Duration of Anticoagulant Therapy for Unprovoked Venous Thromboembolism

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ABSTRACT

Venous thromboembolism (VTE) is a chronic illness that affects nearly 10 million people every year worldwide. Anticoagulant therapy with direct oral anticoagulants is the mainstay of treatment for patients with VTE, and should be continued for at least 3–6 months. Thereafter, a decision should be made to discontinue anticoagulation or continue it indefinitely. This decision is most challenging for patients with a first unprovoked VTE because of uncertainty in estimates for the long-term benefits (e.g., reduction in recurrent VTE) and harms (e.g., increase in major bleeding) of extended anticoagulation, and the trade-offs between them. The overarching aim of this doctoral thesis was to address these key evidence gaps that are pertinent to making decisions regarding the duration of anticoagulation for patients with a first unprovoked VTE. The first three studies of this thesis synthesized contemporary and reliable estimates for the long-term risks and consequences of recurrent VTE and major bleeding, with and without extended anticoagulation (parameters that can influence the clinical and cost-effectiveness of discontinuing versus continuing anticoagulation indefinitely). Broadly, these systematic reviews and meta-analyses found that: 1) the long-term risks and consequences of major bleeding during extended anticoagulation are considerable, particularly with vitamin K antagonists as well as in older patients, patients using antiplatelet therapy, and in patients with kidney disease, a history of bleeding, or anemia; and 2) the long-term risks of recurrent VTE during extended anticoagulation and major bleeding after discontinuing anticoagulation are reassuringly low but not negligible. The fourth study incorporated the synthesized evidence to compare the lifetime clinical benefits, harms, and costs of discontinuing versus continuing anticoagulation indefinitely. This decision analytic modelling study showed that indefinite anticoagulation is unlikely to either result in a net clinical benefit or be cost-effective in all (i.e., unselected) patients with a first unprovoked

VTE. Findings from this thesis can serve to impact clinical practice and health policy by informing patient prognosis to guide shared decision-making regarding the duration of treatment for unprovoked VTE, and informing future research to ultimately identify which patients should receive anticoagulation indefinitely in order to maximize health benefits for the available healthcare resources.

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To my thesis advisory committee – Drs. Kednapa Thavorn, Brian Hutton, Gregoire Le Gal, and Marc Rodger: Many thanks for supporting me, challenging me, and teaching me throughout my doctoral studies. Thank you for your expertise – this work would not be possible without you.

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CHAPTER 1

INTRODUCTION

1.1 CLINICAL PROBLEM

Venous thromboembolism (VTE), defined as deep vein thrombosis (DVT) or pulmonary embolism (PE), is a common, potentially fatal, yet treatable condition. The annual incidence of acute VTE is 1 to 2 cases per 1000 persons.[1] Approximately 20% of patients with PE die within 1 year of diagnosis.[1] Anticoagulant therapy is the mainstay of VTE treatment and should be continued for at least 3-6 months in all patients with acute VTE. After 3-6 months of initial anticoagulation, a decision should be made to either discontinue anticoagulation or continue it indefinitely. This decision requires estimating the net balance between absolute treatment benefits and harms through careful consideration of the long-term risks and case-fatality rates of both recurrent VTE and major bleeding, with and without extended anticoagulation.

In patients with VTE provoked by a major transient risk factor (see Box for examples), the long-term risk of recurrent VTE is low and anticoagulation can be stopped after 3 months.[1-3] In patients with VTE associated with persistent provoking factors such as active cancer, or those who have had prior episodes of unprovoked VTE, the long-term risk of recurrent VTE is high and indefinite anticoagulation is recommended.[1-3] Deciding the duration of anticoagulation in patients with a first episode of VTE that is unprovoked (see Box for definition) or weakly provoked (i.e., associated with a minor transient risk factor; see Box for examples), for whom indefinite anticoagulation is often suggested,[1-3] is more nuanced and challenging because the net clinical benefit of extended anticoagulation is uncertain.

Box 1: International Society on Thrombosis and Haemostasis definition of unprovoked VTE.[4]

VTE is defined as unprovoked if it is not associated with the following provoking risk factors:

Persistent	*Major Transient*	*Minor Transient*
Active cancer, defined as: cancer that has not received potentially curative treatment, or; treatment is ongoing, or; evidence that treatment has not been curative.	Surgery with general anesthesia for > 30 minutes Confined to bed (only 'bathroom privileges') for at least 3 days with an acute illness. Cesarean section	Surgery with general anesthesia for < 30 minutes Admission to hospital for < 3 days with an acute illness Estrogen therapy Pregnancy or puerperium Confined to bed out of hospital for at least 3 days with an acute illness. Leg injury associated with reduced mobility for at least 3 days

A conceptual framework for decision making about treatment duration for patients with a first unprovoked VTE is presented in **Figure 1**. To justify indefinite anticoagulant therapy, the long-term risk of death from recurrent VTE or major bleeding if anticoagulation is discontinued should be balanced by the long-term risk of death from recurrent VTE or major bleeding on extended therapy. In the absence of direct evidence (for or against indefinite anticoagulation) from randomized trials, clinicians and patients rely on combining projected long-term (i.e. beyond 2 years) risks and case-fatality rates of recurrent VTE and major bleeding, with and without extended treatment, in order to estimate net difference in mortality between discontinuing and continuing anticoagulation indefinitely.

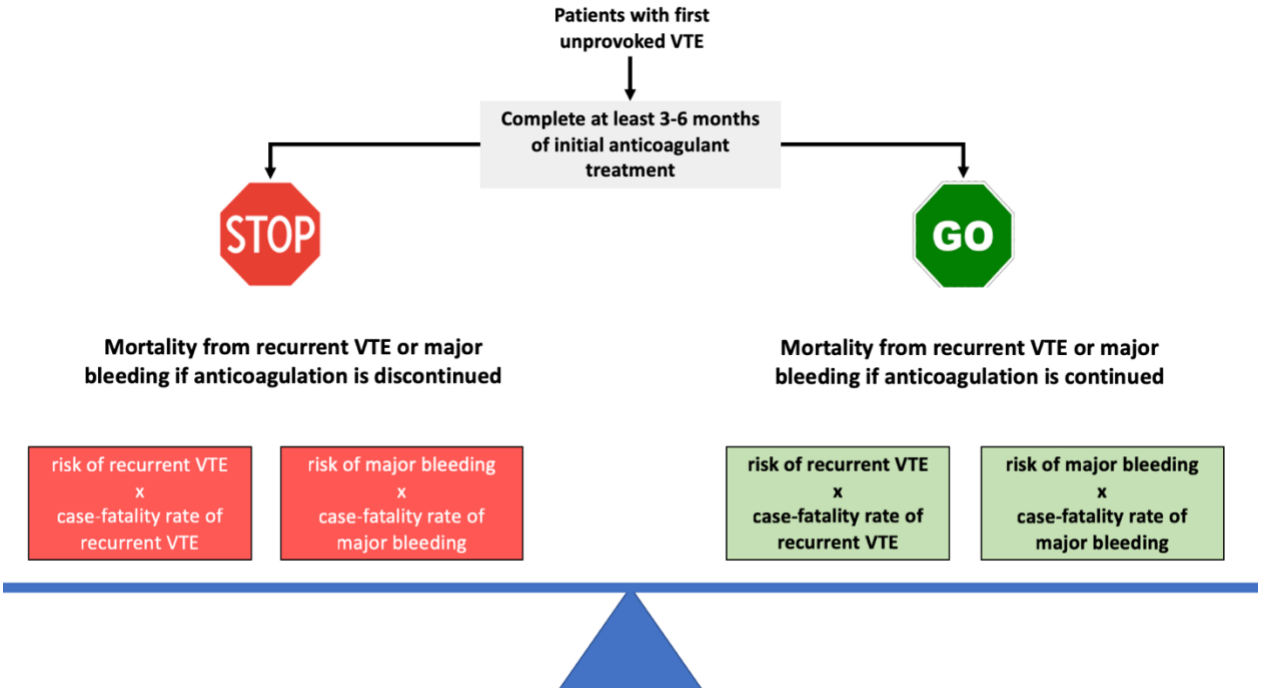

Figure 1: Conceptual framework in which to consider and weigh the long-term risks and consequences of recurrent VTE and major bleeding to guide treatment duration for first unprovoked VTE.

For example, in a typical patient with a first episode of unprovoked VTE, the risk of recurrent VTE after discontinuing anticoagulation is estimated at 36% at 10 years, with a case fatality rate for recurrent VTE of 4% (*as determined by our previous research, described below*).[5] Thus, the risk of death from a first recurrent VTE after discontinuation of anticoagulant treatment would be about (36% x 4%) 1.44% by 10 years.

1.2 PREVIOUS WORK

In a collaborative systematic review and meta-analysis of 18 studies involving 7, 515 patients with first unprovoked VTE who had completed at least 3 months of initial treatment, we found that the long term risk of recurrent VTE was substantial, reaching 10% within the first year, 16% at 2 years, 25% at 5 years, and 36% at 10 years after discontinuing anticoagulation.[5] The case-fatality rate for recurrent VTE was 4%, and the cumulative risk of recurrent fatal VTE was 1.5% at 10 years after discontinuation of treatment.[5]

Because the overall reduction in mortality with indefinite anticoagulation is small, other factors that affect the risk of recurrence (e.g., sex, site of initial VTE) and the risk of bleeding, could influence decisions about whether to continue or stop treatment. We found that the risk of recurrent VTE was significantly different between patient subgroups (**Table 1**). In men and women, the cumulative incidence for recurrent VTE were 41% and 29% at 10 years, respectively. Compared to patients with isolated PE, the rate of recurrent VTE was higher in patients with proximal DVT and patients with concomitant PE and DVT (**Table 1**).[5] In patients with distal DVT, the risk of recurrence was 2% within the first year after discontinuing anticoagulation – significantly lower than the risk in patients with proximal DVT, isolated PE, and concomitant PE and DVT (**Table 1**).[5] These findings emphasize the importance of considering patients' sex and site of initial VTE in deciding which patients should be considered for indefinite anticoagulation.

Table 1: Comparison of the rate of recurrent VTE after discontinuing anticoagulation in subgroups of patients with first unprovoked VTE.[5]

Patient Subgroups	**Recurrent VTE Rate Ratio** (95% CI)
Men vs **Women**	1.4 (1.3 to 1.6)
Distal DVT vs **Proximal DVT**	0.2 (0.04 to 0.5)
Distal DVT vs **isolated PE**	0.2 (0.05 to 0.7)
Distal DVT vs **PE plus DVT**	0.2 (0.03 to 0.5)
Proximal DVT vs **isolated PE**	1.4 (1.1 to 1.7)
Proximal DVT vs **PE plus DVT**	0.9 (0.7 to 1.2)
PE plus DVT vs **isolated PE**	1.5 (1.1 to 1.9)

reference group is bolded.

1.3 KEY EVIDENCE GAPS

While evidence-based estimates for the long-term risk of recurrent VTE after discontinuing anticoagulation are well-established, the long-term risk of major bleeding after discontinuing anticoagulant therapy in patients with first unprovoked VTE is unknown (**Figure 2**). Quantifying this risk is important not only to inform prognosis of patients who discontinue treatment, but also to accurately estimate the incremental risk of major bleeding during extended anticoagulation, that is over and above the risk of major bleeding with no anticoagulant therapy.

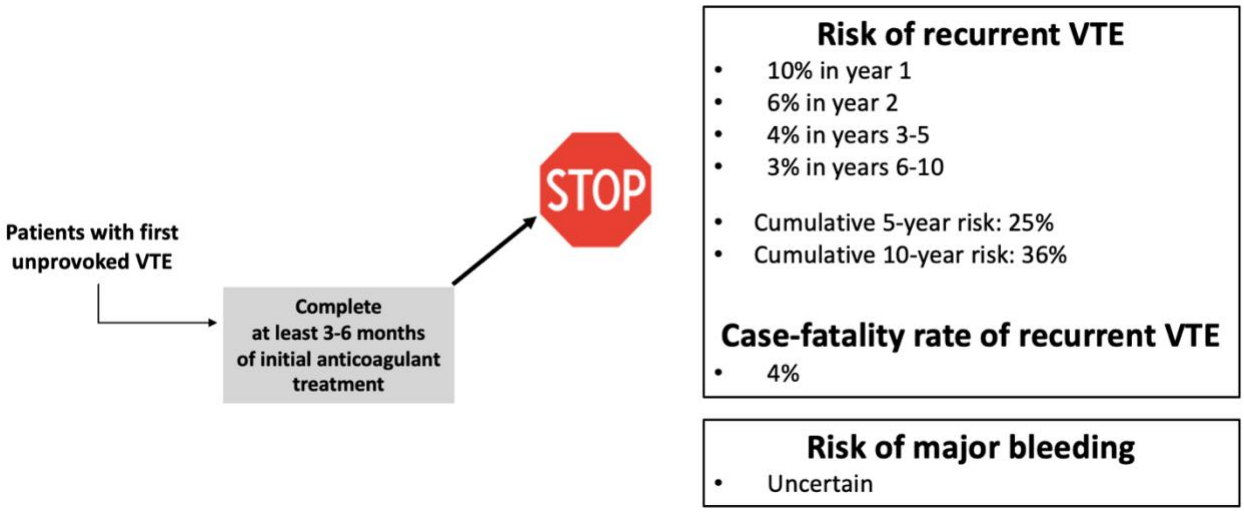

Figure 2: Current evidence and evidence gaps in estimates for the long-term risks and case-fatality rates of recurrent VTE and major bleeding after discontinuing anticoagulation for first unprovoked VTE.

On the other hand, evidence-based estimates for the long-term risk of recurrent VTE during extended anticoagulation, as well as the long-term risk and case-fatality rate of anticoagulant-related major bleeding, with different anticoagulant regimens (i.e., vitamin K antagonists and direct oral anticoagulants [apixaban, dabigatran, edoxaban, and rivaroxaban]) are uncertain (**Figure 3**).

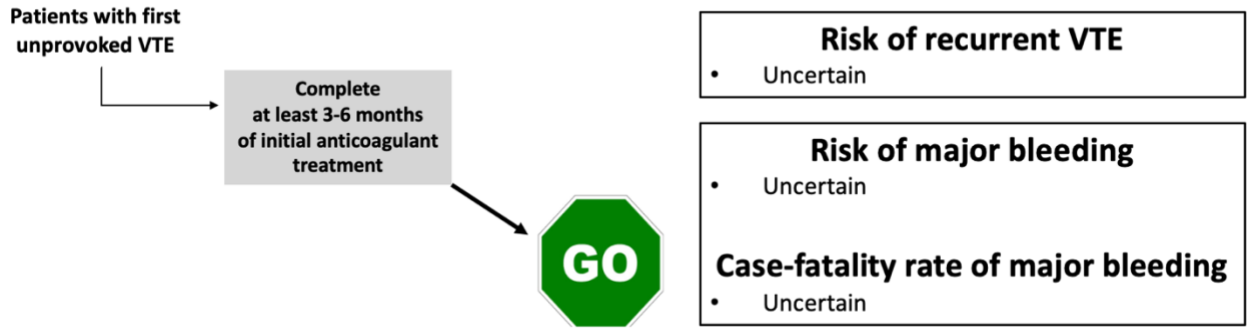

Figure 3: Evidence gaps in estimates for the long-term risks and case-fatality rates of recurrent VTE and major bleeding during extended anticoagulation for first unprovoked VTE.

Additionally, inconveniences/burdens of medical treatment, patient preferences and financial costs associated with VTE management may further influence decision about the duration of anticoagulation for first unprovoked VTE. The total annual healthcare costs related to VTE are estimated to be $600 million in Canada, between €1.5-3.3 billion in Europe, and between $7-10 billion in the United States.[1] In addition to recurrent VTE and anticoagulant-related bleeding, both the post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension are important long-term complications of VTE that reduce quality of life and impose a substantial economic burden.[1] Examining both the clinical (i.e., net clinical benefit) and cost-effectiveness (i.e., net monetary benefit) of continuing anticoagulation indefinitely for a first unprovoked VTE, is therefore imperative as resources are scarce and it is critical to attempt to obtain the greatest reduction of recurrent VTE in the most efficient manner.

