90 See Table S1, S5, and S2 legends for expansion of abbreviations.

- Short vs longer duration of anticoagulation was 6 wk vs 6 mo for Schulman et al, 6 wk vs 3 mo for Pinede et al, and 4 wk vs 3 mo for the other three studies.
- Populations varied among studies: first provoked isolated distal DVT, proximal DVT or PE provoked in Kearon et al; first isolated distal DVT in Pinede et al; first isolated distal DVT, proximal DVT, or PE in Schulman et al; proximal DVT (21% had cancer) in Levine et al; and DVT or PE (29% not objectively confirmed) in British Thoracic Society.
- Timing of randomization relative to the start of treatment varied across studies: Pinede et al, Schulman et al, and British Thoracic Society randomized at diagnosis; Kearon et al and Levine et al randomized to stop or to continue treatment of 2 more months after the initial 4 wk of treatment.
- Generally, study design was strong. No study stopped early for benefit; two stopped early because of slow recruitment (Kearon et al, Pinede et al). In one study (British Thoracic Society), 44 randomized patients were excluded centrally as they did not satisfy eligibility criteria. Patients and caregivers were blinded in two studies (Kearon et al, Levine et al). Adjudicators of outcomes were blinded in all but one study (British Thoracic Society). All studies appeared to have used effective randomization concealment, ITT analysis, and appears to have a low unexplained drop-out frequency.
- No heterogeneity with I² = 0%.
- No imprecision for overall estimates. However, for the subgroup of patients with isolated distal DVT, who are known to have a very low risk of recurrence, there is imprecision and the possibility that the shorter duration of anticoagulation is adequate and not associated with a clinically important higher risk of recurrence.
- Follow-up was for ~1 y in all studies except for Schulman et al in which it was 2 y.
- Differences in mortality are expected to be mediated by differences in recurrent VTE and bleeding.
<table>
<thead>
<tr>
<th>Author/Year (Acronym)</th>
<th>Intervention</th>
<th>No. Patients Analyzed</th>
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<th>Recurrent DVT or PE</th>
<th>Major Bleeding</th>
<th>Total Mortality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kearon et al(^\text{a})/2004</strong> (SOFAST)</td>
<td>VKA stopped (placebo)</td>
<td>84/84</td>
<td>11 mo</td>
<td>5/84 (6%)</td>
<td>0/84</td>
<td>0/84</td>
<td>Population: first DVT or PE. Treated for 1 mo. VTE was asymptomatic in 9% and isolated calf DVT in 18%. One VTE occurred while on warfarin.</td>
</tr>
<tr>
<td></td>
<td>VKA (INR 2.0-3.0) For 2 more mo.</td>
<td>81/81</td>
<td>11 mo</td>
<td>3/81 (4%) RR 0.6 (0.1-2.5)</td>
<td>0/81 RR 1.0 (0.0-51.6)</td>
<td>1/81 (1%) RR 3.1 (0.1-74.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Pinede et al(^\text{a})/2001</strong> (DOTAVK)</td>
<td>VKA (INR 2.0-3.0) for 1.5 mo</td>
<td>105/105</td>
<td>15 mo</td>
<td>2/105 (2%)</td>
<td>1/105 (1%)</td>
<td>Not specified</td>
<td>Population: first isolated calf DVT.</td>
</tr>
<tr>
<td></td>
<td>VKA (INR 2.0-3.0) for 3 mo</td>
<td>92/92</td>
<td>15 mo</td>
<td>3/92 RR 1.7 (0.3-10.0)</td>
<td>3/92 RR 3.4 (0.4-33.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Schulman et al(^\text{a})/1995</strong> (DURAC 1)</td>
<td>VKA (INR 2.0-2.85) for 1.5 mo</td>
<td>443/443</td>
<td>2 y</td>
<td>80/443 (18%)</td>
<td>1/443</td>
<td>22/443 (5%)</td>
<td>First VTE: DVT (distal or proximal) or PE. Only asked about bleeding while on VKAs.</td>
</tr>
<tr>
<td></td>
<td>VKA (INR 2.0-2.85) for 6 mo</td>
<td>454/454</td>
<td>2 y</td>
<td>43/454 (9%) RR 0.5 (0.4-0.7)</td>
<td>0/454 (0.0-2.0)</td>
<td>17/454 (4%) RR 0.7 (0.7-1.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Levine et al(^\text{a})/1995</strong></td>
<td>VKA stopped (placebo)</td>
<td>105/107</td>
<td>9 mo</td>
<td>12/105 (11%)</td>
<td>0/105</td>
<td>9/105 (9%)</td>
<td>Proximal DVT (first episode in 91%). Cancer in 21%.</td>
</tr>
<tr>
<td></td>
<td>VKA (INR 2.0-3.0) for 2 more mo.</td>
<td>109/113</td>
<td>9 mo</td>
<td>7/109 (6%) RR 0.6 (0.2-1.4)</td>
<td>1/109 (1%) RR 2.9 (0.1-70.2) (within 2 mo of randomization)</td>
<td>9/109 (8%) RR 1.0 (0.4-2.5)</td>
<td></td>
</tr>
<tr>
<td><strong>British Thoracic Society et al(^\text{a})/1992</strong></td>
<td>VKA (INR 2.0-3.0) For 1 mo</td>
<td>358/358</td>
<td>1 y</td>
<td>28/358 (11%)</td>
<td>5/358 (1%)</td>
<td>26/358 (7%)</td>
<td>Population: DVT or PE; only 71% objectively diagnosed; proportion with a previous VTE not known. All bleeds were on VKA. Only 1 recurrent VTE among 116 patients with postoperative VTE.</td>
</tr>
<tr>
<td></td>
<td>VKA (INR 2.0-3.0) for 3 mo</td>
<td>354/354</td>
<td>1 y</td>
<td>14/354 (4%) RR 0.5 (0.3-0.9)</td>
<td>4/354 (1%) RR 0.8 (0.2-3.0)</td>
<td>28/354 (8) RR 1.1 (0.6-1.8)</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Author/Year (Acronym)</th>
<th>Intervention</th>
<th>No. Patients Analyzed</th>
<th>Length Follow-up</th>
<th>Recurrent DVT or PE</th>
<th>Major Bleeding</th>
<th>Total Mortality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Different intermediate durations (6 or 12 mo vs 3 mo) of anticoagulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Campbell et al²⁰⁰⁷</td>
<td>VKA (INR 2.0-3.5) for 3 mo</td>
<td>369/396</td>
<td>1 y</td>
<td>31/369 (8%)</td>
<td>0/369 (during 3 mo. treatment)</td>
<td>15/369 (4%)</td>
<td>Population: DVT or PE; proportion with call DVT not known. Only bleeding during treatment is reported; 20% of VTE outcomes were not objectively verified.</td>
</tr>
<tr>
<td></td>
<td>VKA (INR 2.0-3.5) for 6 mo</td>
<td>380/414</td>
<td>1 y</td>
<td>29/380 (8%) RR 0.9 (0.6-1.5)</td>
<td>8/380 (2%) (during 6 mo. treatment) RR 16.5 (1.0-265)</td>
<td>19/369 (5%) RR 1.3 (0.6-2.5)</td>
<td></td>
</tr>
<tr>
<td>Agnelli et al²⁰⁰³ (WODIT PE)</td>
<td>VKA stopped</td>
<td>91/91</td>
<td>2.6 y (mean)</td>
<td>11/91 (12%)</td>
<td>1/91 (1%)</td>
<td>7/91 (8%)</td>
<td>Population: first unprovoked PE. Treated for ≥3 mo. Among the 4 groups, only 1 recurrent VTE while on VKA.</td>
</tr>
<tr>
<td></td>
<td>VKA (INR 2.0-3.0) for 9 more mo</td>
<td>90/90</td>
<td>2.9 y (mean)</td>
<td>11/90 (12%) RR 1.0 (0.5-2.2)</td>
<td>2/90 (2%) RR 2.0 (0.5-21.9)</td>
<td>8/90 (9%) RR 1.16 (0.4-3.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VKA stopped</td>
<td>70/70</td>
<td>2.8 y (mean)</td>
<td>7/70 (10%)</td>
<td>0/70 (0%)</td>
<td>70/70 (0%)</td>
<td>Population: first provoked PE. Treated for ≥3 mo (see above)</td>
</tr>
<tr>
<td></td>
<td>VKA (INR 2.0-3.0) for 3 more mo</td>
<td>75/75</td>
<td>2.9 y (mean)</td>
<td>4/75 (5%) RR 0.5 (0.2-1.7)</td>
<td>1/75 (1%) RR 1.9 (0.1-56)</td>
<td>4/75 (5%) RR 8.4 (0.5-153)</td>
<td></td>
</tr>
<tr>
<td>Agnelli et al²⁰⁰¹ (WODIT DVT)</td>
<td>VKA stopped</td>
<td>133/133</td>
<td>3.2 y (mean)</td>
<td>21/133 (16%)</td>
<td>2/133 (2%)</td>
<td>7/133 (5%)</td>
<td>Population: first unprovoked proximal DVT treated for 3 mo. One patient had recurrent VTE on VKA. Bleeding in the intervention group was while on VKA.</td>
</tr>
<tr>
<td></td>
<td>VKA (INR 2.0-3.0) for 9 mo</td>
<td>134/134</td>
<td>3.1 y (mean)</td>
<td>21/134 (16%) RR 1.0 (0.6-1.7)</td>
<td>4/134 (3%) RR 2.0 (0.4-10.7)</td>
<td>7/134 (5%) RR 1.0 (0.4-2.8)</td>
<td></td>
</tr>
<tr>
<td>Pinede et al²⁰⁰¹ (DOTAVK)</td>
<td>VKA (INR 2.0-3.0) for 3 mo</td>
<td>270/270</td>
<td>15 mo</td>
<td>21/270 (8%)</td>
<td>5/270 (2%)</td>
<td>Not specified</td>
<td>Population: first proximal DVT or PE. Recurrent VTE occurred after VKA in 26/28 of the short duration groups and 21/27 of the long duration groups.</td>
</tr>
<tr>
<td></td>
<td>VKA (INR 1.0-3.0) for 6 mo</td>
<td>269/269</td>
<td></td>
<td>23/269 (9%) RR 1.1 (0.6-1.9)</td>
<td>7/269 (3%) RR 1.4 (0.4-4.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siragusa et al²⁰⁰⁸ (DACUS)</td>
<td>VKA stopped</td>
<td>92/92</td>
<td>1.8 y</td>
<td>27/92 (29%)</td>
<td>1/92 (1%)</td>
<td>Not specified (total of 3 non-VTE/bleed deaths)</td>
<td>Population: first proximal DVT (provoked, 24%; unprovoked, 76%) treated for 3 mo and residual DVT on baseline ultrasound</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Author/Year (Acronym)</th>
<th>Intervention</th>
<th>No. Patients Analyzed</th>
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<th>Major Bleeding</th>
<th>Total Mortality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palareti et al%2006  (PROLONG)</td>
<td>Remain off (stop) VKA</td>
<td>103/105</td>
<td>1.4 y (mean)</td>
<td>18/120 (15%)</td>
<td>0/103</td>
<td>1/103 (1%)</td>
<td>Population: first unprovoked proximal DVT or PE. Treated for ≥ 3 mo. VKA stopped and D-dimer positive 1 mo later. Eight control patient. Restarted VKA, some after superficial phlebitis. One recurrent VTE in VKA group after VKA stopped.</td>
</tr>
<tr>
<td></td>
<td>Restart indefinite VKA (INR 2.0-3.0) (not blinded)</td>
<td>120/122</td>
<td>(maximum, 1.5 y)</td>
<td>2/103 (2%) RR 0.1 (0.0-0.4)</td>
<td>1/120 (1%) RR 2.6 (0.1-62.6)</td>
<td>1/120 (1%) RR 0.9 (0.1-13.6)</td>
<td></td>
</tr>
<tr>
<td>Kearon et al%1999     (LAFIT)</td>
<td>VKA stopped (placebo)</td>
<td>83/83</td>
<td>10 mo (mean)</td>
<td>17/83 (20%)</td>
<td>0/83</td>
<td>3/83 (4%)</td>
<td>Population: first unprovoked proximal DVT or PE (5% had previous provoked VTE). The recurrent VTE in the VKA patient was after stopping VKA.</td>
</tr>
<tr>
<td></td>
<td>VKA (INR 2.0-3.0) for 2 more years</td>
<td>79/79</td>
<td>(maximum, 2 y)</td>
<td>1/79 (1%) RR 0.1 (0.0-0.5)</td>
<td>3/79 (4%) RR 7.4 (0.4-140)</td>
<td>1/79 (1%) RR 0.3 (0.0-3.3)</td>
<td></td>
</tr>
<tr>
<td>Schulman et al%1997   (DURAC 2)</td>
<td>VKA (INR 2.0-2.85) for 6 mo</td>
<td>111/111</td>
<td>4 y</td>
<td>23/111 (2%)</td>
<td>3/111 (3%)</td>
<td>16/111 (14%)</td>
<td>Second VTE: DVT (distal or proximal) or PE. All recurrent VTE in the indefinite VKA group were after stopping VKAs. Bleeding during the first 6 mo of VKA in 1 of 6 mo group and 6 of indefinite group (only asked about bleeding while on VKAs).</td>
</tr>
<tr>
<td></td>
<td>VKA (INR 2.0-2.85) indefinitely</td>
<td>116/116</td>
<td></td>
<td>3/116 (3%) RR 0.1 (0.0-0.4)</td>
<td>10/116 (9%) RR 3.2 (0.9-11.3)</td>
<td>10/116 (9%) RR 0.6 (0.3-3.3)</td>
<td></td>
</tr>
<tr>
<td>Farraj et al%2004</td>
<td>VKA (INR 2.0-3.0) for 6 mo</td>
<td>32/36</td>
<td>3 y</td>
<td>7/32 (22%)</td>
<td>2/32 (6%)</td>
<td>0/32</td>
<td>In total: 2 VTE after 24 mo (24 mo group); 1 VTE on therapy (24 mo group)</td>
</tr>
<tr>
<td></td>
<td>VKA (INR 2.0-2.85) for 24 mo</td>
<td>32/36</td>
<td></td>
<td>3/32 (3%) RR 0.4 (0.1-1.5)</td>
<td>2/32 (6%) RR 1.0 (0.2-6.7)</td>
<td>0/32</td>
<td></td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Author/Year (Acronym)</th>
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<th>Major Bleeding</th>
<th>Total Mortality</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Prandoni et al*2009 (AESOPUS)</td>
<td>VKA stopped if provoked and 3 more months if unprovoked</td>
<td>268/268</td>
<td>33 mo</td>
<td>46/268 (17%)</td>
<td>2/268 (1%)</td>
<td>11/268 (4%)</td>
<td>Population: first provoked (43%) or unprovoked (57%) proximal DVT treated for 3 mo. One VTE in each group while on VKAs. The flexible group was treated for a mean of 4 mo (provoked) and 5 mo (unprovoked) longer.</td>
</tr>
<tr>
<td>Stopped if no residual vein 270/270 thrombosis and until resolved or 9 more mo if provoked or 21 more mo if unprovoked</td>
<td>32/270 (12%)</td>
<td>RR 0.7 (0.4-1.1)</td>
<td>4/270/255 (1%)</td>
<td>RR 2.0 (0.4-10.8)</td>
<td>4/255 (6%)</td>
<td>RR 1.5 (0.7-3.2)</td>
<td></td>
</tr>
<tr>
<td>Ridker et al*2003 (PREVENT)</td>
<td>VKA stopped or not restarted (placebo)</td>
<td>253/253</td>
<td>2.1 y (mean)</td>
<td>37/253 (15%)</td>
<td>2/253 (1%)</td>
<td>8/253 (3%)</td>
<td>Population: unprovoked DVT (distal or proximal) or PE (first episode in 38%). Eight recurrent VTE in the VKA group after stopping VKAs.</td>
</tr>
<tr>
<td>VKA INR 1.5-2.0</td>
<td>255/255</td>
<td>(maximum, 4.3 y)</td>
<td>14/255 (5%)</td>
<td>RR 0.4 (0.2-0.7)</td>
<td>5/255 (2%)</td>
<td>RR 2.5 (0.5-12.7)</td>
<td>4/255 (2%)</td>
</tr>
<tr>
<td>Kearon et al*2003 (ELATE)</td>
<td>VKA INR 1.5-1.9 (blinded)</td>
<td>369/369</td>
<td>2.4 y (mean)</td>
<td>16/369 (4%)</td>
<td>9/369 (2%)</td>
<td>16/369 (4%)</td>
<td>Population: unprovoked proximal DVT or PE (first episode in 31%). Treated for ≥ 3 mo. VKA (INR 2.0-3.0) (mean 12 mo). Five recurrent VTE in INR 1.5-1.9 and three in the INR 2.0-3.0 group after stopping VKAs.</td>
</tr>
<tr>
<td>VKA INR 2.0-3.0</td>
<td>369/369</td>
<td>(blinded)</td>
<td>6/369 (2%)</td>
<td>RR 0.4 (0.1-0.9)</td>
<td>8/369 (2%)</td>
<td>RR 0.9 (0.3-3.3)</td>
<td>8/369 (2%)</td>
</tr>
</tbody>
</table>

AESOPUS = Ultrasound Findings to Adjust the Duration of Anticoagulation; DACUS = Duration of Anticoagulation based on Compression UltraSonography; DOTAVK = Durée Optimale du Traitement AntiVitamines K; DURAC = Duration of Anticoagulation; ELATE = Anticoagulation for Thrombo-Embolism; LAFIT = Long-term Anticoagulation for a First episode of Idiopathic venous Thromboembolism; PREVENT = Prevention of Recurrent Venous Thromboembolism; SOFAST = First Acute Secondary Thrombosis; WODIT DVT = Warfarin Optimal Duration Italian Trial in patients with DVT; WODIT PE = Warfarin Optimal Duration Italian Trial in patients with Pulmonary Embolism. See Table S1, S2, and S7 legends for expansion of other abbreviations.
### Table S25—[Sections 3.1.1-3.1.4] Comparison of Durations of Anticoagulant Therapy for DVT and PE: Methodologic Quality

