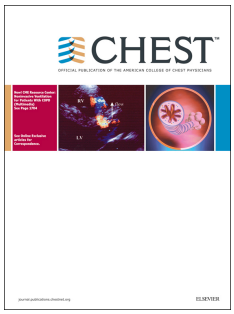
Accepted Manuscript



Antithrombotic Therapy for VTE Disease: CHEST Guideline

Clive Kearon, MD, PhD, Elie A. Akl, MD, MPH, PhD, Joseph Ornelas, PhD, Allen Blaivas, DO, FCCP, David Jimenez, MD, PhD, FCCP, Henri Bounameaux, MD, Menno Huisman, MD, PhD, Christopher S. King, MD, FCCP, Timothy Morris, MD, FCCP, Namita Sood, MD, FCCP, Scott M. Stevens, MD, Janine R.E. Vintch, MD, FCCP, Philip Wells, MD, Scott C. Woller, MD, Col. Lisa Moores, MD, FCCP

PII: S0012-3692(15)00335-9

DOI: 10.1016/j.chest.2015.11.026

Reference: CHEST 203

To appear in: *CHEST*

Received Date: 18 June 2015

Revised Date: 24 November 2015

Accepted Date: 25 November 2015

Please cite this article as: Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris T, Sood N, Stevens SM, Vintch JRE, Wells P, Woller SC, Moores CL, Antithrombotic Therapy for VTE Disease: CHEST Guideline, *CHEST* (2016), doi: 10.1016/j.chest.2015.11.026.

Word Count: 12,840

Antithrombotic Therapy for VTE Disease: CHEST Guideline

Clive Kearon, MD, PhD; Elie A. Akl, MD, MPH, PhD; Joseph Ornelas, PhD; Allen Blaivas, DO, FCCP; David Jimenez, MD, PhD, FCCP; Henri Bounameaux, MD; Menno Huisman, MD, PhD; Christopher S. King, MD, FCCP; Timothy Morris, MD, FCCP; Namita Sood, MD, FCCP; Scott M. Stevens, MD; Janine R. E. Vintch, MD, FCCP; Philip Wells, MD; Scott C. Woller, MD; Col. Lisa Moores, MD, FCCP

Affiliations: McMaster University (Dr. Kearon), Hamilton, ON; American University of Beirut (Dr. Akl), Beirut, Lebanon; CHEST (Dr. Ornelas), Glenview, IL; VA New Jersey Health Care System (Dr. Blaivas), Newark, NJ; Instituto Ramón y Cajal de Investigación Sanitaria (Dr. Jimenez), Madrid, Spain; University of Geneva (Dr. Bounameaux), Geneva, Switzerland; Leiden University Medical Center (Dr. Huisman), Leiden, Netherlands; Virginia Commonwealth University (Dr. King), Falls Church, VA; University of California (Dr. Morris), San Diego, CA; The Ohio State University (Dr. Sood), Columbus, OH; Intermountain Medical Center and the University of Utah (Drs. Stevens and Woller), Murray, UT; Harbor-UCLA Medical Center (Dr. Vintch), Torrance, CA; The University of Ottawa and Ottawa Hospital Research Institute (Dr. Wells), Ottawa, ON; Uniformed Services University of the Health Sciences (Dr. Moores), Bethesda, MD.

Correspondence to: Elie A. Akl, MD, MPH, PhD. Associate Professor of Medicine, Department of Internal Medicine, Faculty of Medicine, American University of Beirut, Lebanon; email: ea32@aub.edu.lb

Disclosures: In the past three years, Dr. Akl was an author on a number of systematic reviews on anticoagulation in patients with cancer. Dr. Bounameaux has received compensation for participation on advisory committees with speaking engagements sponsored by Sanofi-Aventis, Bayer Healthcare and Daiichi-Sankyo. His institution has received grant funding (no salary support) from Daiichi-Sankyo for studying VTE treatment. He has also served as a co-author of original studies using rivaroxaban (Einstein, Einstein PE) and edoxaban (Hokusai). Dr. Huisman has received grant funding and has delivered talks related to long-term and extended anticoagulation and treatment of subsegmental PE. He has also authored several papers related to long-term and extended anticoagulation, treatment of subsegmental PE and compression stocking in preventing post-thrombotic syndrome. Dr. Jimenez's institution has received grant funding (no salary support) from Instituto de salud Carlos III, Sociedad Española de Neumología y Cirugía Torácica, and NeumoMadrid for studying pulmonary embolism. He is a member of Steering Committee of PEITHO, a principal investigator of an original study related to Role of IVC filter in addition to anticoagulation in patients with acute DVT or PE and has participated in the derivation of scores for identification of low risk PE. Dr. Kearon has been compensated for speaking engagements sponsored by Boehringer Ingelheim and Bayer Healthcare related to VTE therapy. His institution has received grant funding (no salary support) from the NIH related to the topic of catheter assisted thrombus removal in patients with leg DVT. He has also published many studies related to long-term anticoagulation and compression stockings in preventing post

thrombotic syndrome. Dr. Moores has frequently lectured on the duration of long-term anticoagulation and is a co-author on several risk-stratification papers. Drs. Moores and King have received honoraria from Chest Enterprises for VTE Prep Courses. Dr. Morris' institution has received grant funding (no salary support) from Portola Pharmaceuticals for APEX clinical trial related to extended prophylaxis against venous thromboembolism with betrixaban. He has also authored textbook chapters related to thrombolytic interventions in patients with acute PE and pulmonary thromboendarterectomy in chronic thromboembolic pulmonary hypertension. Dr. Stevens' and Woller's institution has received grant funding (no salary support) from Canadian Institutes of Health for the D-dimer Optimal Duration Study Phase II (DODS-Extension), from Washington University via the National Institutes of Health (GIFT Trial), Bayer related to VTE (EINSTEIN studies), and from Bristol-Myers Squibb related to apixaban for the Secondary prevention of Thromboembolism (ASTRO-APS). Dr. Vintch's institution has received grant funding (no salary support) from Bristol-Myers Squibb for evaluating the role of apixaban for long-term treatment of VTE. Dr. Wells is a co-investigator on a grant regarding the treatment of subsegmental PE. He has authored several studies (including NOAC) and grants related to the long-term and extended anticoagulation. Dr. Wells has received grant funding from Bristol-Myers Squibb and has received honoraria for talks from Bayer. Drs. Akl, Bounameaux, Kearon and Wells and Woller participated in the last edition of the CHEST Antithrombotic Therapy for VTE Disease Guidelines (AT9). Drs. Blaivas, Ornelas and Sood have nothing to disclose.

Funding Information: This guideline was supported solely by internal funds from CHEST.

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

Disclaimer: American College of Chest Physician guidelines are intended for general information only, are not medical advice, and do not replace professional medical care and physician advice, which always should be sought for any medical condition. The complete disclaimer for this guideline can be accessed at http://www.chestnet.org/Guidelines-and-Resources/Guidelines-and-Consensus-Statements/CHEST-Guidelines

DOI: XX.XXXX/chest.XX-XXXX

Abstract

Background: We update recommendations on 12 topics that were in the 9th edition of these guidelines, and address 3 new topics.

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

Results: For VTE and no cancer, as long-term anticoagulant therapy, we suggest dabigatran (Grade 2B), rivaroxaban (Grade 2B), apixaban (Grade 2B) or edoxaban (Grade 2B) over VKA therapy, and suggest VKA therapy over LMWH (Grade 2C). For VTE and cancer, we suggest LMWH over VKA (Grade 2B), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C) or edoxaban (Grade 2C). We have not changed recommendations for who should stop anticoagulation at 3 months or receive extended therapy. For VTE treated with anticoagulants, we recommend against an IVC filter (Grade 1B). For DVT, we suggest not using compression stockings routinely to prevent PTS (Grade 2B). For subsegmental PE and no proximal DVT, we suggest clinical surveillance over anticoagulation with a low risk of recurrent VTE (Grade 2C), and anticoagulation over clinical surveillance with a high risk (Grade 2C). We suggest thrombolytic therapy for PE with hypotension (Grade 2B), and systemic therapy over catheter directed thrombolysis (Grade 2C). For recurrent VTE on a non-LMWH anticoagulant, we suggest LMWH (Grade 2C), and for recurrent VTE on LMWH we suggest increasing the LMWH dose (Grade 2C).

Conclusion: Of 54 recommendations included in the 30 statements, 20 were strong and none was based on high quality evidence highlighting the need for further research.

CHEST 201X;XX(X):XXXX-XXXX

Abbreviations: AT9 = The 9th Edition of the Antithrombotic Guideline; AT10 = The 10th Edition of the Antithrombotic Guideline; CHEST = American College of Chest Physicians; COI = conflict of interest; CDT = Catheter-Directed Thrombolysis; CT = Computerized Tomography; CTEPH = Chronic Thromboembolic Pulmonary Hypertension; CTPA = Computerized Tomography Pulmonary Angiogram; DVT= deep vein thrombosis; GOC = Guidelines Oversight Committee; INR = International Normalized Ratio; IVC = Inferior Vena Cava; LMWH = Low Molecular Weight Heparin; MeSH = Medical Subject Heading; NOAC = non-vitamin K oral anticoagulant; PE= pulmonary embolism; PESI = Pulmonary Embolism Severity Index; PICO = evidence questions addressing patient population, intervention, comparator, and outcome; PTS = Post-Thrombotic Syndrome; RCT = randomized controlled trial; VKA = Vitamin K Antagonist; VTE = venous thromboembolism; UEDVT = Upper Extremity Deep Vein Thrombosis; US = Ultrasound

Summary of Recommendations

Note on Shaded Text: In this guideline, shading is used within the summary of recommendations to indicate recommendations that are newly added or have been changed since the publication of Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Recommendations that remain unchanged since that edition are not shaded. The order of our presentation of the NOACS (dabigatran, rivaroxaban, apixaban, edoxaban) is based on the chronology of publication of the phase 3 trials in VTE treatment and should not be interpreted as the guideline panel's order of preference for the use of these agents.

Choice of Long-Term (First 3 Months) and Extended (No Scheduled Stop Date) Anticoagulant

1. **In patients with proximal DVT or PE, we recommend long-term (3 months) anticoagulant therapy over no such therapy** (Grade 1B).

2. **In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban or edoxaban over VKA therapy** (all Grade 2B). **For patients with DVT of the leg or PE and no cancer who are not treated with dabigatran, rivaroxaban, apixaban or edoxaban, we suggest VKA therapy over LMWH** (Grade 2C).

Remarks: Initial parenteral anticoagulation is given before dabigatran and edoxaban, is not given before rivaroxaban and apixaban, and is overlapped with VKA therapy. See text for factors that influence choice of therapy.

3. **In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"), as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA therapy** (Grade 2C), **dabigatran** (Grade 2C)**, rivaroxaban** (Grade 2C)**, apixaban** (Grade 2C) **or edoxaban** (Grade 2C).

Remarks: Initial parenteral anticoagulation is given before dabigatran and edoxaban, is not given before rivaroxaban and apixaban, and is overlapped with VKA therapy. See text for factors that influence choice of therapy.

4. **In patients with DVT of the leg or PE who receive extended therapy, we suggest that there is no need to change the choice of anticoagulant after the first 3 months** (Grade 2C).

Remarks: It may be appropriate for the choice of anticoagulant to change in response to changes in the patient's circumstances or preferences during the long-term or extended phases of treatment.

Duration of Anticoagulant Therapy

5. **In patients with a proximal DVT of the leg or 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 (e.g. 6, 12 or 24 months)** (Grade 1B)**, or (iii) extended therapy (no scheduled stop date)** (Grade 1B**).**

6. **In patients with a proximal DVT of the leg or 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)**, and (ii) treatment of a longer time-limited period (e.g. 6, 12 or 24 months)** (Grade 1B). **We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk** (Grade 2B)**, and recommend treatment for 3 months over extended therapy if there is a high risk of bleeding** (Grade 1B)**.**

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

7. **In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor, we suggest treatment with anticoagulation for 3 months over treatment of a shorter period** (Grade 2C), **we recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (e.g. 6, 12 or 24 months)** (Grade 1B), **and we recommend treatment with anticoagulation for 3 months over extended therapy (no scheduled stop date)** (Grade 1B).

Remarks: 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.

8. **In patients with an unprovoked DVT of the leg (isolated distal or proximal) or PE, we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration** (Grade 1B)**, and we recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (e.g. 6, 12 or 24 months)** (Grade 1B).

Remarks: After 3 months of treatment, patients with unprovoked DVT of the leg or PE should be evaluated for the risk-benefit ratio of extended therapy. 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.

9. **In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk (see text), we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy** (Grade 2B)**, and a (ii) high bleeding risk (see text), we recommend 3 months of anticoagulant therapy over extended therapy (no scheduled stop date)** (Grade 1B).

Remarks: Patient sex and D-dimer level measured a month after stopping anticoagulant therapy may influence the decision to stop or extend anticoagulant therapy (see text). In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (e.g. annually).

10. **In patients with a second unprovoked VTE and who have a (i) low bleeding risk (see text), we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months** (Grade 1B)**, (ii) moderate bleeding risk (see text), we suggest extended anticoagulant therapy over 3 months of therapy** (Grade 2B)**, and (iii) high bleeding risk (see text), we suggest 3 months of anticoagulant therapy over extended therapy (no scheduled stop date)** (Grade 2B).

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

11. **In patients with DVT of the leg or PE and active cancer ("cancer-associated thrombosis") and who (i) do not have a high bleeding risk, we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy** (Grade 1B), **and (ii) have a high bleeding risk, we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy** (Grade 2B).

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

Aspirin for Extended Treatment of Venous Thromboembolism

12. **In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, we suggest aspirin over no aspirin to prevent recurrent VTE** (Grade 2C).

Remarks: Because aspirin is expected to be much less effective at preventing recurrent VTE than anticoagulants, we do not consider aspirin a reasonable alternative to anticoagulant therapy in patients who want extended therapy. However, if a patient has decided to stop anticoagulants, prevention of recurrent VTE is one of the benefits of aspirin that needs to be balanced against aspirin's risk of bleeding and inconvenience. Use of aspirin should also be reevaluated when patients stop anticoagulant therapy because aspirin may have been stopped when anticoagulants were started.

Whether and How to Anticoagulate Isolated Distal Deep Vein Thrombosis

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

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

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

Catheter-Directed Thrombolysis for Acute Deep Vein Thrombosis of the Leg

16. **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 post thrombotic 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.

Role of Inferior Vena Caval Filter in Addition to Anticoagulation for Acute Deep Vein Thrombosis or Pulmonary Embolism

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

Compression Stocking to Prevent Post-Thrombotic Syndrome

18. **In patients with acute DVT of the leg, we suggest not using compression stockings routinely to prevent PTS** (Grade 2B).

Remarks: This recommendation focuses on prevention of the chronic complication of PTS and not on the treatment of symptoms. For patients with acute or chronic symptoms, a trial of graduated compression stockings is often justified.

Whether to Anticoagulate Subsegmental Pulmonary Embolism

19. **In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE (see text), we suggest clinical surveillance over anticoagulation** (Grade 2C)**, and (ii) high risk for recurrent VTE (see text), we suggest anticoagulation over clinical surveillance** (Grade 2C)**.**

Remarks: Ultrasound imaging of the deep veins of both legs should be done to exclude proximal DVT. Clinical surveillance can be supplemented by serial ultrasound imaging

of the proximal deep veins of both legs to detect evolving DVT (see text). Patients and physicians are more likely to opt for clinical surveillance over anticoagulation if there is good cardiopulmonary reserve or a high risk of bleeding.

Treatment of Acute Pulmonary Embolism Out of Hospital

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

Systemic Thrombolytic Therapy for Pulmonary Embolism

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

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

23. **In selected patients with acute PE who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, we**

suggest systemically administered thrombolytic therapy over no such therapy (Grade 2C).

Remarks: Patients with PE and without hypotension who have severe symptoms or marked cardiopulmonary impairment should be monitored closely for deterioration. Development of hypotension suggests that thrombolytic therapy has become indicated. Cardiopulmonary deterioration (e.g. symptoms, vital signs, tissue perfusion, gas exchange, cardiac biomarkers) that has not progressed to hypotension may also alter the risk-benefit assessment in favor of thrombolytic therapy in patients initially treated with anticoagulation alone.

Catheter-Based Thrombus Removal for the Initial Treatment of Pulmonary Embolism

24. **In patients with acute PE who are treated with a thrombolytic agent, we suggest systemic thrombolytic therapy using a peripheral vein over catheter directed thrombolysis (CDT)** (Grade 2C).

Remarks: Patients who have a higher risk of bleeding with systemic thrombolytic therapy, and who have access to the expertise and resources required to do CDT, are likely to choose CDT over systemic thrombolytic therapy.

25. **In patients with acute PE associated with hypotension and who have (i) a high bleeding risk, (ii) failed systemic thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect (e.g. within hours), if appropriate**

expertise and resources are available, we suggest catheter assisted thrombus removal over no such intervention (Grade 2C).

Remarks: Catheter assisted thrombus removal refers to mechanical interventions, with or without catheter directed thrombolysis.

Pulmonary Thromboendarterectomy for the Treatment of Chronic Thromboembolic Pulmonary Hypertension

26. **In selected patients with CTEPH who are identified by an experienced thromboendarterectomy team, we suggest pulmonary thromboendarterectomy over no pulmonary thromboendarterectomy** (Grade 2C).

Remarks: Patients with CTEPH should be evaluated by a team with expertise in treatment of pulmonary hypertension. Pulmonary thromboendarterectomy is often life saving and life transforming. Patients with CTEPH who are not candidates for pulmonary thromboendarterectomy may benefit from other mechanical and pharmacological interventions designed to lower pulmonary arterial pressure.

Thrombolytic Therapy in Patients with Upper Extremity Deep Vein Thrombosis

27. **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.

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

Management of Recurrent Venous Thromboembolism on Anticoagulant Therapy

29. **In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or on dabigatran, rivaroxaban, apixaban or edoxaban (and are believed to be compliant), we suggest switching to treatment with LMWH at least temporarily** (Grade 2C).

Remarks: Recurrent VTE while on therapeutic-dose anticoagulant therapy is unusual and should prompt the following assessments: (1) reevaluation of whether there truly was a recurrent VTE; (2) evaluation of compliance with anticoagulant therapy; and (3) consideration of an underlying malignancy. A temporary switch to LMWH will usually be for at least one month.

30. **In patients who have recurrent VTE on long-term LMWH (and are believed to be compliant) we suggest increasing the dose of LMWH by about one-quarter to one-third** (Grade 2C).

Remarks: Recurrent VTE while on therapeutic-dose anticoagulant therapy is unusual and should prompt the following assessments: (1) reevaluation of whether there truly was a recurrent VTE; (2) evaluation of compliance with anticoagulant therapy; and (3) consideration of an underlying malignancy.

CHEST has been developing and publishing guidelines for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively referred to as venous thromboembolism (VTE), for more than 30 years. CHEST published the last (9th) edition of these guidelines in February 2012 (AT9).[1] Since then, a substantial amount of new evidence relating to the treatment of VTE has been published, particularly in relation the use of non-vitamin K oral anticoagulants (NOACs). Moreover, a number of VTE treatment questions that were not addressed in the last edition have been highlighted. This article focuses on new developments and ongoing controversies in the treatment of VTE, updating recommendations for 12 topics that were included in AT9 and providing recommendations for 3 new topics. The target users of this guideline are clinicians.

Methods

Composition and Selection of Topic Panel Members

The Guidelines Oversight Committee (GOC) at CHEST appointed the editor for the guideline update. Then, the editor nominated the project executive committee, the chair and the remaining panelists (see acknowledgements section). The GOC approved all panelists after review of their qualifications and conflict of interest (COI) disclosures. The 15 panelists include general internists, thrombosis specialists, pulmonologists, hematologists and methodologists.

Throughout guideline development, panelists were required to disclose any potential financial or intellectual conflicts of interest by topic.[2] Financial and intellectual conflicts of interest were classified as primary (more serious) or secondary (less serious) (eTable 1). Panelists with primary COI were required to abstain from voting on related topic areas, but could participate in discussions provided they refrained from strong advocacy.

Selection of Topics and Key Questions

First, we listed all of the topic areas from AT9 and added potential new topics proposed by the panel members. Next, all panel members voted on whether each topic should be included in the update. Finally, the full-panel reviewed the results of the vote and decided on the final list. The

panel selected a total of 15 topics: 12 “update topics” from AT9 and 3 “new topics”. For each topic, we developed standardized questions in the PICO (Population, Intervention, Comparator, Outcome) format (eTable 2).

Systematic Search

Systematic methods were used to search for evidence for each question. When available, the National Library of Medicine’s medical subject headings (MeSH) keyword nomenclature was used. We searched MEDLINE via PubMed for original studies and the Cochrane Library for systematic reviews. For update topics, we searched the literature from January 2005 to July 2014. For new topics, we searched the literature from 1946 (Medline inception) to July 2014. All searches were limited to English language publications. We augmented searches by checking reference lists of published articles and personal files, and with ongoing surveillance of the literature by panel members (eFigures 1-4).

When we identified systematic reviews, we assessed their quality according to the AMSTAR tool.[3] We used those that were of highest quality and up-to-date as the source of evidence. In the absence of a satisfactory systematic review, we did our own evidence synthesis using the primary studies identified in AT9 and in the updated search. If the panel judged that the identified randomized controlled trials (RCTs) were inadequate, we expanded the search to include prospective cohort studies.