1.4 THESIS OBJECTIVES

The overarching goal of this thesis is to address key evidence gaps that are pertinent to making decisions regarding the duration of anticoagulant therapy for patients with first unprovoked VTE,

to ultimately determine whether these patients should continue anticoagulation indefinitely, or discontinue it after completing 3-6 months of initial anticoagulant treatment.

This goal will be achieved through the following key objectives:

1. Establish evidence-based estimates for the long-term benefits and harms associated with extended duration of anticoagulation.
2. Examine the trade-offs between the long-term benefits and harms of indefinite anticoagulation with respect to health system costs and life expectancy.

These objectives will be addressed through the following research questions:

1. What is the long-term risk of major bleeding during extended anticoagulation in patients with a first unprovoked VTE that have completed at least 3-6 months of initial treatment?
2. What is the long-term risk of recurrent VTE during extended anticoagulation in patients with a first unprovoked VTE that have completed at least 3-6 months of initial treatment?
3. What is the long-term risk of major bleeding after discontinuing anticoagulation in patients with a first unprovoked VTE that have completed at least 3-6 months of initial treatment?
4. What is the clinical and cost-effectiveness of continuing anticoagulation indefinitely in patients with a first unprovoked VTE that have completed at least 3 months of initial treatment?

1.5 THESIS ORGANIZATION

This thesis is organized in an article format, in accordance with the University of Ottawa doctoral thesis guidelines. A brief overview of each chapter is provided below:

- **Chapter 1** provides an introduction and rationale for the thesis topic.

- **Chapter 2** represents the first article of the thesis, titled "Venous thromboembolism". This article is published in ***The Lancet***.
- **Chapter 3** represents the second article of the thesis, titled "Risk of major bleeding during extended oral anticoagulation in patients with first unprovoked venous thromboembolism: a systematic review and meta-analysis protocol". This article is published in ***Systematic Reviews***.
- **Chapter 4** represents the third article of this thesis, titled "Long-term risk for major bleeding during extended oral anticoagulant therapy for first unprovoked venous thromboembolism: a systematic review and meta-analysis". This article is published in ***Annals of Internal Medicine***.
- **Chapter 5** represents the fourth article of this thesis, titled "Long-term risk of recurrent venous thromboembolism among patients receiving extended oral anticoagulant therapy for first unprovoked venous thromboembolism: a systematic review and meta-analysis". This article is published in ***Journal of Thrombosis and Haemostasis***.
- **Chapter 6** represents the fifth article of this thesis, titled "Long-term risk of major bleeding after discontinuing anticoagulation for unprovoked venous thromboembolism: a systematic review and meta-analysis". This article is published in ***Thrombosis and Haemostasis***.
- **Chapter 7** represents the sixth article of this thesis, titled "Protocol for a Modelling Study to Assess the Clinical and Cost-Effectiveness of Indefinite Anticoagulant Therapy for First Unprovoked Venous Thromboembolism". This article has been accepted for publication in ***BMJ Open***.
- **Chapter 8** represents the seventh and final article of this thesis, titled "Clinical benefits, harms, and cost-effectiveness of indefinite anticoagulation for first unprovoked venous thromboembolism: a modelling study". This article is in preparation for submission to a peer-reviewed journal.

- **Chapter 9** provides a summary of key findings from research studies presented in Chapters 4, 5, 6, and 8, and discusses the implications of research from this thesis.

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CHAPTER 2

Venous Thromboembolism

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https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32658-1/fulltext

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Preface to Chapter 2

This Chapter provides a literature review on venous thromboembolism covering epidemiology, pathophysiology, diagnosis, treatment, and prevention, while highlighting areas of uncertainty, providing guidance for frontline clinicians, and discussing future directions. The author contributions are outlined on page 33 and the appendix starts on page 58. Figure 1 "*Proposed mechanism for development of venous thrombosis*" of the article was designed/sketched by the lead author (Faizan Khan) and recreated in colour by *The Lancet*. As per copyright policies of the publisher (*Elsevier)*, the authors of this article retain the right to use the recreated figure in a thesis, with no permission required.

ABSTRACT

Venous thromboembolism (VTE), comprising both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a chronic illness that affects nearly 10 million people every year worldwide. Strong provoking risk factors for VTE include major surgery and active cancer, but most events are unprovoked. Diagnosis requires a sequential work-up that combines assessment of clinical pretest probability for VTE using a clinical score (e.g., Wells score), D-dimer testing, and imaging. VTE can be considered excluded in patients with both a non-high clinical pretest probability and normal D-dimer concentrations. When required, ultrasonography should be done for a suspected DVT and computed tomography or ventilation–perfusion scintigraphy for a suspected PE. Direct oral anticoagulants (DOACs) are the first-line treatment for almost all patients with VTE (including those with cancer). After completing 3–6 months of initial treatment, anticoagulation can be discontinued in patients with VTE provoked by a major transient risk factor. Patients whose long-term risk of recurrent VTE outweighs the long-term risk of major bleeding, such as those with active cancer or men with unprovoked VTE, should receive indefinite anticoagulant treatment. Pharmacological VTE prophylaxis is generally warranted in patients undergoing major orthopaedic or cancer surgery. Ongoing research is focused on improving diagnostic strategies for suspected DVT, comparing different DOACs, developing safer anticoagulants, and further individualising approaches for the prevention and management of VTE.

INTRODUCTION

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT most often occurs in the leg vein but can also develop in the splanchnic, cerebral, and arm veins. In this Seminar, we focus on recent (past 5 years) advances in epidemiology, pathophysiology, diagnosis, treatment, and prevention of DVT of the legs and PE. Future directions are also discussed.

Search Strategy and Selection Criteria

We searched MEDLINE, Embase, and the Cochrane Library for prospective studies and systematic reviews published in English between Jan 1, 2015, and March 31, 2021, using combinations of the following terms: "deep vein thrombosis", "pulmonary embolism", "venous thromboembolism", "epidemiology", "pathophysiology", "diagnosis", "treatment", and "prevention". We also searched CLOT+, a continuously updated repository of pre-appraised, best evidence to support practising physicians in clinical decisions related to thrombosis. We mainly selected high-quality studies from the past 5 years but considered older publications when more recent evidence was unavailable. We also included pertinent review articles providing in-depth details that could not be covered in this Seminar.

EPIDEMIOLOGY

Afflicting worldwide nearly 10 million people of all ethnicities per year, VTE is a substantial contributor to the global burden of disease.[1] The annual incidence of acute VTE is 1–2 cases per 1000 population,[1–3] which rises exponentially with age for both men and women,[2] and is 4 times higher in high-income than low-income countries.[4] The lifetime risk of VTE does not differ by sex, but women have a higher risk during the ages of 20–40 years reflecting exposure to

reproductive risk factors,[5] whereas men have a higher risk in other age groups. Among patients with active cancer, the annual incidence of first VTE differs according to cancer type (3% for bladder and breast cancers, 4–7% for colon and prostate cancers, 10–12% for lung, stomach, ovary, and brain cancers, and 15% for pancreatic cancer).[6]

VTE is a chronic illness that recurs frequently and is associated with death, major bleeding associated with anticoagulant treatment, and long-term disability. The total annual healthcare costs associated with VTE are estimated to range between €1.5–3.3 billion in Europe, and US$7–10 billion in the USA.[7,8] Although PE-related death rates are declining,[9,10] approximately 20% of patients with PE die within 1 year of diagnosis,[3,10] mostly due to comorbidities (e.g., cancer) rather than recurrent PE. In Europe, PE accounts for 8–13 deaths per 1000 women and 2–7 deaths per 1000 men aged 15–55 years.[11] In addition to recurrent VTE and anticoagulant-related bleeding, both the post-thrombotic syndrome and the post-PE syndrome are important long term complications of VTE that reduce quality of life and result in a substantial economic healthcare burden.[12,13] The post-thrombotic syndrome is a spectrum of signs and symptoms of chronic venous insufficiency, which ranges from mild ankle swelling to debilitating venous claudication or leg ulcers.[12] Moderate-to-severe post thrombotic syndrome occurs in 20–35% of patients with DVT.[14,15] The most severe manifestation of post-PE syndrome is chronic thromboembolic pulmonary hypertension, which affects up to 3% of patients with PE;[16] nearly half of all patients experience functional and exercise limitations at 1 year after an acute PE.[17]

PATHOPHYSIOLOGY

VTE is a multicausal disease believed to be triggered by interactions between multiple provoking factors (**Panel 1)** that can be additive or synergistic. These provoking factors are thought to lead

to clinically overt disease when a so called thrombosis-threshold is reached. Some clinical risk factors are strong and might result in VTE without the presence of any other risk factors. These strong provoking factors can be transient or persistent. Strong transient provoking risk factors, such as major surgery, prolonged immobilisation, and major trauma, account for approximately 20% of all VTE episodes.[2] The most common strong persistent risk factor is active cancer, accounting for approximately 20% of incident VTE.[19] However, most VTE episodes are provoked by weak risk factors or are unprovoked (i.e., no apparent risk factors).[2,18]

A proposed mechanism for the development of venous thrombosis is shown in **Figure 1**. A growing body of evidence suggests a complex interplay between coagulation and inflammation whereby activation of the coagulation cascade triggers the immune system and, in turn, innate immune cells contribute to thrombus formation in a process termed immunothrombosis.[21] Indeed, drugs with anti-inflammatory properties, such as statins, might reduce incident and recurrent VTE.[22,23] Activated leukocytes are the primary source of procoagulant tissue factor-positive microparticles that might stimulate thrombus formation and growth.[24] Neutrophils, the most abundant leukocytes, produce neutrophil extracellular traps (NETs) that are composed of DNA, histones, and antimicrobial proteins.[25] NETs provide a scaffold for red blood cells, platelets, and procoagulant molecules to promote thrombus formation.[25,26] Concentrations of circulating tissue factor-positive microparticles and markers of NETs (e.g., extracellular DNA) are increased in patients with VTE,[27,28] but their use as biomarkers for VTE is not yet established.

Platelets help induce the formation of NETs and augment the procoagulant activity of innate immune cells,[21,29] which might be the mechanism whereby aspirin reduces the risk of

incident and recurrent VTE.[30,31] Red blood cells might be involved in the production of thrombin, platelet activation, and thrombus stabilisation and growth.[32] Moreover, both platelet and red blood cell transfusions appear to increase the risk of VTE.[33,34]

The contribution of genetics to the risk of VTE is not fully characterised. Traditional inherited thrombophilia including protein C, protein S, and antithrombin deficiencies, prothrombin gene mutation, and factor V Leiden are all associated with genes of the coagulation or anticoagulation system.[35] However, a meta-analysis of genome-wide association studies identified several genes associated with inflammation, red blood cells, and platelets, which were also associated with the risk of VTE.[35]

DIAGNOSIS

The diagnostic approach to suspected VTE comprises a sequential workup combining assessment of clinical pretest probability, D-dimer testing, and imaging. The aim of this diagnostic workup, which should be done ideally within 24 hours of presentation, is to identify patients in whom anticoagulation should be initiated (that is, to confirm VTE), and those in whom imaging and anticoagulation can be safely withheld (that is, to exclude VTE). The combined use of clinical pretest probability and D-dimer testing can help exclude VTE, but imaging tests are required to confirm the diagnosis. The signs and symptoms of DVT and PE are non-specific,[36] and so the diagnosis is only confirmed in less than 20% of patients investigated for suspected VTE.[37,38] Thus, it is undesirable to do imaging in all patients in whom VTE is suspected as diagnostic imaging tests are time-consuming, costly, and associated with radiation exposure (e.g., computed tomography) and adverse effects (e.g., contrast-induced nephropathy or allergy to contrast). To increase the efficiency of the diagnostic process and avoid unnecessary

imaging, several prospectively validated diagnostic strategies are available and should be used to guide the sequential workup of suspected VTE.[39–42] Failure to appropriately use these strategies is frequent and results in higher occurrence of VTE during patient follow-up.[43]

Clinical Presentation

The clinical signs and symptoms of DVT include leg pain (80–90% of patients), swelling (80%), redness (25%), localised tenderness on palpation (75–85%), and prominent collateral superficial veins (30%).[44,45] Between 30% and 60% of patients with symptomatic proximal DVT have silent PE.[46] Most patients with PE present with breathlessness (80% of patients), pleuritic chest pain (60–70%), haemoptysis (5–13%), tachycardia (65–70%), or hypoxemia (70%), but can also present with severe haemodynamic compromise (10–20%), including sudden death, shock, hypotension, syncope, or confusion.[47] About 40% of patients with symptomatic PE have proximal DVT and 25% have only distal DVT.[48,49] However, only half of patients with PE and imaging-confirmed DVT have leg symptoms.[48–50]

Clinical Probability Assessment

Clinical assessment of patients for risk factors, signs, and symptoms of DVT or PE at presentation is necessary to estimate a patient's likelihood of having VTE before any further investigations. This first step in the diagnosis of suspected VTE is referred to as clinical pretest probability assessment and guides the selection of subsequent diagnostic tests. Although clinical pretest probability can be assessed by gestalt, standardised assessment using a clinical score (**Table**) is preferred.[40,51]

The Wells score for DVT[52,53] is most widely used for clinical pretest probability

assessment for this condition, and categorises the patient's likelihood of having DVT as likely or unlikely (**Table**). Scores for clinical pretest probability assessment of PE include the Wells score for PE,[54,55] the revised Geneva score,[56,57] and the YEARS criteria,[58] which stratify the patient's likelihood of having PE into categories of likely and unlikely, or low, moderate, and high (**Table**).

The Pulmonary Embolism Rule-Out Criteria[59] (**Table**) is a clinical score developed to exclude PE without the need for further diagnostic testing. PE can be considered excluded in patients with all Pulmonary Embolism Rule-Out Criteria and a low clinical pretest probability, assessed by gestalt, or in clinical settings with a low (<5%) prevalence of PE (e.g., emergency departments in the USA).[60,61]

D-dimer Testing

D-dimers are degradation products of crosslinked fibrin that increase in the setting of acute thrombosis, but also rise physiologically with age and with cancer, infection, or other inflammatory states. Thus, D-dimers testing can help to exclude VTE in those with normal D-dimer concentrations, but elevated concentrations do not confirm VTE. Of note, false negative test results might occur after initiation of anticoagulation.[62] D-dimer testing is recommended in patients assessed as having an unlikely or a non-high (i.e., low or moderate) clinical pretest probability, whereas those assessed as having a high clinical pretest probability should directly undergo imaging without D-dimer testing.