<table>
<thead>
<tr>
<th>Author/Year (Acronym)</th>
<th>Intervention</th>
<th>Study Design</th>
<th>Randomization</th>
<th>Blinding</th>
<th>Loss to Follow-up</th>
<th>Analysis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kearon et al/2004 (SOFAST)</td>
<td>VKA stopped (placebo) VKA (INR 2.0-3.0) for 2 more mo</td>
<td>RCT</td>
<td>CY</td>
<td>Patients: CY Caregivers: CY Adjudications: CY Data Analysts: CY</td>
<td>Placebo: 0/84 VKA: 0/81</td>
<td>ITT</td>
<td>Stopped early because of slow recruitment.</td>
</tr>
<tr>
<td>Pinede et al/2001 (DOT AVK)</td>
<td>VKA (INR 2.0-3.0) for 1.5 and 3 mo VKA (INR 1.0-3.0) for 3 and 6 mo</td>
<td>RCT</td>
<td>CY</td>
<td>Patients: CN Caregivers: CN Adjudications: CY Data Analysts: PN</td>
<td>Not specified Probably low or nil</td>
<td>ITT</td>
<td>Stopped early because of slow recruitment. Patient withdrawals: 4 in short- and 16 in long-duration groups. Total of 22 patients dropped out.</td>
</tr>
<tr>
<td>Schulman et al/1995 (DURAC 1)</td>
<td>VKA (INR 2.0-2.85) for 1.5 mo VKA (INR 2.0-2.85) for 6 mo</td>
<td>RCT</td>
<td>CY</td>
<td>Patients: CN Caregivers: CN Adjudications: VTE, CY Other: PN Data Analysts: PN</td>
<td>Total of 44 patients dropped out during follow-up but partial follow-up achieved</td>
<td>ITT</td>
<td>Five patient were excluded because protein C found after randomization.</td>
</tr>
<tr>
<td>British Thoracic Society et al/1992</td>
<td>VKA (INR 2.0-3.0) For 1 mo VKA (INR 2.0-3.0) for 3 mo</td>
<td>RCT</td>
<td>CY</td>
<td>Patients: CN Caregivers: CN Adjudications: CN Data Analysts: PN</td>
<td>No VKA: 27/354 VKA: 30/358</td>
<td>ITT</td>
<td>Forty-four randomized patients excluded centrally as did not satisfy entry criteria.</td>
</tr>
<tr>
<td>Campbell et al/2007</td>
<td>VKA (INR 2.0.0-3.5) for 3 mo VKA (INR 2.0-3.5) for 6 mo</td>
<td>RCT</td>
<td>CY</td>
<td>Patients: CN Caregivers: CN Adjudications: CN Data Analysts: PN</td>
<td>3-mo VKA: 6/369 6-mo VKA: 4/380</td>
<td>ITT</td>
<td>Sixty-one randomized patients excluded centrally as did not satisfy entry criteria. Stopped early because of low recruitment.</td>
</tr>
<tr>
<td>Agnelli et al/2003 (WODIT PE)</td>
<td>VKA stopped VKA (INR 2.0-3.0) for 9 more mo.</td>
<td>RCT</td>
<td>CY</td>
<td>Patients: CN Caregivers: CN Adjudications: CY Data Analysts: PN</td>
<td>Not specified Probably low or nil</td>
<td>ITT</td>
<td>Two patients in the control groups and 2 patients in the intervention groups crossed over. Five patients in the intended group did not stop VKA. Four patients in the control groups restarted VKAs.</td>
</tr>
<tr>
<td>Agnelli et al/2001 (WODIT DVT)</td>
<td>VKA stopped VKA (INR 2.0-3.0) for 9 mo</td>
<td>RCT</td>
<td>CY</td>
<td>Patients: CN Caregivers: CN Adjudications: CY Data Analysts: PN</td>
<td>Not specified Probably low or nil</td>
<td>ITT</td>
<td>Trial stopped early for lack of adequate benefit. Four patients in the intervention and 2 patients in the control group crossed over.</td>
</tr>
<tr>
<td>Author/Year (Acronym)</td>
<td>Intervention</td>
<td>Study Design</td>
<td>Randomization Concealed</td>
<td>Blinding</td>
<td>Loss to Follow-up</td>
<td>Analysis</td>
<td>Comments</td>
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<tr>
<td>Siragusa et al\textsuperscript{94}/2008 (DACUS)</td>
<td>VKA stopped VKA (INR 1.0-3.0) for 9 mo.</td>
<td>RCT</td>
<td>PY</td>
<td>Patients: CN Caregivers: CN Adjudications: PY Data Analysts: PN</td>
<td>None</td>
<td>ITT</td>
<td>Not known whether the many postenrollment exclusions were postrandomization. Trial stopped early because recurrent VTE was higher than expected.</td>
</tr>
<tr>
<td>Palareti et al\textsuperscript{95}/2006 (PROLONG)</td>
<td>Remain off (stop) VKA Restart indefinitely VKA (INR 2.0-3.0) (not blinded)</td>
<td>RCT</td>
<td>CY</td>
<td>Patients: CN Caregivers: CN Adjudications: CY Data Analysts: PN</td>
<td>No VKA: 3/105 VKA: 0/122</td>
<td>ITT</td>
<td>Four patients excluded because lupus anticoagulant found after randomization.</td>
</tr>
<tr>
<td>Kearon et al\textsuperscript{96}/1999 (LAFIT)</td>
<td>VKA stopped (placebo) VKA (INR 2.0-3.0) for 2 more y</td>
<td>RCT</td>
<td>CY</td>
<td>Patients: CY Caregivers: CY Adjudications: CY Data Analysts: CY</td>
<td>None</td>
<td>ITT</td>
<td>Trial stopped early because of overall benefit. After recurrent VTE, patients were not followed, resulting in shorter follow-up and potential for underestimation of bleeding in the no-VKA group.</td>
</tr>
<tr>
<td>Schulman et al\textsuperscript{97}/1997 (DURAC 2)</td>
<td>VKA (INR 2.0-2.85) for 6 mo VKA (INR 2.0-2.85) indefinitely</td>
<td>RCT</td>
<td>CY</td>
<td>Patients: CN Caregivers: CN Adjudications: VTE, CY Other, PN Data Analysts: PN</td>
<td>Total of 14 patients dropped out during follow-up, but partial follow-up achieved</td>
<td>ITT</td>
<td>Actual mean duration of VKA was 7.7 mo in 6-mo group and 42.7 mo in indefinite (48 mo) group.</td>
</tr>
<tr>
<td>Prandoni et al\textsuperscript{98}/2009 (AESOPUS)</td>
<td>VKA stopped if provoked and 3 more mo if unprovoked Stopped if no residual vein thrombosis and until resolved or 9 more mo if provoked or 21 more mo if unprovoked</td>
<td>RCT</td>
<td>CY</td>
<td>Patients: CN Caregivers: CN Adjudications: VTE, CY Data Analysts: PY</td>
<td>4 subjects in each group</td>
<td>ITT</td>
<td></td>
</tr>
<tr>
<td>Ridker et al\textsuperscript{100}/2003 (PREVENT)</td>
<td>VKA stopped or not restarted (placebo) VKA INR 1.5-2.0</td>
<td>RCT</td>
<td>CY</td>
<td>Patients: CY Caregivers: CY Adjudications: CY Data Analysts: CY</td>
<td>Not specified</td>
<td>ITT</td>
<td>Trial stopped early because of overall benefit. Number of crossovers not described.</td>
</tr>
<tr>
<td>Farraj et al\textsuperscript{99}/2004</td>
<td>VKA (INR 2.0-3.0) for 6 mo VKA (INR 2.0-2.85) for 24 mo</td>
<td>RCT</td>
<td>PY</td>
<td>Patients: CN Caregivers: CN Data Collectors: PN, Adjudicators: PN Data Analysts: PN</td>
<td>0/32 0/32 (see comments)</td>
<td>ITT</td>
<td>Four postrandomization exclusions for each group because of poor compliance.</td>
</tr>
<tr>
<td>Kearon et al\textsuperscript{101}/2003 (ELATE)</td>
<td>VKA INR 1.5-1.9 VKA INR 2.0-3.0 (blinded)</td>
<td>RCT</td>
<td>CY</td>
<td>Patients: CY Caregivers: CY Adjudications: CY Data Analysts: CY</td>
<td>INR 1.5-1.9: 1/369 INR 1.5-1.9: 1/369</td>
<td>ITT</td>
<td>Crossover to INR 2.0-3.0 in 21 patients</td>
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</table>

See Table S1, S2, S7, and S24 legends for expansion of abbreviations.
### Table S26—[Sections 3.1.1-3.1.4] Evidence Profile: Six or Twelve Months vs Three Months as Minimum Duration of Anticoagulation for VTE<sup>a,b</sup>

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With 3 mo</td>
<td>With 6 or 12 mo</td>
</tr>
<tr>
<td>Participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Studies), Follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,061 (6 studies), 1-3 y</td>
<td>No serious risk of bias&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No serious inconsistency</td>
</tr>
<tr>
<td>2,061 (6 studies), 1-3 y</td>
<td>No serious risk of bias&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No serious inconsistency</td>
</tr>
<tr>
<td>1,331 (5 studies), 1-3 y</td>
<td>No serious risk of bias&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No serious inconsistency</td>
</tr>
</tbody>
</table>

**Study Event Rates (%):**
- **Recurrent VTE:**
  - Participants: 2,061 (6 studies), Follow-up: 1-3 y
  - Risk of Bias: No serious
  - Inconsistency: No serious
  - Indirectness: No serious
  - Imprecision: Serious<sup>d</sup>
  - Total Risk: 118/1,025 (11.5)
  - Relative Risk: RR 0.89 (0.69-1.14)
  - Absolute Risk Difference: 13 fewer per 1,000 (from 36 fewer to 16 more)
- **Major bleeding:**
  - Participants: 2,061 (6 studies), Follow-up: 1-3 y
  - Risk of Bias: No serious
  - Inconsistency: No serious
  - Indirectness: No serious
  - Imprecision: No serious
  - Total Risk: 9/1,025 (0.9)
  - Relative Risk: RR 2.49 (1.2-5.16)
  - Absolute Risk Difference: 13 more per 1,000 (from 2 more to 37 more)
- **Mortality:**
  - Participants: 1,331 (5 studies), Follow-up: 1-3 y
  - Risk of Bias: No serious
  - Inconsistency: No serious
  - Indirectness: No serious
  - Imprecision: No serious
  - Total Risk: 29/663 (4.4)
  - Relative Risk: RR 1.3 (0.81-2.08)
  - Absolute Risk Difference: 13 more per 1,000 (from 8 fewer to 47 more)

**Summary of Findings:**
- **Recurrent VTE:**
  - Participants: 2,061 (6 studies), Follow-up: 1-3 y
  - Risk of Bias: No serious
  - Inconsistency: No serious
  - Indirectness: No serious
  - Imprecision: Serious<sup>d</sup>
  - Total Risk: 118/1,025 (11.5)
  - Relative Risk: RR 0.89 (0.69-1.14)
  - Absolute Risk Difference: 13 fewer per 1,000 (from 36 fewer to 16 more)
- **Major bleeding:**
  - Participants: 2,061 (6 studies), Follow-up: 1-3 y
  - Risk of Bias: No serious
  - Inconsistency: No serious
  - Indirectness: No serious
  - Imprecision: No serious
  - Total Risk: 9/1,025 (0.9)
  - Relative Risk: RR 2.49 (1.2-5.16)
  - Absolute Risk Difference: 13 more per 1,000 (from 2 more to 37 more)
- **Mortality:**
  - Participants: 1,331 (5 studies), Follow-up: 1-3 y
  - Risk of Bias: No serious
  - Inconsistency: No serious
  - Indirectness: No serious
  - Imprecision: No serious
  - Total Risk: 29/663 (4.4)
  - Relative Risk: RR 1.3 (0.81-2.08)
  - Absolute Risk Difference: 13 more per 1,000 (from 8 fewer to 47 more)

**Bibliography:** Pinede et al,<sup>87</sup> Campbell et al,<sup>91</sup> Agnelli et al,<sup>92,93</sup> Agnelli et al,<sup>92</sup> Siragusa.<sup>94</sup> See Table S1, S2, and S5 legends for expansion of abbreviations.

<sup>a</sup>Timing of randomization relative to the start of treatment and length of treatment in the non-3-mo group varied across studies: Pinede et al and Campbell et al randomized at diagnosis, and Agnelli et al randomized after the initial 3 mo of treatment to stop, or continue, treatment. The longer duration of treatment was 6 mo in Pinede, Campbell, and Agnelli et al (2003) (provoked PE), and 12 mo in Agnelli (2001) and Agnelli (2003) (unprovoked PE).

<sup>b</sup>Study populations varied across studies: Pinede et al enrolled provoked and unprovoked proximal DVT and PE; Campbell et al enrolled provoked and unprovoked isolated distal DVT, proximal DVT and PE; Agnelli et al (2003) had separate randomizations for provoked PE (3 vs 6 mo) and unprovoked (3 vs 12 mo); and Agnelli et al (2001) enrolled unprovoked proximal DVT.

<sup>c</sup>Generally, study design was strong. No study stopped early for benefit; two stopped early because of slow recruitment (Campbell et al, Pinede et al), and one stopped because of lack of benefit (Agnelli et al [2001]). In one study (Campbell), 20% of VTE outcomes were not objectively confirmed. Patients and caregivers were not blinded in any study. Adjudicators of outcomes were blinded in all but one study (Campbell). All studies used effective randomization concealment and ITT analysis and appear to have a low unexplained drop-out frequency.

<sup>d</sup>CIs include both values suggesting no effect and values suggesting either benefit or harm.

<sup>e</sup>Low number of events and a total number of participants < 2,000.

<sup>f</sup>One study may have confined the assessment of bleeding to when subjects were receiving anticoagulant therapy, which could have inflated the increase in bleeding associated with the longer duration of therapy (Campbell et al).

<sup>g</sup>Differences in mortality are expected to be mediated by differences in recurrent VTE and bleeding.
<table>
<thead>
<tr>
<th>Participants</th>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality Assessment</td>
<td>Risk With No</td>
<td>Risk Difference With</td>
</tr>
<tr>
<td></td>
<td>Extended Anticoagulation</td>
<td>Anticoagulation (95% CI)</td>
</tr>
<tr>
<td>Study Event Rates (%)</td>
<td>With No Extended</td>
<td>With Extended Anticoagulation</td>
</tr>
<tr>
<td></td>
<td>Anticoagulation</td>
<td>Relative Effect (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Risk of Bias</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inconsistency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indirectness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Imprecision</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall Quality of Evidence</td>
<td></td>
</tr>
<tr>
<td>Quality Assessment</td>
<td>Mortality (important outcome)</td>
<td></td>
</tr>
<tr>
<td>Study Event Rates (%)</td>
<td>Risk With No</td>
<td>Risk Difference With</td>
</tr>
<tr>
<td></td>
<td>Extended Anticoagulation</td>
<td>Anticoagulation (95% CI)</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>Participants (Studies), Follow-up</td>
<td>1,184 (4 studies), 10-36 mo</td>
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<tr>
<td>Risk of Bias</td>
<td>No serious risk of bias</td>
<td>63 per 1,000</td>
</tr>
<tr>
<td>Inconsistency</td>
<td>No serious inconsistency</td>
<td>27 fewer per 1,000 (from 44 fewer to 2 more)</td>
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<tr>
<td>Indirectness</td>
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</tr>
<tr>
<td>Imprecision</td>
<td>Serious</td>
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<tr>
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<tr>
<td>Risk of Bias</td>
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<tr>
<td>Inconsistency</td>
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<tr>
<td>Indirectness</td>
<td>due to</td>
<td></td>
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<tr>
<td>Imprecision</td>
<td>imprecision</td>
<td></td>
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<tr>
<td>Relative Effect</td>
<td>38/599 (6.3)</td>
<td>0.57 (0.31-1.03)</td>
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<tr>
<td>(95% CI)</td>
<td>16/585 (2.7)</td>
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<tr>
<td>Mortality (important outcome)</td>
<td>38/599 (6.3)</td>
<td>63 per 1,000</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>16/585 (2.7)</td>
<td>27 fewer per 1,000 (from 44 fewer to 2 more)</td>
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</tr>
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<td>Inconsistency</td>
<td>No serious inconsistency</td>
<td>10 per 1,000</td>
</tr>
<tr>
<td>Indirectness</td>
<td>No serious indirectness</td>
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<td>Imprecision</td>
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<td>Risk of Bias</td>
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<tr>
<td>Inconsistency</td>
<td>21/585 (3.6)</td>
<td>10 per 1,000</td>
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<tr>
<td>Indirectness</td>
<td>Undetected</td>
<td></td>
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<tr>
<td>Imprecision</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Overall Quality of Evidence</td>
<td>undetected</td>
<td></td>
</tr>
<tr>
<td>Risk of Bias</td>
<td>due to</td>
<td></td>
</tr>
<tr>
<td>Inconsistency</td>
<td>imprecision</td>
<td></td>
</tr>
<tr>
<td>Relative Effect</td>
<td>7/599 (12%)</td>
<td>2.63 (1.02-6.76)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>21/585 (3.6%)</td>
<td></td>
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<tr>
<td>Major bleeding at 1 y (critical outcome)</td>
<td>Low risk of bleeding</td>
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</tr>
<tr>
<td>Study Event Rates (%)</td>
<td>3 per 1,000</td>
<td>5 more per 1,000 (from 0 more to 17 more)</td>
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<td></td>
<td>(from 0 more to 17 more)</td>
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</tr>
<tr>
<td></td>
<td>6 per 1,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 more per 1,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(from 0 more to 35 more)</td>
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<tr>
<td></td>
<td>12 per 1,000</td>
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<tr>
<td></td>
<td>20 more per 1,000</td>
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<tr>
<td></td>
<td>(from 0 more to 69 more)</td>
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<td></td>
<td>Low risk of bleeding</td>
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<tr>
<td></td>
<td>3 per 1,000</td>
<td>5 more per 1,000 (from 0 more to 17 more)</td>
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<tr>
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<td>(from 0 more to 17 more)</td>
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<td>6 per 1,000</td>
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<tr>
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<td>(from 0 more to 35 more)</td>
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<td>12 per 1,000</td>
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<tr>
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<td>20 more per 1,000</td>
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<td>(from 0 more to 69 more)</td>
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### Table S27—Continued

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<th>Anticipated Absolute Effects</th>
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<td>Participants</td>
<td>Anticipated Absolute Effects</td>
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<td>(Studies), Follow-up</td>
<td>Risk of Bias</td>
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<tr>
<td>Recurrent VTE at 5 y (critical outcome)</td>
<td>1,184 (4 studies), 10-36 mo</td>
<td>No serious risk of bias</td>
</tr>
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<tr>
<td>Major bleeding at 5 y (critical outcome)</td>
<td>1,184 (4 studies), 10-36 mo</td>
<td>No serious risk of bias</td>
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Burden of anticoagulation not reported
### Summary of Findings

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With No Risk With No</td>
<td>Risk Difference</td>
</tr>
<tr>
<td></td>
<td>Extended Risk With No</td>
<td>Risk Difference</td>
</tr>
<tr>
<td></td>
<td>Anticoagulation Anticoagulation (95% CI)</td>
<td>Anticoagulation (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Overall Quality of Evidence</td>
<td>Relative Effect</td>
</tr>
<tr>
<td>Participants (Studies), Follow-up Risk of Bias Inconsistency Indirectness Imprecision Publication Bias</td>
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<td></td>
</tr>
<tr>
<td>... ... ... ... ... ... ... ... ... ... See comment</td>
<td>See comment</td>
<td>See comment</td>
</tr>
<tr>
<td>... ... ... ... ... ... ... ... ... ... See comment</td>
<td>See comment</td>
<td>See comment</td>
</tr>
</tbody>
</table>

**Quality Assessment**
- **With No Anticoagulation**
  - PTS not reported

**Study Event Rates (%)**

**Anticipated Absolute Effects**
- **Risk With No Anticoagulation**
- **Risk With Extended Anticoagulation**
- **Relative Effect (95% CI)**
- **Risk Difference With Extended Anticoagulation (95% CI)**

---

**Bibliography:**
- Schulman et al (DURAC 2)
- Kearon et al (LAFIT)
- Farraj
- Palareti (PROLONG)

See Table S1, S2, S7, and S10 legends for expansion of abbreviations.

---

**Studies vary in follow-up duration (10 mo to 3 y) and in duration of time-limited VKA (3 to 6 mo).**

**We excluded Rüdiger et al (PREVENT) because target INR was 1.75 (low intensity), which has been shown in an RCT to be less effective than a target of 2.5.**

**I² = 0%.**

**CI includes both values suggesting no effect and values suggesting appreciable harm or appreciable benefit.**

**Small number of events. Decision to rate down also takes into account that two studies were stopped early for benefit.**

**Annual risk of VTE recurrence after discontinuing oral anticoagulation therapy in patients with first VTE provoked by surgery: 1% (Iorio A, Kearon C, Filippucci E, et al. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. Arch Intern Med. 2010;170(19):1710-1716); we assumed a 0.5% yearly risk thereafter (3% over 5 y).**

**Annual risk in patients with first VTE provoked by non surgical factor: about 5% the first year (Iorio et al); we assumed 2.5% yearly thereafter (15% over 5 y).**

**Annual risk in patients with first episode of unprovoked VTE: 9.3% over 1 y in Rodger MA, Kahn SR, Wells PS, et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. CMAJ. 2008;179(5):417-426; 11.0% over 1 y, 19.6% over 3 y, and 29.1% over 5 y in Prandoni et al (2007). We assumed a risk of 10% the first year after discontinuation and 5% yearly thereafter (30% over 5 y).**

**Annual risk in patients with second episode of unprovoked VTE: we assumed an RR of 1.5 compared with a first episode of unprovoked VTE: 15% the first year after discontinuation, 7.5% yearly thereafter (45% over 5 y).**

**Case fatality rate of recurrent VTE after discontinuing oral anticoagulation therapy: 3.6% (Carrier 2010).**

**Annual risk of major bleeding is based on three risk levels: low, intermediate, and high. The corresponding 0.3%, 0.6%, and 1.2% risks are estimates based on control arms of included studies (see Table 3).**

**Case fatality rate of major bleeding during initial oral anticoagulation therapy: 11.3% (Carrier et al) (no data available for after discontinuing oral anticoagulation therapy).**

**Burden of anticoagulation: endured by all patients who continue extended-duration anticoagulation (100%) and applies to patients who stop anticoagulation (no extended-duration anticoagulation) who subsequently experience a recurrent VTE (5%, 10%, 15% at 1 y; 15%, 30%, 45% at 5 y).**

### Table S28 — [Section 3.3] Evidence Profile: LMWH vs VKA for Long-term Treatment of VTE

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Participants</td>
<td>Overall Quality of Evidence</td>
</tr>
<tr>
<td></td>
<td>(Studies), Follow-up</td>
<td>Publication Bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk of Bias</td>
</tr>
<tr>
<td><strong>Mortality</strong> (important outcome)</td>
<td>2,496 (7 studies), 6 mo</td>
<td>No serious</td>
</tr>
<tr>
<td><strong>Recurrent VTE</strong> (critical outcome)</td>
<td>2,727 (8 studies), 6 mo</td>
<td>Serious</td>
</tr>
<tr>
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<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Major bleeding</strong> (critical outcome)</td>
<td>2,737 (8 studies), 6 mo</td>
<td>No serious</td>
</tr>
<tr>
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</table>

(Continued)
### Summary of Findings

<table>
<thead>
<tr>
<th>Participants (Studies), Follow-up</th>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Risk Difference</td>
<td>Risk With LMWH (95% CI)</td>
</tr>
<tr>
<td></td>
<td>With VKA</td>
<td>With LMWH</td>
</tr>
<tr>
<td>Burden of anticoagulation (important outcome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No serious limitations</td>
<td>No serious limitations</td>
<td>No serious limitations</td>
</tr>
</tbody>
</table>
| Warfarin: daily medication, dietary interactions, frequent blood testing/monitoring, increased hospital/clinic visits | LMWH: daily injection, no dietary interactions, no frequent blood testing/monitoring | ... | ...