Study Selection, data abstraction, and data analysis

The criteria for selecting the evidence were based on the PICO elements of the standardized questions and the study design (eTable 2). We followed standard processes (duplicate independent work with agreement checking and disagreement resolution) for title and abstract screening, full text screening, data abstraction, and risk of bias assessment. We abstracted data on the characteristics of: study design, participants, intervention, control, outcomes, funding, and COI. We assessed risk of bias using the Cochrane Risk of Bias Tool in randomized trials[4], and an adapted tool for observational studies[5] (eTable 3).

When existing systematic reviews were not available or were inadequate, we performed meta-analyses when appropriate. For each outcome of interest, we calculated the risk ratios of individual studies then pooled them and assessed statistical heterogeneity using the I^2 statistic. We used fixed-effects model when pooling data from two trials, or when one of the included trials was large relative to the others. Otherwise, we used random-effects model. We used the Review Manager software (Version 5.2) to perform the meta-analyses and construct forest plots. We calculated absolute effects by applying pooled relative risks to baseline risks, ideally estimated from valid prognostic observational data or, in the absence of the latter, from control group risks. When credible data from prognostic observational studies were not available, we used risk estimates from control groups of RCTs included in the meta-analyses (eFigure 5 and 6).

Assessing Quality of Evidence

Based on the GRADE approach, quality of evidence (also known as certainty of evidence) is defined as the extent to which our confidence in the effect estimate is adequate to support a recommendation.[6,7] The quality of evidence is categorized as high (A level), moderate (B level), low (includes very-low) (C level).[6,7] The rating of the quality of evidence reflects the strengths and limitations of the body of evidence and was based on the study design, risk of bias, imprecision, inconsistency, indirectness of results, and likelihood of publication bias, in addition to factors specific to observational studies.[5,6,8-12] Using GRADEpro software (Version 3.6), we generated tables to summarize the judgments of the quality of the evidence, the relative and absolute effect.[13] The GRADE tables include Summary of Findings (SoF) tables presented in the main text, and a more detailed version called Evidence Profiles (EP) presented in the online supplement. The evidence profiles also explicitly link recommendations to the supporting evidence.

Drafting of Recommendations

Following the GRADE approach, the strength of a recommendation is defined as the extent to which we can be confident that the desirable effects of an intervention outweigh its undesirable effects. The strength of recommendation was categorized as strong (grade 1) or weak/conditional (grade 2). In determining the strength of the recommendation, the panel considered the balance of desirable and undesirable consequences (typically trade-off between recurrent VTE and

bleeding events), quality of evidence, resource implications, and patients' average values and preferences for different outcomes and management options.[14-16]

The chair drafted the recommendations after the entire panel had reviewed the evidence and discussed the recommendation. Recommendations were then revised over a series of conference calls and through email exchanges with the entire panel. A major aim was to ensure recommendations were specific and unambiguous.

Methods for achieving consensus

We used a modified Delphi technique [17,18] to achieve consensus on each recommendation. This technique aims to minimize group interaction bias and to maintain anonymity among respondents. Using an online survey (www.surveymonkey.com), panelists without a primary COI voted their level of agreement with each recommendation (including quality of evidence and strength of recommendation) based on a 5-point scale derived from the GRADE grid (strongly agree, weakly agree, neutral, weakly disagree, strongly disagree).[19] Each panelist could also provide open-ended feedback on each recommendation with suggested wording edits or general remarks. To achieve consensus and be included in the final manuscript, each recommendation had to have at least 80% agreement (strong or weak) with a response rate of at least 75% of eligible panel members. All recommendations achieved consensus in the first

round. We then used an iterative approach that involved review by, and approval from, all panel members for the writing of this manuscript.

Peer Review

External reviewers who were not members of the expert panel reviewed the guideline before it was published. These reviewers included content experts, a methodological expert, and a practicing clinician. The final manuscript was reviewed and approved by the CHEST GOC, the CHEST Board of Regents, and the CHEST journal.

Choice of Long-Term (First 3 Months) and Extended (No Scheduled Stop Date) Anticoagulant

Summary of the Evidence

Phases of anticoagulant therapy for VTE

The need for anticoagulant therapy in patients with proximal DVT or PE is presented in AT9.[1] The minimum duration of anticoagulant therapy for DVT or PE is usually three months and this period of treatment is referred to as "long-term therapy".[1] A decision to treat patients for longer than 3 months, which we refer to as "extended anticoagulant therapy", usually implies that anticoagulant therapy will be continued indefinitely.[1]

1. **In patients with proximal DVT or PE, we recommend long-term (3 months) anticoagulant therapy over no such therapy** (Grade 1B).

Choice of anticoagulant for acute and long-term (first 3 months) therapy

AT9 recommendations on choice of anticoagulant therapy were based on comparisons of vitamin K antagonist (VKA) with low-molecular weight heparin (LMWH) that were performed in the preceding two decades[1], and with two of the NOACs (dabigatran[20], rivaroxaban[21]) that had

recently been published. Although we judged that there was no convincing evidence that the efficacy of LMWH compared to VKA differed between VTE patients without and with cancer there are, nevertheless, reasons to make different suggestions for the preferred anticoagulant in patients without and with cancer .[1] We suggested VKA therapy over LMWH in patients without cancer for the following reasons: injections are burdensome; LMWH is expensive; there are low rates of recurrence with VKA in patients with VTE without cancer; and VKA may be as effective as LMWH in patients without cancer. We suggested LMWH over VKA in patients with cancer for the following reasons: there is moderate quality evidence that LMWH was more effective than VKA in patients with cancer; there is a substantial rate of recurrent VTE in patients with VTE and cancer who are treated with VKA; it is often harder to keep patients with cancer who are on VKA in the therapeutic range; LMWH is reliable in patients who have difficulty with oral therapy (e.g. vomiting); LMWH is easier to withhold or adjust than VKA if invasive interventions are required or thrombocytopenia develops.

One new randomized trial compared LMWH (tinzaparin) with warfarin for the first 6 months of treatment in 900 cancer patients with VTE.[22] The findings of this study are consistent with evidence in AT9 that LMWH is more effective than VKA for long-term treatment of VTE, but that there is no difference in major bleeding or death (Table 1, eTable 4). Consequently we still suggest VKA over LMWH in patients without cancer, and LMWH over VKA in patients with cancer, and we have not changed our assessment of the quality of evidence for either of these recommendations (Table 1, eTable 4).

We suggested VKA therapy or LMWH over the NOACs in AT9 because only two randomized trials had compared a NOAC (dabigatran[20], rivaroxaban[21]) with VKA therapy, and none had compared a NOAC with long-term LMWH. In addition, at that time there was little experience using a NOAC for treatment of VTE and a scarcity of long-term follow-up data to support their efficacy and safety. Since then, 4 new randomized trials have compared a NOAC (with[23,24] or without[25,26] initial heparin therapy) with VKA therapy (with initial heparin therapy) for the acute and long-term treatment of VTE.[23-26] The findings of these studies have been analyzed in a number of systematic reviews [27-35], including a network meta-analysis.[35] In addition, there is now extensive clinical experience using NOACs in patients with VTE and atrial fibrillation. For the comparison of each of the NOACs with VKA in the initial and long-term treatment of VTE, current evidence for efficacy is moderate or high quality, for safety (risk of bleeding) is moderate or high quality, and overall is moderate or high quality (Tables 2-5, eTables 5-8).

In the 10th Edition of the Antithrombotic Guideline (AT10), the panel's overall assessment of the relative efficacy and risk of bleeding with different anticoagulant agents is that: (1) the risk reduction for recurrent VTE with all of the NOACs appears to be similar to the risk reduction with VKA[35], including in patients with cancer[36-39]; (2) in patients with VTE and cancer, the risk reduction for recurrent VTE appears to be greater with LMWH than with VKA therapy[1,36,40]; (3) the risk reduction for recurrent VTE with the NOACs compared to LMWH has not been assessed but, based on indirect comparisons, LMWH may be more effective that the NOACs in patients with VTE and cancer[36]; (4) the risk reduction for recurrent VTE with different NOACs has not been directly compared but, based on indirect comparisons, appears to be similar with all of the NOACs[35]; (5) the risk of bleeding with the NOACs, and particularly intracranial bleeding, is less

with the NOACs than with VKA therapy[27,33,35,41,42]; (6) based on patients with atrial fibrillation, gastrointestinal bleeding may be higher with dabigatran, rivaroxaban and edoxaban than with VKA therapy, although this has not been seen in patients with VTE [27,28,33,41,43]; (7) based on indirect comparisons, the risk of bleeding may be lower with apixaban than with the other NOACs[35,44]; and (8) despite the lack of specific reversal agents for the NOACs, the risk that a major bleed will be fatal appears to be no higher for the NOACs than for VKA therapy.[33,34,45] Based on less bleeding with NOACs and greater convenience for patients and healthcare providers, we now suggest that a NOAC is used in preference to VKA for the initial and long-term treatment of VTE in patients without cancer. Factors that may influence which anticoagulant is chosen for initial and long-term treatment of VTE are summarized in Table 6. This decision is also expected to be sensitive to patient preferences. The order of our presentation of the NOACS (dabigatran, rivaroxaban, apixaban, edoxaban) is based on the chronology of publication of the phase 3 trials in VTE treatment and should not be interpreted as the guideline panel's order of preference for the use of these agents.

2. **In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban or edoxaban over VKA therapy** (all Grade 2B). **For patients with DVT of the leg or PE and no cancer who are not treated with dabigatran, rivaroxaban, apixaban or edoxaban, we suggest VKA therapy over LMWH** (Grade 2C).

Remarks: Initial parenteral anticoagulation is given before dabigatran and edoxaban, is not given before rivaroxaban and apixaban, and is overlapped with VKA therapy. See text for factors that influence choice of therapy.

In patients with VTE and cancer ("cancer-associated thrombosis"), as noted earlier in this section, we still suggest LMWH over VKA. In patients with VTE and cancer who are not treated with LMWH, we do not have a preference for either a NOAC or VKA. In the absence of direct comparisons between NOACs, and no convincing indirect evidence that one NOAC is superior to another, we do not have a preference for one NOAC over another NOAC. Factors that may influence which anticoagulant is chosen for initial and long-term treatment of VTE are summarized in Table 6. This decision is also expected to be sensitive to patient preferences.

3. **In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"), as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA therapy** (Grade 2C), **dabigatran** (Grade 2C)**, rivaroxaban** (Grade 2C)**, apixaban** (Grade 2C) **or edoxaban** (Grade 2C).

   Remarks: Initial parenteral anticoagulation is given before dabigatran and edoxaban, is not given before rivaroxaban and apixaban, and is overlapped with VKA therapy. See text for factors that influence choice of therapy.

Choice of anticoagulant for extended therapy (after 3 months and no scheduled stop date)

When AT9 was written, other than a comparison of low and standard intensity anticoagulant therapy[46], there were no comparisons of different types of extended therapy. Since AT9, dabigatran has been compared with VKA therapy for extended treatment of VTE and found to be similarly effective but associated with less bleeding (Table 7, eTable 9).[47] Extended treatment with dabigatran[47], rivaroxaban[21] and apixaban[48] markedly reduces recurrent VTE without being associated with much bleeding (Tables 8-10, eTables 10-12).[49,50] These studies provide moderate quality evidence that dabigatran is as effective and as safe as VKA for extended treatment of VTE (Table 7, eTable 9), and provide moderate quality evidence that each of the NOACs are effective at preventing recurrent VTE without being associated with a high risk of bleeding (Tables 8-10, eTables 10-12).

In AT9, we suggested that if a decision was made to use extended treatment of VTE the same anticoagulant should be used as was used for the initial treatment period. Our intention then was to indicate that there was no obligation to switch from one anticoagulant to a different one after 3 or 6 months of treatment (e.g. from LMWH to VKA in patients with VTE and cancer). We have revised the wording of this recommendation to make it clearer that we neither encourage nor discourage use of the same anticoagulant for initial and extended therapy. Although we anticipate that the anticoagulant that was used for initial treatment will often also be used for the extended therapy, if there are reasons to change the type of anticoagulant, this should be done. We also note that whereas apixaban 5 mg twice-daily is used for long-term treatment, apixaban 2.5 mg twice-daily is used for extended therapy.[48]

4. **In patients with DVT of the leg or PE who receive extended therapy, we suggest that there is no need to change the choice of anticoagulant after the first 3 months** (Grade 2C).

Remarks: It may be appropriate for the choice of anticoagulant to change in response to changes in the patient's circumstances or preferences during the long-term or extended phases of treatment.

Duration of Anticoagulant Therapy

Summary of the Evidence

AT9 recommendations on how long VTE should be treated were based on comparisons of 4 durations of treatment: (1) 4 or 6 weeks; (2) 3 months; (3) longer than 3 months but still a time-limited course of therapy (usually 6 or 12 months); or (4) extended (also termed "indefinite"; no scheduled stopping date) therapy.[1] These four options were assessed in four subgroups of VTE patients with different estimated risks of recurrence after stopping anticoagulant therapy: (1) VTE provoked by surgery (a major transient risk factor; 3% recurrence at 5 years)[51]; (2) VTE provoked by a non-surgical transient risk factor (e.g. estrogen therapy, pregnancy, leg injury, flight of >8 hours; 15% recurrence at 5 years)[51]; (3) unprovoked (also termed "idiopathic") VTE;

not meeting criteria for provoked by a transient risk factor or by cancer (30% recurrence at 5 years)[52,53]; and (4) VTE associated with cancer (also termed "cancer-associated thrombosis"; 15% annualized risk of recurrence; recurrence at 5 years not estimated because of high mortality from cancer)[54,55]. Recurrence risk was further stratified by estimating the risk of recurrence after: (1) an isolated distal DVT was half that after a proximal DVT or PE[56-58]; and (2) a second unprovoked proximal DVT or PE was 50% higher (1.5-fold) than after a first unprovoked event[58,59]. For the decision about whether to stop treatment at 3 months or to treat indefinitely ("extended treatment"), we categorized a patient's risk of bleeding on anticoagulant therapy as low (no bleeding risk factors; 0.8% annualized risk of major bleeding), moderate (one bleeding risk factor; 1.6% annualized risk of major bleeding) or high (two or more bleeding risk factors; ≥6.5% annualized risk of major bleeding) (Table 11). A VKA targeted to an International Normalized Ratio (INR) of about 2.5 was the anticoagulant in all studies that compared different time-limited durations of therapy. We, therefore, assumed that VKA therapy was the anticoagulant when we were making our AT9 recommendations, including for the comparison of extended therapy with stopping treatment at 3 months.

Comparison of different time-limited durations of anticoagulation since AT9

Two additional studies have compared two time-limited durations of anticoagulant therapy. [60,61] In patients with a first unprovoked PE who had completed 6 months of VKA therapy (target INR 2.5), the PADIS study randomized patients to another 18 months of treatment or to placebo, and then followed both groups of patients for an additional 12 months after study drug was stopped

(Table 12, eTable 13).[61] The study's findings were consistent with our recommendations in AT9; the additional 18 months of VKA was very effective at preventing recurrent VTE but, once anticoagulation was stopped, the risk of recurrent VTE was the same in those who had been treated for 6 or for 24 months. This new information has not increased the quality of evidence for comparison of a longer versus a shorter time-limited course of anticoagulation in patients without cancer.

In patients with a first proximal DVT or PE and active cancer who had residual DVT on ultrasound imaging after completing 6 months of LMWH therapy, the Cancer-DACUS study randomized patients to another 6 months of LMWH or to stop therapy and followed patients for 12 months after they stopped LMWH.[60] The additional 6 months of LMWH reduced recurrent VTE but, once anticoagulation was stopped, the risk of recurrent VTE was the same in those who had been treated for 6 or for 12 months. In the same study, all patients without residual DVT after 6 months of LMWH stopped therapy and had a low risk of recurrence during the next year (3 episodes in 91 patients). This study's findings have not changed our recommendations for treatment of VTE in patients with cancer.

Evaluations of extended anticoagulant therapy since AT9

When AT9 was written, extended treatment of VTE with VKA therapy had been evaluated in six studies (mostly patients with unprovoked proximal DVT or PE[46,62-65], or a second episode of VTE[66]), and with a NOAC (rivaroxaban versus placebo) in one study of heterogeneous

patients[21]. Since AT9, no studies have compared extended VKA therapy with stopping anticoagulants, although the large reduction in recurrent VTE with 18 additional months of VKA therapy compared with placebo (i.e. before study drug was stopped) in the PADIS study[61] supports AT9 estimates for the efficacy of extended VKA therapy.

Since AT9, two additional studies have compared extended NOAC therapy (dabigatran[47], apixaban[48]) with stopping treatment (i.e. placebo). These two studies, and the previous study that evaluated extended treatment with rivaroxaban, found that extended therapy with these three NOAC regimens reduced recurrent VTE by at least 80% and was associated with a modest risk of bleeding (Tables 8-10, eTables 10-12).[49] These three studies, however, enrolled heterogeneous populations of patients (i.e. not confined to unprovoked VTE) and only followed patients for 6 to 12 months, which limits the implications of their findings in relationship to extended therapy.

When considering the risks and benefits of extended anticoagulation in this update, the AT10 panel decided to use the same estimates for the reduction in recurrent VTE and the increase in bleeding with anticoagulation that we used in AT9, and that were based on VKA therapy. Our reasoning was: (1) VKA is still widely used for extended treatment of VTE; (2) we felt that there was not enough evidence of differences in efficacy and bleeding during extended therapy to justify separate recommendations for NOACs, either as a group or as individual agents; and (3) our recommendations about whether or not to use extended therapy were not sensitive to assuming that there was a one-third reduction in bleeding with extended therapy compared to the estimated risk of bleeding with extended therapy that are shown in Table 11 and were used in AT9 (e.g. with a NOAC compared to VKA)[27,31,35,49] (the only recommendation to change would

be a strong instead of a weak recommendation in favor of extended therapy in patients with a second unprovoked VTE who had a moderate risk of bleeding).

Better selection of patients for extended VTE therapy

The most common and difficult decision about whether to stop anticoagulants after a time-limited course or to use extended therapy is in patients with a first unprovoked proximal DVT or PE without a high risk of bleeding. In this subgroup of patients, patient sex and D-dimer level measured about one month after stopping anticoagulant therapy can help to further stratify the risk of recurrent VTE.[67-70] Men have about a 75% higher (1.75-fold) risk of recurrence compared to women, while patients with a positive D-dimer result have about double the risk of recurrence compared to those with a negative D-dimer, and the predictive value of these two factors appears to be additive. The risk of recurrence in women with a negative post treatment D-dimer appears to be similar to the risk that we have estimated for patients with a proximal DVT or PE that was provoked by a minor transient risk factor (~15% recurrence at 5 years); consequently, the argument for extended anticoagulation in these women is not strong, suggesting that D-dimer testing will often influence a woman's decision. The risk of recurrence in men with a negative D-dimer is not much less than the overall risk of recurrence that we have estimated for patients with an unprovoked proximal DVT or PE (~25% compared to ~30% recurrence at 5 years); consequently, the argument for extended anticoagulation in these men is still substantial, suggesting that D-dimer testing will often not influence a male's decision. Because there is still uncertainty about how to use D-dimer testing and a patient's sex to make decisions about

796 extended therapy in patients with a first unprovoked VTE, we have not made recommendations
797 based on these factors.
798
799
800 *Revised recommendations*
801
802 These are unchanged from AT9 with the following minor exceptions. First, the recommendations
803 have been reformatted so that there is a separate statement for each comparison rather than
804 combining comparisons in a more complex statement. Second, a qualifying remark has been
805 added to the recommendation that suggests extended therapy over stopping treatment at 3
806 months in patients with a first unprovoked proximal DVT or PE and a low or moderate risk of
807 bleeding; this remark notes that patient sex and D-dimer level measured a month after stopping
808 anticoagulant therapy may influence this treatment decision. If it becomes clear that, during the
809 extended phase of treatment, there are important differences in the risk of recurrence or bleeding
810 with the different anticoagulant agents, agent-specific recommendations for extended therapy
811 may become justified.
812
813
814 5. **In patients with a proximal DVT of the leg or PE provoked by surgery, we**
815 **recommend treatment with anticoagulation for 3 months over (i) treatment of a**
816 **shorter period** (Grade 1B)**, (ii) treatment of a longer time-limited period (e.g. 6, 12 or**
817 **24 months)** (Grade 1B)**, or (iii) extended therapy (no scheduled stop date)** (Grade
818 1B**).**

6. **In patients with a proximal DVT of the leg or 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)**, and (ii) treatment of a longer time-limited period (e.g. 6, 12 or 24 months)** (Grade 1B). **We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk** (Grade 2B)**, and recommend treatment for 3 months over extended therapy if there is a high risk of bleeding** (Grade 1B)**.**

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

7. **In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor, we suggest treatment with anticoagulation for 3 months over treatment of a shorter period** (Grade 2C), **we recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (e.g. 6, 12 or 24 months)** (Grade 1B), **and we recommend treatment with anticoagulation for 3 months over extended therapy (no scheduled stop date)** (Grade 1B).

Remarks: 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.

8. **In patients with an unprovoked DVT of the leg (isolated distal or proximal) or PE, we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration** (Grade 1B)**, and we recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (e.g. 6, 12 or 24 months)** (Grade 1B).