D-dimer assays differ in their method of measurement, sensitivity for VTE, and the threshold for defining a positive or a negative test result. Quantitative, enzyme-linked, immunosorbent assays have a high sensitivity (>95%) but a low specificity for VTE.[63]

Consequently, a negative test result (standard threshold of <500 μg/L) using a highly sensitive D-dimer assay excludes VTE in patients assessed as having an unlikely or a non-high clinical pretest probability (**Table**).[64–66] In the primary care setting without timely access to a highly sensitive D-dimer assay, the use of a strategy incorporating the Wells scores for DVT or PE (**Table**) and a qualitative point-of-care D-dimer is safe[67,68] and recommended.[51] These standard diagnostic strategies can exclude DVT or PE in about a third of ambulatory outpatients with a suspected event, in both the primary and hospital care setting.[64–66] However, the yield of these strategies is lower for patients with an increased risk for VTE, elevated baseline D-dimer concentrations, or both, such as the older patients (>65 years), pregnant women, hospitalised patients, and patients with cancer.[65,66,69]

New diagnostic strategies (**Panel 2**) that have been prospectively validated help to increase the proportion of patients in whom suspected PE can be excluded without the need for imaging.[58,70,71] These strategies use a higher threshold to define either a non-high clinical pretest probability, a negative D-dimer test result, or both. Whether and how these new diagnostic strategies can be used together and sequentially requires further study. Until then, physicians can consider using them in combination, taking into account the prevalence of PE and the setting in which the strategies were validated to safely exclude this condition. When used in combination, imaging and anticoagulation can be withheld even when only one strategy considers PE as excluded, because the safety of all strategies has been established in their pertinent settings.[58,70,71]

In pregnant women, two prospective management cohort studies suggest that D-dimer testing in combination with clinical pretest probability assessment using the YEARS criteria or the revised Geneva score can exclude PE.[69,72] Although the efficiency of these validated

diagnostic strategies diminishes as pregnancy advances, they can be used in all pregnant women to avoid unnecessary imaging and prevent overdiagnosis.[69,72]

Imaging for Suspected DVT

Patients with a suspected DVT either assessed as having a likely clinical pretest probability (**Table**) or with a positive D-dimer test result should undergo imaging. Compression ultrasonography is the first-line, and the most widely used imaging test for patients with a suspected first DVT.[39–41] Two strategies that are interchangeably used in clinical practice include proximal (or limited) leg ultrasonography, which is done as either a scan of the common femoral and the popliteal vein regions, or of all segments of the deep venous system between the groin and the calf trifurcation where the veins of the calf join the popliteal vein; and whole-leg ultrasonography, which includes additional examination of the deep veins of the calf. Failure to fully compress (i.e., collapse) the lumen of the veins with the ultrasound probe is confirmatory of DVT.[36]

DVT can be considered excluded in all patients with a normal whole-leg ultrasound, or in those assessed as having an unlikely clinical pretest probability with a normal proximal leg ultrasound.[39–41,73] Patients assessed as having a likely clinical pretest probability and a normal proximal leg ultrasound should undergo a serial proximal leg ultrasound 1 week after the initial scan to exclude proximal extension of a distal DVT,[39–41,73] and anticoagulation should be withheld between serial ultrasounds. Reserving whole-leg ultrasonography for patients both assessed as having a likely clinical pretest probability and a positive D-dimer test result is recommended, because this strategy allows safe, prompt, and more convenient patient management without the need for serial scans.[74]

Diagnosing recurrent ipsilateral DVT is more challenging, particularly when baseline imaging after completion of at least 3 months of anticoagulation is unavailable for comparison.[75] In patients with non-diagnostic results (i.e., compression ultrasonography does not allow to exclude DVT), direct thrombus magnetic resonance imaging can be considered if available.[76]

Imaging for Suspected PE

Patients assessed as having a likely or high probability of PE (**Table**), or those with a D-dimer concentration above the pertinent threshold (**Panel 2**) require imaging. Ventilation–perfusion scintigraphy and computed tomography pulmonary angiography (CTPA) are the most extensively validated imaging modalities for diagnosing PE, and have similar diagnostic accuracy.[40] As such, physicians can consider using either imaging modality but CTPA often remains the only option in many centres without local access to ventilation–perfusion scintigraphy.

Patients assessed as having a high clinical pretest probability with a non-diagnostic ventilation–perfusion scan should undergo CTPA. All patients with a non-diagnostic CTPA, or those assessed as having a non-high clinical pretest probability with a non-diagnostic ventilation–perfusion scan should undergo a proximal leg ultrasound.[36] The proximal leg ultrasound should be repeated after 1 week of the first scan in patients assessed as having a high clinical pretest probability with a non-diagnostic CTPA. When adhering to this approach, a normal (serial) leg ultrasound excludes PE in patients with non-diagnostic chest scans.[36]

Other diagnostic imaging modalities have been studied, but only ultrasonography can be considered as an alternative initial test for patients with suspected PE.[40,42] The diagnosis of PE

can be considered as established in patients with a confirmed proximal DVT and signs and symptoms of PE.[50] Conversely, a normal leg ultrasound does not exclude PE.[49]

TREATMENT

Treatment of VTE aims to prevent thrombus extension and embolization, cardiopulmonary collapse, death, recurrent VTE, and the risk for long-term complications. Direct oral anticoagulants (DOACs), including the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, and the thrombin inhibitor dabigatran represent major advances in the therapeutic management of VTE.[77] The key aspects of DOACs, including development, pharmacological properties, reversal, efficacy, safety, and dosing in the treatment and prevention of VTE, are detailed in a separate therapeutics review,[78] and are only briefly discussed in this Seminar.

Anticoagulation

Anticoagulation is the first-line treatment for most patients with confirmed VTE.[79,80] Before the introduction of DOACs, anticoagulation with heparin followed by a vitamin K antagonist (VKA) was the cornerstone of treatment for acute VTE in patients without cancer. Low-molecular-weight heparin (LMWH) is associated with a lower risk of recurrent VTE and major bleeding than unfractionated heparin,[81,82] and is the preferred heparin agent in all patients with an estimated glomerular filtration rate of 30 mL/min or more.[41,42,79]

Compared with LMWH followed by VKA therapy, anticoagulation with rivaroxaban, apixaban, dabigatran, or edoxaban is as effective at reducing the risk of recurrent VTE, and associated with a lower risk of major bleeding.[78,83] Therefore, DOACs are the recommended anticoagulants for the treatment of VTE in most patients.[41,42,51,79,80] Because direct comparisons between DOACs are lacking, pharmacological properties of these drugs and characteristics and

preferences of patients should be considered to guide the choice of agent.[78,80]

In patients with VTE and cancer, LMWH is preferred over VKA therapy because of its superior efficacy and comparable safety.[84] In a meta-analysis of trials that compared edoxaban,[85] rivaroxaban,[86] and apixaban[87] with dalteparin for the treatment of VTE in patients with cancer, DOACs appeared to be associated with a 32% lower risk of recurrent VTE and a 36% higher risk of major bleeding than LMWH.[88] Although the combined evidence from these trials support edoxaban, rivaroxaban, and apixaban as efficacious and safe alternatives to treatment with LMWHs in most patients with cancer, selection of the optimal anticoagulant should be individualised based on cancer type, additional risk factors for bleeding, concomitant medications, and patient preferences and values.[89–93] For example, compared with dalteparin, both edoxaban and rivaroxaban increase the risk of bleeding in patients with gastrointestinal cancer,[85,86] whereas apixaban does not.[87] Edoxaban has fewer drug–drug interactions than rivaroxaban and apixaban, but requires a 5-day lead-in with LMWH. In patients with limited drug absorption in the upper gastrointestinal tract, a recent bleeding event, or thrombocytopenia, LMWH remains the preferred anticoagulant given its parenteral administration and titratable dosing.

In patients with antiphospholipid syndrome and a history of VTE, results from the RAPS trial[94] suggested that rivaroxaban might be an effective and safe alternative to warfarin. However, rivaroxaban increased the risk of arterial thrombotic events as compared to warfarin in two trials of patients with either triple positive antiphospholipid syndrome (i.e., positive for lupus anticoagulant, and anti-cardiolipin and anti-β2-glycoprotein-I antibodies) or very high antibody titres.[95,96] Accordingly, such patients should be treated with VKAs.

However, in practice, results of thrombophilia tests are rarely available at the time of

diagnosis, antiphospholipid antibodies can be transiently positive, and anticoagulants can lead to false-positive detection of lupus anticoagulant. Phase 3 trials of DOACs for the treatment of VTE did not routinely test for antiphospholipid antibodies. The prevalence of triple positive antiphospholipid syndrome is 1–2% among patients younger than 50 years with a first unprovoked VTE.[97] Therefore, in patients with a newly confirmed unprovoked event, physicians should consider testing for anticardiolipin and anti-β2-glycoprotein-I antibodies and initiate treatment with a DOAC. Patients with a high antibody titre or positivity for both antibodies can be switched to LMWH followed by warfarin and referred to a thrombosis specialist to guide anticoagulation management. Testing for other thrombophilia is not indicated at the time of diagnosis as test results do not affect the choice of anticoagulant. However, after completing treatment for an acute event, testing might be considered for patients in whom discontinuation of treatment is contemplated, and management can be affected by test results.[98]

Patients with a creatinine clearance of less than 25–30 mL/min were excluded from trials of DOACs for the treatment of VTE, because these agents can accumulate and increase the risk of bleeding in such patients.[78] Therefore, DOACs should be avoided in these patients but might be considered over VKAs in patients with creatinine clearance between 30 mL/min and 50 mL/min.[99]

Similarly, there is limited evidence to guide the use of DOACs in patients with obesity. Existing data suggest that these drugs might be equally effective and safe as VKAs in patients with obesity with a body-mass index of less than 40 kg/m^2 or weight less than 120 kg.[100,101]

VKAs and DOACs cross the placenta and are associated with adverse pregnancy outcomes.[102,103] Thus, pregnant women with VTE should be treated with LMWH.[42,104] However, both VKAs and LMWHs are safe to use during breastfeeding, whereas DOACs are not

recommended pending further evidence of safety.[104]

The optimal approach to management in patients with isolated distal DVT or subsegmental PE is not well defined. The use of whole-leg ultrasonography or multidetector CTPA in patients with suspected VTE results in more frequent diagnosis of distal DVT and subsegmental PE than the use of proximal leg ultrasound or ventilation–perfusion scintigraphy, without safety benefits.[73,105] These findings question whether anticoagulation is required for such additionally detected VTE.[79,106,107] Although terminated prematurely, the CACTUS trial of outpatients with a first symptomatic distal DVT showed that treatment with LMWH, compared with placebo, did not have a benefit in reducing the risk of thrombus extension to proximal veins, recurrent VTE, pain control, or the post-thrombotic syndrome, and increases the risk of bleeding.[108–110] Consequently, and until further evidence, anticoagulation might be withheld in patients with isolated distal DTV or subsegmental PE without proximal DVT if they are at low risk of recurrent VTE (e.g., no cancer or ongoing immobilisation) or at high risk of bleeding.[41,79,106,107] If anticoagulation is withheld, patients with isolated distal DVT should be imaged with serial ultrasound at 1 week after diagnosis to exclude thrombus extension.[41,79] In patients receiving anticoagulation, treatment should be limited to 3 months except for those with cancer.[79,111]

Although therapeutic failure is rare, patients who develop recurrent VTE during treatment can be switched from an oral anticoagulant to therapeutic-dose LMWH, or if receiving full-dose LMWH, can have their dose escalated by 25%.[75,79]

Duration of Anticoagulation

To minimise the risk for early recurrent VTE, patients should be treated for at least 3–6 months.

After that, continuing anticoagulation markedly reduces the risk of recurrent VTE as long as patients remain on therapy.[112–114] Thus, after 3–6 months of treatment, a decision should be made to discontinue anticoagulation or continue it indefinitely. This decision mainly relies on assessing whether the long-term risk and consequences of recurrent VTE if anticoagulation is discontinued offset the long-term risk and consequences of major bleeding if anticoagulation is continued. Patient preferences must also be especially considered when the balance between the risks and benefits of extended anticoagulation is unclear. Also, the balance between risks, consequences, and patient preferences should be reassessed periodically as the decision might change over time.

Major bleeding events occur at an annual rate of approximately 1–2% in patients with VTE receiving extended anticoagulation[115,116] Because anticoagulant-related major bleeds are nearly 3-times more likely to be fatal than recurrent VTE (11% *vs* 4%),[115,117] assessment of the risk of major bleeding (**Figure 2**) takes precedence when deciding the duration of anticoagulation.[111,119] Although existing prediction scores for major bleeding have not yet been validated in prospective management cohort studies, the following risk factors might independently predict the long-term risk of major bleeding: advanced age (e.g., >65 years), antiplatelet therapy, chronic renal impairment (creatinine clearance <50 mL/min), anaemia, and history of bleeding.[118] The presence of two or more of these risk factors is probably associated with a high (>2–3% annually) risk of major bleeding.[79,111,119] Patients at high risk of major bleeding should discontinue anticoagulation.[79] In patients with a non-high risk of major bleeding, the decision to continue anticoagulation indefinitely is primarily influenced by the risk of recurrent VTE after treatment is discontinued (**Figure 2**).[79,111,119]

In patients with VTE provoked by a major transient risk factor (**Panel 1**) or an

unprovoked isolated distal DVT, the risk of recurrent VTE is low[112,117,120] and anticoagulation can be discontinued after 3 months of treatment (**Figure 2**).[41,42,79] By contrast, in patients with antiphospholipid antibodies, active cancer, or a second unprovoked VTE, the risk of recurrent episodes is high[121–125] and indefinite anticoagulation is recommended (**Figure 2**).[41,42,79]

The risks and benefits of extended anticoagulation are more closely balanced in patients with a first unprovoked or weakly provoked proximal DVT or PE, whose risk of recurrent VTE is 10% at 1 year and 36% at 10 years after discontinuing anticoagulation.[117] The risk is higher among men and in patients with isolated proximal DVT.[117] Thus, although indefinite anti-coagulation is generally indicated for a first unprovoked or weakly provoked proximal DVT or PE,[42,119] risk stratification approaches can help to individualise the duration of treatment in these patients. The International Society on Thrombosis and Haemostasis suggests that it is safe to discontinue anticoagulation in patients with a risk of recurrent VTE of less than 5% at 1 year after treatment ends.[126] Although several prediction scores have been proposed to achieve this threshold,[111] the HERDOO2 score (**Figure 2**) is the only prospectively validated score that can identify women with first unprovoked or weakly provoked proximal DVT or PE who can safely discontinue anticoagulation.[127]

Anticoagulants for Extended Treatment

Continuing anticoagulation beyond 3–6 months of treatment results in a reduction of 80% or more in recurrent VTE compared with placebo, and an increase in major bleeding of 1–3-times with DOACs and 4–5-times with VKAs.[30] Although various oral anticoagulants have not been directly compared for extended treatment, data from indirect comparisons suggest that there is no conclusive difference in efficacy, but DOACs might be associated with lower rates of major

bleeding than VKAs.[30] Consequently, extended treatment with DOACs might be preferred over VKAs,[111] although it is practical to continue the same anticoagulant used during the initial 3–6 months of treatment.[79,111]

Unlike extended treatment with low-intensity warfarin (target international normalised ratio of 1.5–1.9),[128] anticoagulation with lower doses of rivaroxaban (10 mg once daily) and apixaban (2.5 mg twice daily) beyond the initial 6 months of treatment appears to be as effective as therapeutic doses, but differences in the risk of clinically relevant bleeding remain unclear.[129,130]

Aspirin is not recommended for extended treatment of VTE, given its lower efficacy and similar safety profile compared with DOACs.[30,130]

Outpatient Treatment

Patients with DVT can be treated as outpatients, except for those at high risk of limb loss or with a contraindication to LMWH or DOACs (e.g., high risk of bleeding or renal failure).[41,79,80,131] The Pulmonary Embolism Severity Index score, or the Hestia criteria can be used to assess the eligibility for safe home outpatient treatment of patients with PE.[42,79,132–134] The recommended criteria to select patients with VTE for outpatient treatment or early discharge within 24 hours is outlined in **Figure 3**.[135]

Thrombolysis

In patients with proximal DVT, thrombolysis in addition to anticoagulation is intended to rapidly achieve thrombus resolution, preserve venous function, and prevent post-thrombotic syndrome. In the CaVenT trial, catheter-directed thrombolysis reduced the risk of post-thrombotic

syndrome over 2 years and 5 years compared with standard anticoagulation,[136,137] whereas the recent ATTRACT and CAVA trials did not confirm these findings.[138,139] Moreover, catheter-directed thrombolysis increased the risk of major bleeding and did not improve quality of life.[138,139] However, subgroup analysis of patients with acute iliofemoral DVT in the ATTRACT trial showed that pharmacomechanical catheter-directed thrombolysis might reduce the occurrence of moderate-to-severe post-thrombotic syndrome.[138] Hence, although the role of pharmacomechanical catheter-directed thrombolysis in patients with iliofemoral DVT remains uncertain, thrombolysis at present can only be recommended for patients if this condition is threatening limb loss (**Figure 3**).[41,79,80]

For patients with PE, systemic thrombolysis aims to rapidly achieve reperfusion and prevent death, and is reserved for those with sustained hypotension or signs and symptoms of shock (**Figure 3**).[42,79,80,140] Current evidence does not support the use of thrombolysis in normotensive patients with PE associated with right ventricular dysfunction, because its benefits are offset by an increased risk of intracranial and extracranial major bleeding.[141]

Vena Cava Filters

Inferior vena cava filters are intended to prevent potentially fatal PE in patients with recent acute VTE. Although they continue to be used extensively for many indications,[142] vena cava filters are best reserved for patients with confirmed recent (<1 month) acute VTE and an absolute contraindication to therapeutic anticoagulation (**Figure 3**).[41,42,79,80] However, efficacy and safety data on the use of filters in these patients are sparse. Retrievable filters are preferred over permanent filters and should be removed once the patient can be anticoagulated.[80]

Elastic Compression Stockings

Although smaller studies suggest up to a 50% reduction in post-thrombotic syndrome,[143] the large, placebo controlled SOX trial showed no benefit associated with elastic compression stockings worn during 2 years.[144] Hence at present, current practice guidelines do not suggest routine use of elastic compression stockings for the prevention of post-thrombotic syndrome in patients with DVT.[51,79,80] However, compression stockings might be used to relieve leg swelling and discomfort, and to treat post-thrombotic syndrome.[12,145]

PREVENTION

Appropriate and timely use of measures to prevent VTE (hereafter referred to as thromboprophylaxis) in patients at risk for VTE are imperative in reducing its global burden. Pharmacological thromboprophylaxis is generally warranted in patient groups in whom the risk of VTE is higher than the risk of bleeding, such as patients undergoing major orthopaedic or cancer surgery.[146] Individual risk assessment should be done in patient groups in whom the risk of VTE is too low (<1%) to justify thromboprophylaxis in every patient.[147] Examples include patients hospitalised for acute medical illness, patients with cancer, and pregnant women.