### PTS (important outcome; assessed with self-reported leg symptoms and signs)

100 (1 study), 2 y

Serious\(^i\) No serious inconsistency Serious\(^m\) No serious imprecision Undetected Low\(^m\) due to risk of bias, indirectness

31/44 (70.5%) 34/56 (60.7%) RR 0.85 (0.77-0.94) 200 per 1,000 30 fewer per 1,000 (from 12 fewer to 46 fewer)

### Bibliography

Included studies: Deitche et al., Hull et al., Hull et al., Lee et al., Lopaciuck et al., Lopez-Beret et al., Meyer et al., Romera et al. Two of these studies enrolled only patients without cancer, and 3 enrolled only patients with cancer, and 3 enrolled both patients with and without cancer (separate data provided for cancer and non-cancer patients in one study). Excluded studies (less than 50% of therapeutic dose LMWH during extended phase): Pini et al., Das et al., Gonzalez-Fajardo et al., Veiga et al., Kalkar et al. (Cesarone 2003 Circ abstract). PTS data from: Hull et al. See Table S1, S2, S5, and S10 legends for expansion of abbreviations.

\(^i\) Limited to LMWH regimens that used ≥50% of the acute treatment dose during the extended phase of treatment.

\(^m\) The initial parenteral anticoagulation was similar in both arms for all except one study (Hull et al [2007]) in which patients randomized to LMWH received initially the same LWMH, whereas patients randomized to VKA received initially UFH.

\(^a\) Two of these studies enrolled only patients without cancer, three enrolled only patients with cancer, and three enrolled both patients with and without cancer (separate data provided for cancer and non-cancer patients in one study).

\(^b\) One study did not report deaths, which is unusual and could reflect selective reporting of outcomes.

\(^c\) GI includes both no effect and harm with LMWH.

\(^d\) None of the studies were blinded, although the diagnosis of recurrent VTE has a subjective component and there could be a lower threshold for diagnosis of recurrent VTE in VKA-treated patients because switching the treatment of such patients to LMWH is widely practiced. At the same time, there is reluctance to diagnose recurrent VTE in patients who are already on LMWH because there is no attractive alternative treatment option.

\(^e\) Risk of recurrent VTE: low corresponds to patients without cancer (3% estimate taken from recent large RCTs of acute treatment); intermediate corresponds to patients with local or recently resected cancer (based on average rate across the six studies in this analysis and appears to be consistent with Prandoni et al [particularly if low risk is increased to 4%]); and high to patients with locally advanced or distant metastatic cancer (Prandoni et al).

\(^f\) No study was blinded; diagnosis of major bleeding has a subjective component.

\(^g\) The 95% CIs for the RR for major bleeding includes a potentially clinically important increase or decrease with LMWH and may vary with the dose of LMWH used during the extended phase of therapy.

\(^h\) Risk of bleeding: low corresponds to patients without risk factor for bleeding (ie, >75 y, cancer, metastatic disease, chronic renal or hepatic failure; platelet count <300,000; requires antiplatelet therapy; history of bleeding without a reversible cause) (Table 2) (based on Prandoni et al and Beyth et al., adjusted to a 6-mo time frame).

\(^i\) Hull et al reported no significant difference in quality of life but suggested greater satisfaction with LMWH over VKA (questionnaire did not directly assess the burden of injections).

\(^j\) No serious limitations. Self-reported leg symptoms and signs after 3 mo of treatment.

\(^k\) The association between leg symptoms and signs at 3 mo and long-term PTS is uncertain.

\(^l\) The baseline risk assumes that patients all wear pressure stockings. Control event rate comes from observational studies in review by Kahn et al., adjusted to 2-y time frame.
Table S29—[Section 3.3] Evidence Profile: Rivaroxaban vs LMWH and VKA Therapy for Short- and Long-term Treatment of VTE**

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With LMWH and VKA Therapy</td>
<td>With Rivaroxaban</td>
</tr>
<tr>
<td>Participants (Studies)</td>
<td>Follow up</td>
<td>Risk of Bias</td>
</tr>
<tr>
<td>Death (important outcome)</td>
<td>3,449 (1 study), 6-12 mo³</td>
<td>No serious risk of bias°</td>
</tr>
<tr>
<td>Recurrent VTE (critical outcome)</td>
<td>3,449 (1 study), 6-12 mo³</td>
<td>No serious risk of bias°</td>
</tr>
<tr>
<td>Major bleeding (critical outcome)</td>
<td>3,429 (1 study), 6-12 mo³</td>
<td>No serious risk of bias°</td>
</tr>
</tbody>
</table>

Burden of anticoagulation (important outcome) not reported

... ... ... ... ... ... Warfarin: daily medication, dietary interactions, frequent blood testing/monitoring, increased hospital/clinic visits Rivaroxaban: daily medication, no dietary interactions, no frequent blood testing/monitoring ... ... ...

Bibliography: Einstein DVT. HR = hazard ratio. See Table S1, S2, S5, and S7 legends for expansion of other abbreviations.

*Rivaroxaban 15 mg bid for 3 wk and then 20 mg/d for a total of 3 (12%), 6 (63%), or 12 (25%) months.
¶Enoxaparin 1 mg/kg bid for ~8 d and then VKA therapy targeted to INR 2.5 for 3, 6, or 12 mo.
**Included patients had acute, symptomatic, objectively verified proximal DVT of the legs (unprovoked, 62%; cancer, 6%; previous VTE, 19%).
†Follow-up was prespecified to be 3 mo (12%), 6 mo (63%), or 12 mo (25%).
‡Allocation was concealed. Patients, providers, and data collectors were not blinded, but outcome adjudicators were blinded. ITT analysis; 1.0% loss to follow-up. Not stopped early for benefit.
§CI includes values suggesting benefit or no effect; relatively low number of events.
‖CI includes values suggesting benefit and harm.
±One definite or possible fatal VTE in rivaroxaban group and one in LMWH/VKA group.
‡Blends contributing to death: one in the rivaroxaban group and five in the warfarin group.
Table S30—[Section 3.3] Evidence Profile: Rivaroxaban vs Placebo for Extended Anticoagulation of VTE<sup>a,b</sup>

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With Placebo</td>
<td>With Rivaroxaban</td>
</tr>
<tr>
<td>Participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Studies), Follow-up</td>
<td>Risk of Bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Study Event Rates (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality (important outcome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,196 (1 study), 6 or 12 mo</td>
<td>No serious risk of bias&lt;sup&gt;d&lt;/sup&gt;</td>
<td>No serious inconsistency</td>
</tr>
<tr>
<td>Recurrent VTE (critical outcome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,196 (1 study), 6 or 12 mo</td>
<td>No serious risk of bias&lt;sup&gt;d&lt;/sup&gt;</td>
<td>No serious inconsistency</td>
</tr>
<tr>
<td>Major bleeding (critical outcome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,188 (1 study), 6 or 12 mo</td>
<td>No serious risk of bias&lt;sup&gt;d&lt;/sup&gt;</td>
<td>No serious inconsistency</td>
</tr>
<tr>
<td>Burden of anticoagulation (important outcome) not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rivaroxaban: daily medication, no dietary interactions, no frequent blood testing/monitoring

PTS (important outcome) not reported

---

Bibliography: Einstein DVT<sup>119</sup> See Table S1, S2, S5, S10, and S29 legends for expansion of abbreviations.

<sup>a</sup>Rivaroxaban 20 mg/d for 6 or 12 mo after initial long-term therapy.

<sup>b</sup>Included patients had acute, symptomatic, objectively verified proximal DVT of the legs or PE (unprovoked, 73%; cancer, 5%; previous VTE, 19%).

<sup>c</sup>Follow-up was prespecified to be 6 mo (60%) or 12 mo (40%).

<sup>d</sup>Allocation was concealed. Patients, providers, data collectors, and outcome adjudicators were blinded. ITT analysis; 0.2% loss to follow-up. Not stopped early for benefit.

<sup>e</sup>CI includes values suggesting benefit or no effect; relatively low number of events.

<sup>f</sup>Calculated from reported data with addition of one event to each event rate in control group.

<sup>g</sup>One definite or possible fatal VTE in rivaroxaban group and one in LMWH/VKA group.

<sup>h</sup>CI includes values suggesting benefit and harm.

<sup>i</sup>Bleeds contributing to death: none in the rivaroxaban group and none in the warfarin group.

<sup>j</sup>PTS: baseline risk over 2 y of 58.8% for PTS and 13.5% for severe PTS (Kahn et al<sup>19</sup>). There is threefold (Prandoni et al<sup>120</sup>) to 10-fold (van Dongen et al<sup>121</sup>) increase in PTS with recurrent VTE in the ipsilateral leg.
### Table S31—[Section 3.3] Dabigatran vs VKA Therapy for Long-term Treatment of VTE

<table>
<thead>
<tr>
<th>Participants (Studies)</th>
<th>Follow-up</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Publication Bias</th>
<th>Overall Quality of Evidence</th>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death (important outcome)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,539 (1 study), 6 mo</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious Undetected</td>
<td>Moderate due to imprecision</td>
<td>21/1,265 (1.7)</td>
<td>21/1,274 (1.6)</td>
<td>HR 0.98 (0.53-1.79)</td>
</tr>
<tr>
<td><strong>Recurrent VTE (critical outcome)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,539 (1 study), 6 mo</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious Undetected</td>
<td>Moderate due to imprecision</td>
<td>24/1,265 (1.9)</td>
<td>30/1,274 (2.4)</td>
<td>HR 1.01 (0.65-1.84)</td>
</tr>
<tr>
<td><strong>Major bleeding (critical outcome)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,539 (1 study), 6 mo</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious Undetected</td>
<td>Moderate due to imprecision</td>
<td>24/1,265 (1.9)</td>
<td>20/1,274 (1.6)</td>
<td>HR 0.82 (0.45-1.48)</td>
</tr>
</tbody>
</table>

| Burden of anticoagulation (important outcome) not reported | Warfarin: daily medication, dietary restrictions, frequent blood testing/monitoring, increased hospital/clinic visits | Dabigatran: daily medication, No dietary restrictions, no frequent blood testing/monitoring |

Bibliography: Schulman et al. See Table S2, S5, and S29 legends for expansion of abbreviations.

- Dabigatran 150 mg bid taken orally for 6 mo after an initial treatment with LMWH or IV UFH.
- Warfarin adjusted to achieve an INR of 2.0 to 3.0 for 6 mo after an initial treatment with LMWH or IV UFH.
- Included patients with acute, symptomatic, objectively verified proximal DVT of the legs or PE.
- Allocation was concealed. Patients, providers, data collectors, and outcome adjudicators were blinded. Modified ITT analysis; 1.1% loss to follow-up. Not stopped early for benefit.
- CI includes values suggesting no effect and values suggesting either benefit or harm; relatively low number of events.
- One fatal VTE in dabigatran group and three fatal VTEs in warfarin group.
- One fatal major bleeding event in dabigatran group and one fatal major bleeding event in warfarin group.
Table S32—[Section 4.1] Elastic Stocking for Prevention of PTS: Clinical Description and Results

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Publication</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brandjes et al(^{27})/1997</td>
<td>RCT</td>
<td>194 patients with first symptomatic proximal DVT</td>
<td>Compression stockings: below-knee customized elastic compression stockings with ankle pressure 30-40 mm Hg (96 patients) Control group: no intervention (96 patients)</td>
<td>Cumulative incidence of mild to moderate and severe PTS</td>
<td>3 and 6 mo, then every 6 mo to a median of 76 mo</td>
<td>Compression stockings: Mild-moderate PTS: 29% (RR, 0.42; 95% CI 0.27-0.66; ( P &lt; .001 )) Severe PTS: 11% (RR, 0.49; 95% CI, 0.25-0.95; ( P &lt; .001 )) Control group: Mild-moderate PTS: 47% Severe PTS: 23%</td>
</tr>
<tr>
<td>Ginsberg et al(^{24})/2001</td>
<td>RCT</td>
<td>47 asymptomatic patients with valvular incompetence 1 y post-DVT</td>
<td>Compression stockings: below-knee elastic compression stockings 20-30 mm Hg (24 patients) Placebo: placebo stocking (23 patients)</td>
<td>PTS symptoms</td>
<td>57 mo (mean)</td>
<td>Compression stockings: PTS symptoms: 0% Placebo: PTS symptoms: 4%</td>
</tr>
<tr>
<td>Prandoni et al(^{20})/2004</td>
<td>RCT</td>
<td>180 patients with first episode of symptomatic, acute proximal DVT</td>
<td>Compression stockings: below-knee elastic compression stockings 30-40 mm Hg (90 patients) Control group: no intervention (90 patients)</td>
<td>Cumulative incidence of mild to moderate and severe PTS</td>
<td>3-5 y</td>
<td>Compression stockings: PTS symptoms: 25% (CI, 15.6%-33.4%) Control group: PTS symptoms: 49% (CI, 38.7%-59.4%)</td>
</tr>
<tr>
<td>Partsch et al(^{49})/2004</td>
<td>2-y follow-up to RCT</td>
<td>37 symptomatic patients with acute DVT followed long term</td>
<td>All anticoagulated with LMWH followed by oral anticoagulation Inelastic bandages + early ambulation (13 patients) Elastic stockings (30 mm Hg) + early ambulation (15 patients) Bed rest for 9 d, no compression (11 patients)</td>
<td>Overall leg pain</td>
<td>2 y</td>
<td>Leg pain: No difference between groups Calf circumference: No difference between groups PTS score: Significantly better outcome with ambulation and bandaging or stockings compared with bed rest (( P &lt; .01 ))</td>
</tr>
<tr>
<td>Ashwanden et al(^{39})/2008</td>
<td>RCT, single center</td>
<td>169 first or recurrent proximal DVT without PTS after 6 mo of compression stockings</td>
<td>Compression stockings: below-knee, 26-36 mm Hg (84 patients) Control group: stopped stockings (85 patients)</td>
<td>PTS shin changes (( \geq C4 ) on CEAP)</td>
<td>0-7 y (mean, 3 y)</td>
<td>PTS compression stockings: 13% Control group: 20% HR: 0.8 (95% CI, 0.3-1.3)</td>
</tr>
</tbody>
</table>

See Table S1, S2, S5, S10, and S29 legends for expansion of other abbreviations.
Table S33—[Section 4.1] Elastic Stocking for Prevention of PTS: Methodologic Quality

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Randomization</th>
<th>Allocation Concealment</th>
<th>Blinding</th>
<th>Loss to Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brandjes et al&lt;sup&gt;1&lt;/sup&gt;/1997</td>
<td>Y</td>
<td>Y (sealed envelopes)</td>
<td>Patients: N Caregivers: N Assessors: Y Data analysis: PY</td>
<td>Intervention group: 4 lost to follow-up, 19 died Control group: 2 lost to follow-up, 18 died</td>
</tr>
<tr>
<td>Ginsberg et al&lt;sup&gt;1&lt;/sup&gt;/2001</td>
<td>Y</td>
<td>Probably, but not specified</td>
<td>Patients: Y Caregivers: Y Assessors: Y data analysis: PY</td>
<td>Intervention: lost to follow-up not reported, 3 died Control group: lost to follow-up not reported</td>
</tr>
<tr>
<td>Prandoni et al&lt;sup&gt;1&lt;/sup&gt;/2004</td>
<td>Y</td>
<td>Y</td>
<td>Patients: N caregivers: N Assessors: Y Data analysis: PY</td>
<td>Intervention: 2 lost to follow-up, 6 died Control group: 13 lost to follow-up</td>
</tr>
<tr>
<td>Ashwanden et al&lt;sup&gt;1&lt;/sup&gt;/2008</td>
<td>Y</td>
<td>Y</td>
<td>Patients: N Caregivers: N Assessors: N Data analysis: N</td>
<td>Intervention: 19 (described) Control group: 13 (described)</td>
</tr>
</tbody>
</table>

See Table S5 legend for expansion of abbreviations.
### Table S34—[Section 4.1] Evidence Profile: Elastic Compression Stockings vs No Elastic Compression Stockings To Prevent PTS of the Leg<sup>a,b</sup>

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants (Studies), Follow-up</td>
<td>With No Elastic Compression Stockings</td>
<td>With Elastic Compression Stockings</td>
</tr>
<tr>
<td>421 (2 studies), 2 y</td>
<td>91/211 (43.1)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>41/210 (19.5)</td>
</tr>
<tr>
<td>374 (2 studies), 5 y</td>
<td>26/188 (13.8)</td>
<td>26/186 (14)</td>
</tr>
</tbody>
</table>

**Study Event Rates (%):**
- **PTS (critical outcome; assessed with Villalta Score):**
  - Participants: 421 (2 studies), 2 y
  - With No Elastic Compression Stockings: 91/211 (43.1)<sup>e</sup>
  - With Elastic Compression Stockings: 41/210 (19.5)
  - Relative Effect: RR 0.46 (0.34-0.63)<sup>e</sup>
  - Risk Difference: 479 per 1,000<sup>f</sup>
  - Anticipated Absolute Effects: 259 fewer per 1,000 (from 177 fewer to 316 fewer)<sup>g</sup>

- **Recurrent VTE (critical outcome):**
  - Participants: 374 (2 studies), 5 y
  - With No Elastic Compression Stockings: 26/188 (13.8)
  - With Elastic Compression Stockings: 26/186 (14)
  - Relative Effect: RR 1.01 (0.61-1.67)<sup>e</sup>
  - Risk Difference: 210 per 1,000
  - Anticipated Absolute Effects: 2 more per 1,000 (from 82 fewer to 141 more)

**Quality of life (important outcome):**

- **0 (0):**
  - Participants: 0
  - Relative Effect: 1

**Summary of Findings:**

- **PTS:** RR 0.46 (0.34-0.63)<sup>e</sup>
  - Anticipated Absolute Effects: 259 fewer per 1,000 (from 177 fewer to 316 fewer)<sup>g</sup>
- **Recurrent VTE:** RR 1.01 (0.61-1.67)<sup>e</sup>
  - Anticipated Absolute Effects: 2 more per 1,000 (from 82 fewer to 141 more)

**Quality Assessment:**

- **Participants (Studies), Follow-up:**
  - Risk of Bias: Serious<sup>c</sup>
  - Inconsistency: No serious inconsistency
  - Indirectness: No serious indirectness
  - Imprecision: No serious imprecision
- **Publication Bias:** Undetected
- **Overall Quality of Evidence:** Moderate due to risk of bias
- **Risk With No Elastic Compression Stockings:** 91/211 (43.1)<sup>e</sup>
- **Risk With Elastic Compression Stockings:** 41/210 (19.5)
- **Relative Effect:** RR 0.46 (0.34-0.63)<sup>e</sup>
- **Risk Difference With Elastic Compression Stockings:** 479 per 1,000<sup>f</sup>
- **Anticipated Absolute Effects:** 259 fewer per 1,000 (from 177 fewer to 316 fewer)<sup>g</sup>

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**Bibliography:**

- Kolbach et al.<sup>123</sup> We excluded Ginsberg et al.<sup>124</sup> and Belcaro et al.<sup>125</sup> because they respectively randomized patients 7 and 12 mo after their DVT rather than at the time of the acute DVT. We also excluded Arpaia et al.<sup>126</sup> because they randomized patients to receive stockings at the time of diagnosis of DVT vs 2 wk later.<sup>126</sup> See Table S1 and S5 legends for expansion of abbreviations.

- Brandjes et al.<sup>127</sup> used graded elastic compression stockings (40 mm Hg of pressure at the ankle, 36 mm Hg at the lower calf, and 21 mm Hg at the upper calf); stockings were applied 2 to 3 wk after the first episode of proximal DVT. Prandoni et al.<sup>128</sup> used flat-knitted stockings (30-40 mm Hg of pressure at the ankle); stockings were started at hospital discharge an average of 1 wk after admission. In both studies, stockings were used for 2 y.