Remarks: After 3 months of treatment, patients with unprovoked DVT of the leg or PE should be evaluated for the risk-benefit ratio of extended therapy. 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.

9. **In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk (see text), we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy** (Grade 2B)**, and a (ii) high bleeding risk (see text), we recommend 3 months of anticoagulant therapy over extended therapy (no scheduled stop date)** (Grade 1B).

Remarks: Patient sex and D-dimer level measured a month after stopping anticoagulant therapy may influence the decision to stop or extend anticoagulant therapy (see text). In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (e.g. annually).

10. **In patients with a second unprovoked VTE and who have a (i) low bleeding risk (see text), we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months** (Grade 1B)**, (ii) moderate bleeding risk (see text), we suggest extended anticoagulant therapy over 3 months of therapy** (Grade 2B)**, and (iii) high bleeding risk (see text), we suggest 3 months of anticoagulant therapy over extended therapy (no scheduled stop date)** (Grade 2B).

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

11. **In patients with DVT of the leg or PE and active cancer ("cancer-associated thrombosis") and who (i) do not have a high bleeding risk, we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy** (Grade 1B), **and (ii) have a high bleeding risk, we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy** (Grade 2B).

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

Aspirin for Extended Treatment of Venous Thromboembolism

Summary of the Evidence

AT9 did not address if there was a role for aspirin, or antiplatelet therapy generally, in the treatment of VTE. Since then, two randomized trials have compared aspirin to placebo for the prevention of recurrent VTE in patients with a first unprovoked proximal DVT or PE who have completed a 3 to 18 month of anticoagulant therapy.[71-73] These trials provide moderate quality evidence that extended aspirin therapy reduces recurrent VTE by about one-third. In these trials, the benefits of aspirin outweighed the increase in bleeding, which was not statistically significant (Table 13, eTable14). The two trials enrolled patients with a first unprovoked VTE who did not have an increased risk of bleeding; patients for whom these guidelines have suggested extended anticoagulant therapy. Extended anticoagulant therapy is expected to reduce recurrent VTE by over 80% and extended NOAC therapy may be associated with the same risk of bleeding as aspirin.[49,50] If patients with a first unprovoked VTE decline extended anticoagulant therapy because they have risk factors for bleeding or because they have a lower than average risk of recurrence, the net benefit of aspirin therapy is expected to be less than in the two trials that evaluated aspirin for extended treatment of VTE.

Based on indirect comparisons, we expect the net benefit of extended anticoagulant therapy in patients with unprovoked VTE to be substantially greater than the benefits of extended aspirin therapy.[49] Consequently, we do not consider aspirin a reasonable alternative to anticoagulant

therapy in patients who want extended therapy. However, if a patient has decided to stop anticoagulants, prevention of recurrent VTE is one of the benefits of aspirin (may also include reductions in arterial thrombosis and colon cancer) that needs to be balanced against aspirin's risk of bleeding and inconvenience. Use of aspirin should also be reevaluated when patients with VTE stop anticoagulant therapy because aspirin may have been stopped when anticoagulants were started (Table 13, eTable 14).

12. **In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, we suggest aspirin over no aspirin to prevent recurrent VTE** (Grade 2C).

Remarks: Because aspirin is expected to be much less effective at preventing recurrent VTE than anticoagulants, we do not consider aspirin a reasonable alternative to anticoagulant therapy in patients who want extended therapy. However, if a patient has decided to stop anticoagulants, prevention of recurrent VTE is one of the benefits of aspirin that needs to be balanced against aspirin's risk of bleeding and inconvenience. Use of aspirin should also be reevaluated when patients stop anticoagulant therapy because aspirin may have been stopped when anticoagulants were started.

Whether and How to Prescribe Anticoagulants to Patients with Isolated Distal Deep Vein Thrombosis

Summary of the Evidence

AT9 discouraged routine whole-leg ultrasound examinations (i.e. including the distal veins) in patients with suspected DVT; thereby reducing how often isolated distal DVT is diagnosed.[1,74] The rationale for not routinely examining the distal veins in patients who have had proximal DVT excluded is that: (1) other assessment may already indicate that isolated distal DVT is either unlikely to be present or unlikely to cause complications if it is present (e.g. low clinical probability of DVT; D-dimer is negative); (2) if these conditions are not met, a repeat ultrasound examination of the proximal veins can be done after a week to detect possible DVT extension and the need for treatment; and (3) false-positive findings for DVT occur more often with ultrasound examinations of the distal compared to the proximal veins.[1,74,75]

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 their DVT is detected on a follow-up ultrasound examination (e.g. after one and two weeks, or sooner if there is concern; there is no widely accepted protocol for surveillance ultrasound (US) testing)[76]. As about 15% of untreated isolated distal DVT are expected to subsequently extend into the popliteal vein and may cause

pulmonary embolism, it is not acceptable to neither anticoagulate nor do surveillance to detect thrombus extension.[1,77-80]

In AT9, we judged that there was high quality evidence that anticoagulant therapy was effective for the treatment of proximal DVT and PE, but uncertainty that the benefits of anticoagulation outweigh its risks in patients with isolated distal DVT because of their lower risk of progressive or recurrent VTE. We suggest the following as risk factors for extension of distal DVT that would favor anticoagulation over surveillance: (1) D-dimer is positive (particularly when markedly so without an alternative reason); (2) thrombosis is extensive (e.g. >5 cm in length, involves multiple veins, >7 mm in maximum diameter); (3) thrombosis is close to the proximal veins; (4) there is no reversible provoking factor for DVT;(5) active cancer;(6) history of VTE; (7) inpatient status.[1,76-78,81-85] We consider thrombosis that is confined to the muscular veins of the calf (i.e., soleus, gastrocnemius) to have a lower risk of extension than thrombosis that involves the axial (i.e. true deep; peroneal, tibial) veins. [77,82,86] Severe symptoms favour anticoagulation, a high risk for bleeding (Table 11) favors surveillance, and the decision to use anticoagulation or surveillance is expected to be sensitive to patient preferences. We anticipate that isolated distal DVT that are detected using a selective approach to whole-leg US will often satisfy criteria for initial anticoagulation whereas distal DVT detected by routine whole-leg ultrasound often will not.

The updated literature search did not identify any new randomized trials that assessed management of patients with isolated distal DVT. Two new systematic reviews[77,78] and a narrative review[84] addressed treatment of isolated distal DVT. In addition to summarizing

977 available data, consistent with AT9, they emphasize the limitations of available evidence. In the
978 absence of substantive new evidence, the panel endorsed the AT9 recommendations without
979 revision. The evidence supporting these recommendations remains low quality because it is not
980 based on direct comparisons of the two management strategies, and ability to predict extension
981 of distal DVT is limited.
982
983
984 13. **In patients with acute isolated distal DVT of the leg and (i) without severe symptoms**
985 **or risk factors for extension (see text), we suggest serial imaging of the deep veins**
986 **for 2 weeks over anticoagulation** (Grade 2C)**, and (ii) with severe symptoms or risk**
987 **factors for extension (see text), we suggest anticoagulation over serial imaging of the**
988 **deep veins** (Grade 2C).
989 *Remarks*: Patients at high risk for bleeding are more likely to benefit from serial imaging.
990 Patients who place a high value on avoiding the inconvenience of repeat imaging and a
991 low value on the inconvenience of treatment and on the potential for bleeding are likely
992 to choose initial anticoagulation over serial imaging
993
994
995 14. **In patients with acute isolated distal DVT of the leg who are managed with**
996 **anticoagulation, we recommend using the same anticoagulation as for patients with**
997 **acute proximal DVT** (Grade 1B).
998

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

Catheter-Directed Thrombolysis for Acute Deep Vein Thrombosis of the Leg

Summary of the Evidence

At the time of AT9 there was one small randomized trial [87] comparing the effect of catheter-directed thrombolysis (CDT) versus anticoagulant alone on development of the post-thrombotic syndrome (PTS), and another larger randomized trial (CAVENT Study) assessing short term (e.g. venous patency and bleeding) but not long term (e.g. PTS) outcomes.[88,89] The CAVENT Study has since reported that CDT reduced PTS, did not alter quality of life, and appears to be cost effective (Table 14, eTable 15).[90-93] A retrospective analysis found that CDT (3649 patients) was associated with an increase in transfusion (2-fold), intracranial bleeding (3-fold), pulmonary embolism (1.5-fold) and vena caval filter insertion (2-fold); long term outcomes and PTS were not reported. [94] A single center prospective registry found that ultrasound-assisted CDT in acute iliofemoral (87 patients) achieved high rates of venous patency, was rarely associated with bleeding, and that only 6% of patients had PTS at one year.[95]

This new evidence has not led to a change in our recommendation for the use of CDT in patients with DVT. Although the quality of the evidence has improved, the overall quality is still low because of very serious imprecision. Unchanged from AT9, we propose that the patients who are most likely to benefit from CDT have iliofemoral DVT, symptoms for <14 days, good functional status, life expectancy of ≥1 year, and a low risk of bleeding (Table 14, Table 15, eTable 15). As the balance of risks and benefits with CDT is uncertain, we consider that anticoagulant therapy

alone is an acceptable alternative to CDT in all patients with acute DVT who do not have impending venous gangrene.

16. **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 post thrombotic 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.

Role of Inferior Vena Caval Filter in Addition to Anticoagulation for Acute Deep Vein Thrombosis or Pulmonary Embolism

Summary of the Evidence

Our recommendation in AT9 was primarily based on findings of the PREPIC randomized trial[96,97] which showed that placement of a permanent inferior vena caval (IVC) filter increased DVT, decreased PE, and did not influence VTE (DVT and PE combined) or mortality (Table 16, eTable 16). Since then, a number of registries have suggested that IVC filters can reduce early mortality in patients with acute VTE, although this evidence has been questioned.[98-102] The recently published PREPIC 2 randomized trial found that placement of an IVC filter for 3 months did not reduce recurrent PE, including fatal PE, in anticoagulated patients with PE and DVT who had additional risk factors for recurrent VTE (Table 16, eTable 16).[103] This new evidence is consistent with our recommendations in AT9. However, because it is uncertain if there is benefit to placement of an IVC filter in anticoagulated patients with severe PE (e.g. with hypotension), and this is done by some experts, our recommendation against insertion of an IVC filter in patients with acute PE who are anticoagulated may not apply to this select subgroup of patients.

Although the PREPIC 2 study has improved the quality of evidence for this recommendation, overall quality is still moderate because of imprecision (Table 16, eTable 16). The AT10 panel decided against combining the results of the PREPIC and PREPIC 2 studies because of

differences in the type of filter used, the duration of filter placement, and differences in the length of follow-up.

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

Compression Stocking to Prevent Post-Thrombotic Syndrome

Summary of the Evidence

AT9 suggested routine use of graduated compression stockings for two years after DVT to reduce the risk of PTS. That recommendation was mainly based on findings of two small single-center randomized trials in which patients and study personnel were not blinded to stocking use (no placebo stocking).[104-106] The quality of the evidence was moderate because of risk of bias due to lack of blinding of an outcome (PTS) that has a large subjective component, and because of serious imprecision of the combined findings of the two trials (Table 17, eTable 17). Since AT9, a much larger multicenter, placebo-controlled trial at low risk of bias found that routine use of graduated compression stockings did not reduce PTS or have other important benefits.[107] Based on this trial, we now suggest that graduated compression stockings not be used routinely to prevent PTS and consider the quality to the evidence to be moderate (Table 17, eTable 17).

The same study found that routine use of graduated compression stockings did not reduce leg pain during the 3 months after DVT diagnosis (Table 17, eTable 2 and 17).[108] This finding, however, does not mean that graduated compression stockings will not reduce acute symptoms of DVT, or chronic symptoms in those who have developed PTS.

18. **In patients with acute DVT of the leg, we suggest not using compression stockings routinely to prevent PTS** (Grade 2B).

Remarks: This recommendation focuses on prevention of the chronic complication of PTS and not on the treatment of symptoms. For patients with acute or chronic symptoms, a trial of graduated compression stockings is often justified.

Whether to Treat Subsegmental Pulmonary Embolism

Summary of the Evidence

Subsegmental PE refers to PE that is confined to the subsegmental pulmonary arteries. Whether these patients should be treated, a question that was not addressed in AT9, has grown in importance because improvements in computerized tomography (CT) pulmonary angiography have increased how often subsegmental PE is diagnosed (i.e. from ~5% to over 10% of PE).[109-112] There is uncertainty whether these patients should be anticoagulated for two reasons. First, because the abnormalities are small, a diagnosis of subsegmental PE is more likely to be a false-positive finding than a diagnosis of PE in the segmental or more proximal pulmonary arteries.[111,113-117] Second, because a true subsegmental PE is likely to have arisen from a small DVT, the risk of progressive or recurrent VTE without anticoagulation is expected to be lower than in patients with a larger PE.[111,112,118,119]

Our literature search did not identify any randomized trials in patients with subsegmental PE. There is, however, high quality evidence for the efficacy and safety of anticoagulant therapy in patients with larger PE, and this is expected to apply similarly to patients with subsegmental PE.[1] Whether the risk of progressive or recurrent VTE is high enough to justify anticoagulation in patients with subsegmental PE is uncertain.[111,112,118] There were no episodes of recurrent VTE in retrospective reports that included a total of about 60 patients with subsegmental PE and no proximal DVT who were not anticoagulated.[111,112] However, in another retrospective analysis,

patients with subsegmental PE appeared to have a similar risk of recurrent VTE during 3 months of anticoagulant therapy as patients with larger PE, and a higher risk than in patients who were suspected of having PE but had PE excluded.[120]

The AT10 panel endorsed that, if no anticoagulant therapy is an option, patients with subsegmental PE should have bilateral ultrasound examinations to exclude proximal DVT of the legs.[111,115] DVT should also be excluded in other high-risk locations, such as in upper extremities with central venous catheters. If DVT is detected, patients require anticoagulation. If DVT is not detected, there is uncertainty whether patients should be anticoagulated. If a decision is made not to anticoagulate, there is the option of doing one or more follow-up ultrasound examinations of the legs to detect (and then treat) evolving proximal DVT.[111,115] Serial testing for proximal DVT has been shown to be a safe management strategy in patients with suspected PE who have non-diagnostic ventilation-perfusion scans, many of whom are expected to have subsegmental PE.[111,112,121]

We suggest that a diagnosis of subsegmental PE is more likely to be correct (i.e. a true-positive) if: (1) the CT pulmonary angiogram (CTPA) is of high quality with good opacification of the distal pulmonary arteries; (2) there are multiple intraluminal defects; (3) defects involve more proximal sub-segmental arteries (i.e. are larger); (4) defects are seen on more than one image; (5) defects are surrounded by contrast rather than appearing to be adherent to the pulmonary artery walls; (6) defects are seen on more than one projection; (7) patients are symptomatic, as opposed to PE being an incidental finding; (8) there is a high clinical pre-test probability for PE; and (9) D-Dimer level is elevated, particularly if the increase is marked and otherwise unexplained.

In addition to whether or not patients truly have subsegmental PE, we consider the following to be risk factors for recurrent or progressive VTE if patients are not anticoagulated -- patients who: are hospitalized or have reduced mobility for another reason; have active cancer (particularly if metastatic or being treated with chemotherapy); or have no reversible risk factor for VTE such as recent surgery. Furthermore, a low cardiopulmonary reserve or marked symptoms that cannot be attributed to another condition favour anticoagulant therapy, while a high risk of bleeding favors no anticoagulant therapy. The decision to anticoagulate or not is also expected to be sensitive to patient preferences. Patients who are not anticoagulated should be told to return for re-evaluation if symptoms persist or worsen.

The evidence supporting our recommendations is low quality because of indirectness and because there is limited ability to predict which patients will have VTE complications without anticoagulation.

19. **In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE (see text), we suggest clinical surveillance over anticoagulation** (Grade 2C)**, and (ii) high risk for recurrent VTE (see text), we suggest anticoagulation over clinical surveillance** (Grade 2C)**.**

Remarks: Ultrasound imaging of the deep veins of both legs should be done to exclude proximal DVT. Clinical surveillance can be supplemented by serial ultrasound imaging

of the proximal deep veins of both legs to detect evolving DVT (see text). Patients and physicians are more likely to opt for clinical surveillance over anticoagulation if there is good cardiopulmonary reserve or a high risk of bleeding.

Treatment of Acute Pulmonary Embolism Out of Hospital

Summary of the Evidence

Our recommendation in AT9 was based on: (1) two trials that randomized patients with acute PE to receive LMWH for only three days in hospital[122] or entirely at home[123] compared with being treated with LMWH in hospital for a longer period; (2) 15 observational studies, nine of which were prospective, that evaluated treatment of acute PE out of hospital[1]; and (3) longstanding experience treating DVT without admission to hospital. Since AT9, no further randomized trials have evaluated out of hospital treatment of acute PE. A number of additional prospective and retrospective observational studies have reported findings consistent with earlier reports, and the findings of all of these studies have been included in recent meta-analyses that have addressed treatment of acute PE out of hospital.[124-126]

Studies that evaluated NOACs for the acute treatment of PE did not report the proportion of patients who were treated entirely out of hospital, but it is probable that this was uncommon. Treatment of acute PE with a NOAC that does not require initial heparin therapy (e.g. rivaroxaban, apixaban) facilitates treatment without hospital admission. Consistent with AT9, we suggest that patients who satisfy all of the following criteria are suitable for treatment of acute PE out of hospital: (1) clinically stable with good cardiopulmonary reserve; (2) no contraindications such as recent bleeding, severe renal or liver disease, or severe thrombocytopenia (i.e. < 70,000 /mm)^3; (3) expected to be compliant with treatment; (4) the

patient feels well enough to be treated at home. Clinical decision rules such as the Pulmonary Embolism Severity Index (PESI), either the original form with score <85 or the simplified form with score of 0, can help to identify low risk patients who are suitable for treatment at home.[127-132] However, we consider clinical prediction rules as aids to decision making and do not require patients to have a predefined score (e.g. low risk PESI score) in order to be considered for treatment at home. Similarly, although we don't suggest the need for routine assessment in patients with acute PE, we agree that the presence of right ventricular dysfunction or increased cardiac biomarker levels should discourage treatment out of hospital.[131,133-139] The quality of the evidence for treatment of acute PE at home remains moderate due to marked imprecision. The updated recommendation has been modified to state that appropriately selected patients may be treated entirely at home, rather than just be discharged early.

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

Systemic Thrombolytic Therapy for Pulmonary Embolism

Summary of the Evidence

It is long established that systemic thrombolytic therapy accelerates resolution of PE as evidenced by more rapid lowering of pulmonary artery pressure, increases in arterial oxygenation, and resolution of perfusion scan defects, and that this therapy increases bleeding.[1] The net mortality benefit of thrombolytic therapy in patients with acute PE, however, has been uncertain and depends on an individual patient's baseline (i.e. without thrombolytic therapy) risk of dying from the acute PE and their risk of bleeding. Patients with the highest risk of dying from PE and the lowest risk of bleeding obtain the greatest net benefit from thrombolytic therapy. Patients with the lowest risk of dying from PE and the highest risk of bleeding obtain the least net benefit from thrombolytic therapy and are likely to be harmed.

Evidence for the use of thrombolytic therapy in patients with acute PE

AT9 recommendations for the use of thrombolytic therapy in acute PE were based on low quality evidence.[1,140] At that time, only about 800 patients with acute PE had been randomized to receive thrombolytic therapy or anticoagulant therapy alone and, consequently, estimates of efficacy, safety and overall mortality were very imprecise. In addition, the trials that enrolled these 800 patients had a high risk of bias, and there was a strong suspicion that there was selective

reporting of studies that favored thrombolytic therapy (i.e. publication bias). Randomized trials have clearly established that thrombolytic therapy increases bleeding in patients with acute myocardial infarction[141], but that evidence was indirect when applied to patients with PE.

Since AT9, two additional small, randomized trials [142,143] and a much larger trial [144] have evaluated systemic thrombolytic therapy in about 1,200 patients with acute PE. The findings of these new studies have been combined with those of earlier studies in a number of meta-analyses.[145-149] These new data, by reducing imprecision for estimates of efficacy and safety and the overall risk of bias, have increased the quality of the evidence from low to moderate for recommendations about the use of systemic thrombolytic therapy in acute PE (Table 18, eTable 18).

Most of the new evidence comes from the PIETHO trial, which randomized 1006 patients with PE and right ventricular dysfunction to tenecteplase and heparin or to heparin therapy alone (with placebo).[144] The most notable findings of this study were that thrombolytic therapy prevented cardiovascular collapse but increased major (including intracranial) bleeding; these benefits and harms were finely balanced, with no convincing net benefit from thrombolytic therapy. An additional finding was that "rescue thrombolytic therapy" appeared to be of benefit in patients who developed cardiovascular collapse after initially being treated with anticoagulant therapy alone.

Management implication of the updated evidence

The improved quality of evidence has not resulted in substantial changes to our recommendations because: (1) the new data supports that the benefits of systemic thrombolytic therapy in patients without hypotension, including those with right ventricular dysfunction or an increase in cardiac biomarkers ("intermediate-risk PE"), are largely offset by the increase in bleeding; and (2) among patients without hypotension, it is still not possible to confidently identify those who will derive net benefit from this therapy.