In people requiring thromboprophylaxis, pharmacological interventions are recommended in the absence of contraindications to anticoagulants at prophylactic dose.[90,91,104,146,148] Elastic compression stockings or intermittent pneumatic compressive devices might be considered when anticoagulation is contraindicated,[146,149] but their addition to pharmacological thromboprophylaxis in patients at moderate or high risk of VTE might not be beneficial.[150] The risk–benefit ratio and contraindications to anticoagulation should be reassessed periodically to determine whether the need, the duration, and the choice of thromboprophylaxis

remains appropriate.[149]

Following total knee or hip arthroplasty, low-dose aspirin after an initial 5 days of rivaroxaban (10 mg once daily) can be used as an alternative to thromboprophylaxis with DOACs in patients without cancer, severe obesity, known thrombophilia, or a history of VTE.[31,146,151,152] Improvements in surgical and anaesthetic management with subsequent shorter duration of hospital stay have reduced the incidence of VTE following orthopaedic surgery.[152] Although extended pharmacological thromboprophylaxis up to 35 days is currently recommended in all patients following total knee or hip arthroplasty, further studies to identify patients who might require a shorter duration of thromboprophylaxis are needed.[152]

The risk of VTE in ambulatory patients with cancer can be assessed using the Khorana score (**Appendix Table S**);[153] in those patients with cancer who have an intermediate-to-high risk of VTE and are starting chemotherapy, apixaban (2.5 mg twice daily) and rivaroxaban (10 mg once daily) compare favourably with placebo in terms of a net risk of VTE and major bleeding,[154,155] and are therefore suggested in patients without drug–drug interactions or a high risk of bleeding.[90,91,93,156] Similarly, in patients with solid tumours who have a high risk of VTE, thromboprophylaxis with LMWH can be considered.[93,157]

Clinical guidelines with strong recommendations for thromboprophylaxis in key populations are outlined in the **Appendix Table S**, and further detail for various populations is discussed elsewhere.[78,90,91,104,146–149]

Global audits reveal that thromboprophylaxis is prescribed inappropriately.[158–160] Preprinted orders, education, and human or computer-based alerts, as well as multifaceted approaches combining different strategies aimed at system-wide implementation have been

proposed to increase the appropriate use of thromboprophylaxis, particularly in hospitalised patients.[161] Strategies incorporating alerts are the most effective in improving rates of thromboprophylaxis and appear to decrease the incidence of symptomatic VTE.[161]

FUTURE DIRECTIONS

New insights into the pathophysiological mechanisms of venous thrombosis have enhanced our understanding of VTE. Advances in diagnostic, therapeutic, and prophylactic strategies have enabled a more individualised approach to patient care, and additional research addressing important clinical questions is ongoing. For example, whether strategies similar to the age--adjusted or pretest probability-adjusted D-dimer can also improve the diagnostic workup of suspected DVT is under investigation (NCT02384135; NCT02038530). Ongoing clinical trials comparing the safety of different DOACs for initial treatment (NCT03266783), and different doses of these drugs for extended treatment of VTE (NCT03285438) will shed light on the optimal choice of anticoagulant. Results from ongoing evaluations (NCT01455818; NCT04263038) of the safety of withholding anticoagulation in patients with sub-segmental PE are awaited to guide management. Decisions regarding the duration of treatment urgently require a standardised approach to assess the risk of major bleeding. Finally, the advent of DOACs has expanded anticoagulant options for the treatment and prevention of VTE; however, bleeding remains the major adverse effect. Therefore, the search for safer anticoagulants continues[162] and initial results on efficacy and safety of drugs that inhibit factor XIa in preventing VTE appear encouraging.[163,164]

Contributors

FK and TT did the literature search and contributed equally to this manuscript. All authors contributed to planning, writing, and revising of the manuscript and approved its final version for submission. The corresponding author had final responsibility for the decision to submit for publication.

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Panel 1. Risk factors for venous thromboembolism

Risk factors are classified as strong or weak and as transient or persistent based on the International Society on Thrombosis and Haemostasis categorization of venous thromboembolism (VTE).[18]

Strong risk factors

Persistent

- Active cancer
- Antiphospholipid syndrome

Transient

- Antiphospholipid syndrome
- Caesarean section
- Heparin-induced thrombocytopenia
- Hospitalisation for acute illness
- Major trauma or fracture
- Prolonged immobility (e.g., bedridden >3 days)
- Surgery >30 minutes

Weak risk factors

Persistent

- Chronic inflammatory disorders
- Nursing home confinement
- Obesity
- Personal or family history of VTE
- Pacemaker placement

Transient

- Nursing home confinement
- Obesity
- Brief immobility (e.g., travel >4 hours)
- Oestrogen therapy
- Infection
- Minor trauma or fracture
- Pacemaker placement
- Pregnancy or puerperium
- Surgery <30 minutes
- Venous catheterization

Panel 2. Criteria of suggested new diagnostic strategies to exclude pulmonary embolism without imaging

Imaging is required in all patients with suspected pulmonary embolism (PE) who do not satisfy these criteria. If clinicians prefer to use a single strategy, the age-adjusted D-dimer strategy using the revised Geneva score might be favored, because the age-adjusted D-dimer strategy is the most extensively validated strategy[66,70] and the revised Geneva score does not incorporate the subjective criterion 'PE is the most likely diagnosis',[56] upon which both the Wells score[54] and the YEARS strategy[58] rely heavily.

Age-adjusted D-dimer strategy[70]

- Recommended in all outpatients with suspected PE
- Clinical pretest probability unlikely as per the Wells score or the revised Geneva score for PE and D-dimer level <age-adjusted threshold, which is is defined as 500 µg/L in patients aged ≤50 years, and as 10 times the patient's age in those >50 years

YEARS strategy[58]

- Recommended in all outpatients with suspected PE
- Requires D-dimer testing for all patients; if D-dimer testing is not readily available, the age-adjusted strategy is preferred over the YEARS strategy in patients with a likely clinical pretest probability
- 1-3 YEARS criteria present and D-dimer <500 µg/L
- 0 YEARS criteria present and D-dimer <1000 µg/L

PEGeD strategy[71]

- Suggested for outpatients settings with a low prevalence (<10%) of PE
- Wells score for PE ≤4 points and D-dimer <1000 µg/L
- Wells score for PE 4.5-6 points and D-dimer <500 µg/L

Table. Scores to assess clinical probability of venous thromboembolism.

	Points
Wells score for deep vein thrombosis (DVT)[52,53]	
Active cancer	+1
Paralysis, paresis, or recent plaster cast on lower extremities	+1
Recent immobilisation >3 days or major surgery within the past 4 weeks	+1
Localised tenderness of deep venous system	+1
Swelling of entire leg	+1
Calf swelling >3 cm compared with asymptomatic side	+1
Unilateral pitting oedema	+1
Collateral superficial veins	+1
Previously documented DVT	+1
Alternative diagnosis at least as likely as DVT	-2
Clinical pretest probability	
Unlikely	Total score ≤2 (prevalence 4%)
Likely	Total score >2 (prevalence 27%)
Wells score for pulmonary embolism (PE)	
Original[54]	
Alternative diagnosis less likely than PE	+3
Clinical signs and symptoms of DVT	+3
Heart rate >100 beats per minute	+1.5
Previous DVT or PE	+1.5
Immobilisation or surgery within the past 4 weeks	+1.5
Active cancer	+1
Haemoptysis	+1
Clinical pretest probability	
Low	Total score ≤1 (prevalence 4%)
Intermediate	Total score 2-6 (prevalence 21%)
High	Total score >6 (prevalence 67%)
Unlikely	Total score ≤4 (prevalence 8%)
Likely	Total score >4 (prevalence 41%)
Simplified[55]	
Alternative diagnosis less likely than PE	+1
Clinical signs and symptoms of DVT	+1

Heart rate >100 beats per minute	+1
Previous DVT or PE	+1
Immobilisation or surgery within the past 4 weeks	+1
Active cancer	+1
Haemoptysis	+1
Clinical pretest probability	
Unlikely	Total score ≤1 (prevalence 11%)
Likely	Total score >1 (prevalence 36%)
Revised Geneva score for PE	
Original[56]	
Heart rate ≥95 beats per minute	+5
Heart rate 75–94 beats per minute	+3
Pain on lower-limb deep venous palpation and unilateral oedema	+4
Unilateral lower-limb pain	+3
Previous DVT or PE	+3
Active cancer	+2
Haemoptysis	+2
Surgery or fracture within the past 4 weeks	+2
Age >65 years	+1
Clinical pretest probability	
Low	Total score <4 (prevalence 9%)
Intermediate	Total score 4-10 (prevalence 28%)
High	Total score >10 (prevalence 72%)
Simplified[57]	
Heart rate ≥95 beats per minute	+2
Heart rate 75–94 beats per minute	+1
Pain on lower-limb deep venous palpation and unilateral oedema	+1
Unilateral lower-limb pain	+1
Previous DVT or PE	+1
Active cancer	+1
Haemoptysis	+1
Surgery or fracture within the past 4 weeks	+1
Age >65 years	+1

Clinical pretest probability	
Unlikely	Total score ≤2 (prevalence 13%)
Likely	Total score >2 (prevalence 42%)
YEARS criteria for PE[58]	
Clinical signs of DVT	+1
Haemoptysis	+1
PE is the most likely diagnosis	+1
Clinical pretest probability	
Low	Total score 0 (prevalence 3%)
High	Total score ≥1 (prevalence 23%)
Pulmonary Embolism Rule-Out Criteria* [59]	
Age <50 years	-
Heart rate <100 beats per minute	-
Pulse oximetry reading on room air >94%	-
No unilateral leg swelling	-
No hemoptysis	-
No recent trauma or surgery	-
No history of venous thromboembolism	-
No oral hormone use	-

Prevalence estimates correspond to emergency department settings.
*Pulmonary embolism (PE) can be considered excluded in patients with all Pulmonary Embolism Rule-Out Criteria and a low clinical pretest probability, assessed by gestalt, or in clinical settings with a low (<5%) prevalence of PE. If any criterion applies, PE cannot be ruled out in these patients.

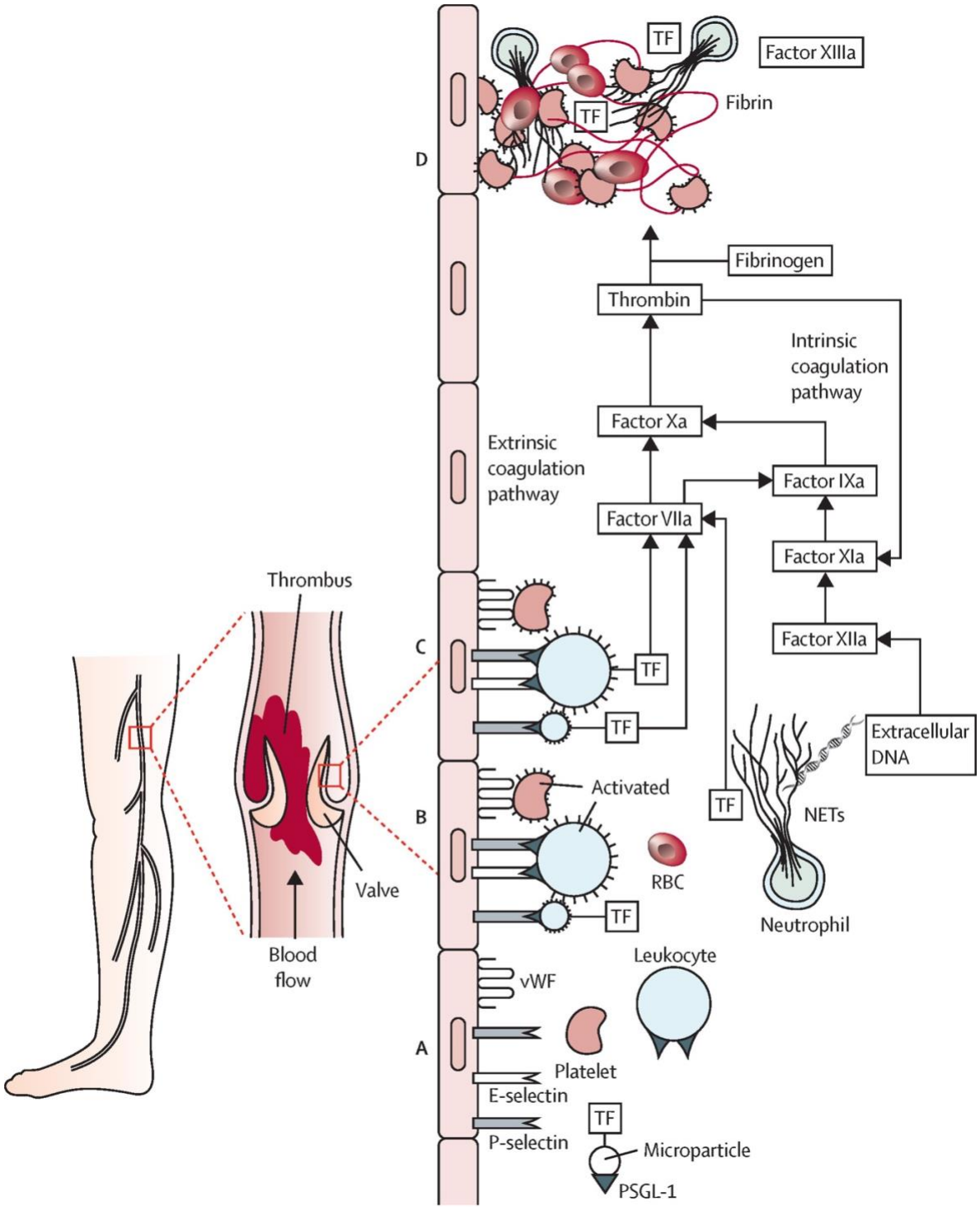

Figure 1: Proposed mechanism for development of venous thrombosis.