- Prandoni et al.<sup>129</sup> excluded patients with recurrent ipsilateral DVT, preexisting leg ulcers, or signs of CVI, bilateral thrombosis, a short life expectancy, or a contraindication for use of stockings (eg, advanced-stage peripheral arterial insufficiency). Brandjes et al. excluded patients with short life, paralysis of the leg, bilateral thrombosis, leg ulcers, or extensive varicosis.

- Patients were not blinded to the treatment assignment, and outcomes were partly based on subjective report of symptoms.

- In Prandoni et al.<sup>128</sup> most events occurred during the first 6 mo: the cumulative incidence of PTS in the control group was 40% after 6 mo, 47% after 1 y, and 49% after 2 y.

- The effect estimate shown here results from a meta-analysis (Mantel-Haenszel fixed-effects model) of the two relevant trials. A fixed-effects model was chosen because of the small number of studies available. This estimate is based on the findings of the VETO (Venous Thrombosis Outcomes) study. This probably underestimates the PTS baseline risk given that overall, 52% of patients reported the current use of compression stockings during study follow-up.

- Severe PTS: assuming the same RR of 0.46 and a baseline risk of 8.1% over 2 y, the absolute reduction is 44 fewer severe PTS per 1,000 (from 30 fewer to 53 fewer) over 2 y.

- We did not rate down the quality of evidence for recurrent VTE for the lack of blinding because this is a more objective outcome than PTS.

- CI includes both negligible effect and appreciable benefit or appreciable harm.

- This estimate is the mean of two estimates derived from two studies: 12.4% probable/definite VTE (Heit et al.<sup>128</sup>) and 29.1% confirmed VTE (Prandoni et al.<sup>128</sup>).

- This is an important outcome that should be considered in future studies.
Table S35—[Section 4.2.1] Evidence Profile: Compression Stockings vs No Compression Stockings for Patients With PTS

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Evidence</td>
<td>With No Compression Stockings</td>
<td>With Compression Stockings</td>
</tr>
<tr>
<td>Overall Quality of Evidence</td>
<td>Anticipated Absolute Effects</td>
<td>Risk With No Compression Stockings</td>
</tr>
<tr>
<td>Study Event Rates (%)</td>
<td>Risk With No Compression Stockings</td>
<td>Risk with Compression Stockings (95% CI)</td>
</tr>
<tr>
<td>Symptomatic relief (critical outcome; assessed with treatment success(^d))</td>
<td>33/57 (57.9)</td>
<td>32/58 (55.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants (Studies), Follow-up</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication Bias</th>
<th>Overall Quality of Evidence</th>
<th>With Compression Stockings</th>
<th>With No Compression Stockings</th>
<th>With Compression Stockings (95% CI)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>115 (2 studies), 12-26 mo</td>
<td>Serious(^a) No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious(^c) Undetected(^e)</td>
<td>Low(^f) due to risk of bias, imprecision</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of life not reported</td>
<td>...</td>
<td>...</td>
<td>...</td>
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<td>...</td>
<td>...</td>
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</tr>
<tr>
<td>Recurrent VTE not reported</td>
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<td>...</td>
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<td></td>
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<tr>
<td>Ulceration not reported(^g)</td>
<td>...</td>
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</tr>
</tbody>
</table>

Bibliography: Ginsberg 2001\(^1\), Frulla, 2005\(^2\) See Table S1, S2, S5, and S10 legends for expansion of abbreviations.

\(^1\)Ginsberg et al: graduated compression stockings, 30-40 mm Hg (calf or thigh length, depending on symptoms). Patients were encouraged to wear stockings as much as possible during waking hours. Frulla (2005): below-knee graded elastic compression stockings (ECS) (30-40 mm Hg at the ankle). Patients in both arms of the study received hydroxyethylrutosides (HR) (we considered the ECS + HR vs HR comparison).

\(^2\)Ginsberg et al: placebo stockings (calf or thigh length, depending on symptoms).

\(^3\)Ginsberg et al included patients with PTS 1 y after chronic, typical proximal DVT. Frulla (2005) included patients with clinical symptoms and signs suggestive of PTS.

\(^4\)Ginsberg et al reported treatment failure (defined a priori based on any of five clinical criteria, including symptoms and ulcer development). Treatment success refers to the absence of treatment failure. Frulla used the Villalta scale.

\(^5\)Ginsberg et al: Adequacy of sequence generation and allocation concealment were unclear; patients and outcome assessors were adequately blinded; unclear whether analysis followed the ITT principle; unclear whether follow-up was complete. Frulla (2005): outcome assessors were blinded; follow-up was complete. ITT principle was adhered to, but sequence generation and allocation concealment were unclear, and patients were not blinded.

\(^6\)Very small number of patients.

\(^7\)Publication bias not detected but not ruled out given that we identified only one small study partially supported by industry (provision of graduated compression stockings).

\(^8\)Indirect evidence from the CLOTS1 (Clots in Legs Or Stockings after Stroke) trial suggests that compression stockings is associated with an RR of 4 for skin complications.

\(^9\)Absence of ulcer included in the treatment success outcome in Ginsberg et al.
Table S36—[Section 4.2.2] Evidence Profile: Intermittent Compression Device vs No Intermittent Compression Device for Patients With Severe PTS

<table>
<thead>
<tr>
<th>Participants (Studies), Follow-up</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication Bias</th>
<th>Overall Quality of Evidence</th>
<th>Study Event Rates (%) With No Intermittent Compression Device</th>
<th>Study Event Rates (%) With Intermittent Compression Device</th>
<th>Relative Effect (95% CI)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic relief (critical outcome; measured with symptom score (includes scoring of pain, swelling, and limitation of activity); range of scores, 10-70; better indicated by higher values)</td>
<td></td>
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</tr>
<tr>
<td>82 (2 studies), 8 wk</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Undetected</td>
<td>41d</td>
<td>Moderate due to imprecision</td>
<td>82 (2 studies), 8 wk</td>
<td>82 (2 studies), 8 wk</td>
<td>0.41</td>
<td>The mean symptomatic relief in the control groups was 0.41 SDs higher (0.02 lower to 0.85 higher)</td>
</tr>
</tbody>
</table>

| Quality of life (critical outcome; measured with VEINES-QOL; range of scores, 0-100; better indicated by higher values) |
| 0 (1 study), 8 wk               | No serious risk of bias | No serious inconsistency | No serious indirectness | Undetected | 0               | 0                           | 0 (1 study), 8 wk | 0 (1 study), 8 wk | 2.3 | The mean quality of life in the intervention groups was 2.3 higher (1.04 lower to 5.64 higher) |

(Continued)
### Quality Assessment

<table>
<thead>
<tr>
<th>Study Event Rates (%)</th>
<th>Summary of Findings</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Recurrent VTE not reported&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ulceration not reported&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants (Studies)</th>
<th>Follow-up</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication Bias</th>
<th>Overall Quality of Evidence</th>
<th>With No Intermittent Compression Device</th>
<th>With Intermittent Compression Device</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With No Intermittent Compression Device</th>
<th>Risk Difference With Intermittent Compression Device (95% CI)</th>
</tr>
</thead>
<tbody>
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</tr>
</tbody>
</table>

**Bibliography:** Ginsberg 1999, O'Donnell, 2008. See Table S1, S5, and S10 legends for expansion of other abbreviations.

<sup>a</sup>Ginsberg et al: Extremity pump used bid for 20 min each session; 50 mm Hg (therapeutic pressure) for 1 mo. O'Donnell et al: Venowave lower-limb venous return assist device to wear for most of the day for 8 wk.

<sup>b</sup>Ginsberg et al: Extremity pump used bid for 20 min each session; 15 mm Hg (placebo pressure) for 1 mo. O'Donnell et al: Venowave lower-limb venous return assist device with no connection between motor and planar sheet for 8 wk.

<sup>c</sup>Patients with previous DVT with symptoms of severe PTS.

<sup>d</sup>Crossover RCTs.

<sup>e</sup>In both studies, sequence generation was adequate; patients were blinded. Analysis adhered to ITT principle, and there were no missing outcome data. In Ginsberg et al (but not in O'Donnell et al), outcome assessors were not blinded, and it was not clear whether allocation was concealed.

<sup>f</sup>$I^2 = 0\%$.

<sup>g</sup>Some concerns with indirectness given relatively short follow-up (8 wk).

<sup>h</sup>Very small number of patients. CI includes both values suggesting no effect and values suggesting a beneficial effect.

<sup>i</sup>Publication bias not detected but not ruled out given that we identified only two small studies with one (Ginsberg et al) partially supported by industry (provision of devices).

<sup>j</sup>O'Donnell et al.

<sup>k</sup>Sequence generation was adequate; patients were blinded; analysis adhered to ITT principle; and there were no missing outcome data. However, outcome assessors were not blinded, and it was not clear whether allocation was concealed.

<sup>l</sup>Publication bias not detected but not ruled out given that we identified only one small study.

<sup>m</sup>O'Donnell et al indicated no cases of recurrent VTE by the end of this study but judged the follow-up period to be short.

<sup>n</sup>O'Donnell et al indicated that one patient in the control group developed a venous ulceration. Three other participants developed nonserious skin-related side effects. Indirect evidence from the CLOTS1 (Clots in Legs Or sTockings after Stroke) trial suggests that compression stockings are associated with an RR of 4 for skin complications. Common side effects are attributed to Venowave were heat sensation, skin irritation, and increased sweating.
Table S37—[Section 4.3] Evidence Profile: Venoactive Medication vs No Venoactive Medication for Patients With PTS

<table>
<thead>
<tr>
<th>Study Event Rates (%)</th>
<th>Study Rates (%)</th>
<th>Relative Effect (95% CI)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptomatic relief</strong> (critical outcome; assessed with PTS score (Villalta scale) &lt; 5 or decreased by 30% at 12 mo compared with baseline in Frulla et al; improved tiredness of the leg at 8 wk in de Jongste et al)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants (Studies), Follow-up Risk of Bias Inconsistency Indirectness Imprecision</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With No Venoactive Medication</td>
<td>With Venoactive Medication</td>
<td>Relative Effect (95% CI)</td>
<td>Risk With No Venoactive Medication</td>
</tr>
<tr>
<td>Symptomatic relief (critical outcome; assessed with PTS score (Villalta scale) &lt; 5 or decreased by 30% at 12 mo compared with baseline in Frulla et al; improved tiredness of the leg at 8 wk in de Jongste et al)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>163 (2 studies)</td>
<td>No serious risk of bias</td>
<td>Serious</td>
<td>No serious indirectness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Quality of life not reported

Recurrent VTE not reported

Ulceration not reported

Side effects (critical outcome)

<table>
<thead>
<tr>
<th>Study Event Rates (%)</th>
<th>Study Rates (%)</th>
<th>Relative Effect (95% CI)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants (Studies), Follow-up Risk of Bias Inconsistency Indirectness Imprecision</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With No Venoactive Medication</td>
<td>With Venoactive Medication</td>
<td>Relative Effect (95% CI)</td>
<td>Risk With No Venoactive Medication</td>
</tr>
<tr>
<td>Symptomatic relief (critical outcome; assessed with PTS score (Villalta scale) &lt; 5 or decreased by 30% at 12 mo compared with baseline in Frulla et al; improved tiredness of the leg at 8 wk in de Jongste et al)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>203 (2 studies)</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

Bibliography: Frulla 2005; de Jongste 1989. See Table S1, S5, and S10 legends for expansion of abbreviations.

1Included studies assessed rutosides; we excluded Monreal et al because it compared two venoactive medications.

1Patients with PTS and history of DVT in PTS leg.

1Investigators assessed other symptoms (pain, heaviness, swelling feeling, restless legs, and cramps) but did not report a composite score. The symptom we chose to report showed the most benefit; the effect estimates for the other symptoms ranged from 0.8 to 1.4, and none was statistically significant.

1In both studies, sequence generation and allocation concealment were unclear. Both studies blinded outcome assessors and had complete follow-up. Although de Jongste et al blinded patients, they did not adhere to the ITT principle and did not use a validated scale to measure symptomatic relief. Although Frulla (2005) adhered to the ITT principle, it did not blind patients.

1P = 77%.

1Small number of patients. CI including both values suggesting harms and values suggesting benefits.

1Publication bias not detected but not ruled out given that we identified only two small studies, and it was unclear whether they were funded by industry.

1V = 7%.
Table S38—[Section 5.4] Evidence Profile: Fondaparinux vs IV UFH for Initial Anticoagulation of Acute PE**

<table>
<thead>
<tr>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study Event Rates (%)</td>
</tr>
<tr>
<td></td>
<td>With UFH</td>
</tr>
<tr>
<td></td>
<td>Overall Quality of Evidence</td>
</tr>
<tr>
<td></td>
<td>Mortality (important outcome)</td>
</tr>
<tr>
<td>Participants</td>
<td>2,213 (1 study), 3 mo</td>
</tr>
<tr>
<td>Follow-up</td>
<td>No serious risk of bias(^d)</td>
</tr>
<tr>
<td>Risk of Bias</td>
<td>No serious risk of bias(^d)</td>
</tr>
<tr>
<td>Inconsistency</td>
<td>No serious indirectness</td>
</tr>
<tr>
<td>Indirectness</td>
<td>Serious(^e)</td>
</tr>
<tr>
<td>Imprecision</td>
<td>Moderate(^d,e) due to imprecision</td>
</tr>
<tr>
<td>Publication Bias</td>
<td></td>
</tr>
<tr>
<td>Overall Quality of Evidence</td>
<td></td>
</tr>
<tr>
<td>Anticipated Difference With Fondaparinux (95% CI)</td>
<td></td>
</tr>
</tbody>
</table>

Bibliography: Büller et al.\(^{136}\) See Table S1, S2, S4, and S7 legends for expansion of abbreviations.

\(^a\)Fondaparinux (5.0, 7.5, or 10.0 mg in patients weighing <50, 50 to 100, or > 100 kg, respectively) SC once daily given for at least 5 days and until the use of VKAs resulted in an INR > 2.0.

\(^b\)UFH continuous IV infusion (ratio of the aPTT to a control value, 1.5-2.5) given for at least 5 days and until the use of VKAs resulted in an INR > 2.0.

\(^c\)All patients had acute symptomatic hemodynamically stable PE.

\(^d\)Allocation was concealed. Patients, providers, and data collectors not blinded. Outcome adjudicators were blinded; 0.6% of randomized patients were lost to follow-up. Not stopped early for benefit.

\(^e\)CI includes values suggesting no effect and values suggesting either benefit or harm; relatively low number of events.

\(^f\)Sixteen fatal VTE in fondaparinux group and 15 fatal VTE in UFH group.

\(^g\)Fourteen patients in the fondaparinux group and 12 in the LMWH group had a major bleeding during the initial period (6-7 d). Of these, one in the fondaparinux group and one in the UFH group were fatal.
### Table S39—[Section 5.5] Evidence Profile: Early Discharge vs Standard Discharge in the Treatment of Acute PE<sup>a,b</sup>

<table>
<thead>
<tr>
<th>Participants (Studies), Follow-up</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Overall Quality of Evidence</th>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>With Standard Discharge</td>
<td>Risk With Standard Discharge</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>With Early Discharge</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Mortality (critical outcome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR 0.58 (0.17-1.97)</td>
<td>26 per 1,000</td>
</tr>
<tr>
<td>471 (2 studies), 3 mo</td>
<td>Serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Undetected</td>
<td>6/228 (2.6)</td>
<td>4/243 (1.6)</td>
</tr>
<tr>
<td>Nonfatal recurrent PE (critical outcome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR 1.23 (0.25-6.03)</td>
<td>9 per 1,000</td>
</tr>
<tr>
<td>471 (2 studies), 3 mo</td>
<td>Serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Undetected</td>
<td>2/228 (0.9)</td>
<td>3/243 (1.2)</td>
</tr>
<tr>
<td>Major bleeding (critical outcome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR 2.74 (0.45-16.71)</td>
<td>4 per 1,000</td>
</tr>
<tr>
<td>471 (2 studies), 3 mo</td>
<td>Serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Undetected</td>
<td>1/228 (0.4)</td>
<td>4/243 (1.6)</td>
</tr>
</tbody>
</table>

Quality of life not reported

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See Table S1, S2, and S5 legends for expansion of abbreviations.

The two RCTs included only patients with low risk: risk classes I or II on the Pulmonary Embolism Severity Index in Aujesky et al<sup>139</sup>; low risk on clinical prediction rule by Uresandi et al<sup>140</sup> in Otero et al.

Otero et al: allocation concealed, no patients lost to follow-up, ITT analysis, no blinding of outcome assessors reported, study stopped early because the rate of short-term mortality was unexpectedly high in the early discharge group (2 [2.8%] vs 0 [0%]). Aujesky et al: unclear whether allocation was concealed, three (1%) patients had missing outcome data, ITT analysis, outcome adjudicators blinded, no early stoppage.

<sup>a</sup>CI includes both values suggesting no effect and values suggesting appreciable harm or appreciable benefit.

<sup>b</sup>Mean length of hospital stay: 3.4 (SD 1.1) vs 9.3 (SD 5.7) in Otero et al and 0.5 (SD 1.0) vs 3.9 (SD 3.1) in Aujesky et al.

<sup>c</sup>The two RCTs included only patients with low risk: risk classes I or II on the Pulmonary Embolism Severity Index in Aujesky et al<sup>139</sup>; low risk on clinical prediction rule by Uresandi et al<sup>140</sup> in Otero et al.

<sup>d</sup>Otero et al: allocation concealed, no patients lost to follow-up, ITT analysis, no blinding of outcome assessors reported, study stopped early because the rate of short-term mortality was unexpectedly high in the early discharge group (2 [2.8%] vs 0 [0%]). Aujesky et al: unclear whether allocation was concealed, three (1%) patients had missing outcome data, ITT analysis, outcome adjudicators blinded, no early stoppage.
Table S40—[Section 5.6.1] Evidence Profile: Systemic Thrombolytic Therapy vs Anticoagulation Alone in Patients With Acute PE<sup>a-d</sup>

<table>
<thead>
<tr>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mortality (critical outcome)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants (Studies), Follow-up</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Overall Quality of Evidence</th>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>847 (12 studies), 30 d</td>
<td>Serious&lt;sup&gt;e&lt;/sup&gt;</td>
<td>No serious inconsistency&lt;sup&gt;e&lt;/sup&gt;</td>
<td>No serious indirectness</td>
<td>Serious&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Undetected&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Low&lt;sup&gt;c&lt;/sup&gt; due to risk of bias and imprecision</td>
<td>26/423 (6.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15/424 (3.5)</td>
<td></td>
</tr>
<tr>
<td>Recurrent PE (important outcome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30/404 (7.4)</td>
<td>RR 0.7 (0.4-1.21)</td>
</tr>
<tr>
<td>801 (9 studies), 30 d</td>
<td>Serious&lt;sup&gt;e&lt;/sup&gt;</td>
<td>No serious inconsistency&lt;sup&gt;e&lt;/sup&gt;</td>
<td>No serious indirectness</td>
<td>Serious&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Undetected&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Low&lt;sup&gt;c&lt;/sup&gt; due to risk of bias and imprecision</td>
<td>18/397 (4.5)</td>
</tr>
<tr>
<td>Major bleeding (critical outcome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>38/424 (9)</td>
<td>RR 1.63 (1.26)&lt;sup&gt;l&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> With No Systemically Administered Thrombolytic Therapy
<sup>b</sup> With Systemically Administered Thrombolytic Therapy
<sup>c</sup> Relative Effect (95% CI)
<sup>d</sup> Mortality (critical outcome)
<sup>e</sup> Recurrent PE (important outcome)
<sup>f</sup> Major bleeding (critical outcome)
<sup>g</sup> No serious indirectness
<sup>h</sup> Low due to risk of bias and imprecision
<sup>i</sup> Low due to risk of bias and imprecision
<sup>j</sup> Moderate due to risk of bias and imprecision
<sup>k</sup> More or less due to risk of bias and imprecision
<sup>l</sup> More or less due to risk of bias and imprecision

(Continued)
<table>
<thead>
<tr>
<th>Study Event Rates (%)</th>
<th>Summary of Findings</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>With No Systemically Administered Thrombolytic Therapy</td>
<td>Overall Quality of Evidence</td>
<td>With Systemically Administered Thrombolytic Therapy</td>
</tr>
<tr>
<td>Participants (Studies), Follow-up Risk of Bias Inconsistency Indirectness Imprecision Publication Bias</td>
<td>Relative Effect (95% CI)</td>
<td>Risk With No Systemically Administered Thrombolytic Therapy</td>
</tr>
<tr>
<td>With No Systemically Administered Thrombolytic Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Quality of Evidence</td>
<td>Relative Effect (95% CI)</td>
<td>Risk With No Systemically Administered Thrombolytic Therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>62 per 1,000</td>
<td>39 more per 1,000 (from 0 more to 104 more)</td>
</tr>
</tbody>
</table>

Bibliography: Nine earlier studies extracted from three systematic reviews (Dong et al., Wan et al., Agnelli et al.) and two recently published studies (Becattini C et al., Fasullo et al.). See Table S1 and S2 legends for expansion of abbreviations.