PE with hypotension

Consistent with AT9, we suggest that patients with acute PE with hypotension (i.e. systolic pressure less than 90 mmHg for 15 minutes) and without high bleeding risk (Table 15) are treated with thrombolytic therapy. The more severe and persistent the hypotension, and the more marked the associated features of shock and myocardial dysfunction or damage, the more compelling the indication for systemic thrombolytic therapy. Conversely, if hypotension is transient or less marked, not associated with features of shock or myocardial dysfunction, and if there are risk factors for bleeding, physicians and patients are likely to initially choose anticoagulant therapy without thrombolytic therapy. If thrombolytic therapy is not used and hypotension persists or becomes more marked, or clinical features of shock or myocardial damage develop or worsen, thrombolytic therapy may then be used.

PE without hypotension

Consistent with AT9, we recommend that most patients with acute PE who do not have hypotension are not treated with thrombolytic therapy. However, patients with PE without hypotension include a broad spectrum of presentations. At the mild end of the spectrum are those who have minimal symptoms and minimal cardiopulmonary impairment. As noted in the section "Setting for initial anticoagulation for PE", many of these patients can be treated entirely at home or can be discharged after a brief admission. At the severe end of the spectrum are those with severe symptoms and more marked cardiopulmonary impairment (even though systolic blood pressure is above 90 mmHg). In addition to clinical features of cardiopulmonary impairment (e.g. heart rate, blood pressure, respiratory rate, jugular venous pressure, tissue hypoperfusion, pulse oximetry), they may have evidence of right ventricular dysfunction on their CTPA or on echocardiography, or evidence of myocardial damage as reflected by increases in cardiac biomarkers (e.g. troponins or brain natriuretic peptide).

We suggest that patients without hypotension who are at the severe end of the spectrum are treated with aggressive anticoagulation and other supportive measures, and not with thrombolytic therapy. These patients need to be closely monitored to ensure that deteriorations are detected. Development of hypotension suggests that thrombolytic therapy has become indicated. Deterioration that has not resulted in hypotension may also prompt the use of thrombolytic therapy. For example, there may be a progressive increase in heart rate, a decrease in systolic blood pressure (which remains above 90 mmHg), an increase in jugular venous pressure, worsening gas exchange, signs of shock (e.g. cold sweaty skin, reduced urine output, confusion),

progressive right heart dysfunction on echocardiography, or an increase in cardiac biomarkers. We do not propose that echocardiography or cardiac biomarkers are measured routinely in all patients with PE, or in all patients with a non-low risk PESI assessment [123,128,150]. This is because, when measured routinely, the results of these assessments do not have clear therapeutic implications. For example, we do not recommend thrombolytic therapy routinely for patients without hypotension who have right ventricular dysfunction and an increase in cardiac biomarkers. However, we encourage assessment of right ventricular function by echocardiography and/or measurement of cardiac biomarkers if, following clinical assessment, there is uncertainty about whether patients require more intensive monitoring or should receive thrombolytic therapy.

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

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

23. **In selected patients with acute PE who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy** (Grade 2C).

Remarks: Patients with PE and without hypotension who have severe symptoms or marked cardiopulmonary impairment should be monitored closely for deterioration. Development of hypotension suggests that thrombolytic therapy has become indicated. Cardiopulmonary deterioration (e.g. symptoms, vital signs, tissue perfusion, gas exchange, cardiac biomarkers) that has not progressed to hypotension may also alter the risk-benefit assessment in favor of thrombolytic therapy in patients initially treated with anticoagulation alone.

Catheter-Based Thrombus Removal for the Initial Treatment of Pulmonary Embolism

Summary of the Evidence

Interventional catheter-based treatments for acute PE include delivery of catheter directed thrombolysis (CDT) if there is not a high risk of bleeding, or catheter-based treatment without thrombolytic therapy if there is a high risk of bleeding.

Catheter directed thrombolysis

The most important limitation of systemic thrombolytic therapy is that it increases bleeding, including intracranial bleeding. CDT, because it uses a lower dose of thrombolytic drug (e.g. about one-third), is expected to cause less bleeding at remote sites (e.g. intracranial or gastrointestinal).[139,151-154] CDT, however, may be as or more effective than systemic thrombolytic therapy for two reasons: (1) it achieves a high local concentration of thrombolytic drug by infusing drug directly into the PE; and (2) thrombus fragmentation due to placement of the infusion catheter in the thrombus or additional maneuvers, or an increase in thrombus permeability due to ultrasound delivered via the catheter, may enhance endogenous or pharmacologic thrombolysis. Thrombolytic therapy is usually infused over many hours or overnight. In emergent situations, systemic thrombolytic therapy can be given while CDT is

being arranged, and active thrombus fragmentation and aspiration (see below) can be combined with CDT.

A single randomized trial of 59 patients found that, compared to anticoagulation alone, ultrasound-assisted CDT improved right ventricular function at 24 hours.[155] Observational studies also suggest that CDT is effective at removing thrombus, lowering pulmonary arterial pressure and improving right ventricular function without being associated with a high risk of bleeding.[151-153,156] Most of these studies are small (less than 30 patients) and retrospective, although a recent prospective registry of 101 patients and a prospective cohort study of 150 patients also support the efficacy of CDT.[156,157] Whereas there was no major bleeding in the registry, there were 15 episodes in the cohort study (10%; no intracranial or fatal bleeds). An older randomized trial of 34 patients with massive PE found that infusion of rt-PA into a pulmonary artery as opposed to a peripheral vein did not accelerate thrombolysis but caused more frequent bleeding at the catheter insertion site.[158] No randomized trials or observational studies have compared contemporary CDT with systemic thrombolytic therapy. For patients who require thrombolytic therapy and do not have a high risk of bleeding, the AT10 panel favored systemic thrombolytic therapy over CDT because, compared to anticoagulation alone, there is a higher quality of evidence in support of systemic thrombolytic therapy than for CDT.

Catheter-based thrombus removal without thrombolytic therapy

Catheter-based mechanical techniques for thrombus removal involve thrombus fragmentation using various types of catheters, some of which are designed specifically for this purpose.[151-154] Fragmentation results in distal displacement of thrombus, with or without suctioning and removal of some thrombus through the catheter. Mechanical methods alone are used when thrombus removal is indicated but there is a high risk of bleeding that precludes thrombolytic therapy. No randomized trial or prospective cohort studies have evaluated catheter-based thrombus removal of PE without thrombolytic therapy.

Evidence for the use of CDT compared to anticoagulation alone, CDT compared to systemic thrombolytic therapy, and catheter-based treatment without thrombolytic therapy is of low quality and our recommendations are weak.

24. **In patients with acute PE who are treated with a thrombolytic agent, we suggest systemic thrombolytic therapy using a peripheral vein over catheter directed thrombolysis (CDT)** (Grade 2C).

Remarks: Patients who have a higher risk of bleeding with systemic thrombolytic therapy, and who have access to the expertise and resources required to do CDT, are likely to choose CDT over systemic thrombolytic therapy.

25. **In patients with acute PE associated with hypotension and who have (i) a high bleeding risk, (ii) failed systemic thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect (e.g. within hours), if appropriate**

expertise and resources are available, we suggest catheter assisted thrombus removal over no such intervention (Grade 2C).

Remarks: Catheter assisted thrombus removal refers to mechanical interventions, with or without catheter directed thrombolysis.

Pulmonary Thromboendarterectomy in for the Treatment of Chronic Thromboembolic Pulmonary Hypertension

Summary of the Evidence

The AT9 recommendation was based on case series that have shown marked improvements in cardiopulmonary status after thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension (CTEPH).[159,160] Although additional case series have been reported, the quality of the evidence for thromboendarterectomy in patients with CTEPH has not improved.[154,161-163] The AT10 panel decided, however, that our previous recommendation for thromboendareterectomy in selected patients with CTEPH was too restrictive and could contribute to suboptimal evaluation and treatment of patients with CTEPH. For example, because of improvements in surgical technique it is now often possible to remove organized thrombi from peripheral pulmonary arteries. In patients with inoperable CTEPH or persistent pulmonary hypertension after pulmonary thromboendarterectomy, there is new evidence from a randomized trial that pulmonary vasodilator therapy may be of benefit.[164] For these reasons, we no longer identify central disease as a selection factor for thromboendarterectomy in patients with CTEPH, and we emphasize that patients with CTEPH should be assessed by a team with expertise in the evaluation and management of pulmonary hypertension.[154,160,165-167]

26. **In selected patients with CTEPH who are identified by an experienced thromboendarterectomy team, we suggest pulmonary thromboendarterectomy over no pulmonary thromboendarterectomy** (Grade 2C).

Remarks: Patients with CTEPH should be evaluated by a team with expertise in treatment of pulmonary hypertension. Pulmonary thromboendarterectomy is often life saving and life transforming. Patients with CTEPH who are not candidates for pulmonary thromboendarterectomy may benefit from other mechanical and pharmacological interventions designed to lower pulmonary arterial pressure.

Thrombolytic Therapy in Patients with Upper Extremity Deep Vein Thrombosis

Summary of the Evidence

The AT9 recommendation was based on: (1) mostly retrospective observational studies suggesting that thrombolysis could improve short and long term venous patency, but a lack of data about whether thrombolysis reduced PTS of the arm; (2) occasional reports of bleeding in patients with upper extremity DVT (UEDVT) who were treated with thrombolysis, and clear evidence that thrombolysis increases bleeding in other settings; and (3) recognition that, compared to anticoagulation alone, thrombolytic therapy is complex and costly.[1 1,168,169] We suggest that thrombolysis is most likely to be of benefit in patients who meet 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. We also suggested CDT over systemic thrombolysis to reduce the dose of thrombolytic drug and the risk of bleeding. There is new moderate quality evidence that CDT can reduce PTS of the leg[91] (Table 14, eTable 15) and that systemic thrombolysis increases bleeding in patients with acute PE[144,148], and low quality evidence that CDT can accelerate breakdown of acute PE[155]. This evidence has indirect bearing on thrombolysis in patients with UEDVT, but it has not changed the overall quality of the evidence or our recommendations for use of thrombolysis in these patients.

27. **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.

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

Management of Recurrent Venous Thromboembolism on Anticoagulant Therapy

Summary of Evidence

There are no randomized trials or prospective cohort studies that have evaluated management of patients with recurrent VTE on anticoagulant therapy. Consequently, management is based on low quality evidence and an assessment of the probable reason for the recurrence. Risk factors for recurrent VTE while on anticoagulant therapy can be divided into two broad categories: (1) treatment factors; and (2) the patient's intrinsic risk of recurrence. How a new event should be treated will depend on the reason(s) for recurrence.

Treatment factors

The risk of recurrent VTE decreases rapidly after starting anticoagulant therapy, with a much higher risk during the first week (or month) compared to the second week (or month).[170,171] A recurrence soon after starting therapy can generally be managed by a time limited (e.g. 1 month) period of more aggressive anticoagulant intensity (e.g. switching from an oral agent back to LMWH, or an increase in LMWH dose). Other treatment factors that are associated with recurrent VTE and will suggest specific approaches to management include: (1) was LMWH being used; (2) was the patient adherent; (3) was VKA subtherapeutic; (4) was anticoagulant

1507 therapy prescribed correctly; (5) was the patient taking a NOAC and a drug that reduced
1508 anticoagulant effect; and (6) had anticoagulant dose been reduced (drugs other than VKA).
1509
1510 There is moderate quality evidence that LMWH is more effective than VKA therapy in patients
1511 with VTE and cancer. A switch to full-dose LMWH, therefore, is often made if there has been an
1512 unexplained recurrent VTE on VKA therapy or a NOAC. If the recurrence happened on LMWH,
1513 the dose of LMWH can be increased. If the dose of LMWH was previously reduced (e.g. by 25%
1514 after 1 month of treatment), it is usually increased to the previous level. If the patient was
1515 receiving full-dose LMWH, the dose may be increased by about 25%. In practice, the increase in
1516 dose is often influenced by the LMWH prefilled syringe dose options that are available. Once-
1517 daily LMWH may also be switched to a twice-daily regimen, particularly if two injections are
1518 required to deliver the increase in LMWH dose. Treatment adherence, including compliance, can
1519 be difficult to assess; for example, symptoms of a recurrent DVT may encourage medication
1520 adherence and a return of coagulation results to the "therapeutic range".
1521
1522
1523 *Patient Factors*
1524
1525 The most important intrinsic risk factor for recurrent VTE while on anticoagulant therapy is
1526 active cancer, with an unexplained recurrence often pointing to yet to be diagnosed disease.
1527 Antiphospholipid syndrome is also associated with recurrent VTE, either because of associated
1528 hypercoagulability or because a lupus anticoagulant has led to underdosing of VKA due to
1529 spurious increases in INR results. Anticoagulated patients may be taking medications that

increase the risk of thrombosis such as estrogens or cancer chemotherapy, in which case these treatments may be withdrawn.

A retrospective observational study found an acceptable risk of recurrence (8.6%) and major bleeding (1.4%) during 3 months follow-up in 70 cancer patients with recurrent VTE while on anticoagulant therapy who either switched from VKA therapy to LMWH (23 patients) or had their LMWH dose increased by about 25% (47 patients).[172] If there is no reversible reason for recurrent VTE while on anticoagulant therapy, and anticoagulant intensity cannot be increased because of risk of bleeding, a vena caval filter can be inserted to prevent PE.[173] However, it is not known if insertion of a filter in these circumstances is worthwhile, and the AT10 panel consider this an option of last resort.

29. **In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or on dabigatran, rivaroxaban, apixaban or edoxaban (and are believed to be compliant), we suggest switching to treatment with LMWH at least temporarily** (Grade 2C).

Remarks: Recurrent VTE while on therapeutic-dose anticoagulant therapy is unusual and should prompt the following assessments: (1) reevaluation of whether there truly was a recurrent VTE; (2) evaluation of compliance with anticoagulant therapy; and (3) consideration of an underlying malignancy. A temporary switch to LMWH will usually be for at least one month.

30. **In patients who have recurrent VTE on long-term LMWH (and are believed to be compliant) we suggest increasing the dose of LMWH by about one-quarter to one-third** (Grade 2C).

Remarks: Recurrent VTE while on therapeutic-dose anticoagulant therapy is unusual and should prompt the following assessments: (1) reevaluation of whether there truly was a recurrent VTE; (2) evaluation of compliance with anticoagulant therapy; and (3) consideration of an underlying malignancy.

Conclusion

There is substantial new evidence since AT9 about how to treat VTE. This evidence led the panel to change many of the AT9 recommendations that are included in this update, and has strengthened the evidence quality that underlies others that are unchanged. We now suggest the use of NOACs over VKA for the treatment of VTE in patients without cancer. While we still suggest LMWH as the preferred long-term treatment for VTE and cancer, we no longer suggest VKA over NOACs in these patients. Although we note factors in individual patients that may favor selection of one NOAC over another in patients without or with cancer, or may favor selection of either a NOAC or VKA in patients with cancer, we have not expressed an overall preference for one NOAC over another, or for either a NOAC or VKA in patients with cancer, because: (1) there are no direct comparisons of different NOACs; (2) NOACs have not been compared to VKA in a broad spectrum of patients with VTE and cancer; and (3) indirect comparisons have not shown convincingly different outcomes with different NOACs. Another notable change in AT10 is that, based on a new low risk of bias study, we now suggest that graduated compression stocking are not routinely used to prevent PTS. Recommendations that are unchanged but are now supported by better evidence include: (1) discouragement of IVC filter use in anticoagulated patients; (2) encouragement of indefinite anticoagulant therapy after a first unprovoked PE; and (3) discouragement of thrombolytic therapy in PE patients who are not hypotensive and are not deteriorating on anticoagulation.

Of the 54 recommendations that are included in the 30 statements in this update, 20 (38%) are strong recommendations (Grade 1) and none are based on high quality (Grade A) evidence. The absence of high quality evidence highlights the need for further research to guide VTE treatment decisions. As new evidence becomes available, these guidelines will need to be updated. Goals of our group and CHEST include transition to continually updated "living guidelines". The modular format of this update is designed to facilitate this development, with individual topics and questions being addressed as new evidence becomes available. We will also facilitate implementation of our recommendations into practice by developing new and convenient ways to disseminate our recommendations. This will enable achievement of another of our goals — reduction in the burden of VTE in individual patients and in the general population.

Acknowledgments

The roles of the panelists include the following:

Clive Kearon, MD, PhD – chair, executive committee member, topic editor for "Treatment of Acute Pulmonary Embolism Out of Hospital" and "Pulmonary Thromboendarterectomy in the Treatment of Chronic Thromboembolic Pulmonary Hypertension"

Elie Akl, MD, MPH, PhD – methodologist, executive committee member, topic editor for "Compression Stocking to Prevent Post-Thrombotic Syndrome" and "Thrombolytic Therapy in Patients with Upper Extremity Deep Vein Thrombosis"

Joseph Ornelas, PhD – methodologist, executive committee member

Allen Blaivas, DO, FCCP – GOC Liaison, executive committee member, topic editor for "Compression Stocking to Prevent Post-Thrombotic Syndrome" and "Thrombolytic Therapy in Patients with Upper Extremity Deep Vein Thrombosis"

David Jimenez, MD, PhD, FCCP - executive committee member, topic editor for "Pulmonary Thromboendarterectomy in the Treatment of Chronic Thromboembolic Pulmonary Hypertension" and "Management of Recurrent Venous Thromboembolism on Anticoagulant Therapy"

Henri Bounameaux, MD – topic editor for “Whether and How to Anticoagulate Patients with Isolated Distal Deep Vein Thrombosis” and “Catheter-Directed Thrombolysis for Acute Deep Vein Thrombosis of the Leg”

Menno Huisman, MD, PhD – topic editor for “Catheter-Directed Thrombolysis for Acute Deep Vein Thrombosis of the Leg” and “Duration of Anticoagulant Therapy”

Christopher King, MD, FCCP – topic editor for “Whether to Anticoagulate Subsegmental Pulmonary Embolism” and “Management of Recurrent Venous Thromboembolism on Anticoagulant Therapy”

Timothy Morris, MD, FCCP – topic editor for “Catheter-Based Thrombus Removal for the Initial Treatment of Pulmonary Embolism” and “Choice of Long-Term (First 3 Months) and Extended (No Scheduled Stop Date) Anticoagulant”

Namita Sood, MD, FCCP – topic editor for “Whether and How to Anticoagulate Isolated Distal Deep Vein Thrombosis “ and “Treatment of Acute Pulmonary Embolism Out of Hospital”

Scott Stevens, MD – topic editor for “Systemic Thrombolytic Therapy for Pulmonary Embolism” and “Catheter-Based Thrombus Removal for the Initial Treatment of Pulmonary Embolism”

Janine Vintch, MD, FCCP – topic editor for "Systemic Thrombolytic Therapy for Pulmonary Embolism" and "Duration of Anticoagulant Therapy"

Philip Wells, MD – topic editor for "Catheter-Based Thrombus Removal for the Initial Treatment of Pulmonary Embolism" and "Aspirin for Extended Treatment of Venous Thromboembolism"

Scott Woller, MD – topic editor for "Systemic Thrombolytic Therapy for Pulmonary Embolism" and "Choice of Long-Term (First 3 Months) and Extended (No Scheduled Stop Date) Anticoagulant"

Col. Lisa Moores, MD, FCCP – overall guideline editor, executive committee member, topic editor for "Whether to Anticoagulate Subsegmental Pulmonary Embolism" , "Role of Inferior Vena Caval Filter in Addition to Anticoagulation in Patients with Acute Deep Vein Thrombosis or Pulmonary Embolism" and "Aspirin for Extended Treatment of Venous Thromboembolism"

All the authors would like to acknowledge the contributions of previous authors of the CHEST Antithrombotic Guidelines.

References

1. Kearon C, Akl EA, Comerota AJ, et al. 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(2 Suppl):e419S-494S.
2. Guyatt G, Akl EA, Hirsh J, et al. The Vexing Problem of Guidelines and Conflict of Interest: A Potential Solution. *Annals of Internal Medicine.* 2010;152(11):738-741.
3. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC medical research methodology.* 2007;7:10.
4. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.
5. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *Journal of Clinical Epidemiology.*64(4):407-415.
6. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology.*64(4):401-406.
7. Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force. *Chest.* 2006;129(1):174-181.
8. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence—publication bias. *Journal of Clinical Epidemiology.*64(12):1277-1282.
9. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. *Journal of Clinical Epidemiology.*64(12):1283-1293.
10. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 7. Rating the quality of evidence—inconsistency. *Journal of Clinical Epidemiology.*64(12):1294-1302.
11. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 8. Rating the quality of evidence—indirectness. *Journal of Clinical Epidemiology.*64(12):1303-1310.
12. Guyatt GH, Oxman AD, Sultan S, et al. GRADE guidelines: 9. Rating up the quality of evidence. *Journal of Clinical Epidemiology.*64(12):1311-1316.
13. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology.*64(4):383-394.
14. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *Journal of Clinical Epidemiology.*66(7):719-725.
15. Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation's direction and strength. *Journal of Clinical Epidemiology.*66(7):726-735.
16. MacLean S, Mulla S, Akl EA, et al. 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. *Chest.* 2012;141(2 Suppl):e1S-23S.