Pathophysiological mechanisms leading to thrombosis are traditionally explained by the Virchow's triad: stasis, vascular wall damage or dysfunction, and hypercoagulability. Venous

thrombi are thought to begin in the valve pockets of large veins, which are susceptible to blood stasis, particularly during prolonged immobilisation.[20] Stasis and vascular wall damage or dysfunction can lead to hypoxia or inflammation—processes that downregulate the natural anticoagulant properties of the endothelium and thereby induce a hypercoagulable state.[20] Activation of procoagulant venous endothelial cells leads to an increased expression of surface adhesion molecules such as P-selectin and von Willebrand factor (A) that facilitate subsequent binding of circulating leukocytes, microparticles, and platelets (B).[20] Activated leukocytes express the procoagulant tissue factor that is thought to initiate the extrinsic pathway of the coagulation cascade (the intrinsic [contact] pathway is activated via factors XII and XI), leading to the activation of factor X, production of thrombin (C), and culminating in the formation of thrombus comprising fibrin, red blood cells, and platelets (D).[20]

NETs=neutrophil extracellular traps. PSGL-1=P-selectin glycoprotein ligand-1. RBC=red blood cell. TF=tissue factor. vWF=von Willebrand factor

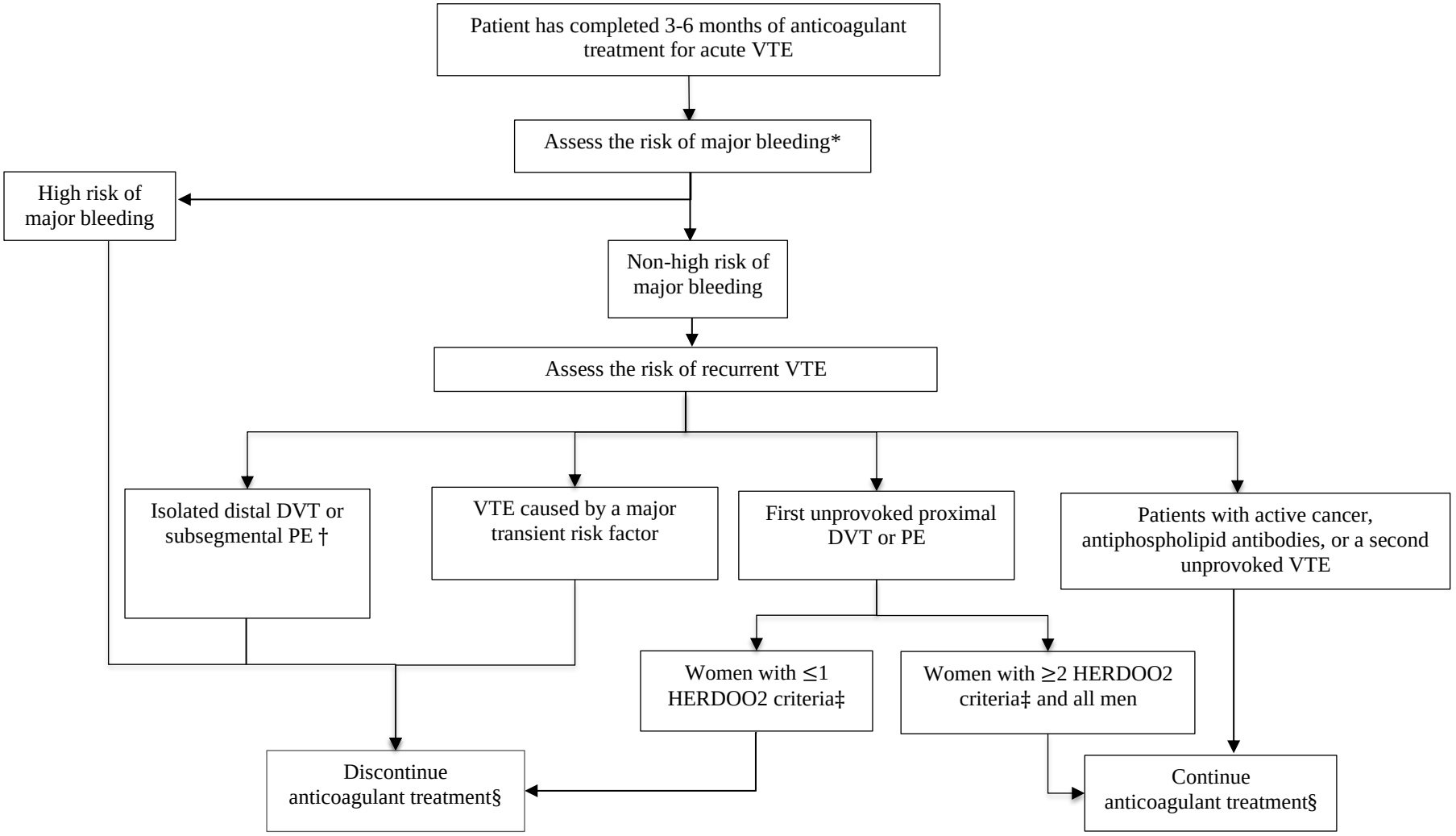

Figure 2: Approach to deciding the duration of anticoagulation for venous thromboembolism.

DVT=deep vein thrombosis. PE=pulmonary embolism. VTE=venous thromboembolism.
*Existing prediction scores for major bleeding have not yet been validated in prospective management cohort studies; the following

risk factors might independently predict the long-term risk of major bleeding: advanced age (e.g., >65 years), antiplatelet therapy, chronic renal impairment (creatinine clearance <50 mL/min), anaemia, and history of bleeding;[118] the presence of two or more of these risk factors is probably associated with a high (>2–3% annually) risk of major bleeding.[79,111,119] †Extended treatment is recommended in patients with cancer. ‡HERDOO2 criteria: hyperpigmentation, oedema, or redness in either leg; VIDAS D-dimer concentration of
250 μg/L or more measured while receiving anticoagulation therapy; obesity with body-mass index of 30 kg/m2 or more; or age ≥65 years. §Periodically reassess the balance between risks and benefits of discontinuing or continuing anticoagulant treatment, incorporating patient preferences.

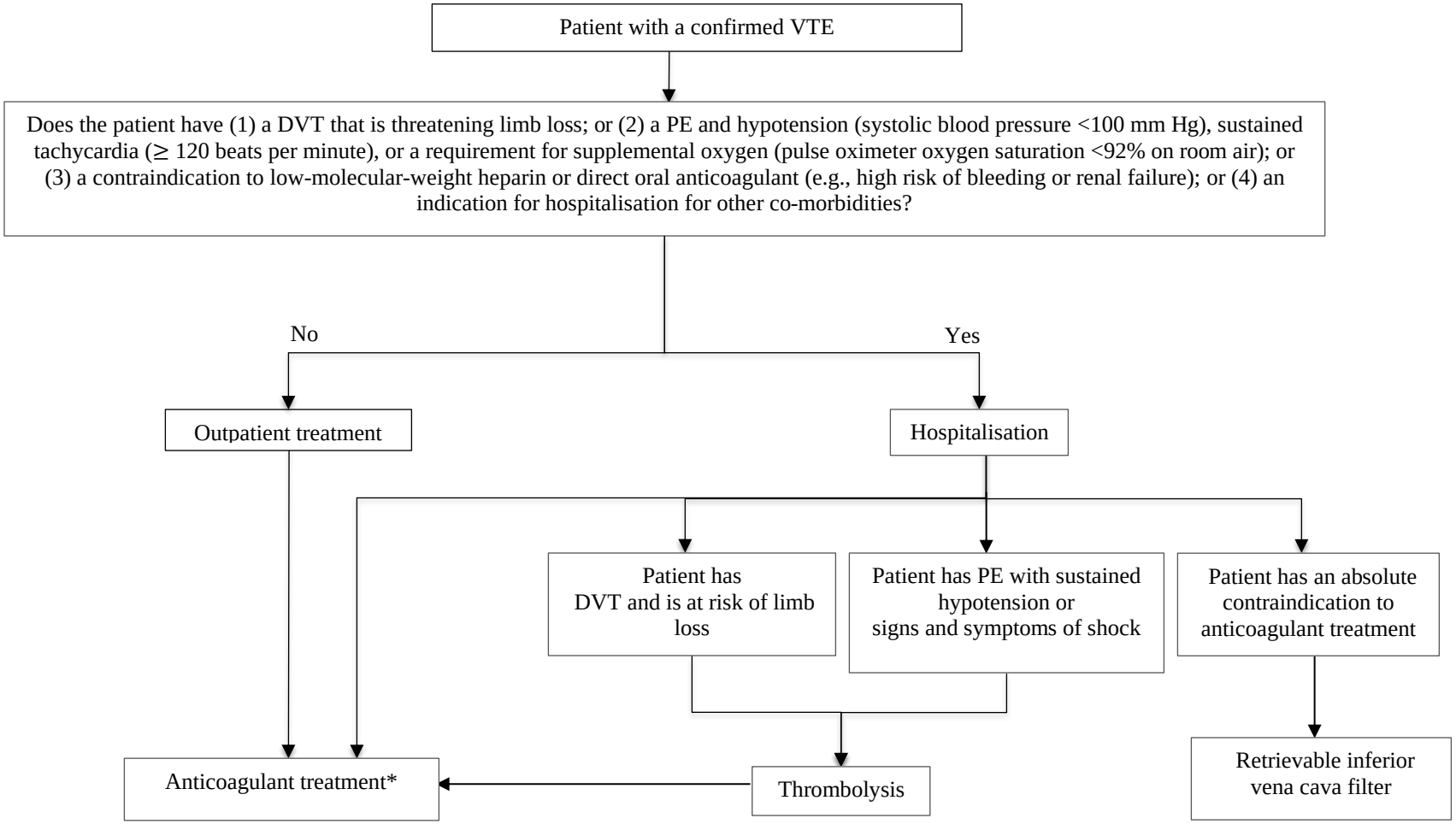

Figure 3: Approach to the initial treatment of venous thromboembolism

DVT=deep vein thrombosis. PE=pulmonary embolism. VTE=venous thromboembolism.
*Anticoagulation might be withheld in patients with isolated DVT or subsegmental PE without proximal DVT, who are at low risk of recurrent VTE (e.g., no cancer or ongoing immobilisation) or high risk of bleeding.

APPENDIX

Table S: Indications with strong recommendations from recent guidelines of thromboprophylaxis in key populations.

Population	Recommendations
Acutely ill hospitalized medical patients[148,149]	• Offer inpatient, rather than inpatient plus extended-duration outpatient thromboprophylaxis.
Cancer patients[90,91]	• Offer anticoagulant thromboprophylaxis to: - hospitalized patients with active cancer and an acute medical illness or reduced mobility. - patients undergoing major cancer surgery, starting preoperatively and for at least 7-10 days postoperatively. - patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone. • Offer extended anticoagulant thromboprophylaxis up to 4 weeks postoperatively to patients at high risk of venous thromboembolism (e.g., patients with reduced mobility, obesity, or history of venous thromboembolism) undergoing major open or laparoscopic abdominal or pelvic cancer surgery. • Offer/consider* anticoagulant thromboprophylaxis in outpatients at intermediate-to-high risk of venous thromboembolism as per the Khorana score†. • Do not offer anticoagulant thromboprophylaxis: - routinely to all outpatients with cancer. • to cancer patients admitted for the sole purpose of minor procedures or chemotherapy infusion, nor to patients undergoing stem-cell/ bone marrow transplantation.
Critically ill medical patients[147,148]	• Offer anticoagulant thromboprophylaxis.
Pregnant women[104]	• Offer antepartum anticoagulant thromboprophylaxis in women with a history of unprovoked or estrogen-associated venous thromboembolism. • Offer postpartum anticoagulant thromboprophylaxis in all women with a history of venous thromboembolism. • Offer postpartum antithrombotic thromboprophylaxis in women with a family history of venous thromboembolism who have antithrombin deficiency.
Surgical patients[146,149]	• Offer anticoagulant thromboprophylaxis:

	- to patients with fragility fractures of the pelvis, hip or proximal femur. - to patients undergoing elective hip or knee replacement surgery. • Offer mechanical thromboprophylaxis: - on admission to patients undergoing elective spinal surgery. - with intermittent pneumatic compression on admission to patients with serious or major trauma. - to patients undergoing bariatric surgery and add anticoagulant thromboprophylaxis in patients whose risk of venous thromboembolism outweighs their risk of bleeding. - to patients undergoing abdominal (gastrointestinal, gynaecological, or urological) surgery and add anticoagulant thromboprophylaxis in patients whose risk of venous thromboembolism outweighs their risk of bleeding. • Do not offer anticoagulant thromboprophylaxis to patients with ruptured cranial vascular malformations or patients with intracranial hemorrhage until the lesion has been secured or the condition has stabilized.

All recommendations apply only to patients who are not already receiving long-term anticoagulation.

* The strength of this recommendation varies from conditional to strong across the considered guidelines.

† Patients with pancreatic, stomach, or brain cancer as well as those with at least 2 of the following have an intermediate-to-high risk of VTE: high risk cancer type (lung, lymphoma, gynecologic, bladder, testicular, myeloma, kidney); a pre-chemotherapy platelet count ≥350 $\times 10^9$/L; a hemoglobin <100 g/L or use of red blood cell growth factors; a pre-chemotherapy leukocyte count >11 $\times 10^9$/L; and a body mass index ≥35 kg/m^2.

CHAPTER 3

Risk of Major Bleeding During Extended Oral Anticoagulation in Patients with First Unprovoked Venous Thromboembolism

A Systematic Review and Meta-Analysis Protocol

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https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/s13643-019-1175-5

Preface to Chapter 3

This Chapter details the rationale and planned methodology for a systematic review and meta-analysis aimed to quantify the risk for major bleeding events during extended oral anticoagulation in patients with a first unprovoked venous thromboembolism. The author contributions are outlined on page 70.

ABSTRACT

Background: The optimal duration of anticoagulation after a first unprovoked venous thromboembolism (VTE) remains controversial. Deciding to stop or continue anticoagulant therapy indefinitely after completing 3 to 6 months of initial treatment requires balancing the long-term risk of recurrent VTE if anticoagulation is stopped against the long-term risk of major bleeding if anticoagulation is continued. However, knowledge of the long-term risk for major bleeding events during extended anticoagulation in this patient population is limited. We plan to conduct a systematic review and meta-analysis to quantify the risk for major bleeding events during extended oral anticoagulation in patients with first unprovoked VTE.

Methods: Electronic databases including MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials will be systematically searched with the assistance of an information specialist (from inception to March 1, 2019) to identify randomized controlled trials and prospective cohort studies reporting major bleeding during extended oral anticoagulation in patients with first unprovoked VTE, who have completed at least 3 months of initial anticoagulant therapy. Study selection, risk of bias assessment and extraction will be performed independently by at least two investigators. The number of major bleeding events and person-years of follow-up will be used to calculate the rate (events per 100 person-years) with its 95% confidence interval for each study cohort, during clinically relevant time periods of extended anticoagulant therapy. Results will be pooled using random-effects meta-analysis.

Discussion: The planned systematic review and meta-analysis will provide reliable estimates of the risk for major bleeding events during extended anticoagulation. This information will help inform patient prognosis and assist clinicians with balancing the risks and benefits of treatment to guide management of unprovoked VTE.