*Included studies used different thrombolytic agents with varying doses and durations of administration; no statistical heterogeneity was noted.

*Thrombolysis was in addition to anticoagulation (most of the studies used heparin followed by warfarin; three studies used warfarin only).

*One study included exclusively patients with hemodynamic compromise (shock); six excluded them, whereas the rest either included a number of such patients or did not specify related eligibility criteria. Of studies not restricted to patients with hemodynamic compromise (n = 11), only three were clearly restricted to patients with right ventricular dysfunction; the rest either did not specify related eligibility criteria or included both patients with and without right ventricular dysfunction. As a result, it was not possible to perform reliable categorization of studies to conduct subgroup analyses based on the presence or absence of right ventricular dysfunction or hemodynamic compromise.

*Studies included patients at low risk of bleeding.

*Report of methodologic quality was poor in most studies. Of the 12 eligible studies, allocation was concealed in five, three were single blinded (outcome assessor), six were double blinded, and three were not blinded. Most studies did not report on missing outcome data. None of the studies was stopped early for benefit. For the increase in bleeding with thrombolytic therapy, quality of evidence is increased from low to moderate because there is high quality evidence of this association in patients with myocardial infarction and the indirectness of this evidence to patients with PE is minor.

*I² = 0%.

*CI includes values suggesting both benefit and no effect or harm; small number of events.

*Inverted funnel plots suggested possible publication bias in favor of thrombolytics.

*Recurrent PE stratification based on the simplified Pulmonary Embolism Severity Index validated in the RIETE (Registro Informatizado de la Enfermedad Tromboembólica) cohort.

*Some studies suggest that the baseline risk of mortality in patients with hemodynamic instability is high as 30% (Wood et al.). In that case, the absolute number of death associated with thrombolytics would be 90 fewer per 1,000 (from 189 fewer to 93 more).

*CI includes values suggesting both harm and no effect; small number of events.

*Indirect evidence from studies of thrombolysis for myocardial infarction and acute stroke provide more-precise estimates of increase major bleeding with thrombolytics use.

*Major bleeding risk stratification derived from the RIETE cohort. The median risk of bleeding over the first 10 d reported in the eligible trials was 3.1%. In that case, the absolute number of major bleeds with thrombolysis would be 20 per 1,000 (from 0 more to 52 more).
### Table S41—[Section 5.6.1] Systemic Thrombolytic Therapy vs Anticoagulation Alone in Patients With Acute PE: Clinical Description and Results

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Interventions</th>
<th>No. Patients Analyzed</th>
<th>Length of Follow-up</th>
<th>Recurrent DVT and PE (%) RR (95% CI)</th>
<th>Major Bleeding (%) RR (95% CI)</th>
<th>Total Mortality (%) RR (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tibbutt et al¹⁰/1974</td>
<td>SK 600,000 units intrapulmonary followed by 100,000 units for 72 h</td>
<td>SK: 11/13 (84.6%)</td>
<td>72 h</td>
<td>SK: 0/11</td>
<td>SL: 1/11 (9.1%)</td>
<td>SK: 0/11</td>
<td>All hydrocortisone 100 mg and at 60 h of treatment warfarin initial dose 25 mg for 6 mo. Seven patients who failed to complete the treatment regimen were excluded from the analysis. Patients reporting major bleeding required a blood transfusion. Some 6-mo follow-up data available.</td>
</tr>
<tr>
<td></td>
<td>Heparin 5,000 units intrapulmonary followed by 2,500 units for 72 h</td>
<td>Heparin: 12/17 (70.6%)</td>
<td></td>
<td>Heparin: 0/12</td>
<td>Heparin: 1/12 (8.3%)</td>
<td>RR 0.92 (0.06-12.95)</td>
<td>Heparin: 0/12</td>
</tr>
<tr>
<td>Ly et al¹⁰/1978</td>
<td>SK 250,000 units followed by 100,000 units/h for 72 h</td>
<td>SK: 14/14</td>
<td>10 d</td>
<td>SK: 1/14 (7.1%)</td>
<td>SK: 4/14 (28.6%)</td>
<td>SK: 1/14 (7.1%)</td>
<td>Primary outcome was angiographic reperfusion. Five of the 25 patients received nonrandomized therapy. Uncertain if deaths were in patients who were randomized or not randomized.</td>
</tr>
<tr>
<td></td>
<td>Heparin 15,000 units followed by 1,250 units/h for 7 d</td>
<td>Heparin: 11/11</td>
<td></td>
<td></td>
<td>Heparin: 2/11 (18.2%)</td>
<td>RR 2.55 (0.12-24.56)</td>
<td></td>
</tr>
<tr>
<td>Dotter et al¹⁰/1979</td>
<td>SK 250,000 units followed by 100,000 units/h for 18-72 h</td>
<td>SK: 15/15</td>
<td>In hospital</td>
<td>SK: 0/15</td>
<td>SK: 3/15 (20.0%)</td>
<td>SK: 1/15 (6.7%)</td>
<td>All: warfarin/VKA. Primary outcome was angiographic reperfusion (not clearly stated).</td>
</tr>
<tr>
<td></td>
<td>Heparin 1,500 units per kg for 2-7 d</td>
<td>Heparin: 16/16</td>
<td></td>
<td>Heparin: 1/16 (6.3%)</td>
<td>Heparin: 4/16 (25.0%)</td>
<td>Heparin: 2/16 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>Jerjes-Sanchez et al¹⁰/1995</td>
<td>SK 1,500,000 units over 1 h followed by a bolus of heparin 10,000 units + constant infusion of 1,000 units/h</td>
<td>SK: 4/4</td>
<td>In hospital</td>
<td>SK: 0/4 (0%)</td>
<td>SK: 0/4 (0%)</td>
<td>SK: 0/4 (0%)</td>
<td>Primary outcome not stated. Trial stopped early for benefit. All patients had cardiogenic shock at randomization. Heparin-treated patients appear to have failed heparin therapy before randomization, whereas the SK patients had not.</td>
</tr>
<tr>
<td></td>
<td>Heparin 10,000 units followed by 1,000 units/h</td>
<td>Heparin: 4/4</td>
<td></td>
<td>Heparin: 4/4 (100%)</td>
<td>Heparin: 0/4 (0%)</td>
<td>Heparin: 4/4 (100%)</td>
<td></td>
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</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Interventions</th>
<th>No. Patients Analyzed</th>
<th>Length of Follow-up</th>
<th>Recurrent DVT and PE (%) RR (95% CI)</th>
<th>Major Bleeding (%) RR (95% CI)</th>
<th>Total Mortality (%) RR (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UPET Study Group et al</strong>&lt;sup&gt;1970&lt;/sup&gt;</td>
<td>Urokinase: infusion of 2,000 CTA units/lb followed by 2,000 CTA units/lb per h</td>
<td>Urokinase 82/82</td>
<td>2 wk</td>
<td>Urokinase: 12/82 (14.6%)</td>
<td>Urokinase: 37/82 (45.1%)</td>
<td>Urokinase: 6/82 (7.3%)</td>
<td>All: heparin for a minimum of 5 d. The major bleeding reported includes moderate + severe bleeding. Angiographic follow-up data available up to 12 mo.</td>
</tr>
<tr>
<td></td>
<td>Heparin: infusion of 75 units/lb followed by 10 units/lb per h</td>
<td>Heparin: 78/78</td>
<td></td>
<td>Heparin: 15/78 (19.2%) RR 1.31 (0.66-2.63)</td>
<td>Heparin: 21/78 (26.9%) RR 0.60 (0.39-0.92)</td>
<td>Heparin: 7/78 (8.9%) RR 1.23 (0.43-3.49)</td>
<td></td>
</tr>
<tr>
<td><strong>Marini et al</strong>&lt;sup&gt;67/1988&lt;/sup&gt;</td>
<td>High-dose: urokinase 3,300,000 units over 12 h</td>
<td>High-dose urokinase: 10/10</td>
<td>7 d</td>
<td>High-dose urokinase: 0/10</td>
<td>High-dose urokinase: 0/10</td>
<td>High-dose urokinase: 0/10</td>
<td>Primary outcome was lung scan perfusion. Thrombolysis arms did not receive heparin. All patients: OACs continued for 1 y.</td>
</tr>
<tr>
<td></td>
<td>Low-dose: urokinase 800,000 units over 12 h daily for 3 d</td>
<td>Low-dose urokinase: 10/10</td>
<td></td>
<td>Low-dose urokinase: 0/10</td>
<td>Low-dose urokinase: 0/10</td>
<td>Low-dose urokinase: 0/10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heparin 30,000 units/d for 7 d followed by OAC</td>
<td>Heparin: 0/10</td>
<td></td>
<td>Heparin: 0/10</td>
<td>Heparin: 0/10</td>
<td>Heparin: 0/10</td>
<td></td>
</tr>
<tr>
<td><strong>Dalla-Volta et al</strong>&lt;sup&gt;142/1992&lt;/sup&gt;</td>
<td>rt-PA 10 mg followed by 90 mg over 2 h</td>
<td>rt-PA alteplase: 20/20</td>
<td>30 d</td>
<td>rt-PA alteplase: 1/20 (3.0%)</td>
<td>rt-PA alteplase: 3/20 (15.0%)</td>
<td>rt-PA alteplase: 2/20 (10.0%)</td>
<td>Primary outcome was angiographic reperfusion.</td>
</tr>
<tr>
<td></td>
<td>Heparin 10,000 units followed by 1,750 units/h for 7-10 d</td>
<td>Heparin: 16/16</td>
<td></td>
<td>Heparin: 0/16 RR 2.43 (0.11-55.89)</td>
<td>Heparin: 2/16 (12.5%) RR 1.20 (0.23-6.34)</td>
<td>Heparin: 16/16 RR 4.05 (0.21-78.76)</td>
<td></td>
</tr>
<tr>
<td><strong>Goldhaber et al</strong>&lt;sup&gt;199/1993&lt;/sup&gt;</td>
<td>rt-PA alteplase 100 mg over 2 h followed by heparin 1,000 units/h</td>
<td>rt-PA: 46/46</td>
<td>In hospital 14-21 d</td>
<td>rt-PA: 0/46</td>
<td>rt-PA: 3/46 (6.5%)</td>
<td>rt-PA: 0/46</td>
<td>Primary outcome was echocardiographic right ventricular function.</td>
</tr>
<tr>
<td></td>
<td>Heparin 5,000 units followed by 1,000 units/h</td>
<td>Heparin: 55/55</td>
<td></td>
<td>Heparin: 5/55 (9.1%) RR 0.11 (0.01-1.91)</td>
<td>Heparin: 1/55 (1.8%) RR 3.39 (0.39-33.33)</td>
<td>Heparin: 2/55 (3.6%) RR 0.24 (0.01-8.44)</td>
<td></td>
</tr>
<tr>
<td><strong>Konstantinides et al</strong>&lt;sup&gt;193/2002&lt;/sup&gt;</td>
<td>Alteplase 100 mg followed by alteplase 90 mg over 2 h + heparin 1,000 units/h</td>
<td>Alteplase: 118/118</td>
<td>30 d</td>
<td>Alteplase: 4/118 (3.4%) Alteplase: 1/118 (0.8%)</td>
<td>Alteplase: 4/118 (3.4%) Alteplase: 1/118 (0.8%)</td>
<td>Alteplase: 4/118 (3.4%) Alteplase: 1/118 (0.8%)</td>
<td>Primary outcome was death or need for escalation of therapy (later decision could be made after unblinding).</td>
</tr>
<tr>
<td></td>
<td>Heparin 5,000 units followed by 1,000 units/h + placebo</td>
<td>Heparin + placebo: 138/138</td>
<td></td>
<td>Heparin + placebo: 4/138 (2.9%) RR 1.17 (0.30-4.57)</td>
<td>Heparin + placebo: 5/138 (3.6%) RR 0.23 (0.03-1.97)</td>
<td>Heparin + placebo: 3/138 (2.2%) RR 1.56 (0.36-6.83)</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Interventions</th>
<th>No. Patients Analyzed</th>
<th>Length of Follow-up</th>
<th>Recurrent DVT and PE (%) RR (95% CI)</th>
<th>Major Bleeding (%) RR (95% CI)</th>
<th>Total Mortality (%) RR (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levine et al18/1990</td>
<td>rt-PA 0.6mg/kg over 2 min</td>
<td>rt-PA: 33/33</td>
<td>10 d</td>
<td>rt-PA: 0/33</td>
<td>rt-PA: 0/33</td>
<td>rt-PA: 1/33 (3.0%)</td>
<td>Primary outcome was lung scan reperfusion</td>
</tr>
<tr>
<td></td>
<td>Placebo plus heparin 5,000 units followed by 30,000/d</td>
<td>Placebo: 25/25</td>
<td></td>
<td>Placebo: 0/25</td>
<td>Placebo: 0/25</td>
<td>Placebo: 0/25 RR 2.29 (0.10-54.06)</td>
<td></td>
</tr>
<tr>
<td>PIOPED Investigators 18/1990</td>
<td>rt-PA 40-80 mg at 1 mg/min</td>
<td>rt-PA: 9/9</td>
<td>7 d</td>
<td>rt-PA: 0/9</td>
<td>rt-PA: 1/9 (11.1%)</td>
<td>rt-PA: 0/9</td>
<td>Primary outcome not stated</td>
</tr>
<tr>
<td></td>
<td>Placebo + heparin (doses determined by physician)</td>
<td>Placebo: 4/4</td>
<td></td>
<td>Placebo: 0/4</td>
<td>Placebo: 0/4 RR 1.50 (0.07-30.59)</td>
<td>Placebo: 0/4</td>
<td>Heparin doses determined by attending physician in both groups One death occurred 19 d after treatment</td>
</tr>
<tr>
<td>Fasullo et al 15/2011</td>
<td>Alteplase 100 mg over 2 h</td>
<td>Alteplase: 37/37</td>
<td>10 d</td>
<td>Alteplase: 0/37</td>
<td>Alteplase: 2/37 (5.4%)</td>
<td>Alteplase: 0/37</td>
<td>All had right ventricular dysfunction. Primary outcome was echocardiographic changes. Three recurrent PE were fatal. One additional fatal and nonfatal PE in heparin arm by 180 d. No fatal or intracranial bleeds.</td>
</tr>
<tr>
<td></td>
<td>Placebo + heparin 5,000 units followed by 1,000 units/h</td>
<td>Placebo: 35/35</td>
<td></td>
<td>Placebo: 3/35 (8.5%)</td>
<td>Placebo: 1/35 (2.9%)</td>
<td>Placebo: 5/35 (14.2%)</td>
<td></td>
</tr>
<tr>
<td>Becattini et al 10/2010</td>
<td>Tenectaplace: ~2 mg/kg bolus</td>
<td>Tenectaplace: 28/28</td>
<td>30 d</td>
<td>Tenectaplace: 2/28</td>
<td>Tenectaplace: 2/28</td>
<td>Tenectaplace: 0/28</td>
<td>All had right ventricular dysfunction. Primary outcome was echocardiographic changes. No fatal PE or major bleeding; one intracranial bleed (tenectaplace).</td>
</tr>
<tr>
<td></td>
<td>Placebo + heparin (80 International Units/kg and 18 International Units/kg per h)</td>
<td>Placebo: 32/32</td>
<td></td>
<td>Placebo: 1/32</td>
<td>Placebo: 1/32</td>
<td>Placebo: 1/32</td>
<td></td>
</tr>
</tbody>
</table>

CTA = Committee on Thrombolytic Agents; OAC = oral anticoagulant; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; UPET = Urokinase Pulmonary Embolism Trial. See Table S1, S2, and S11 legends for expansion of other abbreviations.
### Table S42—:[Section 5.6.1] Systemic Thrombolytic Therapy vs Anticoagulation Alone in Patients With Acute PE: Methodologic Quality

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Intervention</th>
<th>Study Design</th>
<th>Randomize</th>
<th>Blinding</th>
<th>Lost to Follow-up</th>
<th>Analysis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tibbutt et al 1974</td>
<td>SK 600,000 units intrapulmonary followed by 100,000 units for 72 h</td>
<td>RCT</td>
<td>PY</td>
<td>SK: 0/11 (0%)</td>
<td>Per protocol</td>
<td>All hydrocortisone 100 mg and at 60 h of treatment, warfarin initial dose 25 mg for 6 mo.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heparin 5,000 units intrapulmonary followed by 2,500 units for 72 h</td>
<td></td>
<td></td>
<td></td>
<td>Heparin: 0/12 (0%)</td>
<td>Seven patients who failed to complete the treatment regimen were excluded from the analysis.</td>
<td></td>
</tr>
<tr>
<td>Lyet et al 1978</td>
<td>SK 250,000 units followed by 100,000 units/h for 72 h</td>
<td>RCT</td>
<td>CY</td>
<td>SK: 0/14 (0%)</td>
<td>As treated</td>
<td>Included 5 nonrandomized patients, and uncertain if deaths occurred in those who were randomized or not randomized.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heparin 15,000 U followed by 1250 U/h for 7 days</td>
<td></td>
<td></td>
<td></td>
<td>Heparin: 0/11 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dotter et al 1979</td>
<td>SK 250,000 units followed by 100,000 units/h for 18-72 h</td>
<td>RCT</td>
<td>PY</td>
<td>SK plus heparin: 0/15 (0%)</td>
<td>ITT</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heparin 1.500 units per kg for 2-7 d</td>
<td></td>
<td></td>
<td></td>
<td>Heparin: 0/16 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jerjes-Sanchez et al 1995</td>
<td>SK 1,500,000 units over 1 h followed by a bolus of heparin 10,000 units + constant infusion of 1,000 units/h</td>
<td>RCT</td>
<td>CY</td>
<td>SK + heparin: 0/4 (0%)</td>
<td>ITT</td>
<td></td>
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<tr>
<td></td>
<td>Heparin 10,000 units followed by 1,000 units/h</td>
<td></td>
<td></td>
<td></td>
<td>Heparin: 0/4 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPET Study Group 1970</td>
<td>Urokinase: infusion of 2,000 CTA units/lb followed by 2,000 CTA units/lb per h Heparin: infusion of 75 units/lb followed by 10 units/lb per h</td>
<td>RCT</td>
<td>CY</td>
<td>As treated</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Urokinase: 0/82 (0%)</td>
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</tbody>
</table>

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<table>
<thead>
<tr>
<th>Author-Year</th>
<th>Intervention</th>
<th>Study Design</th>
<th>Randomize</th>
<th>Blinding</th>
<th>Lost to Follow-up</th>
<th>Analysis</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Marini et al1988 | High dose: urokinase 3,300,000 units over 12 h | RCT | PY | Patients: PN  
Caregivers: CN  
Data Collectors: PN  
Adjudicators: PN  
Data Analysts: PN | High-dose urokinase:  
0/10 (0%) | ITT | |
| | Low dose: urokinase 800,000 units over 12 h daily for 3 d  
Heparin 30,000 units/d for 7 d followed by OAC | | | | | | |
| Dalla-Volta et al1992 | rt-PA (alteplase) 10 mg followed by 90 mg over 2 h | RCT | PY | Patients: PN  
Caregivers: CN  
Data Collectors: PN  
Adjudicators: PN  
Data Analysts: PN | rt-PA: 0/20 (0%) | ITT | rt-PA (alteplase) + heparin vs heparin |
| | Heparin 10,000 units followed by 1.750 units/h for 7-10 d | | | | Heparin: 0/16 (0%) | | |
| Goldhaber et al1993 | rt-PA 100 mg over 2 h followed by heparin 1,000 units/h | RCT | CY | Patients: PN  
Caregivers: CN  
Data Collectors: PN  
Adjudicators: PN  
Data Analysts: PN | rt-PA: 0/46 (0%) | ITT | |
| | Heparin 5,000 units followed by 1,000 units/h | | | | Heparin: 0/55 (0%) | | |
| Konstantinides et al2002 | rt-PA (alteplase) 100 mg followed by alteplase 90 mg over 2 h + heparin 1,000 units/h | RCT | CY | Patients: PY  
Caregivers: CN  
Data Collectors: PY  
Adjudicators: PN  
Data Analysts: PY | rt-PA: 0/118 (0%) | ITT | All: UFH 5,000 units. |
| | Heparin 5,000 units followed by 1,000 units/h | | | | UFH: 0/138 (0%) | | |
| Levine et al2000 | rt-PA 0.6 mg/kg over 2 min | RCT | PY | Patients: CY  
Caregivers: CY  
Data Collectors: CY  
Adjudicators: CY  
Data Analysts: CY | rt-PA: 0/33(0%) | ITT | All: UFH initial bolus of 5,000 units followed by continuous infusion at starting dose of 30,000 for the first 24 h. |
| | Placebo + heparin 5,000 units followed by 30,000/d | | | | Heparin: 0/25(0%) | | |