17. Jones J, Hunter D. Consensus methods for medical and health services research. *Bmj.* 1995;311(7001):376-380.
18. Lewis SZ, Diekemper R, Ornelas J, Casey KR. Methodologies for the development of CHEST guidelines and expert panel reports. *Chest.* 2014;146(1):182-192.
19. Jaeschke R, Guyatt GH, Dellinger P, et al. Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. *BMJ.* 2008;337:a744.
20. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med.* 2009;361(24):2342-2352.
21. Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med.* 2010;363(26):2499-2510.
22. Lee AY, Kamphuisen PW, Meyer G, et al. Tinzaparin vs Warfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer: A Randomized Clinical Trial. *JAMA.* 2015;314(7):677-686.
23. Hokusai VTEI, Buller HR, Decousus H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med.* 2013;369(15):1406-1415.
24. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation.* 2014;129(7):764-772.
25. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369(9):799-808.
26. Investigators E-P, Buller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med.* 2012;366(14):1287-1297.
27. van Es N, Coppens M, Schulman S, Middeldorp S, Buller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. *Blood.* 2014;124(12):1968-1975.
28. Holster IL, Valkhoff VE, Kuipers EJ, Tjwa ET. New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. *Gastroenterology.* 2013;145(1):105-112 e115.
29. Gomez-Outes A, Terleira-Fernandez AI, Lecumberri R, Suarez-Gea ML, Vargas-Castrillon E. Direct oral anticoagulants in the treatment of acute venous thromboembolism: a systematic review and meta-analysis. *Thromb Res.* 2014;134(4):774-782.
30. Fox BD, Kahn SR, Langleben D, Eisenberg MJ, Shimony A. Efficacy and safety of novel oral anticoagulants for treatment of acute venous thromboembolism: direct and adjusted indirect meta-analysis of randomised controlled trials. *BMJ.* 2012;345:e7498.
31. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. *J Thromb Haemost.* 2014;12(3):320-328.
32. Mantha S, Ansell J. Indirect comparison of dabigatran, rivaroxaban, apixaban and edoxaban for the treatment of acute venous thromboembolism. *J Thromb Thrombolysis.* 2015;39(2):155-165.

33. Chai-Adisaksopha C, Crowther M, Isayama T, Lim W. The impact of bleeding complications in patients receiving target-specific oral anticoagulants: a systematic review and meta-analysis. *Blood.* 2014;124(15):2450-2458.
34. Wu C, Alotaibi GS, Alsaleh K, Linkins LA, Sean McMurtry M. Case-fatality of recurrent venous thromboembolism and major bleeding associated with aspirin, warfarin, and direct oral anticoagulants for secondary prevention. *Thromb Res.* 2015;135(2):243-248.
35. Castellucci LA, Cameron C, Le Gal G, et al. Clinical and safety outcomes associated with treatment of acute venous thromboembolism: a systematic review and meta-analysis. *JAMA.* 2014;312(11):1122-1135.
36. Carrier M, Cameron C, Delluc A, Castellucci L, Khorana AA, Lee AY. Efficacy and safety of anticoagulant therapy for the treatment of acute cancer-associated thrombosis: a systematic review and meta-analysis. *Thromb Res.* 2014;134(6):1214-1219.
37. Vedovati MC, Germini F, Agnelli G, Becattini C. Direct Oral Anticoagulants in Patients With VTE and Cancer: A Systematic Review and Meta-analysis. *Chest.* 2015;147(2):475-483.
38. Di Minno MN, Ageno W, Dentali F. Meta-analysis of the efficacy and safety of new oral anticoagulants in patients with cancer-associated acute venous thromboembolism: comment. *J Thromb Haemost.* 2014;12(12):2136-2138.
39. Franchini M, Bonfanti C, Lippi G. Cancer-associated thrombosis: investigating the role of new oral anticoagulants. *Thromb Res.* 2015;135(5):777-781.
40. Bochenek T, Nizankowski R. The treatment of venous thromboembolism with low-molecular-weight heparins. A meta-analysis. *Thromb Haemost.* 2012;107(4):699-716.
41. Bloom BJ, Filion KB, Atallah R, Eisenberg MJ. Meta-analysis of randomized controlled trials on the risk of bleeding with dabigatran. *Am J Cardiol.* 2014;113(6):1066-1074.
42. Touma L, Filion KB, Atallah R, Eberg M, Eisenberg MJ. A meta-analysis of randomized controlled trials of the risk of bleeding with apixaban versus vitamin K antagonists. *Am J Cardiol.* 2015;115(4):533-541.
43. Abraham NS, Singh S, Alexander GC, et al. Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study. *BMJ.* 2015;350:h1857.
44. Kang N, Sobieraj DM. Indirect treatment comparison of new oral anticoagulants for the treatment of acute venous thromboembolism. *Thromb Res.* 2014;133(6):1145-1151.
45. Majeed A, Hwang HG, Connolly SJ, et al. Management and outcomes of major bleeding during treatment with dabigatran or warfarin. *Circulation.* 2013;128(21):2325-2332.
46. Kearon C, Ginsberg JS, Kovacs MJ, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *New England Journal Medicine.* 2003;349:631-639.
47. Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med.* 2013;368(8):709-718.
48. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med.* 2013;368(8):699-708.
49. Castellucci LA, Cameron C, Le Gal G, et al. Efficacy and safety outcomes of oral anticoagulants and antiplatelet drugs in the secondary prevention of venous thromboembolism: systematic review and network meta-analysis. *BMJ.* 2013;347:f5133.

50. Sobieraj DM, Coleman CI, Pasupuleti V, Deshpande A, Kaw R, Hernandez AV. Comparative efficacy and safety of anticoagulants and aspirin for extended treatment of venous thromboembolism: A network meta-analysis. *Thromb Res.* 2015;135(5):888-896.
51. 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.
52. Boutitie F, Pinede L, Schulman S, et al. Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials. *BMJ.* 2011;342:d3036.
53. Prandoni P, Noventa F, Ghirarduzzi A, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. *Haematologica.* 2007;92(2):199-205.
54. Prandoni P, Lensing AWA, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. *Annals of Internal Medicine.* 1996;125:1-7.
55. Palareti G, Legnani C, Lee A, et al. A comparison of the safety and efficacy of oral anticoagulation for the treatment of venous thromboembolic disease in patients with or without malignancy. *Thromb Haemost.* 2000;84(5):805-810.
56. Baglin T, Douketis J, Tosetto A, et al. Does the clinical presentation and extent of venous thrombosis predict likelihood and type of recurrence? A patient level meta-analysis. *J Thromb Haemost.* 2010;8:2436-2442.
57. Boutitie FP, L.;Schulman,S.; Agnelli,G.; Raskob,G.; Julian,J.; Hirsh,J.; Kearon,C. Influence of preceding duration of anticoagulant therapy and initial presentation of venous thromboembolism on risk of recurrence after stopping therapy: analysis of individualparticipant data from seven trials. *BMJ.* 2011;In Press(x):x.
58. Hansson PO, Sorbo J, Eriksson H. Recurrent venous thromboembolism after deep vein thrombosis: incidence and risk factors. *Archives of Internal Medicine.* 2000;160(6):769-774.
59. Schulman S, Wahlander K, Lundstrîm T, Clason SB, Eriksson H, for the TIIII. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. *New England Journal Medicine.* 2003;349:1713-1721.
60. Napolitano M, Saccullo G, Malato A, et al. Optimal duration of low molecular weight heparin for the treatment of cancer-related deep vein thrombosis: the Cancer-DACUS Study. *J Clin Oncol.* 2014;32(32):3607-3612.
61. Couturand F SO, Pernod G, Mismetti P, Jego P, Duhamel E, Provost K, Bal dit Sollier C, Presles E, Castellant P, Parent F, Salaun P, Bressollette L, Nonent M, Lorillon P, Girard P, Lacut K, Guégan M, Bosson J, Laporte S, Leroyer C, Décousus H, Meyer G, Mottier D, for the PADIS-PE Investigators. Two years versus six months of oral anticoagulation after a first episode of unprovoked pulmonary embolism. The PADIS-PE multicenter, double-blind, randomized, trial. 2015.
62. Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *New England Journal of Medicine.* 1999;340:901-907.

63. Ridker PM, Goldhaber S Z, Danielson E, et al. Long-term, low-intensity warfarin therapy for prevention of recurrent venous thromboembolism. *New England Journal Medicine.* 2003;348:1425-1434.
64. Farraj RS. Anticoagulation period in idiopathic venous thromboembolism. How long is enough? *Saudi Med J.* 2004;25(7):848-851.
65. Palareti G, Cosmi B, Legnani C, et al. D-dimer testing to determine the duration of anticoagulation therapy. *N.Engl.J Med.* 2006;355(17):1780-1789.
66. Schulman S, Granqvist S, Holmstrom M, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. *The New England Journal of Medicine.* 1997;336:393-398.
67. Douketis J, Tosetto A, Marcucci M, et al. Risk of recurrence after venous thromboembolism in men and women: patient level meta-analysis. *BMJ.* 2011;342:d813.
68. Douketis J, Tosetto A, Marcucci M, et al. Patient-level meta-analysis: effect of measurement timing, threshold, and patient age on ability of D-dimer testing to assess recurrence risk after unprovoked venous thromboembolism. *Ann Intern Med.* 2010;153(8):523-531.
69. Palareti G, Cosmi B, Legnani C, et al. D-dimer to guide the duration of anticoagulation in patients with venous thromboembolism: a management study. *Blood.* 2014;124(2):196-203.
70. Kearon C, Spencer FA, O'Keeffe D, et al. D-dimer testing to select patients with a first unprovoked venous thromboembolism who can stop anticoagulant therapy: a cohort study. *Ann Intern Med.* 2015;162(1):27-34.
71. Brighton TA, Eikelboom JW, Mann K, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. *N Engl J Med.* 2012;367(21):1979-1987.
72. Becattini C, Agnelli G, Schenone A, et al. Aspirin for preventing the recurrence of venous thromboembolism. *N Engl J Med.* 2012;366(21):1959-1967.
73. Simes J, Becattini C, Agnelli G, et al. Aspirin for the prevention of recurrent venous thromboembolism: the INSPIRE collaboration. *Circulation.* 2014;130(13):1062-1071.
74. Bates SM, Jaeschke R, Stevens SM, et al. Diagnosis of Deep Vein Thrombosis: ACCP Evidence-Based Clinical Practice Guidelines (Ninth Edition). *Chest.* 2012.
75. Righini M, Paris S, Le Gal G, Laroche JP, Perrier A, Bounameaux H. Clinical relevance of distal deep vein thrombosis. Review of literature data. *Thromb Haemost.* 2006;95(1):56-64.
76. Masuda EM, Kistner RL. The case for managing calf vein thrombi with duplex surveillance and selective anticoagulation. *Dis Mon.* 2010;56(10):601-613.
77. Masuda EM, Kistner RL, Musikasinthorn C, Liquido F, Geling O, He Q. The controversy of managing calf vein thrombosis. *Journal of Vascular Surgery.* 2012;55(2):550-561.
78. De Martino RR, Wallaert JB, Rossi AP, Zbehlik AJ, Suckow B, Walsh DB. A meta-analysis of anticoagulation for calf deep venous thrombosis. *Journal of Vascular Surgery.* 2012;56(1):228-237.e221.
79. Spencer F, Kroll A, Lessard D, et al. Isolated calf deep vein thrombosis in the community setting: the Worcester Venous Thromboembolism study. *Journal of Thrombosis and Thrombolysis.* 2012;33(3):211-217.
80. Hughes MJ, Stein PD, Matta F. Silent pulmonary embolism in patients with distal deep venous thrombosis: systematic review. *Thromb Res.* 2014;134(6):1182-1185.

81. Kearon C. Natural history of venous thromboembolism. *Circulation.* 2003;107:I-22-21-30.
82. Macdonald PS, Kahn SR, Miller N, Obrand D. Short-term natural history of isolated gastrocnemius and soleal vein thrombosis. *J Vasc Surg.* 2003;37(3):523-527.
83. Parisi R, Visona A, Camporese G, et al. Isolated distal deep vein thrombosis: efficacy and safety of a protocol of treatment. Treatment of Isolated Calf Thrombosis (TICT) Study. *Int Angiol.* 2009;28(1):68-72.
84. Palareti G. How I treat isolated distal deep vein thrombosis (IDDVT). *Blood.* 2014;123(12):1802-1809.
85. Galanaud JP, Sevestre MA, Genty C, et al. Incidence and predictors of venous thromboembolism recurrence after a first isolated distal deep vein thrombosis. *J Thromb Haemost.* 2014;12(4):436-443.
86. Schwarz T, Buschmann L, Beyer J, Halbritter K, Rastan A, Schellong S. Therapy of isolated calf muscle vein thrombosis: a randomized, controlled study. *J Vasc Surg.* 2010;52(5):1246-1250.
87. Elsharawy M, Elzayat E. Early results of thrombolysis vs anticoagulation in iliofemoral venous thrombosis. A randomised clinical trial. *Eur.J Vasc Endovasc.Surg.* 2002;24(3):209-214.
88. Enden T, Klow NE, Sandvik L, et al. Catheter-directed thrombolysis vs. anticoagulant therapy alone in deep vein thrombosis: results of an open randomized, controlled trial reporting on short-term patency. *J Thromb Haemost.* 2009;7(8):1268-1275.
89. Enden T, Sandvik L, Klow NE, et al. Catheter-directed Venous Thrombolysis in acute iliofemoral vein thrombosis--the CaVenT study: rationale and design of a multicenter, randomized, controlled, clinical trial (NCT00251771). *Am Heart J.* 2007;154(5):808-814.
90. Haig Y, Enden T, Slagsvold CE, Sandvik L, Sandset PM, Klow NE. Determinants of early and long-term efficacy of catheter-directed thrombolysis in proximal deep vein thrombosis. *J Vasc Interv Radiol.* 2013;24(1):17-24; quiz 26.
91. Enden T, Haig Y, Klow NE, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. *Lancet.* 2012;379(9810):31-38.
92. Enden T, Resch S, White C, Wik HS, Klow NE, Sandset PM. Cost-effectiveness of additional catheter-directed thrombolysis for deep vein thrombosis. *J Thromb Haemost.* 2013;11(6):1032-1042.
93. Watson LI, Armon MP. Thrombolysis for acute deep vein thrombosis. *Cochrane Database Syst Rev.* 2004(4):Cd002783.
94. Bashir R, Zack CJ, Zhao H, Comerota AJ, Bove AA. Comparative outcomes of catheter-directed thrombolysis plus anticoagulation vs anticoagulation alone to treat lower-extremity proximal deep vein thrombosis. *JAMA internal medicine.* 2014;174(9):1494-1501.
95. Engelberger RP, Fahrni J, Willenberg T, et al. Fixed low-dose ultrasound-assisted catheter-directed thrombolysis followed by routine stenting of residual stenosis for acute ilio-femoral deep-vein thrombosis. *Thromb Haemost.* 2014;111(6):1153-1160.
96. Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. *N Engl J Med.* 1998;338:409-415.

97. Eight-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism: the PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) randomized study. *Circulation.* 2005;112(3):416-422.
98. Stein PD, Matta F. Vena cava filters in unstable elderly patients with acute pulmonary embolism. *Am J Med.* 2014;127(3):222-225.
99. Stein PD, Matta F, Keyes DC, Willyerd GL. Impact of vena cava filters on in-hospital case fatality rate from pulmonary embolism. *Am J Med.* 2012;125(5):478-484.
100. Muriel A, Jimenez D, Aujesky D, et al. Survival effects of inferior vena cava filter in patients with acute symptomatic venous thromboembolism and a significant bleeding risk. *J Am Coll Cardiol.* 2014;63(16):1675-1683.
101. Prasad V, Rho J, Cifu A. The inferior vena cava filter: how could a medical device be so well accepted without any evidence of efficacy? *JAMA internal medicine.* 2013;173(7):493-495; discussion 495.
102. Girard P, Meyer G, Parent F, Mismetti P. Medical literature, vena cava filters and evidence of efficacy. A descriptive review. *Thromb Haemost.* 2014;111(4):761-769.
103. Mismetti P, Laporte S, Pellerin O, et al. Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a randomized clinical trial. *JAMA.* 2015;313(16):1627-1635.
104. Brandjes DP, Buller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet.* 1997;349(9054):759-762.
105. Prandoni P, Lensing AW, Prins MH, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. *Ann.Intern.Med.* 2004;141(4):249-256.
106. Kahn SR, Comerota AJ, Cushman M, et al. The postthrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation.* 2014;130(18):1636-1661.
107. Kahn SR, Shapiro S, Wells PS, et al. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. *Lancet.* 2014;383(9920):880-888.
108. Kahn SR, Shapiro S, Ducruet T, et al. Graduated compression stockings to treat acute leg pain associated with proximal DVT. A randomised controlled trial. *Thromb Haemost.* 2014;112(6):1137-1141.
109. Wiener RS, Schwartz LM, Woloshin S. When a test is too good: how CT pulmonary angiograms find pulmonary emboli that do not need to be found. *BMJ.* 2013;347:f3368.
110. Carrier M, Righini M, Wells PS, et al. Subsegmental pulmonary embolism diagnosed by computed tomography: incidence and clinical implications. A systematic review and meta-analysis of the management outcome studies. *J Thromb Haemost.* 2010;8(8):1716-1722.
111. Carrier M, Righini M, Le Gal G. Symptomatic subsegmental pulmonary embolism: what is the next step? *J Thromb Haemost.* 2012;10(8):1486-1490.
112. Stein PD, Goodman LR, Hull RD, Dalen JE, Matta F. Diagnosis and management of isolated subsegmental pulmonary embolism: review and assessment of the options. *Clin Appl Thromb Hemost.* 2012;18(1):20-26.
113. Costantino G, Norsa AH, Amadori R, et al. Interobserver agreement in the interpretation of computed tomography in acute pulmonary embolism. *Am J Emerg Med.* Vol 272009:1109-1111.

114. Lucassen WA, Beenen LF, Buller HR, et al. Concerns in using multi-detector computed tomography for diagnosing pulmonary embolism in daily practice. A cross-sectional analysis using expert opinion as reference standard. *Thromb Res.* 2013;131(2):145-149.
115. Stein PD, Fowler SE, Goodman LR, et al. Multidetector computed tomography for acute pulmonary embolism. *N Engl J Med.* 2006;354(22):2317-2327.
116. Courtney DM, Miller C, Smithline H, Klekowski N, Hogg M, Kline JA. Prospective multicenter assessment of interobserver agreement for radiologist interpretation of multidetector computerized tomographic angiography for pulmonary embolism. *J Thromb Haemost.* 2010;8(3):533-539.
117. Pena E, Kimpton M, Dennie C, Peterson R, G LEG, Carrier M. Difference in interpretation of computed tomography pulmonary angiography diagnosis of subsegmental thrombosis in patients with suspected pulmonary embolism. *J Thromb Haemost.* 2012;10(3):496-498.
118. Le Gal G, Righini M, Parent F, van Strijen M, Couturaud F. Diagnosis and management of subsegmental pulmonary embolism. *J Thromb Haemost.* 2006;4(4):724-731.
119. Le Gal G, Righini M, Sanchez O, et al. A positive compression ultrasonography of the lower limb veins is highly predictive of pulmonary embolism on computed tomography in suspected patients. *Thromb Haemost.* 2006;95(6):963-966.
120. den Exter PL, van Es J, Klok FA, et al. Risk profile and clinical outcome of symptomatic subsegmental acute pulmonary embolism. *Blood.* 2013;122(7):1144-1149; quiz 1329.
121. Kearon C, Ginsberg JS, Hirsh J. The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. *Ann Intern Med.* 1998;129(12):1044-1049.
122. Otero R, Uresandi F, Jimenez D, et al. Home treatment in pulmonary embolism. *Thromb Res.* 2010;126(1):e1-5.
123. Aujesky D, Roy PM, Verschuren F, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. *Lancet.* 2011;378(9785):41-48.
124. Piran S, Le Gal G, Wells PS, et al. Outpatient treatment of symptomatic pulmonary embolism: a systematic review and meta-analysis. *Thromb Res.* 2013;132(5):515-519.
125. Vinson DR, Zehtabchi S, Yealy DM. Can selected patients with newly diagnosed pulmonary embolism be safely treated without hospitalization? A systematic review. *Annals of emergency medicine.* 2012;60(5):651-662 e654.
126. Zondag W, Kooiman J, Klok FA, Dekkers OM, Huisman MV. Outpatient versus inpatient treatment in patients with pulmonary embolism: a meta-analysis. *Eur Respir J.* 2013;42(1):134-144.
127. Chan CM, Woods C, Shorr AF. The validation and reproducibility of the pulmonary embolism severity index. *J Thromb Haemost.* 2010;8(7):1509-1514.
128. Jimenez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med.* 2010;170(15):1383-1389.
129. Moores L, Aujesky D, Jimenez D, et al. Pulmonary Embolism Severity Index and troponin testing for the selection of low-risk patients with acute symptomatic pulmonary embolism. *J Thromb Haemost.* 2010;8(3):517-522.