Systematic review registration: PROSPERO CRD42019128597

INTRODUCTION

Venous thromboembolism (VTE), defined as deep vein thrombosis (DVT) or pulmonary embolism (PE), is a common, potentially fatal, yet treatable condition. Anticoagulation is the mainstay of VTE treatment and is divided into 3 phases: the initial phase (first 5 to 10 days after diagnosis), the long-term phase (from initial phase to 3-6 months), and the extended phase (beyond 3-6 months).[1] Anticoagulant therapy for at least 3 months is recommended in all patients with acute VTE.[1] Thereafter, balancing the long-term risk of recurrent VTE, defined by etiology of the VTE and the presence of persistent risk factors, against the long-term risk of major bleeding from anticoagulation informs treatment duration. Etiology of VTE is defined as provoked or unprovoked.[2] Patients with an unprovoked event have a high risk of recurrent VTE after discontinuation of anticoagulation (10% after 1 year, 36% after 10 years).[3] Therefore, the 2016 American College of Chest Physicians and the 2014 European Society of Cardiology guidelines both suggest indefinite anticoagulation in patients with unprovoked VTE, unless they have a high risk of bleeding.[1,4]

A previous meta-analysis by Linkins and colleagues[5] reported a major bleeding rate of approximately 3% per year during extended anticoagulation. However, the analysis was based on a heterogeneous population of VTE patients (i.e., mix of provoked and unprovoked VTE), and the duration of extended anticoagulation in most included studies was limited to 3 months (i.e., 6 months of total treatment duration). To inform the decision on whether patients with a first unprovoked VTE should continue anticoagulation indefinitely, understanding the *long-term* risk of major bleeding on extended anticoagulation is crucial.

Since the publication of the meta-analysis by Linkins et al. in 2003, numerous prospective studies involving patients with a first unprovoked VTE have reported on the risk of major bleeding during extended anticoagulation with patient follow-up lasting beyond 3 months and up

to a maximum follow-up of 4 years.[6] This provides the opportunity to summarize and establish reliable and precise estimates of the *long-term* risk of major bleeding on extended oral anticoagulant therapy in patients with first unprovoked VTE.

OBJECTIVE

The aim of this systematic review and meta-analysis is to determine and quantify the rate of major bleeding events during extended oral anticoagulation in patients with a first unprovoked VTE, who have completed at least 3 months of initial treatment.

METHODS

This protocol was developed following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) Statement,[7] and is registered in the PROSPERO international register of prospective systematic reviews database (CRD42019128597). Any modifications made to the study methods during conduct of the review will be reported and justified in the publication of the final report. The final publication will be reported according to guidance from the PRISMA statement.[8]

Eligibility Criteria

Studies meeting the following criteria will be included in the systematic review.

Population

The targeted group of participants will be adults with a first episode of objectively confirmed, symptomatic major VTE (proximal DVT or PE) that is either unprovoked or provoked by minor transient risk factors, according to the International Society on Thrombosis and Haemostasis (ISTH) definition[2]. Patients will be eligible if they have received treatment with an approved oral anticoagulant therapy, continued for a minimum of six additional months beyond completion of 3

months of anticoagulation with either 1) intravenous heparin or LMWH for 3 months; or 2) intravenous heparin or low molecular weight heparin (LMWH) for at least 5 days followed by dabigatran, edoxaban, or a vitamin K antagonist; or 3) apixaban or rivaroxaban. Studies will be excluded if they only include patients with VTE associated with major transient and/or persistent provoking risk factors according to the ISTH definition[2].

Interventions and Comparators

The review will include studies wherein participants have received treatment with an approved oral anticoagulant therapy, continued for a minimum of six additional months beyond completion of 3 months of anticoagulation. As the study objective is to establish the rate of major bleeding during extended anticoagulation, a comparator is not applicable. As such, all studies, including each arm of a randomized controlled trial (RCT), will be evaluated as an independent observational cohort, with follow-up starting at the time that oral anticoagulants are continued for secondary prevention (i.e., beyond completion of at least 3 months of *initial* treatment).

Outcome

The primary outcome will be the rate of major bleeding (as defined by the ISTH[9]) on extended oral anticoagulation.

Study Design

Studies eligible for this systematic review will consist of both RCTs and prospective cohort studies. Case reports, case series, case-control or cross sectional studies, as well as retrospective cohort and registry-based studies, will be excluded.

Search Strategy

In conjunction with an information specialist, electronic databases including MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials will be systematically searched

(from inception to March 01, 2019) with no language restrictions. Search terms will be related to VTE, major bleeding, anticoagulants, and study design. We will use medical subject heading (MeSH) terms. We will supplement our search with keywords and adjust vocabulary and syntax across databases. The search strategy for EMBASE and MEDLINE was reviewed by an information specialist and is presented in **Table 1** and **Table 2**, respectively. Reference lists of retrieved articles will be hand-searched to identify additional relevant studies, while grey literature will not be considered.

Data Management and Selection Process

Results from the literature search will be uploaded to Covidence.[10] Screening of titles/abstracts as well as full-text articles will be performed by at least two independent investigators of the review team. Discrepancies will be resolved by consensus discussion or by a third person if needed. The process of study selection will be presented using the PRISMA flow diagram.[8] In the case of published reports including duplicate patients, only the publication with the longest follow-up of patients will be included.

Data Collection

Data from included studies will be collected using a standardized data extraction form. Data extraction will be conducted by at least two reviewers independently, with clarifications requested from the study's authors when necessary. A third person will verify a subset of the studies to ensure accurate data collection. The standardized data extraction form will be piloted by two reviewers independently for the first five full-text articles. After comparing the results of the pilot phase for data extraction, further changes will be made to the standardized data extraction form, if needed. Disagreements between reviewers will be resolved by consensus or by

a third person if required.

We will collect the following information from included studies:

a) Study information: year of study publication, author, and journal information
b) Study characteristics: design, period, country(ies), funding source, and criteria used to define VTE and its etiology.
c) Participant characteristics: number of eligible patients, number of eligible male patients, mean age, site of initial VTE, type and dose of anticoagulant used during the initial treatment period, person-years of follow-up, and number of patients lost to follow-up.
d) Intervention characteristics: type and dose of anticoagulant agent used during the extended treatment period.
e) Outcomes: major, clinically relevant non-major, intracranial and fatal bleeding (as defined by the ISTH or by individual studies), as well as recurrent VTE and recurrent fatal PE. Each study's chosen definition of bleeding outcomes will be rigorously documented.

Outcomes and Prioritization

The primary outcome will be the rate of major bleeding during extended oral anticoagulation. Major bleeding is a patient-relevant outcome and the primary safety outcome of all recent phase III anticoagulation trials.[11] Secondary outcomes will include the rate of clinically relevant non-major bleeding, intracranial bleeding, fatal bleeding, recurrent VTE and fatal recurrent PE during extended oral anticoagulation. We will also calculate the case-fatality rate of major bleeding and recurrent VTE during extending anticoagulation, from the total number of fatal (bleeding and recurrent PE events) divided by the total number of major bleeding and recurrent VTE events, respectively. Bleeding outcomes will be defined as per ISTH definition[9] for the primary analysis, and secondary analysis will include bleeding outcomes as defined by the individual studies.

These secondary outcomes were chosen because of their clinical relevance and importance in assessing the net clinical benefit of extended anticoagulation.

Risk of Bias Assessment

At least two reviewers will independently assess the risk of bias at the individual study level. For a subset of studies, a third reviewer will verify the accuracy of the risk of bias assessment done by the first two reviewers. Conflicts will be resolved by consensus or by a third reviewer if needed. Given each arm of a RCT will be evaluated as an independent observational cohort, the risk of bias for each study will be assessed using the Newcastle-Ottawa scale for prospective cohort studies.[12]

Data Synthesis

The rate (expressed as events per 100 person-years) of the primary and secondary outcomes will be calculated from each observational cohort from the number of events and person-years of follow-up. If feasible from the available data, these rates will be calculated and reported at standardized time intervals during extended anticoagulation (i.e. at 6, 12, 18, 24, 36, 60, and 120 months following completion of the *initial* 3- to 6-month period of anticoagulation) to account for the different lengths of follow up from each study. To assess clinical and statistical heterogeneity, we will compare study design, patients' characteristics, and studied interventions of included studies prior to pooling results. Statistical heterogeneity will be measured using Cochrane's Q (statistically significant at $p<0.10$) and the I^2 statistic (>75% considered to represent high heterogeneity).

If pooling is deemed appropriate, we will combine the total number of major bleeding events and person-years of follow up across all included study cohorts to calculate a weighted

estimate of the absolute rate of major bleeding per 100 person-years of follow up. If and when possible, this pooled rate will be calculated for each of the standardized time periods defined above. Furthermore, the cumulative incidence of major bleeding events at each of the standardized time intervals will be estimated from the absolute rate of major bleeding events at each time period, if feasible from the available data. These analyses will be repeated for all secondary outcomes. A random effects model will be used for data synthesis due to the expected diversity of the studied interventions.

All analyses for the meta-analysis will be performed using StatsDirect version 3 (Cheshire, United Kingdom) software.[13]

Planned sensitivity analyses

Sensitivity analyses will be undertaken to establish the robustness of primary findings. We will perform the following sensitivity analyses excluding study cohorts whose event rates are outliers, as well as excluding studies judged to be at high risk of bias. Estimates from overall and sensitivity analyses will be compared to gauge the impact of potential heterogeneity and biases on the primary results.

Planned subgroup analyses

If feasible from the available data, subgroup analyses will be performed based on the study design (i.e., cohorts derived from RCTs versus prospective observational studies), type of anticoagulation used for extended treatment, and patient characteristics. Several patient characteristics of interest were previously shown to be associated with bleeding in VTE patients receiving anticoagulation or used to define risk of recurrent VTE and case-fatality in this patient population. Accordingly, we will include the following characteristics: sex,[14-19] age (less than 65

years old and 65 years old or over),[1,20-22] prior major bleeding,[1,20-26] concomitant use of anti-platelet therapy,[1,20] anemia (i.e., hemoglobin less than 90, 100, 110, 120, and 130g/L),[23-27] creatinine clearance less than 30, 50 and 60 mL/min,[1,28] and site of initial VTE event (i.e., isolated proximal DVT, isolated PE, or DVT and PE).[29] Findings from all analyses will be presented in the final report.

Meta-Bias Assessment

Meta-bias will be assessed through the use of funnel plots to evaluate potential reporting bias if applicable. Additionally, we will compare random effect estimates to fixed effect estimates to evaluate whether small sample bias is present. Finally, selective outcome reporting will be assessed by comparing the reported outcome from the included studies to their published protocol, where available.

DISCUSSION

In this systematic review and meta-analysis, we aim to provide reliable estimates regarding the risk of major bleeding events at clinically relevant time points during extended anticoagulation in patients with a first unprovoked VTE. This knowledge will inform clinical practice guidelines, and help clinicians and patients balance the risks and benefits of anticoagulation to guide treatment duration.

Abbreviations: DVT: Deep vein thrombosis; PE: Pulmonary embolism; PRISMA: Preferred reporting items for systematic reviews and meta-analysis; PRISMA-P: Preferred reporting items for systematic reviews and meta-analysis protocols; ISTH: International Society on Thrombosis and Haemostasis; LMWH: Low-molecular-weight heparin; RCT: Randomized controlled trial; VTE: Venous thromboembolism.

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Authors' contributions: FK, MK, and TT contributed equally to this work. **FK**, MK, TT, and MAR conceived the idea and design for this systematic review. **FK**, MK, TT, BH, DAF, and MAR developed the methodology for the systematic review protocol. The contents of this manuscript were drafted by **FK**, MK, TT with input from all members of the authorship team.

The manuscript was reviewed by GLG, BH, DAF and MAR for important intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials: Not applicable.

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Competing interests: TT reports receiving travel and congress fees from Pfizer**.** GLG reports other support from Portola Pharmaceuticals, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, LEO Pharma, Daiichi Sankyo, Bayer, Sanofi, and bioMerieux outside the submitted work. BH reports receiving honoraria from Cornerstone Research Group for provision of methodologic advice related to systematic reviews and meta-analysis. MAR reports receiving research support from Biomerieux, outside of the submitted work. **FK**, MK and DAF declare that they have no relevant competing interests.

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Table 1: EMBASE Search Strategy

No.	Searches
1	Venous Thrombosis/
2	(ven* adj2 thrombos*).ti,ab.
3	Deep Vein Thrombosis/
4	(deep adj3 thrombos*).ti,ab.
5	Pulmonary Embolism/
6	(pulmonary adj2 embolism*).ti,ab.
7	Venous Thromboembolism/
8	(ven* adj2 thromboembolism*).ti,ab.
9	Recurrent Venous Thromboembolism/
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	secondary prevention/
12	secondary prevention*.ti,ab.
13	(relapse adj2 prevention*).ti,ab.
14	(extended adj2 therap*).ti,ab.
15	11 or 12 or 13 or 14
16	Hemorrhage/
17	(hemorrhag* or haemorrhag*).ti,ab.
18	16 or 17
19	Anticoagulants/
20	Antithrombins/
21	(anticoagulant* or anti-coagulant* or antithrombin* or anti-thrombin*).tw.
22	(thrombin adj3 inhibit*).tw.
23	(Factor Xa adj2 (antagonist? or inhibit* or block*)).tw.
24	heparin/ or exp heparin, low-molecular-weight/
25	(heparin* or beparine or clarin or contusol or disebrin or eleparon or elheparin or elheparon or epiheparin or gag 98 or helberina or hepaflex or hepalean or heparitin* or hepcon or hepsal or inhepar or inviclot or lipo-hepin or lipohepin or liquemin or liquemine or menaven or monoparin or mucoitin or multiparin or nevparin or noparin or panheparin or panhepin or panheprin or parinix or praecivenin or pularin or thromb*or niparin or vetren or vaster).tw.
26	liquaemin.tw.
27	dalteparin*.tw.
28	fragmin*.tw.
29	enoxaparin*.tw.
30	clexane.tw.
31	lovenox.tw.
32	fraxiparin*.tw.
33	nadroparin*.tw.
34	Warfarin/
35	(warfarin or warfant or tedicumar or savaysa or endoxaban or befarin or adoisine or carfin or circuvit or coumadan or coumafene or coumaphene or dagonal or tintorane or uniwarfin or waran or warfar or warnerin or farin or jantoven or

	kumatox or maforan or orfarin or panwarfarin or panwarfin or prothromadin or warfil* or sofarin).tw.
36	coumadin*.tw.
37	aldocumar.tw.
38	marevan.tw.
39	(Vitamin K adj2 (antagonist? or inhibit* or block*)).tw.
40	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
42	RETRACTED ARTICLE/
43	or/41-42
44	(animal$ not human$).sh,hw.
45	(book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/
46	(random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/
47	43 not (44 or 45 or 46)
48	exp cohort analysis/
49	exp longitudinal study/
50	exp prospective study/
51	exp follow up/
52	cohort$.tw.
53	or/48-52
54	47 or 53
55	10 and 15 and 18 and 40 and 54
56	10 and 18 and 40 and 54