(Continued)
### Table S42—Continued

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Intervention</th>
<th>Study Design</th>
<th>Randomize</th>
<th>Concealed</th>
<th>Blinding</th>
<th>Lost to Follow-up</th>
<th>Analysis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIOPED</td>
<td>rt-PA 40-80mg at 1 mg/min</td>
<td>RCT</td>
<td>PY</td>
<td>Patients: CY</td>
<td>rt-PA: 0/9(0%)</td>
<td>ITT</td>
<td>All heparin doses determined by attending physician.</td>
<td></td>
</tr>
<tr>
<td>Caregivers: CY</td>
<td></td>
<td>Data Collectors: PY</td>
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<tr>
<td>Adjudicators: PY</td>
<td></td>
<td>Data Analysts: PY</td>
<td></td>
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<tr>
<td>Placebo plus heparin (doses determined by physician)</td>
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<td></td>
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<tr>
<td>Heparin: 0/4(0%)</td>
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<tr>
<td>Fusullo et al 154/2011</td>
<td>Alteplase 100 mg over 2 h</td>
<td>RCT</td>
<td>CY</td>
<td>Patients: CY</td>
<td>rt-PA: 0/37</td>
<td>ITT</td>
<td>Primary outcome was echocardiographic changes.</td>
<td></td>
</tr>
<tr>
<td>Caregivers: CY</td>
<td></td>
<td>Data Collectors: PY</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Adjudicators: CY</td>
<td></td>
<td>Data Analysts: PY</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + heparin 5,000 units followed by 1,000 units/h</td>
<td></td>
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<tr>
<td>Heparin: 0/35</td>
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<tr>
<td>rt-PA (alteplase) + heparin vs heparin</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Becattini et al 153/2010</td>
<td>Tenectaplas: ~2 mg/kg bolus</td>
<td>RCT</td>
<td>CY</td>
<td>Patients: CY</td>
<td>Tenectaplas: 0/28(0%)</td>
<td>ITT</td>
<td>Primary outcome was echocardiographic changes.</td>
<td></td>
</tr>
<tr>
<td>Caregivers: CY</td>
<td></td>
<td>Data Collectors: CY</td>
<td></td>
<td></td>
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<tr>
<td>Adjudicators: CY</td>
<td></td>
<td>Data Analysts: PY</td>
<td></td>
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<tr>
<td>Placebo + heparin (80 International Units/kg and 18 International Units/kg per h)</td>
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<tr>
<td>Heparin: 0/30(0%)</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

See Table S1, S2, S5, S11, and S41 legends for expansion of other abbreviations.


<table>
<thead>
<tr>
<th>Table S43—[Section 8.1] Evidence Profile: Fondaparinux vs Placebo for Acute SVT&lt;sup&gt;a-c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality Assessment</td>
</tr>
<tr>
<td>Participants (Studies), Follow-up</td>
</tr>
<tr>
<td>3,002 (1 study), 3 mo</td>
</tr>
<tr>
<td>Mortality (important outcome)</td>
</tr>
<tr>
<td>VTE (critical outcome)</td>
</tr>
<tr>
<td>3,002 (1 study), 3 mo</td>
</tr>
<tr>
<td>SVT recurrence (important outcome)</td>
</tr>
<tr>
<td>3,002 (1 study), 3 mo</td>
</tr>
<tr>
<td>Major bleeding (critical outcome)</td>
</tr>
<tr>
<td>2,987 (1 study), 47 d</td>
</tr>
<tr>
<td>Quality of life not measured</td>
</tr>
</tbody>
</table>

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Bibliography: CALISTO study by Decousus et al.<sup>161</sup> CALISTO = Comparison of ARIXTRA™ in lower LImb Superfi  cial Thrombophlebitis with placebo; SVT = superfi  cial vein thrombosis. See Table S1 and S5 legends for expansion of other abbreviations.

<sup>a</sup>Fondaparinux 2.5 mg for 45 d.
<sup>b</sup>Patients in the two treatment groups benefi  ted from close clinical monitoring with adequate diagnostic procedures in the event of new and persistent symptoms.
<sup>c</sup>Patients with infusion-related SVT were excluded from CALISTO.
<sup>d</sup>Allocation concealed. Outcome adjudicators, steering committee, patients, providers, and data collectors blinded. Follow-up rate was 98%. ITT analysis for efficacy outcomes. Not stopped early for benefi  t.
<sup>e</sup>CI includes values suggesting large benefi  t and values suggesting large harm.
<sup>f</sup>We rated down by only one level because the low event rate and large sample size.
<sup>g</sup>Small number of events.
<sup>h</sup>Baseline risk derived from a large prospective cohort study.<sup>162</sup>
<sup>i</sup>The upper limit of the CI for absolute effect (10 more bleeds) is not low enough to suggest a clear balance of benefi  ts vs harms.
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Publication</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>STENOX Study&lt;sup&gt;10&lt;sup&gt;</td>
<td>Parallel RCT, multicenter</td>
<td>436 patients with ultrasound-confirmed acute symptomatic SVT (≥5 cm length) of the lower extremity</td>
<td>Enoxaparin 40 mg SC daily</td>
<td>Day 12 (end of treatment): Screening ultrasound or symptomatic recurrence: VTE SVT recurrence/extension to saphenofemoral junction 3-mo VTE SVT recurrence/extension Major bleeding Death</td>
<td>3 mo</td>
<td>VTE day 12: Placebo: 4/112 (3.6%) (PE 0); Enoxaparin 40 mg: 1/110 (0.9%) (PE 0); RR 0.25 (95% CI, 0.03-2.24) Enoxaparin 1.5 mg/kg: 1/106 (0.9%) (PE 0); RR 0.26 (95% CI, 0.03-2.33) Tenoxicam: 2/99 (2.0%) (PE 1); RR 0.57 (95% CI, 0.11-3.02) P = ns for all comparisons of active treatment vs placebo SVT recurrence/extension day 12: Placebo: 33/112 (29.5%); Enoxaparin 40 mg: 9/110 (8.3%); RR 0.28 (95% CI, 0.14-0.55) Enoxaparin 1.5 mg/kg: 6/106 (5.7%); RR 0.19 (95% CI, 0.08-0.44) Tenoxicam: 13/99 (13.1%); RR 0.45 (95% CI, 0.25-0.80) VTE 3 mo: Placebo: 5/112 (4.5%) (PE 0); Enoxaparin 40 mg: 6/110 (5.7%); (PE 2); RR 1.22 (95% CI, 0.38-3.89) Enoxaparin 1.5 mg/kg: 4/106 (3.9%); (PE 0); RR 0.85 (95% CI, 0.23-3.06) Tenoxicam: 4/99 (4.3%) (PE 1); RR 0.91 (95% CI, 0.25-3.28) P = ns for all comparisons of active treatment vs placebo SVT recurrence/extension 3 mo: Placebo: 37/112 (33.0%); Enoxaparin 40 mg: 16/110 (14.5%); RR 0.44 (95% CI, 0.26-0.74)</td>
</tr>
</tbody>
</table>

<sup>10</sup>Continued
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Publication</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prandoni for Vesalio Investigators Group/2005</td>
<td>Parallel RCT, multicenter</td>
<td>164 patients with ultrasound-confirmed acute SVT of the greater saphenous vein</td>
<td>High-dose weight-adjusted nadroparin (190 anti-Xa International Units/kg for 10 d followed by 95 anti-Xa International Units/kg for 20 d)</td>
<td>Composite outcome of asymptomatic or symptomatic SVT extension, asymptomatic or symptomatic DVT, symptomatic PE at 3 mo</td>
<td>3 mo follow-up</td>
<td>3 mo</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Publication</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marchiori et al&lt;sup&gt;166&lt;/sup&gt;/2002</td>
<td>Parallel RCT, single center</td>
<td>60 patients with ultrasound-confirmed first acute SVT of greater saphenous vein</td>
<td>Low-dose UFH (5,000 International Units bid SC for 4 wk) High-dose UFH (12,500 International Units for 1 wk then 10,000 International Units for 3 wk)</td>
<td>VTE</td>
<td>6 mo</td>
<td>VTE during treatment period: Low dose: 4/30 (13.3%) (3 asymptomatic DVT, 1 PE) High dose: 0/30 (0%); RR 0.11 (95% CI, 0.01-1.98; P = ns) Extension/recurrence SVT during treatment period: Low dose: 7/30 (23.3%) High dose: 3/30 (10%); RR 0.40 (95% CI, 0.11-1.40; P = ns) Overall VTE during follow-up period: Low dose: 6/30 (20%) High dose: 1/30 (3.3%); RR 0.17 (95% CI, 0.02-1.30; P = ns) Overall extension/recurrence SVT during follow-up period: Low dose: 11/30 (36.7%) High dose: 8/30 (26.7%); RR 0.73 (95% CI, 0.34, 1.55; P = ns)</td>
</tr>
</tbody>
</table>

### Table S44—Continued

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose nadroparin (2,850 anti-Xa International Units for 30 d)</td>
<td>Improvement in clinical symptoms and signs at 1 mo</td>
<td></td>
<td>SVT High dose: 2/83 (2.4%) (1 occurred while on treatment) Low dose: 5/81 (6.2%) (all occurred while on treatment) RR 2.56 (95% CI, 0.51-12.83) Major bleeding</td>
</tr>
<tr>
<td>No placebo group NSAIDS and aspirin use discouraged</td>
<td>Death</td>
<td></td>
<td>VTE High dose: 4/83 (4.8%) (3 symptomatic events; 1 [PE] occurred while on treatment) Low dose: 2/81 (2.5%) (both symptomatic DVT) RR 0.51 (95% CI, 0.10-2.72) Rate of improvement in clinical symptoms and signs similar both groups Major bleeding: 0 Death: 0</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Publication</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belcaro et al [167]/1999 Parallel RCT, multicenter 562 patients with ultrasound-confirmed SVT and large varicose veins or venous incompetence</td>
<td>A. Elastic compression stockings alone</td>
<td>Extension of SVT at 3 mo 6 mo</td>
<td>No major bleeding, HIT, or death in any group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B. Elastic compression stockings and simple flush ligation</td>
<td>Extension of SVT at 6 mo</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>C. Elastic compression stockings and complete stripping and perforator ligation</td>
<td>New DVT at 3 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D. Elastic compression stockings and low-dose SC heparin</td>
<td>Extension at 6 mo: A: 32/78 (41%); B: 11/78 (14.1%); RR 0.34 (95% CI, 0.19-0.63) C: 0/70; RR 0.02 (95% CI, 0.00-0.27) D: 4/71 (5.6%); RR 0.14 (95% CI, 0.05-0.37) E: 4/76 (5.2%); RR 0.13 (95% CI, 0.05-0.35) F: 5/71 (7.0%); RR 0.17 (95% CI, 0.07-0.42)</td>
<td></td>
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<tr>
<td></td>
<td>E. Elastic compression stockings and LMWH</td>
<td>P &lt; .05 for groups C, D, E, F vs A or B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F. Elastic compression stockings and VKA</td>
<td>New DVT at 3 mo: A: 6/78 (7.7%); B: 2/78 (2.5%); RR 0.33 (95% CI, 0.07-1.60) C: 2/70 (2.8%); RR 0.37 (95% CI, 0.06-1.78) D: 0/71 (0%); RR 0.08 (95% CI, 0.0-0.14) E: 1/76 (1.3%); RR 0.08 (95% CI, 0.01-0.59) F: 0/71 (0%); RR 0.08 (95% CI, 0.0-0.14)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lozano et al [168]/2003 Parallel RCT, single center 60 patients with ultrasound-confirmed above-knee internal saphenous SVT</td>
<td>Saphenofemoral disconnection under local anesthesia with short-term use of a compression bandage</td>
<td>Recurrence/extension of SVT 6 mo</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>VTE</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Complications of surgery</td>
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</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Publication</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sullivan et al 2001</td>
<td>Systematic review of 6 studies (includes Belcaro (14 patients) and 5 small case series)</td>
<td>Patients with objectively confirmed above-knee SVT</td>
<td>Ligation of greater saphenous vein at saphenofemoral junction with or without vein stripping (n = 246)</td>
<td>SVT progression</td>
<td>Surgical group: 4-6 mo</td>
<td>Surgical complications: 18/148 (12%) Medical group: 10/71 (14%); RR 1.16 (95% CI, 0.56-2.38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anticoagulation (IV heparin followed by VKA for 6wks-6 mo) (n = 88)</td>
<td>DVT</td>
<td>Surgical group: 6 d to 14 mo</td>
<td>DVT: Surgical group: 7/204 (3.4%) Medical group: 2/88 (2.2%); RR 0.66 (95% CI, 0.14-3.13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PE</td>
<td>Medical group: 6 d to 14 mo</td>
<td>PE: Surgical group: 2/98 (2.0%) Medical group: 0/17 (0%); RR 1.10 (95% CI, 0.06-2.19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Surgical complications: 6/78 (7.7%)</td>
<td>Surgical complications: 6/78 (7.7%) (hematoma, seroma, infection)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bleeding complications: 0/17 (0%)</td>
<td>Bleeding complications: 0/17 (0%)</td>
</tr>
</tbody>
</table>

Table S44—Continued
Table S44—Continued

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Publication</th>
<th>Participants</th>
<th>Intervention^b</th>
<th>Outcomes^c</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Górski et al^{[9]}/2005</td>
<td>Parallel RCT, multicenter</td>
<td>46 patients with ultrasound-confirmed SVT</td>
<td>Topical liposomal heparin spray gel (4 sprays of 438 International Units tid)</td>
<td>Pain by visual analog scale (0-10) 21 d</td>
<td>Data extrapolated from graphs and figures in article by reviewer</td>
<td></td>
</tr>
<tr>
<td>Andreozzi et al^{[3]}/1996</td>
<td>Parallel RCT, multicenter</td>
<td>56 patients with SVT of the lower limbs</td>
<td>A: Dermatan sulfate 100 mg SC once daily</td>
<td>Pain</td>
<td>30 d</td>
<td>Data extrapolated from graphs and figures in article by reviewer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B: Dermatan sulfate 100 mg SC bid</td>
<td>Increase in functional ability</td>
<td>Resolution of pain, day 30: Group A: 47% Group B: 83% Group C: 79%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C: Dermatan sulfate 200 mg intramuscular once daily</td>
<td>Local edema</td>
<td>P not stated</td>
<td></td>
</tr>
</tbody>
</table>

^a^ Participants

^b^ Intervention

^c^ Outcomes

DVT: Deep vein thrombosis

SVT: Supraventricular tachycardia
Table S44—Continued

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Publication</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment given for 30 d</td>
<td></td>
<td></td>
<td>Increase in ability to perform normal daily activities, day 30: Group A: 44% Group B: 67% Group C: 84% P &lt; .05 groups B and C vs group A Local edema, day 30: Progressive improvement in all 3 groups; no significant differences between groups</td>
</tr>
</tbody>
</table>

The CALISTO study that compared fondaparinux with no fondaparinux is described in Table 28 and Table S42. HIT = heparin-induced thrombocytopenia; NSAID = nonsteroidal antiinflammatory drug; STENOX = Superficial Thrombophlebitis Treated by Enoxaparin. See Table S1, S2, S5, S21, and S43 legends for expansion of other abbreviations.

*Study design: RCT, cohort.

*Drugs: VKA, UFH, LMWH, NSAIDs, aspirin, topical treatments, surgery vs placebo, no treatment, each other or different durations or regimens of the same agent.

*Outcomes: extension of thrombus, symptomatic relief, DVT and PE, major bleeding, surgical complications, and death.
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Randomization</th>
<th>Allocation Concealment</th>
<th>Blinding</th>
<th>Loss to Follow-up/ ITT</th>
</tr>
</thead>
<tbody>
<tr>
<td>STENOX Study Group(^{163/2003})</td>
<td>Central randomization</td>
<td>Visually identical drugs and packaging; triple dummy design</td>
<td>Investigators, patients, and assessors blinded</td>
<td>9 lost to follow-up/ ITT</td>
</tr>
<tr>
<td>Titon et al(^{164/1994})</td>
<td>Randomized to one of three treatment groups; method of randomization not specified</td>
<td>Open label</td>
<td>Not blinded</td>
<td>8 lost to follow-up/ not specified</td>
</tr>
<tr>
<td>Prandoni for Vesalio group et al(^{165/2005})</td>
<td>Computer-generated random number sequence assigned to each patient to determine treatment group</td>
<td>Double dummy</td>
<td>Patients and adjudicators of outcome events blind</td>
<td>0 lost to follow-up/ ITT</td>
</tr>
<tr>
<td>Marchiori et al(^{166/2002})</td>
<td>Randomized to treatment group by computer-generated list</td>
<td>Not specified</td>
<td>Assessors blinded</td>
<td>0 lost to follow-up/ not specified</td>
</tr>
<tr>
<td>Belcaro et al(^{167/1999})</td>
<td>Not specified</td>
<td>Not blinded</td>
<td>Not blinded</td>
<td>118 lost to follow-up/not specified</td>
</tr>
<tr>
<td>Lozano et al(^{168/2003})</td>
<td>Method not specified</td>
<td>Not blinded</td>
<td>Not blinded</td>
<td>3 lost to follow-up/not specified</td>
</tr>
<tr>
<td>Sullivan et al(^{169/2001})</td>
<td>Review of six studies; includes one RCT (Belcaro [14 patients]) and five small case series</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Andreozzi et al(^{170/1996})</td>
<td>Patients randomly assigned to one of three therapeutic groups (method not specified)</td>
<td>Open label</td>
<td>Not blinded</td>
<td>Not specified/not specified</td>
</tr>
<tr>
<td>Górski et al(^{171/2005})</td>
<td>Performed according to a prespecified randomization list; treatment allocated according to next number on list; no stratification was performed</td>
<td>Open trial</td>
<td>Not blinded</td>
<td>6 lost to follow-up/ITT</td>
</tr>
</tbody>
</table>

See Table S5, S12, S43, and S44 legends for expansion of abbreviations.
### Table S46—[Section 9.1] Initial Treatment of Acute UEDVT With Anticoagulant Therapy: Clinical Description and Results (Randomized Trials [None Performed] and Prospective Observational Studies of at Least 20 Patients)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Publication</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savage et al172/1999</td>
<td>Prospective cohort, two center</td>
<td>46 outpatients with UEDVT (includes 16 with CVC)</td>
<td>Dalteparin daily for 5-7 d (200 International Units/kg) and VKA with target INR of 2.0-3.0</td>
<td>Symptomatic recurrence/extension of DVT PE Major bleeding Death</td>
<td>3 mo</td>
<td>Recurrence/extension DVT: 1/46 (2%) PE: 0/46 Major bleeding: 1/46 (2%) (on VKA) Death: 7/46 (15%) (none from PE or bleeding)</td>
</tr>
<tr>
<td>Karabay et al173/2003</td>
<td>Prospective cohort, single center</td>
<td>36 inpatients with UEDVT (includes 13 with CVC)</td>
<td>Nadroparin SC bid, 86 anti-Xa International Units/kg for up to 7 d, then VKA (started on day 3; target INR 2-2.5) for mean of 4.7 mo</td>
<td>Symptom relief Lysis of thrombus on ultrasound Recurrent DVT PE Death</td>
<td>1 y</td>
<td>Significant symptom relief, day 7: 32/36 (89%) Lysis, day 10: ≥ 35%: 16/36 (45%) &lt; 35%: 17/36 (47%) None: 3/36 (8%) Recurrent DVT: 0/36 PE: 0/36 Death: 9/36 (25%) (none due to PE or bleeding)</td>
</tr>
<tr>
<td>Prandoni et al120/2004</td>
<td>Prospective cohort, number of centers not stated</td>
<td>53 patients with first UEDVT (included 6 with CVC)</td>
<td>Therapeutic-dose heparin (81% received UFH, 19% received LMWH) then VKA (median, 3 mo)</td>
<td>Recurrent VTE Death</td>
<td>Median of 48 mo</td>
<td>Results not presented according to initial treatment with UFH vs LMWH Recurrent VTE: 3/53 (5.7%) (2 arm, 1 leg) Cumulative incidence 1, 2, and 5 y: 2.0%, 4.2%, 7.7% Death: 11/53 (20.8%) (due to cancer, PE, congestive heart failure [numbers not provided])</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Publication(^a)</th>
<th>Participants</th>
<th>Intervention(^b)</th>
<th>Outcomes(^c)</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kovacs et al(^a) 2007</td>
<td>Prospective cohort, multicenter</td>
<td>74 cancer patients with confirmed UEDVT (all had CVC)</td>
<td>Dalteparin daily for 5-7 d (200 International Units/kg) and VKA to achieve target INR of 2.0-3.0</td>
<td>Recurrent VTE PE Major bleeding Death Catheter failure due to DVT or inability to infuse</td>
<td>3 mo</td>
<td>Recurrent VTE: 0/74 PE: 0/74 Major bleeding: 3/74 (4%) Death: 7/74 (6 cancer, 1 major bleed) Catheter failure due to DVT or inability to infuse: 0/74</td>
</tr>
</tbody>
</table>

CVC = central venous catheter; UEDVT = upper-extremity DVT. See Table S2, S7, and S41 legends for expansion of other abbreviations.