130. Ozsu S, Abul Y, Orem A, et al. Predictive value of troponins and simplified pulmonary embolism severity index in patients with normotensive pulmonary embolism. *Multidisciplinary respiratory medicine.* 2013;8(1):34.
131. Righini M, Roy PM, Meyer G, Verschuren F, Aujesky D, Le Gal G. The Simplified Pulmonary Embolism Severity Index (PESI): validation of a clinical prognostic model for pulmonary embolism. *J Thromb Haemost.* 2011;9(10):2115-2117.
132. Zondag W, den Exter PL, Crobach MJ, et al. Comparison of two methods for selection of out of hospital treatment in patients with acute pulmonary embolism. *Thromb Haemost.* 2013;109(1):47-52.
133. Jimenez D, Uresandi F, Otero R, et al. Troponin-based risk stratification of patients with acute nonmassive pulmonary embolism: systematic review and metaanalysis. *Chest.* 2009;136(4):974-982.
134. Lankeit M, Jimenez D, Kostrubiec M, et al. Validation of N-terminal pro-brain natriuretic peptide cut-off values for risk stratification of pulmonary embolism. *Eur Respir J.* 2014;43(6):1669-1677.
135. Becattini C, Agnelli G, Germini F, Vedovati MC. Computed tomography to assess risk of death in acute pulmonary embolism: a meta-analysis. *Eur Respir J.* 2014;43(6):1678-1690.
136. Coutance G, Cauderlier E, Ehtisham J, Hamon M, Hamon M. The prognostic value of markers of right ventricular dysfunction in pulmonary embolism: a meta-analysis. *Critical care.* 2011;15(2):R103.
137. Spirk D, Aujesky D, Husmann M, et al. Cardiac troponin testing and the simplified Pulmonary Embolism Severity Index. The SWIss Venous ThromboEmbolism Registry (SWIVTER). *Thromb Haemost.* 2011;106(5):978-984.
138. Lankeit M, Gomez V, Wagner C, et al. A strategy combining imaging and laboratory biomarkers in comparison with a simplified clinical score for risk stratification of patients with acute pulmonary embolism. *Chest.* 2012;141(4):916-922.
139. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J.* 2014;35(43):3033-3069, 3069a-3069k.
140. Dong B, Jirong Y, Wang Q, Wu T. Thrombolytic treatment for pulmonary embolism. *Cochrane Database Syst Rev.* 2006;2; :Art.No: CD004437.pub004432. DOI: 004410.001002/14651858.CD14004437.pub14651852.
141. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. *Lancet.* 1994;343(8893):311-322.
142. Kline JA, Nordenholz KE, Courtney DM, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. *J Thromb Haemost.* 2014;12(4):459-468.
143. Sharifi M, Bay C, Skrocki L, Rahimi F, Mehdipour M. Moderate Pulmonary Embolism Treated With Thrombolysis (from the "MOPETT" Trial). *The American Journal of Cardiology.* 2013;111(2):273-277.
144. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med.* 2014;370(15):1402-1411.

145. Wang TF, Squizzato A, Dentali F, Ageno W. The role of thrombolytic therapy in pulmonary embolism. *Blood.* 2015;125(14):2191-2199.
146. Marti C, John G, Konstantinides S, et al. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. *Eur Heart J.* 2015;36(10):605-614.
147. Nakamura S, Takano H, Kubota Y, Asai K, Shimizu W. Impact of the efficacy of thrombolytic therapy on the mortality of patients with acute submassive pulmonary embolism: a meta-analysis. *J Thromb Haemost.* 2014;12(7):1086-1095.
148. Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *JAMA.* 2014;311(23):2414-2421.
149. Riera-Mestre A, Becattini C, Giustozzi M, Agnelli G. Thrombolysis in hemodynamically stable patients with acute pulmonary embolism: a meta-analysis. *Thromb Res.* 2014;134(6):1265-1271.
150. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir.Crit Care Med.* 2005;172:1041-1046.
151. Kuo WT, Gould MK, Louie JD, Rosenberg JK, Sze DY, Hofmann LV. Catheter-directed therapy for the treatment of massive pulmonary embolism: systematic review and meta-analysis of modern techniques. *J Vasc Interv Radiol.* 2009;20(11):1431-1440.
152. Kuo WT. Endovascular therapy for acute pulmonary embolism. *J Vasc Interv Radiol.* 2012;23(2):167-179 e164; quiz 179.
153. Avgerinos ED, Chaer RA. Catheter-directed interventions for acute pulmonary embolism. *Journal of Vascular Surgery.* 2015;61(2):559-565.
154. Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation.* 2011;123(16):1788-1830.
155. Kucher N, Boekstegers P, Muller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation.* 2014;129(4):479-486.
156. Kuo WT, Banerjee A, Kim PS, et al. Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT): Initial Results from a Prospective Multicenter Registry. *Chest.* 2015.
157. Piazza G, Hohlfelder B, Jaff MR, et al. A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism: The SEATTLE II Study. *JACC Cardiovasc Interv.* 2015;8(10):1382-1392.
158. Verstraete M, Miller GAH, Bounameaux H, et al. Intravenous and intrapulmonary recombinant tissue-type plasminogen activator in the treatment of acute massive pulmonary embolism. *Circulation.* 1988;77(2):353-360.
159. Pepke-Zaba J, Delcroix M, Lang I, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. *Circulation.* 2011;124(18):1973-1981.
160. Fedullo P, Kerr KM, Kim NH, Auger WR. Chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med.* 2011;183(12):1605-1613.

161. Mayer E, Jenkins D, Lindner J, et al. Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. *The Journal of thoracic and cardiovascular surgery.* 2011;141(3):702-710.
162. Hayes, Inc. Pulmonary thromboendarterectomy for treatment of pulmonary hypertension (Structured abstract). *Health Technology Assessment Database.* 2012(1).
163. Rahnavardi M, Yan TD, Cao C, Vallely MP, Bannon PG, Wilson MK. Pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension: a systematic review (Structured abstract). *Annals of Thoracic and Cardiovascular Surgery.* 2011;17(5):435-445.
164. Ghofrani HA, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med.* 2013;369(4):319-329.
165. Deano RC, Glassner-Kolmin C, Rubenfire M, et al. Referral of patients with pulmonary hypertension diagnoses to tertiary pulmonary hypertension centers: the multicenter RePHerral study. *JAMA internal medicine.* 2013;173(10):887-893.
166. Andreassen AK, Ragnarsson A, Gude E, Geiran O, Andersen R. Balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension. *Heart (British Cardiac Society).* 2013;99(19):1415-1420.
167. Taichman DB, Ornelas J, Chung L, et al. Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report. *Chest.* 2014;146(2):449-475.
168. Kucher N. Clinical practice. Deep-vein thrombosis of the upper extremities. *N Engl J Med.* 2011;364(9):861-869.
169. Naeem M, Soares G, Ahn S, Murphy TP. Paget-Schroetter syndrome: A review and Algorithm (WASPS-IR). *Phlebology.* 2015.
170. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ, III. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. *Archives of Internal Medicine.* 2000;160(6):761-768.
171. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N.Engl.J Med.* 2003;349(2):146-153.
172. Carrier M, Le Gal G, Cho R, Tierney S, Rodger M, Lee AY. Dose escalation of low molecular weight heparin to manage recurrent venous thromboembolic events despite systemic anticoagulation in cancer patients. *J Thromb Haemost.* 2009;7(5):760-765.
173. Farge D, Debourdeau P, Beckers M, et al. International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *J Thromb Haemost.* 2013;11(1):56-70.

Table 1: Summary of Findings - LMWH vs VKA for long term treatment of VTE [1]

Bibliography: Deitcher et al. (ONCENOX)[1], Hull et al. (LITE)[2], Hull et al. (LITE Home)[3], Lee et al. (CLOT)[4], Lopaciuk et al.[5], Lopez-Beret et al.[6], Meyer et al.[7], Romera et al.[8], Lee et al. (CATCH)[9]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI) [2]	Anticipated absolute effects	
				Risk with VKA	Risk difference with LMWH (95% CI)
All Cause Mortality	3396 (9 studies) 6 months	⊕⊕⊕⊖ **MODERATE**[4] due to risk of bias	**RR 1.01** (0.89 to 1.14)	**Non-Cancer**[3]	
				17 per 1000	**0 more per 1000** (from 2 fewer to 2 more)
				Non-Metastatic Cancer[3]	
				42 per 1000	**0 more per 1000** (from 5 fewer to 6 more)
				Metastatic Cancer[3]	
				253 per 1000	**3 more per 1000** (from 28 fewer to 35 more)
Recurrent VTE	3627 (9 studies) 6 months	⊕⊕⊕⊖ **MODERATE**[6] due to risk of bias	**RR 0.65** (0.51 to 0.83)	**Low**[5]	
				30 per 1000	**11 fewer per 1000** (from 5 fewer to 15 fewer)
				Moderate[5]	
				80 per 1000	**28 fewer per 1000** (from 14 fewer to 39 fewer)
				High[5]	
				200 per 1000	**70 fewer per 1000** (from 34 fewer to 98 fewer)
Major bleeding	3637 (9 studies) 6 months	⊕⊕⊕⊖ **MODERATE**[8,9] due to imprecision	**RR 0.86** (0.56 to 1.32)	**Low**[7]	
				20 per 1000	**3 fewer per 1000** (from 9 fewer to 6 more)
				High[7]	
				80 per 1000	**11 fewer per 1000** (from 35 fewer to 26 more)

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
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.

[1] The initial parenteral anticoagulation was similar in both arms for all except one study (Hull et al.[2]) in which patients randomized to LMWH received initially the same LWMH whereas patients randomized to VKA received initially UFH

[2] The relative effect (RR; 95% CI) of LMWH versus VKA was assessed, and compared, in the subgroup of trials that enrolled patients without (Hull et al. (LITE)[2], Lopez-Beret et al..[6]) and with (Deitcher et al. (ONCENOX)[1], Hull et al. (LITE)[2], Lee et al. (CLOT)[4], Lee et al. (CATCH)[9], Lopez-Beret et al.[6], Meyer et al.[7]) cancer: Recurrent VTE: cancer RR 0.59 (0.44 to 0.78) vs. no cancer RR 0.99 (0.46

to 2.13); P=0.21 for subgroup difference. Major Bleeding: cancer RR 0.96 (0.65 to 1.42) vs. no cancer RR 0.43 (0.17 to 1.17); P=0.14 for subgroup difference. All Cause Mortality: cancer RR 1.00 (0.88 to 1.33) vs. no cancer RR 1.85 (0.59 to 5.77); P=0.29 for subgroup difference.

[3] Low corresponds to patients without cancer and patients with non-metastatic cancer. High corresponds to patients with metastatic cancer. These control event rates were derived from the RIETE registry (an ongoing prospective registry of consecutive patients with acute VTE) (Prandoni et al.[10])

[4] One study did not report deaths, which is unusual and could reflect selective reporting of outcomes.

[5] Risk of recurrent VTE: Low corresponds to patients without cancer (3% estimate taken from recent large RCTs of acute treatment), intermediate to patients with local or recently resected cancer (appears to be consistent with Prandoni [particularly if low risk is increased to 4%]), and high to patients with locally advanced or distant metastatic cancer. (Prandoni et al.[11])

[6] None of the studies was blinded while 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 as 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 as there is no attractive alternative treatment option.

[7] Risk of bleeding: Low corresponds to patients without risk factor for bleeding (i.e., > 75 years, cancer, metastatic disease; chronic renal or hepatic failure; platelet count <80,0000; requires antiplatelet therapy; history of bleeding without a reversible cause). (Prandoni et al.[10], Byeth et al.[12])

[8] Confidence interval includes both no effect and harm with LMWH

[9] 95% confidence intervals for the risk ratio for major bleeding includes a potentially clinically important increase or decrease with LMWH, and may also vary with the dose of LMWH used during the extended phase of therapy

Table 2: Summary of Findings - Dabigatran vs VKA for long-term treatment of VTE [1,2]

Bibliography: Schulman et al. (RE-COVER I & II)[13]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with VKA	Risk difference with Dabigatran (95% CI)
All Cause Mortality	5107 (2 studies)	⊕⊕⊕⊖ **MODERATE**[4] due to imprecision	**RR 1.0** (0.67 to 1.50)[3]	**18 per 1000**[3]	**0 fewer per 1000** (from 6 fewer to 9 more)
Recurrent VTE	5107 (2 studies)	⊕⊕⊕⊖ **MODERATE**[4] due to imprecision	**RR 1.12** (0.77 to 1.62)[3]	**22 per 1000**[3]	**3 more per 1000** (from 5 fewer to 13 more)
Major Bleeding	5107 (2 studies)	⊕⊕⊕⊖ **MODERATE**[4] due to imprecision	**RR 0.73** (0.48 to 1.10)[3]	**20 per 1000**[3]	**5 fewer per 1000** (from 10 fewer to 2 more)

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
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.

[1] Patients with acute VTE treated initially with low-molecular-weight or unfractionated heparin
[2] Dabigatran 150 mg twice daily vs. warfarin
[3] Pooled analysis of Schulman et al. (Re-Cover I)[14] and Schulman et al. (Re-Cover II)[13] performed by Schulman et al.[13]
[4] CI includes values suggesting no effect and values suggesting either benefit or harm

Table 3: Summary of Findings - Rivaroxaban vs LMWH and VKA for acute and long-term treatment of VTE[1,2]

Bibliography: Prins et al.[15]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH and VKA	Risk difference with Rivaroxaban (95% CI)
All Cause Mortality	8281 (2 studies) 3 months	⊕⊕⊕⊖ **MODERATE**[4] due to imprecision	**RR 0.97** (0.73 to 1.27)	**24 per 1000**[3]	**1 fewer per 1000** (from 6 fewer to 6 more)
Recurrent VTE	8281 (2 studies) 3 months	⊕⊕⊕⊖ **MODERATE**[4] due to imprecision	**RR 0.90** (0.68 to 1.2)	**23 per 1000**[3]	**2 fewer per 1000** (from 7 fewer to 5 more)
Major Bleeding	8246 (2 studies) 3 months	⊕⊕⊕⊕ **HIGH**	**RR 0.55** (0.38 to 0.81)	**17 per 1000**[3]	**8 fewer per 1000** (from 3 fewer to 11 fewer)

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
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.

[1] Included patients had acute, symptomatic, objectively verified proximal DVT of the legs or PE (unprovoked 73%; cancer 5%; previous VTE 19%)
[2] Rivaroxaban 20 mg daily for 6 or 12 month after initial long-term therapy
[3] Pooled analysis of Bauersachs et al. (EINSTEIN-DVT)[16] and Buller et al. (EINSTEIN-PE)[17] performed by Prins et al.[15]
[4] CI includes values suggesting no effect and values suggesting either benefit or harm

Table 4: Summary of Findings - Apixaban vs LMWH and VKA for acute and long-term treatment of VTE [1,2]

Bibliography: Agnelli et al. (AMPLIFY)[18]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH and VKA	Risk difference with Apixaban (95% CI)
All Cause Mortality	5365 (1 study)	⊕⊕⊕⊖ **MODERATE**[3] due to imprecision	**RR 0.79** (0.53 to 1.19)	**19 per 1000**	**4 fewer per 1000** (from 9 fewer to 4 more)
Recurrent VTE	5244 (1 study)	⊕⊕⊕⊖ **MODERATE**[3] due to imprecision	**RR 0.84** (0.6 to 1.18)	**27 per 1000**	**4 fewer per 1000** (from 11 fewer to 5 more)
Major Bleeding	5365 (1 study)	⊕⊕⊕⊕ **HIGH**	**RR 0.31** (0.17 to 0.55)	**18 per 1000**	**13 fewer per 1000** (from 8 fewer to 15 fewer)

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
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.

[1] Apixaban 10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months
[2] Subcutaneous enoxaparin, followed by warfarin
[3] CI includes values suggesting no effect and values suggesting either benefit or harm

Table 5: Summary of Findings - Edoxaban vs VKA for acute and long-term treatment of VTE [1,2]

Bibliography: Buller et al. (Hokusai)[19]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with VKA	Risk difference with Edoxaban (95% CI)
All Cause Mortality	8240 (1 study)	⊕⊕⊕⊖ **MODERATE**[4] due to imprecision	**RR 1.05** (0.82 to 1.33)	**31 per 1000**[3]	**2 more per 1000** (from 6 fewer to 10 more)
Recurrent VTE	8240 (1 study)	⊕⊕⊕⊖ **MODERATE**[3,4] due to imprecision	**RR 0.83** (0.57 to 1.21)	**35 per 1000**	**6 fewer per 1000** (from 15 fewer to 7 more)
Major Bleeding	8240 (1 study)	⊕⊕⊕⊖ **MODERATE**[4] due to imprecision	**RR 0.85** (0.6 to 1.21)	**16 per 1000**	**2 fewer per 1000** (from 6 fewer to 3 more)

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
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.

[1] Patients with acute VTE who had initially received heparin
[2] Edoxaban 60 mg once daily, or 30 mg once daily if patients with creatinine clearance of 30 to 50 ml per minute or a body weight below 60 kg
[3] Death, with PE not ruled out
[4] CI includes values suggesting no effect and values suggesting either benefit or harm

Table 6: Factors that may influence which anticoagulant is chosen for initial and long-term treatment of VTE

Factor	Preferred anticoagulant	Qualifying remarks
Cancer	LMWH	More so if: just diagnosed, extensive VTE, metastatic cancer, very symptomatic; vomiting; on cancer chemotherapy.
Parenteral therapy to be avoided	Rivaroxaban; apixaban	VKA, dabigatran and edoxaban require initial parenteral therapy.
Once daily oral therapy preferred	Rivaroxaban; edoxaban; VKA	
Liver disease and coagulopathy	LMWH	NOACs contraindicated if INR raised due to liver disease; VKA difficult to control and INR may not reflect antithrombotic effect.
Renal disease and creatinine clearance <30 ml/min	VKA	NOACs and LMWH contraindicated with severe renal impairment. Dosing of NOACs with levels of renal impairment differ with the NOAC and among jurisdictions.
Coronary artery disease	VKA, rivaroxaban, apixaban, edoxaban	Coronary artery events appear to occur more often with dabigatran than with VKA. This has not been seen with the other NOACs, and they have demonstrated efficacy for coronary artery disease. Antiplatelet therapy should be avoided if possible in patients on anticoagulants because of increased bleeding.
Dyspepsia or history of gastrointestinal bleeding	VKA, apixaban,	Dabigatran increased dyspepsia. Dabigatran, rivaroxaban and edoxaban may be associated with more gastrointestinal bleeding than VKA.
Poor compliance	VKA	INR monitoring can help to detect problems. However, some patients may be more compliant with a NOAC because it is less complex.
Thrombolytic therapy use	Unfractionated heparin infusion	Greater experience with its use in patients treated with thrombolytic therapy
Reversal agent needed	VKA, unfractionated heparin	
Pregnancy or pregnancy risk	LMWH	Potential for other agents to cross the placenta
Cost, coverage, licensing	Varies among regions and with individual circumstances	

Table 7: Summary of Findings - Dabigatran vs VKA for extended treatment of VTE [1,2,3,4]

Bibliography: Schulman et al. (REMEDY)[20]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with VKA	Risk difference with Dabigatran (95% CI)
All Cause Mortality	2856 (1 study)	⊕⊕⊕⊖ **MODERATE**[5,6] due to imprecision	**RR 0.89** (0.47 to 1.71)	**13 per 1000**	**1 fewer per 1000** (from 7 fewer to 9 more)
Recurrent VTE	2856 (1 study)	⊕⊕⊕⊖ **MODERATE**[5,6,7] due to imprecision	**RR 1.44** (0.79 to 2.62)	**13 per 1000**	**6 more per 1000** (from 3 fewer to 20 more)
Major Bleeding	2856 (1 study)	⊕⊕⊕⊖ **MODERATE**[5,6] due to imprecision	**RR 0.52** (0.27 to 1.01)	**18 per 1000**	**8 fewer per 1000** (from 13 fewer to 0 more)

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
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.

[1] Included patients had acute, symptomatic, objectively verified proximal DVT of the legs or PE
[2] Dabigatran 150 mg twice daily taken orally for 6 months after an initial treatment with LMWH or IV UFH
[3] Warfarin adjusted to achieve an INR of 2.0 to 3.0 for 6 months after an initial treatment with LMWH or IV UFH
[4] Active-Control study outcomes used from Schulman et al. (REMEDY)[20]
[5] 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.
[6] CI includes values suggesting no effect and values suggesting either benefit or harm
[7] Primary end point was composite of recurrent or fatal VTE or unexplained death

Table 8: Summary of Findings - Dabigatran vs Placebo for extended treatment of VTE [1,2,3]

Bibliography: Schulman et al. (RESONATE)[20]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Dabigatran (95% CI)
All Cause Mortality	1343 (1 study)	⊕⊕⊕⊖ **MODERATE**[4] due to imprecision	Not estimable[5]	-	-
Recurrent VTE	1343 (1 study)	⊕⊕⊕⊕ **HIGH**	**RR 0.08** (0.02 to 0.25)	**56 per 1000**	**51 fewer per 1000** (from 42 fewer to 55 fewer)
Major Bleeding	1343 (1 study)	⊕⊕⊕⊖ **MODERATE**[4] due to imprecision	Not estimable[6]	-	-

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
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.