Table 2: MEDLINE Search Strategy

No.	Searches
1	exp Venous Thrombosis/
2	(ven* adj2 thrombos*).ti,ab.
3	exp Deep Vein Thrombosis/
4	(deep adj3 thrombos*).ti,ab.
5	exp Pulmonary Embolism/
6	(pulmonary adj2 embolism*).ti,ab.
7	Venous Thromboembolism/
8	(ven* adj2 thromboembolism*).ti,ab.
9	Recurrent Venous Thromboembolism/
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	secondary prevention/
12	secondary prevention*.ti,ab.
13	(relapse adj2 prevention*).ti,ab.
14	(extended adj2 therap*).ti,ab.
15	11 or 12 or 13 or 14
16	exp Hemorrhage/
17	(hemorrhag* or haemorrhag*).ti,ab.
18	16 or 17
19	Anticoagulants/
20	Antithrombins/
21	(anticoagulant* or anti-coagulant* or antithrombin* or anti-thrombin*).tw.
22	(thrombin adj3 inhibit*).tw.
23	(Factor Xa adj2 (antagonist? or inhibit* or block*)).tw.
24	heparin/ or exp heparin, low-molecular-weight/
25	(heparin* or beparine or clarin or contusol or disebrin or eleparon or elheparin or elheparon or epiheparin or gag 98 or helberina or hepaflex or hepalean or heparitin* or hepcon or hepsal or inhepar or inviclot or lipo-hepin or lipohepin or liquemin or liquemine or menaven or monoparin or mucoitin or multiparin or nevparin or noparin or panheparin or panhepin or panheprin or parinix or praecivenin or pularin or thromb*or niparin or vetren or vaster).tw.
26	liquaemin.tw.
27	dalteparin*.tw.
28	fragmin*.tw.
29	enoxaparin*.tw.
30	clexane.tw.
31	lovenox.tw.
32	fraxiparin*.tw.
33	nadroparin*.tw.
34	Warfarin/
35	(warfarin or warfant or tedicumar or savaysa or endoxaban or befarin or adoisine or carfin or circuvit or coumadan or coumafene or coumaphene or dagonal or tintorane or uniwarfin or waran or warfar or warnerin or farin or jantoven or

	kumatox or maforan or orfarin or panwarfarin or panwarfin or prothromadin or warfil* or sofarin).tw.
36	coumadin*.tw.
37	aldocumar.tw.
38	marevan.tw.
39	(Vitamin K adj2 (antagonist? or inhibit* or block*)).tw.
40	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41	randomized controlled trial.pt.
42	controlled clinical trial.pt.
43	random allocation.sh.
44	double-blind method.sh.
45	single-blind method.sh.
46	41 or 42 or 43 or 44 or 45
47	clinical trial.pt.
48	(clin$ adj25 trial$).ti,ab.
49	(singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
50	placebos.sh.
51	placebo$.ti,ab.
52	random$.ti,ab.
53	research design.sh.
54	exp cohort studies/
55	cohort$.tw.
56	controlled clinical trial.pt.
57	epidemiologic methods/
58	48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57
59	46 or 58
60	10 and 15 and 18 and 40 and 59
61	10 and 18 and 40 and 59

CHAPTER 4

Long-Term Risk for Major Bleeding During Extended Oral Anticoagulant Therapy for First Unprovoked Venous Thromboembolism

A Systematic Review and Meta-analysis

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Preface to Chapter 4

This Chapter presents the results of the systematic review and meta-analysis designed in Chapter 3. The aims of this study were to determine the incidence of major bleeding (including intracranial and fatal bleeding) among patients with a first unprovoked venous thromboembolism (VTE) that are receiving extended anticoagulation (up to 5 years) with direct oral anticoagulants or vitamin K antagonists. The case-fatality rate of major bleeding as well as differences in bleeding risk based on sex, age, site of initial VTE, kidney function, history of bleeding, concomitant use of antiplatelet therapy, level of anemia, and study design were also determined. The author contributions are outlined on page 98 and the study appendix starts on page 110.

ABSTRACT

Background: The long-term risk for major bleeding in patients receiving extended (beyond the initial 3 to 6 months) anticoagulant therapy for a first unprovoked venous thromboembolism (VTE) is uncertain.

Purpose: To determine the incidence of major bleeding during extended anticoagulation of up to 5 years among patients with a first unprovoked VTE, overall, and in clinically important subgroups.

Data Sources: MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials from inception to 23 July 2021.

Study Selection: Randomized controlled trials (RCTs) and prospective cohort studies reporting major bleeding among patients with a first unprovoked VTE who were to receive oral anticoagulation for a minimum of 6 additional months after completing at least 3 months of initial anticoagulant treatment.

Data Extraction: Two reviewers independently abstracted data and assessed study quality. Unpublished data required for analyses were obtained from authors of included studies.

Data Synthesis: Among the 14 RCTs and 13 cohort studies included in the analysis, 9982 patients received a vitamin K antagonist (VKA) and 7220 received a direct oral anticoagulant (DOAC). The incidence of major bleeding per 100 person-years was 1.74 events (95% CI, 1.34 to 2.20 events) with VKAs and 1.12 events (95% CI, 0.72 to 1.62 events) with DOACs. The 5-year cumulative incidence of major bleeding with VKAs was 6.3% (95% CI, 3.6% to 10.0%). Among patients receiving either a VKA or a DOAC, the incidence of major bleeding was statistically significantly higher among those who were older than 65 years or had creatinine clearance less than 50 mL/min, a history of bleeding, concomitant use of antiplatelet therapy, or a hemoglobin level less than 100 g/L. The case-fatality rate of major bleeding was 8.3% (95% CI, 5.1% to

12.2%) with VKAs and 9.7% (95% CI, 3.2% to 19.2%) with DOACs.

Limitation: Data were insufficient to estimate incidence of major bleeding beyond 1 year of extended anticoagulation with DOACs.

Conclusion: In patients with a first unprovoked VTE, the long-term risks and consequences of anticoagulant-related major bleeding are considerable. This information will help inform patient prognosis and guide decision making about treatment duration for unprovoked VTE.

INTRODUCTION

Venous thromboembolism (VTE) is a major contributor to the global burden of disease: The annual incidence of acute VTE is 1 to 2 cases per 1000 persons.[1,2] Most VTE episodes are classified as unprovoked or associated with minor transient risk factors (that is, weakly provoked; see **Appendix Table S1** for examples).[1,3] VTE should be treated with anticoagulant therapy for at least 3 to 6 months;[4-6] during this period, the risk for a potentially fatal recurrent VTE if treatment is discontinued clearly exceeds the risk for a potentially fatal major bleeding event associated with anticoagulation.[7,8] Deciding whether to continue anticoagulant therapy beyond the initial 3 to 6 months (termed extended anticoagulation) requires estimating the net balance between absolute treatment benefits and harms through careful consideration of the long-term risks and case-fatality rates of both recurrent VTE if anticoagulation is discontinued and major bleeding if anticoagulation is continued. This framework for decision making about treatment duration is most relevant to patients with a first unprovoked or weakly provoked VTE, for whom indefinite anticoagulation is often suggested,[3,9] but the net clinical benefit of extended anticoagulation is uncertain.

In a recent meta-analysis, we determined that the overall risk for recurrent VTE after discontinuation of anticoagulant therapy for a first unprovoked or weakly provoked VTE is 10% at 1 year and 36% at 10 years, with 4% of recurrent VTE events resulting in death.[10] Although the clinical benefits of extended anticoagulation are clear—more than 80% reduction in risk for recurrent VTE as long as treatment is continued[11,12]—estimates for counterbalancing absolute long-term risk for major bleeding during extended anticoagulation for a first unprovoked or weakly provoked VTE are not well established. This evidence gap makes it difficult to estimate the net balance between benefits and harms of extended anticoagulation, thereby hampering decision making about long-term management of this common patient population.

A previous systematic review and meta-analysis of randomized controlled trials (RCTs) and prospective cohort studies reported a major bleeding incidence of 2.74 events (95% CI, 2.71 to 2.77 events) per 100 per- son-years during extended anticoagulation with vitamin K antagonists (VKAs) in patients with VTE.[8] This estimate was based on 9 studies that included 2422 patients who received extended anticoagulation with VKAs beyond the initial 3 months of treatment.[8] However, the duration of extended anticoagulation in most of the 9 studies was limited to 3 additional months (that is, total treatment duration of 6 months), leaving an important knowledge gap about long-term bleeding risk.[8] Also, that meta-analysis[8] did not focus on patients with unprovoked VTE, did not provide bleeding risk estimates in clinically important subgroups or assess risk for major bleeding over time, and included only studies published up to May 2001. Since then, several prospective studies, some with an extended treatment duration of up to 5 years, and studies of direct oral anticoagulants (DOACs) have been published. Therefore, updated information about the potential harms of extended anticoagulant therapy is needed.

We formed the MAJESTIC (**MAJ**or bl**E**eding ri**S**k during ex**T**ended ant**IC**oagulation) collaboration to undertake a systematic review and meta-analysis, with the objective of determining the risk for major bleeding during extended anticoagulation of up to 5 years among patients with a first unprovoked VTE and in clinically important subgroups.

METHODS

This systematic review and meta-analysis was done in accordance with our study protocol, which was registered in PROSPERO (CRD42019128597) and has been published.[13] Our study is reported in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement.[14]

Search Strategy and Study Selection

In collaboration with an academic information specialist, we searched MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials from the date of inception to 23 July 2021 (search strategy for Embase is presented in **Appendix Table S2**). No language restrictions were applied, and content experts were consulted to identify other potentially eligible studies. Two reviewers (F.K. and T.T. or M.K.) independently screened titles, abstracts, and full-text articles. Disagreements were resolved by discussion or by consultation with a third reviewer (M.A.R. or G.L.G.).

Eligibility Criteria

Studies were eligible for inclusion if they met the following criteria: 1) were an RCT or a prospective cohort study; 2) included patients with a first symptomatic VTE that had been objectively confirmed and was categorized as either unprovoked or provoked by minor transient risk factors according to the definition from the International Society on Thrombosis and Haemostasis (ISTH) (**Appendix Table S1**); 3) had a treatment group that received an approved oral anticoagulant regimen (that is, apixaban, dabigatran, edoxaban, rivaroxaban, or VKA [international normalized ratio, 2.0 to 3.0]) for a minimum of 6 additional months beyond completion of at least 3 months of initial anticoagulation; and 4) reported major bleeding during extended anticoagulation. The publication with the longest follow-up was included when several articles reported on duplicate patient populations.

Outcomes

The primary outcome was a first major bleeding event, as defined by the ISTH criteria or by the individual studies. The ISTH criteria define major bleeding as overt bleeding that is associated with a decrease in hemoglobin concentration of at least 20 g/L, requires transfusion of at least 2

units of red blood cells or whole blood, occurs in a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or is fatal or contributes to death. Secondary outcomes were intracranial bleeding and fatal bleeding.

Data Extraction

Two reviewers (F.K. and T.T.) independently extracted the following data from each eligible study, with clarifications requested from the study's authors when necessary: study design, duration of initial anticoagulant treatment, maximum duration of follow-up and regimen during extended anticoagulation, definition of unprovoked VTE, and definition of major bleeding.

We contacted the principal investigators of each potentially relevant study to request aggregate data on number of bleeding events (major, intracranial, and fatal) and number of person-years (to ensure appropriate censoring of deaths, patients lost to follow-up, and patients withdrawn from the study) during extended anticoagulation, stratified by type of anticoagulant (VKA or DOAC, when applicable), among patients with a first unprovoked VTE (and within-study subgroups outlined in *Subgroup and Sensitivity Analyses*). Our requests to principal investigators also ensured that these aggregate data excluded major bleeding events that did not occur while patients were receiving extended anticoagulation and excluded patients who did not satisfy our eligibility criteria (for example, those who had cancer, had a history of VTE, or had not completed at least 3 months of initial anticoagulant treatment).

Risk-of-Bias Assessment

Because our objective was to determine the incidence of major bleeding during follow-up of patients receiving extended anticoagulation, we assessed each study, including each group of an RCT, as an independent observational cohort. As such, we used a modified version of the

Newcastle-Ottawa Scale[15] based on 3 selection and 3 outcome criteria, including whether a representative sample of eligible patients was included, the outcome of interest was not present at the start of patient follow-up, the outcome of interest was independently and blindly adjudicated, and follow-up was sufficiently long and complete. Criteria assessing comparability were considered irrelevant in the context of this systematic review and meta-analysis. Two reviewers (F.K. and T.T.) independently assessed risk of bias among the included studies for the primary outcome of major bleeding, and clarifications were requested from the study authors when necessary. Following quality assessment standards of previous meta-analyses,[10,16] we considered studies that scored at least 4 points on the modified Newcastle-Ottawa Scale to have low risk of bias.

Data Synthesis and Analysis

Primary Analysis

Using the numbers of events and person-years of follow-up acquired from the principal investigators of included studies, we calculated the incidence rate (expressed as events per 100 person-years) of a first major bleeding event in each study cohort. Unless heterogeneity was high, a random-effects model with the DerSimonian–Laird method was used to obtain pooled estimates of the incidence across all studies, and individual study cohorts were weighted according to their inverse variance.[17] We also calculated the incidence rate ratio (IRR) to statistically compare major bleeding rates between subgroups. A treatment group continuity correction was used if 1 or both subgroups of a study cohort had 0 events.

To assess bleeding risk over time, we categorized the incidence of major bleeding into the following 3 intervals of follow-up during extended anticoagulation: year 1, year 2, and years 3 to 5. Using our calculated incidence (based on exact person-time at risk during each of the studied intervals, obtained from authors of included studies), we estimated the 2- and 5-year cumulative

incidence of major bleeding as follows: We first estimated the cumulative proportion of patients who did not have major bleeding as the product of the proportion of patients who did not have major bleeding during each of the studied intervals; we then estimated the cumulative proportion of patients who had major bleeding as the complement of the cumulative proportion of patients who did not have major bleeding.[10] For example, the 5-year cumulative incidence of major bleeding was estimated as follows: If the incidence of major bleeding per 100 person-years was 2.0 events in the first year, 1.5 events in the second year, and 1.0 events in years 3 to 5, then the proportion of patients who did not have major bleeding in years 1 to 5 was estimated as $(98.0\%_{\text{year 1}}) \times (98.5\%_{\text{year 2}}) \times ([99.0\%]^{3}_{\text{years 3-5}}) = 93.7\%$. The proportion of patients who had major bleeding in years 1 to 5 was then estimated as 100% - 93.7% = 6.3%.

To estimate the lower and upper limits of the 95% CI for the cumulative incidence, we used the lower and upper limits of the incidence rates in the calculation described in the previous paragraph.

Finally, we calculated the case-fatality rate of major bleeding as the total (that is, during the entire follow-up period) number of fatal bleeding events divided by the total number of major bleeding events.

Heterogeneity between studies was assessed using the I^2 statistic; values of 75% or higher were interpreted as evidence of substantial heterogeneity.[18] All meta- analyses were done using StatsDirect, version 3.3.5 (StatsDirect).[19]

Subgroup and Sensitivity Analyses

To establish the long-term risk for major bleeding in clinically important subgroups, we did prespecified, within-study subgroup analyses based on the following patient characteristics: sex, age (>65 vs. ≤65 years), site of initial VTE (isolated proximal deep venous thrombosis [DVT] vs.

isolated pulmonary embolism [PE] vs. concomitant DVT and PE), creatinine clearance (<50 vs. ≥50 mL/min), his- tory of bleeding, concomitant use of antiplatelet therapy, and hemoglobin concentration (<100 vs. ≥100 g/L). We also did subgroup analyses according to study design (RCT vs. prospective cohort). Last, we did sensitivity analyses restricted to studies in which the duration of initial anticoagulant treatment was exclusively 3 months and those restricted to studies that used the ISTH definition of major bleeding.

Role of the Funding Source

The funding sources had no role in the study design, analysis, interpretation of data, writing of the manuscript, or decision to submit the manuscript for publication.

RESULTS

The systematic literature search identified 5219 records. After full-text review, 28 studies (supplemented with 9 additional studies identified from other sources) were considered potentially relevant for inclusion in the meta-analysis (**Figure 1**). After contacting the principal investigators of all 37 potentially relevant studies for further clarification of data, we deemed 9 studies[20-28] ineligible because they had the wrong patient population (**Appendix Table S3**). Among the remaining 28 studies deemed eligible for inclusion, data required for our analysis were obtained from 27 studies; [11,29-53] 1 study[54] was excluded because information required for our analysis was unavailable (**Figure 1** and **Appendix Table S3**).

Characteristics of Included Studies and Patients

Among the 27 studies[11,29-53] included in the analysis, 14 were RCTs and 13 were prospective cohort studies (**Appendix Table S4**). A total of 17 202 patients with a first unprovoked or weakly provoked VTE who had completed at least 3 months of initial anticoagulant treatment were included in the analysis (**Appendix Table S5**). Seventeen studies used the ISTH definition of

major bleeding (**Appendix Table S4**). The overall risk of bias among the included studies was considered to be low (**Appendix Table S4**); the component Newcastle-Ottawa Scale scores for all studies are presented in **Appendix Table S6**.