\(^a\)Study design: prospective cohort studies.

\(^b\)Drugs: IV UFH or LMWH followed by OACs.

\(^c\)Outcomes: recurrent DVT and PE, major bleeding, total mortality, and early symptom relief.
Table S47—[Section 9.1] Initial Treatment of Acute UEDVT With Anticoagulant Therapy: Methodologic Quality

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Randomization</th>
<th>Allocation Concealment</th>
<th>Blinding</th>
<th>Loss to Follow-up/ITT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savage et al[172]1999</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>1 lost to follow-up/N/A</td>
</tr>
<tr>
<td>Karabay et al[173]2003</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0 lost to follow-up/N/A</td>
</tr>
<tr>
<td>Prandoni et al[174]2004</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>2 lost to follow-up/N/A</td>
</tr>
<tr>
<td>Kovacs et al[175]2006</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0 lost to follow-up/N/A</td>
</tr>
</tbody>
</table>

See Table S12 and S46 legends for expansion of abbreviations.

Table S48—[Section 9.2] Initial Treatment of Acute UEDVT With Thrombolytic Therapy: Clinical Description and Results (Randomized Trials [None Performed] and Prospective Observational Studies of at Least 10 Patients)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Publication,**</th>
<th>Participants</th>
<th>Intervention§</th>
<th>Outcomes∥</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horne et al[176]2000</td>
<td>Prospective cohort, single center</td>
<td>18 patients with axillary or subclavian DVT</td>
<td>Catheter-directed rt-PA (2 mg/cm of thrombus to maximum of 20 mg) then VKA for 3 mo</td>
<td>Immediate patency</td>
<td>6 mo</td>
<td>Immediate patency: 10/18 (56%)  Establishment of antegrade flow  Bleeding events: 11/18 (61%)  Bleeds (all minor): 5/18 (28%)</td>
</tr>
<tr>
<td>Lee et al[177]2006</td>
<td>Prospective case series, single center</td>
<td>35 patients with primary UEDVT who had complete resolution of acute symptoms with CDT (n = 29) or IV heparin (n = 6)</td>
<td>Oral VKA for mean of 5.2 mo</td>
<td>Recurrent DVT</td>
<td>54 mo</td>
<td>Ipsilateral recurrent DVT: 8/35 (23%)</td>
</tr>
</tbody>
</table>

Early prospective observational studies with < 10 patients and retrospective studies are described in Table 3 of the eighth edition of these guidelines. See Table S2, S10, S11, and S46 legends for expansion of abbreviations.

**Study design: retrospective and prospective cohort studies.

§Drugs: thrombolytic therapy compared with different types of lytic therapy or with anticoagulants.

∥Outcomes: recurrent DVT and PE, vein patency, major bleeding, total mortality, and PTS of the arm.

Table S49—[Section 9.2] Initial Treatment of Acute UEDVT With Thrombolytic Therapy: Methodologic Quality

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Randomization</th>
<th>Allocation Concealment</th>
<th>Blinding</th>
<th>Loss to Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horne et al[176]2000</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
<td>Not specified</td>
</tr>
<tr>
<td>Lee et al[177]2006</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
<td>0 lost to follow-up</td>
</tr>
</tbody>
</table>

See Table S12 legend for expansion of abbreviation.
Table S50—[Section 9.3] Long-term Treatment of Acute UEDVT: Clinical Description and Results

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Publication</th>
<th>Participants</th>
<th>Intervention$^a$</th>
<th>Outcomes$^b$</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savage et al$^{172}$/1999</td>
<td>Prospective cohort, two center</td>
<td>46 outpatients with confirmed UEDVT (includes 16 with CVC)</td>
<td>Dalteparin 200 International Units/kg daily for 5-7 d and VKA to achieve target INR of 2.0-3.0 for 3 mo</td>
<td>Symptomatic recurrence/extension of DVT PE Major bleeding Death</td>
<td>3 mo</td>
<td>Recurrence/extension: 1/46 (2%) PE: 0 Major bleeding: 1/46 (2%) (on VKA) Death: 7/46 (15%) (none from PE or bleeding)</td>
</tr>
<tr>
<td>Karabay et al$^{173}$/2003</td>
<td>Prospective cohort, single center</td>
<td>36 inpatients with confirmed UEDVT (includes 13 with CVC)</td>
<td>Nadroparin SC bid, 86 anti-Xa International Units/kg for up to 7 d, then VKA (started on day 3; target INR 2-2.5) for mean of 4.7 mo</td>
<td>Symptom relief Lysis of thrombus on ultrasound Recurrent DVT PE Death PTS</td>
<td>1 y</td>
<td>Significant symptom relief, day 7: 32/36 (89%) Lysis, day 10: ≥ 35%: 16/36 (45%) &lt; 35%; 17/36 (47%) None: 3/36 (8%) Recurrent DVT: 0 PE: 0 Death: 9/36 (25%) (none due to PE or bleeding) PTS: 0</td>
</tr>
<tr>
<td>Martinelli et al$^{177}$/2004</td>
<td>Case-control study with prospective follow-up of cases, single center</td>
<td>98 patients with primary UEDVT (none with CVC)</td>
<td>VKA for mean 6 mo (77 patients), heparin SC (14 patients), or antiplatelet agents (7 patients) for ≤ 3 mo</td>
<td>Recurrent VTE after anticoagulants stopped</td>
<td>Median of 5.1 y</td>
<td>Recurrent VTE: 12/98 (12%) overall (all UEDVT) Annual incidence recurrent VTE: 2.4% (95% CI, 1.2%-4.0%) (results not provided by treatment group)</td>
</tr>
<tr>
<td>Prandoni et al$^{178}$/2004</td>
<td>Prospective cohort, number of centers not stated</td>
<td>53 patients with confirmed first UEDVT (included 6 with CVC)</td>
<td>Therapeutic-dose heparin (81% received UFH, 19% received LMWH) then VKA (median, 3 mo)</td>
<td>Recurrent VTE</td>
<td>Median of 48 mo</td>
<td>Results not presented according to initial treatment with UFH vs LMWH</td>
</tr>
</tbody>
</table>

(Continued)
Early prospective observational studies with <20 patients, and retrospective studies, are described in Table 3 of the Eight edition of these guidelines. See Table S2, S7, S10, and S46 legends for expansion of abbreviations.

- Drugs: VKA, UFH, LMWH vs placebo, control or each other.
- Outcomes: recurrent DVT and PE, major bleeding, total mortality, and PTS of the arm.

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Publication</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kovacs et al/2007</td>
<td>Prospective cohort, multicenter</td>
<td>74 cancer patients with confirmed UEDVT (all had CVC)</td>
<td>Dalteparin 200 International Units/kg daily for 5-7 d and VKA to achieve target INR of 2.0-3.0</td>
<td>Recurrent VTE, PE, Major bleeding, Death, Catheter failure due to DVT or inability to infuse</td>
<td>3 mo</td>
<td>Recurrent VTE: 0, PE: 0, Major bleeding: 3 (4%), Death: 7 (6 cancer, 1 major bleed), Catheter failure due to DVT or inability to infuse: 0</td>
</tr>
</tbody>
</table>

Recurrent VTE: 3/53 (5.7%) (2 arm, 1 leg) Cumulative incidence 1, 2, and 5 y: 2.0%, 4.2%, 7.7% Death: 11/53 (20.8%) (due to cancer, PE, congestive heart failure [breakdown not provided]) PTS: 12/53 (22.6%); 2 y Cumulative incidence: 27.3%
### Table S51—[Section 9.3] Long-term Treatment of Acute UEDVT: Methodologic Quality

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Randomization</th>
<th>Allocation Concealment</th>
<th>Blinding</th>
<th>Loss to Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savage et al(^{172})/1999</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>1 lost to follow-up</td>
</tr>
<tr>
<td>Karahay et al(^{173})/2003</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0 lost to follow-up</td>
</tr>
<tr>
<td>Martinelli et al(^{177})/2004</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Not specified</td>
</tr>
<tr>
<td>Prandoni et al(^{178})/2004</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>2 patients lost to follow-up</td>
</tr>
<tr>
<td>Kovacs et al(^{174})/2007</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0 lost to follow-up</td>
</tr>
</tbody>
</table>

See Table S12 and S46 legends for expansion of abbreviations.


Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines
Chest 2012;141; e419S-e494S
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Chest February 2012 141:2 suppl e1S–e23S; doi:10.1378/chest.11–2290
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Primary and Secondary Prevention of Cardiovascular Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines
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ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: AMERICAN COLLEGE OF CHEST PHYSICIAN EVIDENCE–BASED CLINICAL PRACTICE GUIDELINES ONLINE ONLY ARTICLES
Patient Values and Preferences in Decision Making for Antithrombotic Therapy: A Systematic Review
Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines
Background: Development of clinical practice guidelines involves making trade–offs between desirable and undesirable consequences of alternative management strategies. Although the relative value of health states to patients should provide the basis for these trade–offs, few guidelines have systematically summarized the relevant evidence. We conducted a systematic review relating to values and preferences of patients considering antithrombotic therapy.
http://chestjournal.chestpubs.org/gca?gca=chest%3B141%2F2_supp...hest%3B141%2F2_suppl%2Fe737S&submit=Get+All+Checked+Abstracts
Methods: We included studies examining patient preferences for alternative approaches to antithrombotic prophylaxis and studies that examined, in the context of antithrombotic prophylaxis or treatment, how patients value alternative health states and experiences with treatment. We conducted a systematic search and compiled structured summaries of the results. Steps in the process that involved judgment were conducted in duplicate.

Results: We identified 48 eligible studies. Sixteen dealt with atrial fibrillation, five with VTE, four with stroke or myocardial infarction prophylaxis, six with thrombolysis in acute stroke or myocardial infarction, and 17 with burden of antithrombotic treatment.

Conclusion: Patient values and preferences regarding thromboprophylaxis treatment appear to be highly variable. Participant responses may depend on their prior experience with the treatments or health outcomes considered as well as on the methods used for preference elicitation. It should be standard for clinical practice guidelines to conduct systematic reviews of patient values and preferences in the specific content area.

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ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: AMERICAN COLLEGE OF CHEST PHYSICIAN EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES ONLINE ONLY ARTICLES

Parenteral Anticoagulants

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

This article describes the pharmacology of approved parenteral anticoagulants. These include the indirect anticoagulants, unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs), fondaparinux, and danaparoid, as well as the direct thrombin inhibitors hirudin, bivalirudin, and argatroban. UFH is a heterogeneous mixture of glycosaminoglycans that bind to antithrombin via a unique pentasaccharide sequence and catalyze the inactivation of thrombin, factor Xa, and other clotting enzymes. Heparin also binds to cells and plasma proteins other than antithrombin causing unpredictable pharmacokinetic and pharmacodynamic properties and triggering nonhemorrhagic side effects, such as heparin–induced thrombocytopenia (HIT) and osteoporosis. LMWHs have greater inhibitory activity against factor Xa than thrombin and exhibit less binding to cells and plasma proteins than heparin. Consequently, LMWH preparations have more predictable pharmacokinetic and pharmacodynamic properties, have a longer half-life than heparin, and are associated with a lower risk of nonhemorrhagic side effects. LMWHs can be administered once daily or bid by subcutaneous injection, without coagulation monitoring. Based on their greater convenience, LMWHs have replaced UFH for many clinical indications. Fondaparinux, a synthetic pentasaccharide, catalyzes the inhibition of factor Xa, but not thrombin, in an antithrombin-dependent fashion. Fondaparinux binds only to antithrombin. Therefore, fondaparinux–associated HIT or osteoporosis is unlikely to occur. Fondaparinux exhibits complete bioavailability when administered subcutaneously, has a longer half-life than LMWHs, and is given once daily by subcutaneous injection in fixed doses, without coagulation monitoring. Three additional parenteral direct thrombin inhibitors and danaparoid are approved as alternatives to heparin in patients with HIT.

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ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: AMERICAN COLLEGE OF CHEST PHYSICIAN EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES ONLINE ONLY ARTICLES

Oral Anticoagulant Therapy

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Background: The objective of this article is to summarize the published literature concerning the pharmacokinetics and pharmacodynamics of oral anticoagulant drugs that are currently available for clinical use and other aspects related to their management.

Methods: We carried out a standard review of published articles focusing on the laboratory and clinical characteristics of the vitamin K antagonists; the direct thrombin inhibitor, dabigatran etexilate; and the direct factor Xa inhibitor, rivaroxaban

Results: The antithrombotic effect of each oral anticoagulant drug, the interactions, and the monitoring of anticoagulation intensity are described in detail and discussed without providing specific recommendations. Moreover, we describe and discuss the clinical applications and optimal dosages of oral anticoagulant therapies, practical issues related to their initiation and monitoring, adverse events such as bleeding and other potential side effects, and available strategies for reversal.

Conclusions: There is a large amount of evidence on laboratory and clinical characteristics of vitamin K antagonists. A growing body of evidence is becoming available on the first new oral anticoagulant drugs available for clinical use, dabigatran and rivaroxaban.

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ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: AMERICAN COLLEGE OF CHEST PHYSICIAN EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES ONLINE ONLY ARTICLES

Antiplatelet Drugs

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

The article describes the mechanisms of action, pharmacokinetics, and pharmacodynamics of aspirin, dipyridamole, cilostazol, the thienopyridines, and the glycoprotein IIb/IIIa antagonists. The relationships among dose, efficacy, and safety are discussed along with a mechanistic overview of results of randomized clinical trials. The article does not provide specific management recommendations but highlights important practical aspects of antiplatelet therapy, including optimal dosing, the variable balance between benefits and risks when antiplatelet therapies are used alone or in combination with other antiplatelet drugs in different clinical settings, and the implications of persistently high platelet reactivity despite such treatment.

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New Antithrombotic Drugs

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

This article focuses on new antithrombotic drugs that are in or are entering phase 3 clinical testing. Development of these new agents was prompted by the limitations of existing antiplatelet, anticoagulant, or fibrinolytic drugs. Addressing these unmet needs, this article (1) outlines the rationale for development of new antithrombotic agents; (2) describes the new antiplatelet, anticoagulant, and fibrinolytic drugs; and (3) provides clinical perspectives on the opportunities and challenges faced by these novel agents.

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Evidence-Based Management of Anticoagulant Therapy

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Background: High-quality anticoagulation management is required to keep these narrow therapeutic index medications as effective and safe as possible. This article focuses on the common important management questions for which, at a minimum, low-quality published evidence is available to guide best practices.


Results: Most practical clinical questions regarding the management of anticoagulation, both oral and parenteral, have not been adequately addressed by randomized trials. We found sufficient evidence for summaries of recommendations for 23 questions, of which only two are strong rather than weak recommendations. Strong recommendations include targeting an international normalized ratio of 2.0 to 3.0 for patients on vitamin K antagonist therapy (Grade 1B) and not routinely using pharmacogenetic testing for guiding doses of vitamin K antagonist (Grade 1B). Weak recommendations deal with such issues as loading doses, initiation overlap, monitoring frequency, vitamin K supplementation, patient self-management, weight and renal function adjustment of doses, dosing decision support, drug interactions to avoid, and prevention and management of bleeding complications. We also address anticoagulation management services and intensive patient education.

Conclusions: We offer guidance for many common anticoagulation–related management problems. Most anticoagulation management questions have
not been adequately studied.

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Approach to Outcome Measurement in the Prevention of Thrombosis in Surgical and Medical Patients

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

This article provides the rationale for the approach to making recommendations primarily used in four articles of the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines: orthopedic surgery, nonorthopedic surgery, nonsurgical patients, and stroke. Some of the early clinical trials of antithrombotic prophylaxis with a placebo or no treatment group used symptomatic VTE and fatal PE to measure efficacy of the treatment. These trials suggest a benefit of thromboprophylaxis in reducing fatal PE. In contrast, most of the recent clinical trials comparing the efficacy of alternative anticoagulants used a surrogate outcome, asymptomatic DVT detected at mandatory venography. This outcome is fundamentally unsatisfactory because it does not allow a trade–off with serious bleeding; that trade–off requires knowledge of the number of symptomatic events that thromboprophylaxis prevents. In this article, we review the merits and limitations of four approaches to estimating reduction in symptomatic thrombosis: (1) direct measurement of symptomatic thrombosis, (2) use of asymptomatic events for relative risks and symptomatic events from randomized controlled trials for baseline risk, (3) use of baseline risk estimates from studies that did not perform surveillance and relative effect from asymptomatic events in randomized controlled trials, and (4) use of available data to estimate the proportion of asymptomatic events that will become symptomatic. All approaches have their limitations. The optimal choice of approach depends on the nature of the evidence available.

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Prevention of VTE in Nonsurgical Patients

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Background: This guideline addressed VTE prevention in hospitalized medical patients, outpatients with cancer, the chronically immobilized, long-distance travelers, and those with asymptomatic thrombophilia.


Results: For acutely ill hospitalized medical patients at increased risk of thrombosis, we recommend anticoagulant thromboprophylaxis with low-molecular–weight heparin (LMWH), low-dose unfractionated heparin (LDUH) bid, LDUH tid, or fondaparinux (Grade 1B) and suggest against extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay (Grade 2B). For acutely ill hospitalized medical patients at low risk of thrombosis, we recommend against the use of pharmacologic prophylaxis or mechanical prophylaxis (Grade 1B). For acutely ill hospitalized medical patients at increased risk of thrombosis who are bleeding or are at high risk for major bleeding, we suggest mechanical thromboprophylaxis with graduated compression stockings (GCS) (Grade 2C) or intermittent pneumatic compression (IPC) (Grade 2C). For critically ill patients, we suggest using LMWH or LDUH thromboprophylaxis (Grade 2C). For critically ill patients who are bleeding or are at high risk for major bleeding, we suggest mechanical thromboprophylaxis with GCS and/or IPC at least until the bleeding risk decreases (Grade 2C). In outpatients with cancer who have no additional risk factors for VTE we suggest against routine prophylaxis with LMWH or LDUH (Grade 2B) and recommend against the prophylactic use of vitamin K antagonists (Grade 1B).

Conclusions: Decisions regarding prophylaxis in nonsurgical patients should be made after consideration of risk factors for both thrombosis and bleeding, clinical context, and patients' values and preferences.

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Prevention of VTE in Nonorthopedic Surgical Patients

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Background: VTE is a common cause of preventable death in surgical patients.

Methods: We developed recommendations for thromboprophylaxis in nonorthopedic surgical patients by using systematic methods as described in Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines in this supplement.

Results: We describe several alternatives for stratifying the risk of VTE in general and abdominal-pelvic surgical patients. When the risk for VTE is very low (< 0.5%), we recommend that no specific pharmacologic (Grade 1B) or mechanical (Grade 2C) prophylaxis be used other than early ambulation. For patients at low risk for VTE (< 1.5%), we suggest mechanical prophylaxis, preferably with intermittent pneumatic compression (IPC), over no prophylaxis (Grade 2C). For patients at moderate risk for VTE (< 6%) who are not at high risk for major bleeding complications, we recommend low-molecular-weight heparin (LMWH) (Grade 2B), low-dose unfractionated heparin (Grade 2B), or mechanical prophylaxis with IPC (Grade 2C) over no prophylaxis. For patients at high risk for VTE (< 1.5%) who are not at high risk for major bleeding complications, we recommend pharmacologic prophylaxis with LMWH (Grade 2B) or low-dose unfractionated heparin (Grade 1B) over no prophylaxis. In these patients, we suggest adding mechanical prophylaxis with elastic stockings or IPC to pharmacologic prophylaxis (Grade 2C). For patients at high risk for VTE undergoing abdominal or pelvic surgery for cancer, we recommend extended-duration, postoperative, pharmacologic prophylaxis (4 weeks) with LMWH over limited-duration prophylaxis (Grade 1B). For patients at moderate to high risk for VTE who are at high risk for major bleeding complications or those in whom the consequences of bleeding are believed to be particularly severe, we suggest use of mechanical prophylaxis, preferably with IPC, over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated (Grade 2C). For patients in all risk groups, we suggest that an inferior vena cava filter not be used for primary VTE prevention (Grade 2C) and that surveillance with venous compression ultrasonography should not be performed (Grade 2C). We developed similar recommendations for other nonorthopedic surgical populations.