[1] Patients with VTE who had completed at least 3 initial months of therapy
[2] Dabigatran 150 mg twice daily
[3] Placebo-Control study outcomes used from Schulman et al. (RESONATE)[20]
[4] Event rate low in a large sample size
[5] Event rate with Dabigatran was 0/681 (0%); event rate with placebo was 2/662 (0.3%); anticipated absolute effect - risk difference with Dabigatran is 3 fewer per 1000 (from 11 fewer to 3 more)
[6] Event rate with Dabigatran was 2/681 (0.3%); event rate with placebo was 0/662 (0%); anticipated absolute effect - risk difference with Dabigatran is 3 more per 1000 (from 3 fewer to 11 more)

Table 9: Summary of Findings - Rivaroxaban vs Placebo for extended treatment of VTE [1, 2]

Bibliography: Bauersachs et al. (EINSTEIN-Extension)[16]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	**Risk difference with Rivaroxaban** (95% CI)
All Cause Mortality	1196 (1 study)	⨁⨁⨁⨀ **MODERATE**[3] due to imprecision	**RR 0.49** (0.04 to 5.43)	**3 per 1000**	**2 fewer per 1000** (from 3 fewer to 15 more)
Recurrent VTE	1196 (1 study)	⨁⨁⨁⨁ **HIGH**	**RR 0.19** (0.09 to 0.4)	**71 per 1000**	**57 fewer per 1000** (from 42 fewer to 64 fewer)
Major Bleeding	1188 (1 study)	⨁⨁⨁⨀ **MODERATE** due to risk of bias	Not estimable[4]	-	-

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
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.

[1] Patients who had completed 6 to 12 months of treatment for VTE
[2] Rivaroxaban 20mg daily or placebo, specific to the continued treatment study
[3] CI includes values suggesting no effect and values suggesting either benefit or harm
[4] Event rate with Rivaroxaban was 4/598 (0.67%); event rate with placebo was 0/590 (0%); anticipated absolute effect - risk difference with Rivaroxaban is 4 more per 1000 (from 1 less to 17 more)

Table 10: Summary of Findings - Apixaban vs Placebo for extended treatment of VTE [1,2]

Bibliography: Agnelli et al. (AMPLIFY-EXT)[21]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Apixaban (95% CI)
All Cause Mortality	1669 (1 study) 12 months	⊕⊕⊕⊖ **MODERATE**[3,4] due to imprecision	**RR 0.49** (0.2 to 1.22)	**17 per 1000**	**9 fewer per 1000** (from 14 fewer to 4 more)
Recurrent VTE	1669 (1 study) 12 months	⊕⊕⊕⊕ **HIGH**	**RR 0.19** (0.11 to 0.33)	**88 per 1000**	**71 fewer per 1000** (from 59 fewer to 78 fewer)
Major Bleeding	1669 (1 study) 12 months	⊕⊕⊕⊖ **MODERATE**[3,4] due to imprecision	**RR 0.49** (0.09 to 2.64)	**5 per 1000**	**2 fewer per 1000** (from 4 fewer to 8 more)

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
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.

[1] Patients with VTE who had completed 6 to 12 months of anticoagulation therapy
[2] Apixaban 2.5 mg twice-daily dose vs. placebo
[3] Significantly wide CIs, including appreciable benefit / harm and no effect line
[4] Low number of events

Table 11: Risk factors for bleeding with anticoagulant therapy and estimated risk of major bleeding in low, moderate and high risk categories*

Risk factors[A]			
Age >65 years[22-31] Age >75 years [22-26,28,30,32-40] Previous bleeding[23,29-31,36,39-42] Cancer[25,29,33,36,43] Metastatic cancer[11,42] Renal failure[23,29-31,34,36,39,44] Liver failure[24,26,33,34] Thrombocytopenia[33,42] Previous stroke[23,30,33,45] Diabetes[23,24,34,38,40] Anaemia[23,26,33,36,40] Antiplatelet therapy[24,33,34,40,46] Poor anticoagulant control[27,34,41] Co-morbidity and reduced functional capacity[29,34,42] Recent surgery[26,47 B] Frequent falls[33] Alcohol abuse[29,30,33,40] Non-steroidal anti-inflammatory drug[48]			
Categorization of Risk of Bleeding[C]			
	Estimated absolute risk of major bleeding		
	Low risk[D] (0 risk factors)	Moderate risk[D] (1 risk factor)	High risk[D] (≥2 risk factors)
Anticoagulation 0-3 months[E]			
baseline risk (%)	0.6	1.2	4.8
increased risk (%)	1.0	2.0	8.0
total risk (%)	1.6[F]	3.2	12.8[G]
Anticoagulation after first 3 months[5]			
baseline risk (% per yr)	0.3[H]	0.6	≥2.5
increased risk (% per yr)	0.5	1.0	≥4.0
total risk (% per yr)	0.8[I]	1.6[I]	≥6.5

*From AT9. Since AT9: References for bleeding with individual factors have been added [31,44,48]; non-steroidal anti-inflammatory drug has been added as a risk factor; a systematic review has described the risk in VTE trial patients who were randomized to no antithrombotic therapy [49]; and a number of recent publications have compared clinical prediction rules for bleeding in various populations [31,50-54].

A. Most studies assessed risk factors for bleeding in patients who were on VKA therapy. The risk of bleeding with different anticoagulants is not addressed in this table. The increase in bleeding associated with a risk factor will vary with: 1) severity of the risk factor (e.g. location and extent of metastatic disease; platelet count); 2) temporal relationships (e.g. interval from surgery or a previous bleeding episode[35]; and 3) how effectively a previous cause of bleeding was corrected (e.g. upper gastrointestinal bleeding).

B. Important for parenteral anticoagulation (e.g. first 10 days) but less important for long-term or extended anticoagulation.

C. Although there is evidence that risk of bleeding increases with the prevalence of risk factors[25,26,30,31,33,34,36,39,40,42,55,56], the categorization scheme suggested above has not been validated. Furthermore, a single risk factor, when severe, will result in a high risk of bleeding (e.g. major surgery within the past 2 days; severe thrombocytopenia).

D. Compared to low risk patients, moderate risk patients are assumed to have a 2-fold risk and high-risk patients are assumed to have an 8-fold risk of major bleeding[23,25,26,33,34,36,42,57].

E. We estimate that anticoagulation is associated with a 2.6-fold increase in major bleeding based on comparison of extended anticoagulation with no extended anticoagulation (Table 6). The relative risk of major bleeding during the first 3 month of therapy may be greater that during extended VKA therapy because: 1) the intensity of anticoagulation with initial parenteral therapy may be greater that with VKA therapy; 2) anticoagulant control will be less stable during the first 3 months; and 3) predispositions to anticoagulant-induced bleeding may be uncovered during the first 3 months of therapy[27,36,41]. However, studies of patients with acute coronary syndromes do not suggest a higher than 2.6 relative risk of major bleeding with parenteral anticoagulation (e.g. UFH or LMWH) compared to control[58,59].

F. 1.6% corresponds to the average of major bleeding with initial UFH or LMWH therapy followed by VKA therapy (Table 7). We estimated baseline risk by assuming a 2.6 relative risk of major bleeding with anticoagulation (footnote 1).

G. Consistent with frequency of major bleeding observed by Hull in "high risk" patients[47].

H. Our estimated baseline risk of major bleeding for low risk patients (and adjusted up for moderate and high risk groups as per footnote D).

I. Consistent with frequency of major bleeding during prospective studies of extended anticoagulation for VTE[27,57,60-62] (Table 6).

Table 12: Summary of Findings - Six, Twelve or Twenty-four Months vs Three or Six Months as minimum duration of anticoagulation for VTE [1,2]

Bibliography: Campbell et al.[63], Pinede et al. (DOTAVK)[64], Agnelli et al. (WODIT-PE Provoked and Unprovoked)[65], Agnelli et al. (WODIT-DVT)[66], Couturand et al. (PADIS-PE)[67], Siragusa et al. (DACUS)[68], Eischer et al.(AUREC-FVIII)[69]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No extended	Risk difference with Extended (95% CI)
Mortality	1736 (7 studies) 1-3 years	⊕⊕⊕⊖ **MODERATE**[3,4,5] due to imprecision	**RR 1.39** (0.91 to 2.12)	**41 per 1000**	**16 more per 1000** (from 4 fewer to 46 more)
Recurrent VTE	2466 (8 studies) 1-3 years	⊕⊕⊕⊖ **MODERATE**[3,4,5] due to imprecision	**RR 0.88** (0.71 to 1.09)	**128 per 1000**	**18 fewer per 1000** (from 40 fewer to 8 more)
Major Bleeding	2466 (8 studies) 1-3 years	⊕⊕⊕⊖ **MODERATE**[3,4,5] due to imprecision	**RR 1.78** (0.95 to 3.34)	**12 per 1000**	**9 more per 1000** (from 1 fewer to 27 more)

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
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.

[1] Studies vary in follow-up duration (10 months to 3 years) and in duration of time-limited VKA (3 to 6 months).
[2] VKA as NOACs are not included
[3] Timing of randomization relative to the start of treatment and length of treatment varied across studies: Pinede et al.[64] and Campbell et al.[63] randomized at diagnosis; and Agnelli et al.[65], Eischer et al.[69] and Couturaud et al.[67] randomized after the initial 3 mo (Agnelli et al.[65]) or 6 mo (Eischer et al.[69] Couturaud et al.[67]) of treatment to stop or continued treatment. The longer duration of treatment was 6 mo in Agnelli et al. (provoked PE)[65] and Pinede et al.[64], 12 months in Agnelli et al. (unprovoked DVT; unprovoked PE)[65,66], 24 months in Couturaud et al.[67], and 30 months in Eischer et al.[69] Generally, study design was strong. No study stopped early for benefit; three stopped early because of slow recruitment (Campbell et al.[63], Pinede et al.[64], Eischer et al.[69]) and one because of lack of benefit (Agnelli et al.[65]). In one study (Campbell et al.[63]), 20% of VTE outcomes were not objectively confirmed. Patients and caregivers were blinded in Couturaud et al.[67], but none of the other studies. Adjudicators of outcomes were blinded in all but one study (Campbell et al.[63]). All studies used effective randomization concealment, intention-to-treat analysis, and a low unexplained drop-out frequency.
[4] Study populations varied across studies: Pinede et al.[64] enrolled provoked and unprovoked proximal DVT and PE; Campbell et al.[63], enrolled provoked and unprovoked isolated distal DVT, proximal DVT, and PE; Agnelli et al.[65] had separate randomizations for provoked PE (3 vs 6 mo) and unprovoked (3 vs 12 mo); Agnelli et al.[66] enrolled unprovoked proximal DVT; Eischer et al.[69] enrolled unprovoked isolated DVT, proximal DVT and PE with high levels of factor VIII; and Couturaud et al.[67] enrolled unprovoked PE.
[5] CIs include both values suggesting no effect and values suggesting either benefit or harm.

Table 13: Summary of Findings - Aspirin vs Placebo for extended treatment of VTE

Bibliography: Simes et al. (INSPIRE)[70]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Aspirin (95% CI)
All Cause Mortality	1224 (2 studies) up to 4 years	⊕⊕⊖⊖ **LOW**[3,4,5] due to imprecision	**HR 0.82** (0.45 to 1.52)[2]	**Moderate risk population**[1]	
				5 per 1000	**1 fewer per 1000** (from 3 fewer to 3 more)
Recurrent VTE	1224 (2 studies) up to 4 years	⊕⊕⊕⊖ **MODERATE**[3,5] due to imprecision	**HR 0.65** (0.49 to 0.86)[2]	**184 per 1000**	**60 fewer per 1000** (from 24 fewer to 89 fewer)
Major Bleeding	1224 (2 studies) up to 4 years	⊕⊕⊕⊖ **MODERATE**[3,4] due to imprecision	**HR 1.31** (0.48 to 3.53)[2]	**12 per 1000**	**4 more per 1000** (from 6 fewer to 29 more)

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **HR:** Hazard ratio;

GRADE Working Group grades of evidence
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.

[1] Estimate taken from Douketis et al.[71]
[2] Estimate based on Simes et al. (INSPIRE)[70] of synthesis of Brighton et al. (ASPIRE)[72] and Becattini et al. (WARFASA)[73]
[3] Both of the included studies were stopped early with knowledge of overall rates of VTE. Decision to stop was not made with unblinded data. Only 1/3 of the intended patients in the study
[4] CI includes values suggesting no effect and values suggesting either benefit or harm
[5] Greater than 50% change in risk reduction

Table 14: Summary of Findings - Catheter assisted thrombus removal vs anticoagulation alone for acute leg DVT

Bibliography: Watson et al.[74] used for all outcomes except Patency and QoL. Enden et al.[75] used for Patency estimates. Enden et al.[76] used for QoL estimates.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Anticoagulation alone	Risk difference with Catheter assisted thrombus removal (95% CI)
All Cause Mortality	209 (1 study) 3 months	⊕⊕⊖⊖ **LOW**[2,3] due to imprecision	**RR 0.43** (0.08 to 2.16)	**46 per 1000**[1]	**26 fewer per 1000** (from 43 fewer to 54 more)
Recurrent VTE	189 (1 study) 3 months	⊕⊕⊖⊖ **LOW**[2,3] due to imprecision	**RR 0.61** (0.3 to 1.25)[5]	**Moderate risk population**[4]	
				48 per 1000	**19 fewer per 1000** (from 34 fewer to 12 more)
Major bleeding	224 (2 studies) 3 months	⊕⊕⊖⊖ **LOW**[2,3] due to imprecision	**RR 7.69** (0.4 to 146.9)[5]	**Moderate risk population**[4,6]	
				29 per 1000	**194 more per 1000** (from 17 fewer to 1000 more)
Postthrombotic syndrome	189 (1 study) 2 years	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	**RR 0.74** (0.55 to 1)[9]	**Moderate risk population**[7]	
				588 per 1000	**153 fewer per 1000** (from 265 fewer to 0 more)[8]
Patency	189 (1 study) 6 months	⊕⊕⊕⊖ **MODERATE**[3] due to imprecision	**RR 1.42** (1.09 to 1.85)	**455 per 1000**[10]	**191 more per 1000** (from 41 more to 386 more)
Quality of Life	189 (1 study) 24 months	⊕⊕⊕⊖ **MODERATE**[13] due to risk of bias			The mean quality of life in the intervention groups was **0.2 higher** (2.8 lower to 3 higher)[11,12]

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
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.

[1] Reported deaths from Enden et al. (CAVENT)[75]
[2] Confidence interval includes values suggesting both benefit and harm
[3] Low number of events
[4] Baseline risks for non-fatal recurrent VTE and for major bleeding derived from Douketis et al.[77]
[5] Estimate taken from Watson et al.[74]. The one study included for this outcome was Enden et al. (CAVENT)[75]

[6] Most of bleeding events occur during the first 7 days
[7] This estimate is based on the findings of the VETO study.[78]
[8] For severe PTS, assuming the same RR of 0.46 and a baseline risk of 13.8%[78], the absolute reduction is 75 fewer severe PTS per 1000 (from 29 fewer to 138 fewer) over 2 years
[9] This estimate is based on the Watson et al.[74]. The one study included for this outcome was Enden et al. (CAVENT).[75] For PTS at 6 months, published data from Enden et al. (CAVENT)[75] provides an estimate RR of 0.93 (0.61, 1.42) via Watson et al.[74]
[10] Reported patency from Enden et al. (CAVENT)[75]
[11] Disease-specific QOL (VEINES-QOL) estimate used at 24 months according to treatment allocation
[12] Generic QoL (EQ-5D) at 24 months according to treatment allocation estimate is MD 0.04 (-0.01 to 0.17)
[13] Open-label

Table 15: Risk factors for bleeding with, and contraindications to use of, thrombolytic therapy (both systemic and locally administered)

Major contraindications[1]
Structural intracranial disease
Previous intracranial hemorrhage
Ischemic stroke within 3 months
Active bleeding
Recent brain or spinal surgery
Recent head trauma with fracture or brain injury
Bleeding diathesis
Relative contraindications[2]
Systolic blood pressure >180
Diastolic bleed pressure >110
Recent bleeding (non-intracranial)
Recent surgery
Recent invasive procedure
Ischemic stroke more that 3 months previously
Anticoagulated (e.g. VKA therapy)
Traumatic cardiopulmonary resuscitation
Pericarditis or pericardial fluid
Diabetic retinopathy
Pregnancy
Age >75 years
Low body weight (eg, <60 kg)
Female
Black race

1. 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. Patients with one or more major contraindication are usually considered to be "high risk for bleeding with thrombolytic therapy" The factors listed in this table are consistent with other recommendations for the use of thrombolytic therapy in patients with PE.[79-83]

2. Risk factors for bleeding during anticoagulant therapy that are noted in Table 11 “Risk factors for bleeding with anticoagulant therapy and estimated risk of major bleeding in low, moderate and high risk categories” 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 (e.g. extent of trauma or recent surgery); and 2) temporal relationships (e.g. interval from surgery or a previous bleeding episode; believed to decrease markedly after ~2 weeks). Risk factors for bleeding at critical sites (e.g. intracranial or intraocular) or non-compressible sites are stronger contraindications for thrombolytic therapy.
Depending on the nature, severity, temporality and number of relative contraindications, patients may be considered "high risk of bleeding with thrombolytic therapy" or "non-high risk for thrombolytic therapy". Patients with no risk factors, one or two minor risk factors (e.g. female and black race), are usually considered "low risk of bleeding with thrombolytic therapy".
Among 32,000 Medicare patients (≥65 years) with myocardial infraction who were treated with thrombolytic therapy, the following factors were independently associated with intracranial haemorrhage: age ≥75 years (odds ratio [OR] 1.6); Black (OR1.6); female (OR 1.4); previous stroke (OR 1.5); systolic blood pressure ≥160 mmHg (OR 1.8); women ≤65 kg or men ≤ 80Kg (OR 1.5); INR >4 (OR 2.2)[84]. The rate of intracranial haemorrhage increased from 0.7% with 0 or 1 of these risk factors, to 4.1% with ≥5 risk factors.
Among 32,000 patients with myocardial infraction who were treated with thrombolytic therapy in 5 clinical trials, the following factors were independently associated with moderate or severe bleeding: older age (OR 1.04 per year); Black (OR1.4); female (OR 1.5); hypertension (OR 1.2); lower weight (OR 0.99 per kg).[81]
We estimate that systemic thrombolytic therapy is associated with relative risk of major bleeding of 3.5 within 35 days (relative risk ~7 for intracranial bleeding); about three quarters of the excess of major bleeds with thrombolytic therapy occur in the first 24 hours.[85]

Table 16: Summary of Findings - Temporary Inferior Vena Caval Filter vs No Temporary Inferior Vena Caval Filter in addition to anticoagulation for acute DVT or PE [1,2]

Bibliography: Mismetti et al. (PREPIC 2)[86]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Temporary Inferior Vena Caval Filter in addition to anticoagulation	Risk difference with Temporary Inferior Vena Caval Filter (95% CI)
All Cause Mortality	399 (1 study) 3 months	⨁⨁⨁⨀ **MODERATE**[3,4] due to imprecision	**RR 1.25** (0.6 to 2.6)	**60 per 1000**	**15 more per 1000** (from 24 fewer to 96 more)
Recurrent PE	399 (1 study) 3 months	⨁⨁⨁⨀ **MODERATE**[3,4] due to imprecision	**RR 2.00** (0.51 to 7.89)	**15 per 1000**	**15 more per 1000** (from 7 fewer to 104 more)
Major Bleeding	399 (1 study) 3 months	⨁⨁⨁⨀ **MODERATE**[3,4] due to imprecision	**RR 0.80** (0.32 to 1.98)	**50 per 1000**	**10 fewer per 1000** (from 34 fewer to 49 more)

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
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.

[1] All patients received full-dose anticoagulant therapy according to guidelines for at least 6 months
[2] Filter removal was attempted in 164 patients and successful for 153 (93.3%)
[3] CI includes values suggesting no effect and values suggesting either benefit or harm
[4] Small number of events

Table 17: Summary of Findings - Elastic Compression Stockings vs No Elastic Compression Stockings to Prevent PTS of the leg

Bibliography: Kahn et al. (SOX)[87] for PTS and recurrent VTE; Kahn et al.[88] for acute leg pain

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No elastic compression stockings	Risk difference with Elastic compression stockings (95% CI)
PTS Villalta Score[1]	803 (1 study) 6 months	⊕⊕⊕⊖ **MODERATE**[4] due to imprecision	**RR 1.01** (0.86 to 1.18)[3]	**Moderate risk population**[2]	
				479 per 1000	**5 more per 1000** (from 67 fewer to 86 more)
Recurrent VTE	803 (1 study) 6 months	⊕⊕⊕⊖ **MODERATE**[4,7] due to imprecision	**RR 0.84** (0.54 to 1.31)[6]	**Moderate risk population**[5]	
				210 per 1000	**34 fewer per 1000** (from 97 fewer to 65 more)
Acute Leg Pain	742 (1 study) 60 days	⊕⊕⊕⊖ **MODERATE**[7,9] due to imprecision		The mean acute leg pain in the control groups was **1.13 leg pain severity assessed on an 11-point numerical pain rating scale**[8]	The mean acute leg pain in the intervention groups was **0.26 higher** (0.03 lower to 0.55 higher)[8]
Quality of Life	803 (1 study)	⊕⊕⊕⊕ **HIGH**			The mean quality of life in the intervention groups was **0.12 lower** (1.11 lower to 0.86 higher)[10,11]

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
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.

[1] For included studies, number of post-thrombotic syndrome events as assessed by Villalta's criteria
[2] This estimate is based on the findings of the VETO study[78]
[3] There were three studies originally included for this outcome (Brandjes et al.[89], Prandoni et al.[90] and Kahn et al. (SOX).[87]) There was very high heterogeneity between the three studies, I^2 =92% (p<0.01). The pooled effect of the three studies was RR 0.63 (0.35 to 1.13). Yet, because of the high risk of bias associated with Brandjes et al.[89] and Prandoni et al.[90], it was decided to focus on the estimate of the low risk trial, Kahn et al. (SOX)[87], which is used here
[4] Low number of events
[5] This estimate is the mean of two estimates derived from two studies: 12.4% probable/definite VTE[91] and 29.1% confirmed VTE.[92]
[6] There were three studies originally included for this outcome (Brandjes et al.[89], Prandoni et al.[90] and Kahn et al. (SOX).[87]). The pooled effect of the three studies was RR 0.91 (0.65 to 1.27). Yet, because of the high risk of bias associated with Brandjes et al.[89] and Prandoni et al.[90], it was decided to focus on the estimate of the low risk trial, Kahn et al. (SOX)[87], which is used here
[7] CI includes values suggesting no effect and values suggesting either benefit or harm
[8] Estimate derived from Kahn et al.[88]
[9] Wide CI that includes no effect
[10] Estimate based on VEINES-QOL score improvement of 5.8 points (SD 7.5) for active ECS versus 5.9 (SD 7.1) for placebo ECS
[11] SF-36 physical component score improved by 8.4 points (SD 13.6) for active ECS versus 9.9 (SD 13.2) for placebo ECS (difference

between groups of -1.53 points, 95% CI -3.44 to 0.39; p=0.12)

Table 18: Summary of Findings - Systemic thrombolytic therapy vs. anticoagulation alone for acute PE

Bibliography: Chatterjee et al.[93]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Anticoagulation alone	**Risk difference with Systemic thrombolytic therapy** (95% CI)
All Cause Mortality	2115 (17 studies)	⊕⊕⊕⊖ **MODERATE**[3] due to imprecision	**OR 0.53** (0.32 to 0.88)[2]	**39 per 1000**[1]	**18 fewer per 1000** (from 5 fewer to 26 fewer)
Recurrent PE	2043 (15 studies)	⊕⊕⊕⊖ **MODERATE**[3] due to imprecision	**OR 0.40** (0.22 to 0.74)[4]	**30 per 1000**[1]	**18 fewer per 1000** (from 8 fewer to 24 fewer)
Major bleeding	2115 (16 studies)	⊕⊕⊕⊕ **HIGH**	**OR 2.73** (1.91 to 3.91)[5]	**34 per 1000**[1]	**54 more per 1000** (from 29 more to 87 more)
Intracranial Hemorrhage	2043 (15 studies)	⊕⊕⊕⊖ **MODERATE**[3] due to imprecision	**OR 4.63** (1.78 to 12.04)[6]	**2 per 1000**[1]	**7 more per 1000** (from 2 more to 21 more)

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
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.

[1] Majority (83%) of participants in Chatterjee et al.[93] were "moderate" risk.
[2] Estimate from Chatterjee et al.[93]. Other estimates from meta-analyses on this topic include: Dong et al.[94] - OR 0.89 (0.45, 1.78) Cao et al.[95] - RR 0.64 (0.29, 1.40) Marti et al.[96] - OR 0.59 (0.36 - 0.96) Nakamura et al.[97] - RR 0.72 (0.39, 1.31) Chatterjee et al. (Intermediate-Risk PE Only)[93] - OR 0.46 (0.25 - 0.92) Marti et al. (Intermediate-Risk PE Only)[96] - OR 0.42 (0.17 - 1.03)
[3] Low number of events
[4] Estimate from Chatterjee et al.[93]. Other estimates from meta-analyses on this topic include: Dong et al.[94]- OR 0.63 (0.33, 1.20) Cao et al.[95] - RR 0.44 (0.19, 1.05) Marti et al.[96] - OR 0.50 (0.27 - 0.94) Nakamura et al.[97] - RR 0.60 (0.21, 1.69)
[5] Estimate from Chatterjee et al.[93]. Other estimates from meta-analyses on this topic include: Dong et al.[94] - OR 1.61 (0.91, 2.86) Cao et al.[95] - RR 1.16 (0.51, 2.60) Marti et al.[96] - OR 2.91 (1.95 - 4.36) Nakamura et al.[97] - RR 2.07 (0.58, 7.35)
[6] Estimate from Chatterjee et al.[93]

References

1. Deitcher SR, Kessler CM, Merli G, et al. Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period. *Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis.* 2006;12(4):389-396.
2. Hull RD, Pineo GF, Brant RF, et al. Self-managed long-term low-molecular-weight heparin therapy: the balance of benefits and harms. *The American journal of medicine.* 2007;120(1):72-82.
3. Hull RD, Pineo GF, Brant R, et al. Home therapy of venous thrombosis with long-term LMWH versus usual care: patient satisfaction and post-thrombotic syndrome. *The American journal of medicine.* 2009;122(8):762-769 e763.
4. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N.Engl.J Med.* 2003;349(2):146-153.
5. Lopaciuk S, Bielska-Falda H, Noszczyk W, et al. Low molecular weight heparin versus acenocoumarol in the secondary prophylaxis of deep vein thrombosis. *Thromb Haemost.* 1999;81(1):26-31.
6. Lopez-Beret P, Orgaz A, Fontcuberta J, et al. Low molecular weight heparin versus oral anticoagulants in the long-term treatment of deep venous thrombosis. *J Vasc Surg.* 2001;33(1):77-90.
7. Meyer G, Marjanovic Z, Valcke J, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. *Arch Intern Med.* 2002;162(15):1729-1735.
8. Romera A, Cairols MA, Vila-Coll R, et al. A randomised open-label trial comparing long-term sub-cutaneous low-molecular-weight heparin compared with oral-anticoagulant therapy in the treatment of deep venous thrombosis. *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery.* 2009;37(3):349-356.
9. Lee AY, Kamphuisen PW, Meyer G, et al. Tinzaparin vsWarfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer: A Randomized Clinical Trial. *Journal of the American Medical Association.* 2015;314:677-686.
10. Prandoni P, Trujillo-Santos J, Surico T, et al. Recurrent thromboembolism and major bleeding during oral anticoagulant therapy in patients with solid cancer: findings from the RIETE registry. *Haematologica.* 2008;93(9):1432-1434.
11. Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood.* 2002;100(10):3484-3488.

12. Beyth RJ, Milligan PE, Gage BF. Risk factors for bleeding in patients taking coumarins. *Current hematology reports.* 2002;1(1):41-49.
13. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation.* 2014;129(7):764-772.
14. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *The New England journal of medicine.* 2009;361(24):2342-2352.
15. Prins MH, Lensing AW, Bauersachs R, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thrombosis journal.* 2013;11(1):21.
16. Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *The New England journal of medicine.* 2010;363(26):2499-2510.
17. Investigators E-P, Buller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *The New England journal of medicine.* 2012;366(14):1287-1297.
18. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *The New England journal of medicine.* 2013;369(9):799-808.
19. Hokusai VTEI, Buller HR, Decousus H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *The New England journal of medicine.* 2013;369(15):1406-1415.
20. Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *The New England journal of medicine.* 2013;368(8):709-718.
21. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. *The New England journal of medicine.* 2013;368(8):699-708.
22. van der Meer FJ, Rosendaal FR, Vandenbroucke JP, Briet E. Bleeding complications in oral anticoagulant therapy. An analysis of risk factors. *Arch Intern Med.* 1993;153(13):1557-1562.
23. Beyth RJ, Quinn LM, Landefeld S. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *American Journal of Medicine.* 1998;105:91-99.
24. Douketis JD, Arneklev K, Goldhaber SZ, Spandorfer J, Halperin F, Horrow J. Comparison of bleeding in patients with nonvalvular atrial fibrillation treated with ximelagatran or warfarin: assessment of incidence, case-fatality rate, time course and sites of bleeding, and risk factors for bleeding. *Arch Intern Med.* 2006;166(8):853-859.
25. Kuijer PMM, Hutten BA, Prins MH, Buller HR. Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism. *Archives of Internal Medicine.* 1999;159:457-460.

26. Landefeld CS, McGuire E, 3rd, Rosenblatt MW. A bleeding risk index for estimating the probability of major bleeding in hospitalized patients starting anticoagulant therapy. *Am J Med.* 1990;89(5):569-578.
27. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: An inception-cohort, prospective collaborative study (ISCOAT). *The Lancet.* 1996;348:423-428.
28. Torn M, Bollen WL, van der Meer FJ, van der Wall EE, Rosendaal FR. Risks of oral anticoagulant therapy with increasing age. *Arch Intern Med.* 2005;165(13):1527-1532.
29. White RH, Beyth RJ, Zhou H, Romano PS. Major bleeding after hospitalization for deep-venous thrombosis. *Am J Med.* 1999;107(5):414-424.
30. Olesen JB, Lip GY, Hansen PR, et al. Bleeding risk in 'real world' patients with atrial fibrillation: comparison of two established bleeding prediction schemes in a nationwide cohort. *J Thromb Haemost.* 2011;9(8):1460-1467.
31. Kooiman J, van Hagen N, Iglesias Del Sol A, et al. The HAS-BLED Score Identifies Patients with Acute Venous Thromboembolism at High Risk of Major Bleeding Complications during the First Six Months of Anticoagulant Treatment. *PloS one.* 2015;10(4):e0122520.
32. Fihn SD, Callahan CM, Martin DC, McDonell MB, Henikoff JG, White RH. The risk for and severity of bleeding complications in elderly patients treated with warfarin. The National Consortium of Anticoagulation Clinics. *Ann Intern Med.* 1996;124(11):970-979.
33. Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am.Heart J.* 2006;151(3):713-719.
34. Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. *J Am Coll Cardiol.* 2011;57(2):173-180.
35. Nieto JA, Bruscas MJ, Ruiz-Ribo D, et al. Acute venous thromboembolism in patients with recent major bleeding. The influence of the site of bleeding and the time elapsed on outcome. *J Thromb Haemost.* 2006;4(11):2367-2372.
36. Ruiz-Gimenez N, Suarez C, Gonzalez R, et al. Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE Registry. *Thromb Haemost.* 2008;100(1):26-31.
37. van der Meer FJ, Rosendaal FR, Vandenbroucke JP, Briet E. Assessment of a bleeding risk index in two cohorts of patients treated with oral anticoagulants. *Thromb Haemost.* 1996;76(1):12-16.
38. Pengo V, Legnani C, Noventa F, Palareti G. Oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and risk of bleeding. A Multicenter Inception Cohort Study. *Thromb Haemost.* 2001;85(3):418-422.
39. Fang MC, Go AS, Chang Y, et al. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. *J Am Coll Cardiol.* 2011;58(4):395-401.

40. Shireman TI, Mahnken JD, Howard PA, Kresowik TF, Hou Q, Ellerbeck EF. Development of a contemporary bleeding risk model for elderly warfarin recipients. *Chest.* 2006;130(5):1390-1396.
41. Fihn SD, McDonell M, Martin D, et al. Risk factors for complications of chronic anticoagulation. A multicenter study. Warfarin Optimized Outpatient Follow-up Study Group. *Ann Intern Med.* 1993;118(7):511-520.
42. Nieto JA, Solano R, Ruiz-Ribo MD, et al. Fatal bleeding in patients receiving anticoagulant therapy for venous thromboembolism: findings from the RIETE registry. *J Thromb Haemost.* 2010;8(6):1216-1222.
43. Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JG, Buller HR. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. *J Clin Oncol.* 2000;18(17):3078-3083.
44. Jun M, James MT, Manns BJ, et al. The association between kidney function and major bleeding in older adults with atrial fibrillation starting warfarin treatment: population based observational study. *BMJ.* 2015;350:h246.
45. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med.* 1994;120(11):897-902.
46. Dentali F, Ageno W, Becattini C, et al. Prevalence and clinical history of incidental, asymptomatic pulmonary embolism: a meta-analysis. *Thromb Res.* 2010;125(6):518-522.
47. Hull RD, Raskob GE, Rosenbloom D, et al. Heparin for 5 days as compared with 10 days in the initial treatment of proximal venous thrombosis. *The New England Journal of Medicine.* 1990;322:1260-1264.
48. Lamberts M, Lip GY, Hansen ML, et al. Relation of nonsteroidal anti-inflammatory drugs to serious bleeding and thromboembolism risk in patients with atrial fibrillation receiving antithrombotic therapy: a nationwide cohort study. *Ann Intern Med.* 2014;161(10):690-698.
49. Castellucci LA, Le Gal G, Rodger MA, Carrier M. Major bleeding during secondary prevention of venous thromboembolism in patients who have completed anticoagulation: a systematic review and meta-analysis. *J Thromb Haemost.* 2014;12(3):344-348.
50. Burgess S, Crown N, Louzada ML, Dresser G, Kim RB, Lazo-Langner A. Clinical performance of bleeding risk scores for predicting major and clinically relevant non-major bleeding events in patients receiving warfarin. *J Thromb Haemost.* 2013;11(9):1647-1654.
51. Scherz N, Mean M, Limacher A, et al. Prospective, multicenter validation of prediction scores for major bleeding in elderly patients with venous thromboembolism. *J Thromb Haemost.* 2013;11(3):435-443.
52. Poli D, Antonucci E, Testa S, et al. The predictive ability of bleeding risk stratification models in very old patients on vitamin K antagonist treatment for venous thromboembolism: results of the prospective collaborative EPICA study. *J Thromb Haemost.* 2013;11(6):1053-1058.
53. Roldan V, Marin F, Fernandez H, et al. Predictive value of the HAS-BLED and ATRIA bleeding scores for the risk of serious bleeding in a "real-world"

population with atrial fibrillation receiving anticoagulant therapy. *Chest.* 2013;143(1):179-184.

54. Apostolakis S, Lane DA, Buller H, Lip GY. Comparison of the CHADS2, CHA2DS2-VASc and HAS-BLED scores for the prediction of clinically relevant bleeding in anticoagulated patients with atrial fibrillation: the AMADEUS trial. *Thromb Haemost.* 2013;110(5):1074-1079.
55. Dahri K, Loewen P. The risk of bleeding with warfarin: a systematic review and performance analysis of clinical prediction rules. *Thromb Haemost.* 2007;98(5):980-987.
56. Palareti G, Cosmi B. Bleeding with anticoagulation therapy - who is at risk, and how best to identify such patients. *Thromb Haemost.* 2009;102(2):268-278.
57. Kearon C, Ginsberg JS, Kovacs MJ, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *New England Journal Medicine.* 2003;349:631-639.
58. Collins R, MacMahon S, Flather M, et al. Clinical effects of anticoagulant therapy in suspected acute myocardial infarction: systematic overview of randomised trials. *BMJ.* 1996;313(7058):652-659.
59. Yusuf S, Mehta SR, Xie C, et al. Effects of reviparin, a low-molecular-weight heparin, on mortality, reinfarction, and strokes in patients with acute myocardial infarction presenting with ST-segment elevation. *JAMA.* 2005;293(4):427-435.
60. Palareti G, Cosmi B, Legnani C, et al. D-dimer testing to determine the duration of anticoagulation therapy. *N.Engl.J Med.* 2006;355(17):1780-1789.
61. Schulman S, Granqvist S, Holmstrom M, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. *The New England journal of medicine.* 1997;336:393-398.
62. Wells PS, Forgie MA, Simms M, et al. The outpatient bleeding risk index: validation of a tool for predicting bleeding rates in patients treated for deep venous thrombosis and pulmonary embolism. *Arch Intern Med.* 2003;163(8):917-920.
63. Campbell IA, Bentley DP, Prescott RJ, Routledge PA, Shetty HG, Williamson IJ. Anticoagulation for three versus six months in patients with deep vein thrombosis or pulmonary embolism, or both: randomised trial. *Bmj.* 2007;334(7595):674.
64. Pinede L, Ninet J, Duhaut P, et al. Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. *Circulation.* 2001;103(20):2453-2460.
65. Agnelli G, Prandoni P, Becattini C, et al. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. *Ann Intern Med.* 2003;139(1):19-25.
66. Agnelli G, Prandoni P, Santamaria MG, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin

Optimal Duration Italian Trial Investigators. *The New England journal of medicine.* 2001;345(3):165-169.

67. Couturand F SO, Pernod G, Mismetti P, Jego P, Duhamel E, Provost K, Bal dit Sollier C, Presles E, Castellant P, Parent F, Salaun P, Bressollette L, Nonent M, Lorillon P, Girard P, Lacut K, Guégan M, Bosson J, Laporte S, Leroyer C, Décousus H, Meyer G, Mottier D, for the PADIS-PE Investigators. Two years versus six months of oral anticoagulation after a first episode of unprovoked pulmonary embolism. The PADIS-PE multicenter, double-blind, randomized, trial. 2015.
68. Siragusa S, Malato A, Anastasio R, et al. Residual vein thrombosis to establish duration of anticoagulation after a first episode of deep vein thrombosis: the Duration of Anticoagulation based on Compression UltraSonography (DACUS) study. *Blood.* 2008;112(3):511-515.
69. Eischer L, Gartner V, Schulman S, Kyrle PA, Eichinger S, investigators A-F. 6 versus 30 months anticoagulation for recurrent venous thrombosis in patients with high factor VIII. *Annals of hematology*. 2009;88(5):485-490.
70. Simes J, Becattini C, Agnelli G, et al. Aspirin for the prevention of recurrent venous thromboembolism: the INSPIRE collaboration. *Circulation.* 2014;130(13):1062-1071.
71. Douketis JD, Gu CS, Schulman S, Ghirarduzzi A, Pengo V, Prandoni P. The risk for fatal pulmonary embolism after discontinuing anticoagulant therapy for venous thromboembolism. *Ann Intern Med.* 2007;147(11):766-774.
72. Brighton TA, Eikelboom JW, Mann K, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. *The New England journal of medicine.* 2012;367(21):1979-1987.
73. Becattini C, Agnelli G, Schenone A, et al. Aspirin for preventing the recurrence of venous thromboembolism. *The New England journal of medicine.* 2012;366(21):1959-1967.
74. Watson L, Broderick C, Armon MP. Thrombolysis for acute deep vein thrombosis. *The Cochrane database of systematic reviews.* 2014;1:CD002783.
75. Enden T, Haig Y, Klow NE, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. *Lancet.* 2012;379(9810):31-38.
76. Enden T, Wik HS, Kvam AK, Haig Y, Klow NE, Sandset PM. Health-related quality of life after catheter-directed thrombolysis for deep vein thrombosis: secondary outcomes of the randomised, non-blinded, parallel-group CaVenT study. *BMJ open.* 2013;3(8):e002984.
77. Douketis JD, Foster GA, Crowther MA, Prins MH, Ginsberg JS. Clinical risk factors and timing of recurrent venous thromboembolism during the initial 3 months of anticoagulant therapy. *Arch Intern Med.* 2000;160(22):3431-3436.
78. Kahn SR, Shrier I, Julian JA, et al. Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis. *Ann Intern Med.* 2008;149(10):698-707.
79. Piazza G, Goldhaber SZ. Fibrinolysis for acute pulmonary embolism. *Vasc Med.* 2010;15(5):419-428.

80. Jaff MR, McMurtry MS, Archer SL, et al. Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension: A Scientific Statement From the American Heart Association. *Circulation.* 2011.
81. Mehta RH, Stebbins A, Lopes RD, et al. Race, Bleeding, and Outcomes in STEMI Patients Treated with Fibrinolytic Therapy. *Am J Med.* 2011;124(1):48-57.
82. Todd JL, Tapson VF. Thrombolytic therapy for acute pulmonary embolism: a critical appraisal. *Chest.* 2009;135(5):1321-1329.
83. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *European heart journal.* 2014;35(43):3033-3069, 3069a-3069k.
84. Brass LM, Lichtman JH, Wang Y, Gurwitz JH, Radford MJ, Krumholz HM. Intracranial hemorrhage associated with thrombolytic therapy for elderly patients with acute myocardial infarction: results from the Cooperative Cardiovascular Project. *Stroke.* 2000;31(8):1802-1811.
85. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. *Lancet.* 1994;343(8893):311-322.
86. Mesmetti, PREPIC 2 Study Group. Retrievable vena cava filter for patients with acute pulmonary embolism: A randomized clinical trial. 2015.
87. Kahn SR, Shapiro S, Wells PS, et al. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. *Lancet.* 2014;383(9920):880-888.
88. Kahn SR, Shapiro S, Ducruet T, et al. Graduated compression stockings to treat acute leg pain associated with proximal DVT. A randomised controlled trial. *Thromb Haemost.* 2014;112(6):1137-1141.
89. Brandjes DP, Buller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet.* 1997;349(9054):759-762.
90. Prandoni P, Lensing AW, Prins MH, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. *Ann.Intern.Med.* 2004;141(4):249-256.
91. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. *Arch Intern Med.* 2000;160(6):761-768.
92. Prandoni P, Noventa F, Ghirarduzzi A, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. *Haematologica.* 2007;92(2):199-205.
93. Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *Jama.* 2014;311(23):2414-2421.

94. Dong BR, Hao Q, Yue J, Wu T, Liu GJ. Thrombolytic therapy for pulmonary embolism. *The Cochrane database of systematic reviews.* 2009(3):CD004437.
95. Cao Y, Zhao H, Gao W, Wang Y, Cao J. Systematic review and meta-analysis for thrombolysis treatment in patients with acute submassive pulmonary embolism. *Patient preference and adherence.* 2014;8:275-282.
96. Marti C, John G, Konstantinides S, et al. *Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis.* 2014.
97. Nakamura S, Takano H, Kubota Y, Asai K, Shimizu W. Impact of the efficacy of thrombolytic therapy on the mortality of patients with acute submassive pulmonary embolism: a meta-analysis. *Journal of thrombosis and haemostasis : JTH.* 2014;12(7):1086-1095.