Conclusions: Optimal thromboprophylaxis in nonorthopedic surgical patients will consider the risks of VTE and bleeding complications as well as the values and preferences of individual patients.

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Prevention of VTE in Orthopedic Surgery Patients

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Background: VTE is a serious, but decreasing complication following major orthopedic surgery. This guideline focuses on optimal prophylaxis to reduce postoperative pulmonary embolism and DVT.


Results: In patients undergoing major orthopedic surgery, we recommend the use of one of the following rather than no antithrombotic prophylaxis: low-molecular-weight heparin; fondaparinux; dabigatran, apixaban, rivaroxaban (total hip arthroplasty or total knee arthroplasty but not hip fracture surgery); low-dose unfractionated heparin; adjusted-dose vitamin K antagonist; aspirin (all Grade 1B); or an intermittent pneumatic compression device (IPCD) (Grade 1C) for a minimum of 10 to 14 days. We suggest the use of low-molecular-weight heparin in preference to the other agents we have recommended as alternatives (Grade 2C/2B), and in patients receiving pharmacologic prophylaxis, we suggest adding an IPCD during the hospital stay (Grade 2C). We suggest extending thromboprophylaxis for up to 35 days (Grade 2B). In patients at increased bleeding risk, we suggest an IPCD or no prophylaxis (Grade 2C). In patients who decline injections, we recommend using apixaban or dabigatran (all Grade 1B). We suggest against using inferior vena cava filter placement for primary prevention in patients with contraindications to both pharmacologic and mechanical thromboprophylaxis (Grade 2C). We recommend against Doppler (or duplex) ultrasonography screening before hospital discharge (Grade 1B). For patients with isolated lower-extremity injuries requiring leg immobilization, we suggest no thromboprophylaxis (Grade 2B). For patients undergoing knee arthroscopy without a history of VTE, we suggest no thromboprophylaxis (Grade 2B).

Conclusions: Optimal strategies for thromboprophylaxis after major orthopedic surgery include pharmacologic and mechanical approaches.
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ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: AMERICAN COLLEGE OF CHEST PHYSICIAN EVIDENCE–BASED CLINICAL PRACTICE GUIDELINES ONLINE ONLY ARTICLES

Perioperative Management of Antithrombotic Therapy

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Background: This guideline addresses the management of patients who are receiving anticoagulant or antiplatelet therapy and require an elective surgery or procedure.


Results: In patients requiring vitamin K antagonist (VKA) interruption before surgery, we recommend stopping VKAs 5 days before surgery instead of a shorter time before surgery (Grade 1B). In patients with a mechanical heart valve, atrial fibrillation, or VTE at high risk for thromboembolism, we suggest bridging anticoagulation instead of no bridging during VKA interruption (Grade 2C); in patients at low risk, we suggest no bridging instead of bridging (Grade 2C). In patients who require a dental procedure, we suggest continuing VKAs with an oral prohemostatic agent or stopping VKAs 2 to 3 days before the procedure instead of alternative strategies (Grade 2C). In moderate- to high-risk patients who are receiving acetylsalicylic acid (ASA) and require noncardiac surgery, we suggest continuing ASA around the time of surgery instead of stopping ASA 7 to 10 days before surgery (Grade 2C). In patients with a coronary stent who require surgery, we recommend deferring surgery > 6 weeks after bare-metal stent placement and > 6 months after drug–eluting stent placement instead of undertaking surgery within these time periods (Grade 1C); in patients requiring surgery within 6 weeks of bare–metal stent placement or within 6 months of drug–eluting stent placement, we suggest continuing antiplatelet therapy perioperatively instead of stopping therapy 7 to 10 days before surgery (Grade 2C).

Conclusions: Perioperative antithrombotic management is based on risk assessment for thromboembolism and bleeding, and recommended approaches aim to simplify patient management and minimize adverse clinical outcomes.

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Diagnosis of DVT

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Background: Objective testing for DVT is crucial because clinical assessment alone is unreliable and the consequences of misdiagnosis are serious. This guideline focuses on the identification of optimal strategies for the diagnosis of DVT in ambulatory adults.


Results: We suggest that clinical assessment of pretest probability of DVT, rather than performing the same tests in all patients, should guide the diagnostic process for a first lower extremity DVT (Grade 2B). In patients with a low pretest probability of first lower extremity DVT, we recommend initial testing with D–dimer or ultrasound (US) of the proximal veins over no diagnostic testing (Grade 1B), venography (Grade 1B), or whole–leg US (Grade 2B). In patients with moderate pretest probability, we recommend initial testing with a highly sensitive D–dimer, proximal compression US, or whole–leg US rather than no testing (Grade 1B) or venography (Grade 1B). In patients with a high pretest probability, we recommend proximal compression or whole–leg US over no testing (Grade 1B) or venography (Grade 1B).

Conclusions: Favored strategies for diagnosis of first DVT combine use of pretest probability assessment, D–dimer, and US. There is lower–quality evidence available to guide diagnosis of recurrent DVT, upper extremity DVT, and DVT during pregnancy.

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Antithrombotic Therapy for VTE Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Background: This article addresses the treatment of VTE disease.

Methods: We generated strong (Grade 1) and weak (Grade 2) recommendations based on high-quality (Grade A), moderate-quality (Grade B), and low-quality (Grade C) evidence.

Results: For acute DVT or pulmonary embolism (PE), we recommend initial parenteral anticoagulant therapy (Grade 1B) or anticoagulation with rivaroxaban. We suggest low–molecular–weight heparin (LMWH) or fondaparinux over IV unfractionated heparin (Grade 2C) or subcutaneous unfractionated heparin (Grade 2B). We suggest thrombolytic therapy for PE with hypotension (Grade 2C). For proximal DVT or PE, we recommend treatment of 3 months over shorter periods (Grade 1B). For a first proximal DVT or PE that is provoked by surgery or by a nonsurgical transient risk factor, we recommend 3 months of therapy (Grade 1B; Grade 2B if provoked by a nonsurgical transient risk factor and low or moderate bleeding risk); that is unprovoked, we suggest extended therapy if bleeding risk is low or moderate (Grade 2B) and recommend 3 months of therapy if bleeding risk is high (Grade 1B); and that is associated with active cancer, we recommend extended therapy (Grade 1B; Grade 2B if high bleeding risk) and suggest LMWH over vitamin K antagonists (Grade 2B). We suggest vitamin K antagonists or LMWH over dabigatran or rivaroxaban (Grade 2C). We suggest compression stockings to prevent the postthrombotic syndrome (Grade 2B). For extensive superficial vein thrombosis, we suggest prophylactic-dose fondaparinux or LMWH over no anticoagulation (Grade 2B), and suggest fondaparinux over LMWH (Grade 2C).

Conclusion: Strong recommendations apply to most patients, whereas weak recommendations are sensitive to differences among patients, including their preferences.

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Treatment and Prevention of Heparin-Induced Thrombocytopenia

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Background: Heparin–induced thrombocytopenia (HIT) is an antibody–mediated adverse drug reaction that can lead to devastating thromboembolic complications, including pulmonary embolism, ischemic limb necrosis necessitating limb amputation, acute myocardial infarction, and stroke.


Results: Among the key recommendations for this article are the following: For patients receiving heparin in whom clinicians consider the risk of HIT to be > 1%, we suggest that platelet count monitoring be performed every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first) (Grade 2C). For patients receiving heparin in whom clinicians consider the risk of HIT to be < 1%, we suggest that platelet counts not be monitored (Grade 2C). In patients with HIT with thrombosis (HITT) or isolated HIT who have normal renal function, we suggest the use of argatroban or lepirudin or danaperoid over other nonheparin anticoagulants (Grade 2C). In patients with HIT and renal insufficiency, we suggest the use of argatroban over other nonheparin anticoagulants (Grade 2C). In patients with acute HIT or subacute HIT who require urgent cardiac surgery, we suggest the use of bivalirudin over other nonheparin anticoagulants or heparin plus antiplatelet agents (Grade 2C).

Conclusions: Further studies evaluating the role of fondaparinux and the new oral anticoagulants in the treatment of HIT are needed.

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Antithrombotic Therapy for Atrial Fibrillation

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Background: The risk of stroke varies considerably across different groups of patients with atrial fibrillation (AF). Antithrombotic prophylaxis for stroke is associated with an increased risk of bleeding. We provide recommendations for antithrombotic treatment based on net clinical benefit for patients with AF at varying levels of stroke risk and in a number of common clinical scenarios.

Methods: We used the methods described in the Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines article of this supplement.

Results: For patients with nonrheumatic AF, including those with paroxysmal AF, who are (1) at low risk of stroke (eg, CHADS2 [congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack] score of 0), we suggest no therapy rather than antithrombotic therapy, and for patients choosing antithrombotic therapy, we suggest aspirin rather than oral anticoagulation or combination therapy with aspirin and clopidogrel; (2) at intermediate risk of stroke (eg, CHADS2 score of 1), we recommend oral anticoagulation rather than no therapy, and we suggest oral anticoagulation rather than aspirin or combination therapy with aspirin and clopidogrel; and (3) at high risk of stroke (eg, CHADS2 score of ≥ 2), we recommend oral anticoagulation rather than no therapy, aspirin, or combination therapy with aspirin and clopidogrel. Where we recommend or suggest in favor of oral anticoagulation, we suggest dabigatran 150 mg bid rather than adjusted-dose vitamin K antagonist therapy.

Conclusions: Oral anticoagulation is the optimal choice of antithrombotic therapy for patients with AF at high risk of stroke (CHADS2 score of ≥ 2). At lower levels of stroke risk, antithrombotic treatment decisions will require a more individualized approach.

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Antithrombotic and Thrombolytic Therapy for Valvular Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Background: Antithrombotic therapy in valvular disease is important to mitigate thromboembolism, but the hemorrhagic risk imposed must be considered.


Results: In rheumatic mitral disease, we recommend vitamin K antagonist (VKA) therapy when the left atrial diameter is > 55 mm (Grade 2C) or when complicated by left atrial thrombus (Grade 1A). In candidates for percutaneous mitral valvotomy with left atrial thrombus, we recommend VKA therapy until thrombus resolution, and we recommend abandoning valvotomy if the thrombus fails to resolve (Grade 1A). In patients with patent foramen ovale (PFO) and stroke or transient ischemic attack, we recommend initial aspirin therapy (Grade 1B) and suggest substitution of VKA if recurrence (Grade 2C). In patients with cryptogenic stroke and DVT and a PFO, we recommend VKA therapy for 3 months (Grade 1B) and consideration of PFO closure (Grade 2C). We recommend against the use of anticoagulant (Grade 1C) and antplatelet therapy (Grade 1B) for native valve endocarditis. We suggest holding VKA therapy until the patient is stabilized without neurologic complications for infective endocarditis of a prosthetic valve (Grade 2C). In the first 3 months after bioprosthetic valve implantation, we recommend aspirin for aortic valves (Grade 2C), the addition of clopidogrel to aspirin if the aortic valve is transcatheter (Grade 2C), and VKA therapy with a target international normalized ratio (INR) of 2.5 for mitral valves (Grade 2C). After 3 months, we suggest aspirin therapy (Grade 2C). We recommend early bridging of mechanical valve patients to VKA therapy with unfractionated heparin (DVT dosing) or low–molecular–weight heparin (Grade 2C). We recommend long–term VKA therapy for all mechanical valves (Grade 1B): target INR 2.5 for aortic (Grade 1B) and 3.0 for mitral or double valve (Grade 2C). In patients with mechanical valves at low bleeding risk, we suggest the addition of low–dose aspirin (50–100 mg/d) (Grade 1B). In valve repair patients, we suggest aspirin therapy (Grade 2C). In patients with thrombosed prosthetic valve, we recommend fibrinolysis for right–sided valves and left–sided valves with thrombus area < 0.8 cm² (Grade 2C). For patients with left–sided prosthetic valve thrombosis and thrombus area ≥ 0.8 cm², we recommend early surgery (Grade 2C).

Conclusions: These antithrombotic guidelines provide recommendations based on the optimal balance of thrombotic and hemorrhagic risk.

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Antithrombotic and Thrombolytic Therapy for Ischemic Stroke

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Objectives: This article provides recommendations on the use of antithrombotic therapy in patients with stroke or transient ischemic attack (TIA).

Methods: We generated treatment recommendations (Grade 1) and suggestions (Grade 2) based on high (A), moderate (B), and low (C) quality evidence.

Results: In patients with acute ischemic stroke, we recommend IV recombinant tissue plasminogen activator (r-tPA) if treatment can be initiated within 3 h (Grade 1A) or 4.5 h (Grade 2C) of symptom onset; we suggest intraarterial r-tPA in patients ineligible for IV tPA if treatment can be initiated within 6 h (Grade 2C); we suggest against the use of mechanical thrombectomy (Grade 2C) although carefully selected patients may choose this intervention; and we recommend early aspirin therapy at a dose of 160 to 325 mg (Grade 1A). In patients with acute stroke and restricted mobility, we suggest the use of prophylactic-dose heparin or intermittent pneumatic compression devices (Grade 2B) and suggest against the use of elastic compression stockings (Grade 2B). In patients with a history of noncardioembolic ischemic stroke or TIA, we recommend long-term treatment with aspirin (75–100 mg once daily), clopidogrel (75 mg once daily), aspirin/extended release dipyridamole (25 mg/200 mg bid), or cilostazol (100 mg bid) over no antiplatelet therapy (Grade 1A), oral anticoagulants (Grade 1B), the combination of clopidogrel plus aspirin (Grade 1B), or triflusal (Grade 2B). Of the recommended antiplatelet regimens, we suggest clopidogrel or aspirin/extended-release dipyridamole over aspirin (Grade 2B) or cilostazol (Grade 2C). In patients with a history of stroke or TIA and atrial fibrillation we recommend oral anticoagulation over no antithrombotic therapy, aspirin, and combination therapy with aspirin and clopidogrel (Grade 1B).

Conclusions: These recommendations can help clinicians make evidence-based treatment decisions with their patients who have had strokes.

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Primary and Secondary Prevention of Cardiovascular Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Background: This guideline focuses on long–term administration of antithrombotic drugs designed for primary and secondary prevention of cardiovascular disease, including two new antiplatelet therapies.


Results: We present 23 recommendations for pertinent clinical questions. For primary prevention of cardiovascular disease, we suggest low-dose aspirin (75–100 mg/d) in patients aged > 50 years over no aspirin therapy (Grade 2B). For patients with established coronary artery disease, defined as patients 1-year post–acute coronary syndrome, with prior revascularization, coronary stenoses > 50% by coronary angiogram, and/or evidence for cardiac ischemia on diagnostic testing, we recommend long-term low–dose aspirin or clopidogrel (75 mg/d) (Grade 1A). For patients with acute coronary syndromes who undergo percutaneous coronary intervention (PCI) with stent placement, we recommend for the first year dual antiplatelet therapy with low–dose aspirin in combination with ticagrelor 90 mg bid, clopidogrel 75 mg/d, or prasugrel 10 mg/d over single antiplatelet therapy (Grade 1B). For patients undergoing elective PCI with stent placement, we recommend aspirin (75–325 mg/d) and clopidogrel for a minimum duration of 1 month (bare–metal stents) or 3 to 6 months (drug–eluting stents) (Grade 1A). We suggest continuing low–dose aspirin plus clopidogrel for 12 months for all stents (Grade 2C). Thereafter, we recommend single antiplatelet therapy over continuation of dual antiplatelet therapy (Grade 1B).

Conclusions: Recommendations continue to favor single antiplatelet therapy for patients with established coronary artery disease. For patients with acute coronary syndromes or undergoing elective PCI with stent placement, dual antiplatelet therapy for up to 1 year is warranted.

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Antithrombotic Therapy in Peripheral Artery Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Background: This guideline focuses on antithrombotic drug therapies for primary and secondary prevention of cardiovascular disease as well as for the relief of lower-extremity symptoms and critical ischemia in persons with peripheral arterial disease (PAD).


Results: The most important of our 20 recommendations are as follows. In patients aged ≥ 50 years with asymptomatic PAD or asymptomatic carotid stenosis, we suggest aspirin (75–100 mg/d) over no therapy (Grade 2B) for the primary prevention of cardiovascular events. For secondary prevention of cardiovascular disease in patients with symptomatic PAD (including patients before and after peripheral arterial bypass surgery or percutaneous transluminal angioplasty), we recommend long-term aspirin (75–100 mg/d) or clopidogrel (75 mg/d) (Grade 1A). We recommend against the use of warfarin plus aspirin in patients with symptomatic PAD (Grade 1B). For patients undergoing peripheral artery percutaneous transluminal angioplasty with stenting, we suggest single rather than dual antiplatelet therapy (Grade 2C). For patients with refractory claudication despite exercise therapy and smoking cessation, we suggest addition of cilostazol (100 mg bid) to aspirin (75–100 mg/d) or clopidogrel (75 mg/d) (Grade 2C). In patients with critical limb ischemia and rest pain unable to undergo revascularization, we suggest the use of prostanoids (Grade 2C). In patients with acute limb ischemia due to acute thrombosis or embolism, we recommend surgery over peripheral arterial thrombolysis (Grade 1B).

Conclusions: Recommendations continue to favor single antiplatelet therapy for primary and secondary prevention of cardiovascular events in most patients with asymptomatic PAD, symptomatic PAD, and asymptomatic carotid stenosis. Additional therapies for relief of limb symptoms should be considered only after exercise therapy, smoking cessation, and evaluation for peripheral artery revascularization.

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VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Background: The use of anticoagulant therapy during pregnancy is challenging because of the potential for both fetal and maternal complications. This guideline focuses on the management of VTE and thrombophilia as well as the use of antithrombotic agents during pregnancy.


Results: We recommend low–molecular–weight heparin for the prevention and treatment of VTE in pregnant women instead of unfractionated heparin (Grade 1B). For pregnant women with acute VTE, we suggest that anticoagulants be continued for at least 6 weeks postpartum (for a minimum duration of therapy of 3 months) compared with shorter durations of treatment (Grade 2C). For women who fulfill the laboratory criteria for antiphospholipid antibody (APLA) syndrome and meet the clinical APLA criteria based on a history of three or more pregnancy losses, we recommend antepartum administration of prophylactic or intermediate–dose unfractionated heparin or prophylactic low–molecular–weight heparin combined with low–dose aspirin (75–100 mg/d) over no treatment (Grade 1B). For women with inherited thrombophilia and a history of pregnancy complications, we suggest not to use antithrombotic prophylaxis (Grade 2C). For women with two or more miscarriages but without APLA or thrombophilia, we recommend against antithrombotic prophylaxis (Grade 1B).

Conclusions: Most recommendations in this guideline are based on observational studies and extrapolation from other populations. There is an urgent need for appropriately designed studies in this population.

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Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Background: Neonates and children differ from adults in physiology, pharmacologic responses to drugs, epidemiology, and long-term consequences of thrombosis. This guideline addresses optimal strategies for the management of thrombosis in neonates and children.


Results: We suggest that where possible, pediatric hematologists with experience in thromboembolism manage pediatric patients with thromboembolism (Grade 2C). When this is not possible, we suggest a combination of a neonatologist/pediatrician and adult hematologist supported by consultation with an experienced pediatric hematologist (Grade 2C). We suggest that therapeutic unfractionated heparin in children is titrated to achieve a target anti–Xa range of 0.35 to 0.7 units/mL or an activated partial thromboplastin time range that correlates to this anti–Xa range or to a protamine titration range of 0.2 to 0.4 units/mL (Grade 2C). For neonates and children receiving either daily or bid therapeutic low–molecular–weight heparin, we suggest that the drug be monitored to a target range of 0.5 to 1.0 units/mL in a sample taken 4 to 6 h after subcutaneous injection or, alternatively, 0.5 to 0.8 units/mL in a sample taken 2 to 6 h after subcutaneous injection (Grade 2C).

Conclusions: The evidence supporting most recommendations for antithrombotic therapy in neonates and children remains weak. Studies addressing appropriate drug target ranges and monitoring requirements are urgently required in addition to site– and clinical situation–specific thrombosis management strategies.

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