Incidence of Major Bleeding

The incidence of major bleeding per 100 person- years was 1.74 events (95% CI, 1.34 to 2.20 events) among 9982 patients receiving extended anticoagulation with a VKA and 1.12 events (95% CI, 0.72 to 1.62 events) among 7220 patients receiving a DOAC (IRR, 1.66 [95% CI, 1.18 to 2.39]) (**Table 1**; **Appendix Tables S7 and S8**). The incidence rate of major bleeding with VKAs overlapped in each of the studied intervals of follow-up. The 5-year cumulative incidence of major bleeding with VKAs was 6.3% (95% CI, 3.6% to 10.0%) (**Table 1**). Data were insufficient to estimate incidence of major bleeding beyond 1 year of extended anticoagulation with DOACs.

Subgroup Analyses

In patients receiving a VKA, the incidence of major bleeding was statistically significantly higher among women than men (IRR, 1.55 [95% CI, 1.17 to 2.06]) (**Figure 2**), whereas in those receiving a DOAC, we found no statistically significant difference according to sex (IRR, 1.00 [95% CI, 0.51 to 1.95]). The 5-year cumulative incidence of major bleeding with VKAs was 8.5% (95% CI, 4.0% to 15.0%) in women and 6.5% (95% CI, 4.2% to 9.2%) in men (**Appendix Table S9**).

The incidence of major bleeding was statistically significantly higher among those older than 65 years than those aged 65 years or younger (IRR, 1.84 [95% CI, 1.32 to 2.57] with VKAs and 2.92 [95% CI, 1.50 to 5.70] with DOACs) (**Figure 2**). The 5-year cumulative incidence of major bleeding with VKAs was 8.3% (95% CI, 4.0% to 14.3%) among patients older than 65

years and 4.4% (95% CI, 2.5% to 6.7%) in those aged 65 years or younger (**Appendix Table S10**).

We found no statistically significant difference in the incidence of major bleeding between patients with initial isolated proximal DVT and those with isolated PE (IRR, 0.77 [95% CI, 0.54 to 1.09] for VKAs and 1.65 [95% CI, 0.49 to 8.66] for DOACs); between patients with initial isolated proximal DVT and those with concomitant PE and DVT (IRR, 0.98 [95% CI, 0.67 to 1.42] with VKAs and 0.80 [95% CI, 0.34 to 2.10] with DOACs); or between patients with isolated PE and those with concomitant PE and DVT (IRR, 1.27 [95% CI, 0.88 to 1.85] with VKAs and 0.49 [95% CI, 0.83 to 2.02] with DOACs) (**Appendix Table S11**). The 5-year cumulative incidence of major bleeding with VKAs was 6.8% (95% CI, 2.5% to 14.0%) for patients with isolated proximal DVT, 7.6% (95% CI, 3.3% to 13.3%) for patients with isolated PE, and 7.9% (95% CI, 4.1% to 12.7%) for patients with concomitant PE and DVT (**Appendix Table S11**).

The incidence of major bleeding was statistically significantly higher among those with creatinine clearance less than 50 mL/min than those with creatinine clearance of 50 mL/min or higher (IRR, 2.83 [95% CI, 1.90 to 4.22] with VKAs and 3.71 [95% CI, 1.51 to 9.13] with DOACs) (**Figure 2**). The 5-year cumulative incidence of major bleeding with VKAs was 21.9% (95% CI, 7.8% to 40.2%) among patients with creatinine clearance less than 50 mL/min and 6.0% (95% CI, 4.0% to 8.5%) in those with creatinine clearance of 50 mL/min or higher (**Appendix Table S12**).

The incidence of major bleeding was statistically significantly higher among those with a history of bleeding than those without (IRR, 3.47 [95% CI, 1.86 to 6.50] with VKAs and 18.81 [95% CI, 9.54 to 37.07] with DOACs) (**Figure 2**). The 5-year cumulative incidence of major bleeding with VKAs was 20.9% (95% CI, 3.9% to 46.4%) among patients with a history of

bleeding and 12.7% (95% CI, 2.5% to 33.4%) in those without (**Appendix Table S13**).

The incidence of major bleeding was statistically significantly higher among those with concomitant use of antiplatelet therapy than those without (IRR, 2.89 [95% CI, 1.93 to 4.34] with VKAs and 17.18 [95% CI, 6.68 to 44.18] with DOACs) (**Figure 2**). The 5-year cumulative incidence of major bleeding with VKAs was 15.6% (95% CI, 5.8% to 29.6%) among patients with concomitant use of antiplatelet therapy and 6.6% (95% CI, 3.9% to 9.9%) in those without (**Appendix Table S14**).

The incidence of major bleeding was statistically significantly higher among those with hemoglobin levels less than 100 g/L than those with hemoglobin levels of 100 g/L or higher (IRR, 6.51 [95% CI, 3.23 to 13.13] with VKAs and 17.41 [95% CI, 7.67 to 39.55] with DOACs) (**Figure 2**). The 5-year cumulative incidence of major bleeding with VKAs was 15.6% (95% CI, 3.8% to 57.2%) among patients with hemoglobin levels less than 100 g/L and 7.2% (95% CI, 4.5% to 10.6%) in those with hemoglobin levels of 100 g/L or higher (**Appendix Table S15**).

We found no statistically significant difference in the incidence of major bleeding between study cohorts derived from RCTs and those derived from prospective cohort studies (IRR, 1.10 [95% CI, 0.80 to 1.51] with VKAs and 0.59 [95% CI, 0.30 to 1.15] with DOACs) (**Appendix Table S16**). No RCTs had follow-up beyond 2 years of extended anticoagulation with VKAs (**Appendix Table S16**). The 5-year cumulative incidence of major bleeding with VKAs among cohorts derived from prospective cohort studies was 6.4% (95% CI, 3.2% to 10.6%) (**Appendix Table S16**).

Case-Fatality Rate of Major Bleeding

The pooled case-fatality rate of major bleeding was 8.3% (95% CI, 5.1% to 12.2%) among patients receiving a VKA and 9.7% (95% CI, 3.2% to 19.2%) among those receiving a DOAC (**Table 2** and **Appendix Table S17**).

Sensitivity Analyses

Estimates of major bleeding rates in the primary analyses did not differ from those in analyses restricted to studies in which the duration of initial anticoagulant treatment was exclusively 3 months or to studies that used the ISTH definition of major bleeding (**Appendix Tables S7 and S8**).

DISCUSSION

In this systematic review and meta-analysis of 27 studies and 17 202 patients with a first unprovoked or weakly provoked VTE receiving extended anticoagulant therapy, we found that the incidence of major bleeding per 100 person-years was 1.7 events with VKAs and 1.1 events with DOACs. The 5-year cumulative incidence of major bleeding with VKAs was 6%. In patients receiving either a VKA or a DOAC, the incidence of major bleeding was statistically significantly higher among those who were older than 65 years or had creatinine clearance less than 50 mL/min, history of bleeding, concomitant use of antiplatelet therapy, or a hemoglobin level less than 100 g/L.

We also provide contemporary estimates for the clinical effect of anticoagulant-related major bleeding, defined as risk for intracranial and fatal bleeding, as well as the case-fatality rate of major bleeding. Of note, in our meta-analysis of patients with VTE, the case-fatality rate of major bleeding seemed to be similar with DOACs (9.7% [95% CI, 3.2% to 19.2%]) and VKAs (8.3% [95% CI, 5.1% to 12.2%])—a finding different from that reported in a previous meta-analysis of phase 3 RCTs comparing DOACs (7.6% [95% CI, 6.5% to 8.7%]) with VKAs (11.0% [95% CI, 9.2% to 13.1%]) in patients with atrial fibrillation.[55]

Given the need for precise estimates of the absolute long-term risk and case-fatality rate of major bleeding during extended anticoagulant therapy to guide decisions about treatment duration in unprovoked VTE, our findings are likely to affect clinical practice. For patients with a

first unprovoked proximal DVT or PE who have completed at least 3 to 6 months of initial treatment, the 2016 guidelines from the American College of Chest Physicians and 2020 guidelines from the American Society of Hematology suggest continuing anticoagulation indefinitely over discontinuing it, except for those considered to have high risk for major bleeding.[5,6] Because the case-fatality rate of major bleeding is 2- to 3-fold higher than that of recurrent VTE,[10] it has been proposed that patients with a major bleeding risk of 3% or higher per year be classified as having high risk and thus not be considered for indefinite anticoagulation, regardless of their risk for recurrent VTE.[5,56,57] However, no standardized approach currently exists to identify such a subgroup of patients with unprovoked VTE. Expert consensus opinion and previous individual studies aimed at identifying patients with VTE at high risk for anticoagulant-related major bleeding have proposed that female sex, advanced age (such as >65 years), renal insufficiency, history of bleeding, concomitant use of antiplatelet therapy, and anemia are common independent risk factors for bleeding.[56-59]. The American College of Chest Physicians guidelines suggest that the prevalence of these risk factors could be used to categorize the risk for bleeding as low (no risk factors) or high (≥2 risk factors).[5] Our meta-analysis supports the existence of a clinically meaningful difference in long-term risk for anticoagulant-related major bleeding among patients with a first unprovoked VTE stratified according to presence or absence of the following risk factors: age older than 65 years, creatinine clearance less than 50 mL/min, history of bleeding, concomitant use of anti- platelet therapy, and hemoglobin level less than 100 g/L.

Taken together, our results provide clinicians, patients, and policy-makers with a management framework in which to consider the long-term risks for and consequences of major bleeding if anticoagulation is continued beyond the initial 3 to 6 months. When weighed against the long-term risks for and consequences of recurrent VTE if anticoagulation is discontinued, our

results could be used to balance the benefits and harms of extended anticoagulation for unprovoked VTE. For example, a patient with a first unprovoked VTE who has completed at least 3 months of initial anticoagulant treatment and either is receiving concomitant antiplatelet therapy or has a history of bleeding (factors associated with a point estimate for major bleeding risk ≥3% per year in our analysis) may not be a candidate for extended anticoagulation with a VKA: If anticoagulation is discontinued, the risk for death from recurrent VTE at 5 years would be about 1.0% (25% risk for recurrent VTE at 5 years multiplied by 4% case-fatality rate of recurrent VTE);[10] if anticoagulation is continued, the risk for death from major bleeding at 5 years would be greater than 1.2% (>15% risk for major bleeding at 5 years multiplied by 8% case-fatality rate of major bleeding, as determined in our analysis). Over a 10-year horizon, the risk for death from recurrent VTE if anticoagulation is discontinued would be about 1.4% (36% risk for recurrent VTE at 10 years multiplied by 4% case-fatality rate of recurrent VTE)[10] and the risk for death from major bleeding if anticoagulation is continued would be greater than 2.4% (>30% risk at 10 years multiplied by 8% case-fatality rate of major bleeding).

Last, we found that the incidence of major bleeding during extended anticoagulation is lower with DOACs than VKAs—a finding consistent with that established for the initial treatment of VTE.[60] However, in our analysis, only 1 study cohort exclusively received extended anticoagulation with DOACs beyond 13 months. As such, our systematic review emphasizes the need for future prospective studies focused on establishing the long-term (beyond 1 year of extended anticoagulation) risk for major bleeding with DOACs.

Our study has several notable strengths. First, our systematic review involved a comprehensive search and included unpublished data from studies with an overall low risk of bias. Second, many of the included studies had a heterogeneous patient population that included persons with VTE provoked by major transient or persistent risk factors, as well as those with a

history of VTE. However, with help from principal investigators of included studies, we extracted and combined data on more than 17 000 patients who had a first episode of unprovoked or weakly provoked VTE and were prospectively followed for major bleeding during extended anticoagulant therapy with a VKA or DOAC. Moreover, we standardized durations of follow-up across study cohorts and used exact person-time at risk during each of the studied intervals to assess the risk for major bleeding over time, and we compared bleeding risks in several patient subgroups that are clinically important.

Limitations of this study include limited data (from insufficient number of studies) to compare bleeding risk between reduced- and therapeutic-dose DOACs and limited data beyond 1 year of extended anticoagulation with DOACs. Most DOAC cohorts included in our analysis received extended anticoagulation with rivaroxaban; thus, our estimates for the incidence of major bleeding with DOACs may not always be generalizable to all DOACs. Also, we found moderate statistical heterogeneity for the primary outcome of major bleeding; however, this heterogeneity was largely explained through the various prespecified subgroup and sensitivity analyses. Moreover, we used the DerSimonian–Laird random-effects model, which may have underestimated the true between-study variance, potentially producing overly narrow 95% CIs for our meta-analyses involving fewer than 10 study cohorts and moderate statistical heterogeneity.[61] Finally, owing to constraints in time; resource use; and access to raw, individual-level data, particularly from the included industry-sponsored studies, we did not do an individual-patient data meta-analysis, which would have allowed us to compute direct estimates of the cumulative incidence over time and adjust estimates by various risk factors (and potential interactions between risk factors).

In conclusion, this systematic review and meta- analysis determined the risk for major bleeding during extended anticoagulation of up to 5 years among patients with a first unprovoked

VTE and in clinically important subgroups. Findings from this study will help inform physician–patient discussions about long-term risks and consequences of anticoagulant-related major bleeding and help balance the net benefits and harms of extended anticoagulation to guide treatment duration for unprovoked VTE.

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Table 1: Incidence of Major Bleeding*.

Interval of Follow-up During Extended Anticoagulation	Study Cohorts, *n*	Events, *n*			Person-Years, *n*	Incidence Rate per 100 Person-Years (95% CI)		
		Major Bleeding	Intracranial Bleeding	Fatal Bleeding		Major Bleeding	Intracranial Bleeding	Fatal Bleeding
Overall								
VKA	24	207	37	15	12 251	1.74 (1.34–2.20)	0.39 (0.25–0.57)	0.16 (0.10–0.24)
DOAC	11	40	9	2	3934	1.12 (0.72–1.62)	0.29 (0.14–0.50)	0.10 (0.03–0.23)
Year 1								
VKA	24	128	26	9	6989	2.00 (1.56–2.50)	0.53 (0.35–0.74)	0.18 (0.10–0.30)
DOAC	11	40	9	2	3768	1.20 (0.74–1.77)	0.31 (0.15–0.53)	0.11 (0.03–0.24)
Year 2†								
VKA	18	48	7	2	2707	1.65 (0.99–2.48)	0.42 (0.20–0.72)	0.21 (0.07–0.41)
Years 3–5†								
VKA	5	31	4	4	2555	0.95 (0.35–1.83)	0.22 (0.08–0.44)	0.20 (0.07–0.42)

	Cumulative Incidence (95% CI), %		
	Major Bleeding	Intracranial Bleeding	Fatal Bleeding
After 2 y†			
VKA	3.6 (2.5–4.9)	0.9 (0.5–1.5)	0.4 (0.2–0.7)
After 5 y†			
VKA	6.3 (3.6–10.0)	1.6 (0.8–2.7)	1.0 (0.4–1.9)

DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.

* I^2 range, 31%–54% for major bleeding and 0%–1% for intracranial and fatal bleeding.

† For DOACs in these follow-up intervals, data were insufficient to estimate incidence.

Table 2: Case-Fatality Rate of Major Bleeding.*

Type of Anticoagulant	Study Cohorts, *n*	Fatal Bleeding Events, *n*	Major Bleeding Events, *n*	Case-Fatality Rate (95% CI), *%*
Any	33	17	247	8.4 (5.4–12.1)
Vitamin K antagonists	22	15	207	8.3 (5.1–12.2)
Direct oral anticoagulants	11	2	40	9.7 (3.2–19.2)

* I^2 = 0% for all case-fatality rates.

Figure 1: Evidence Search and Selection.

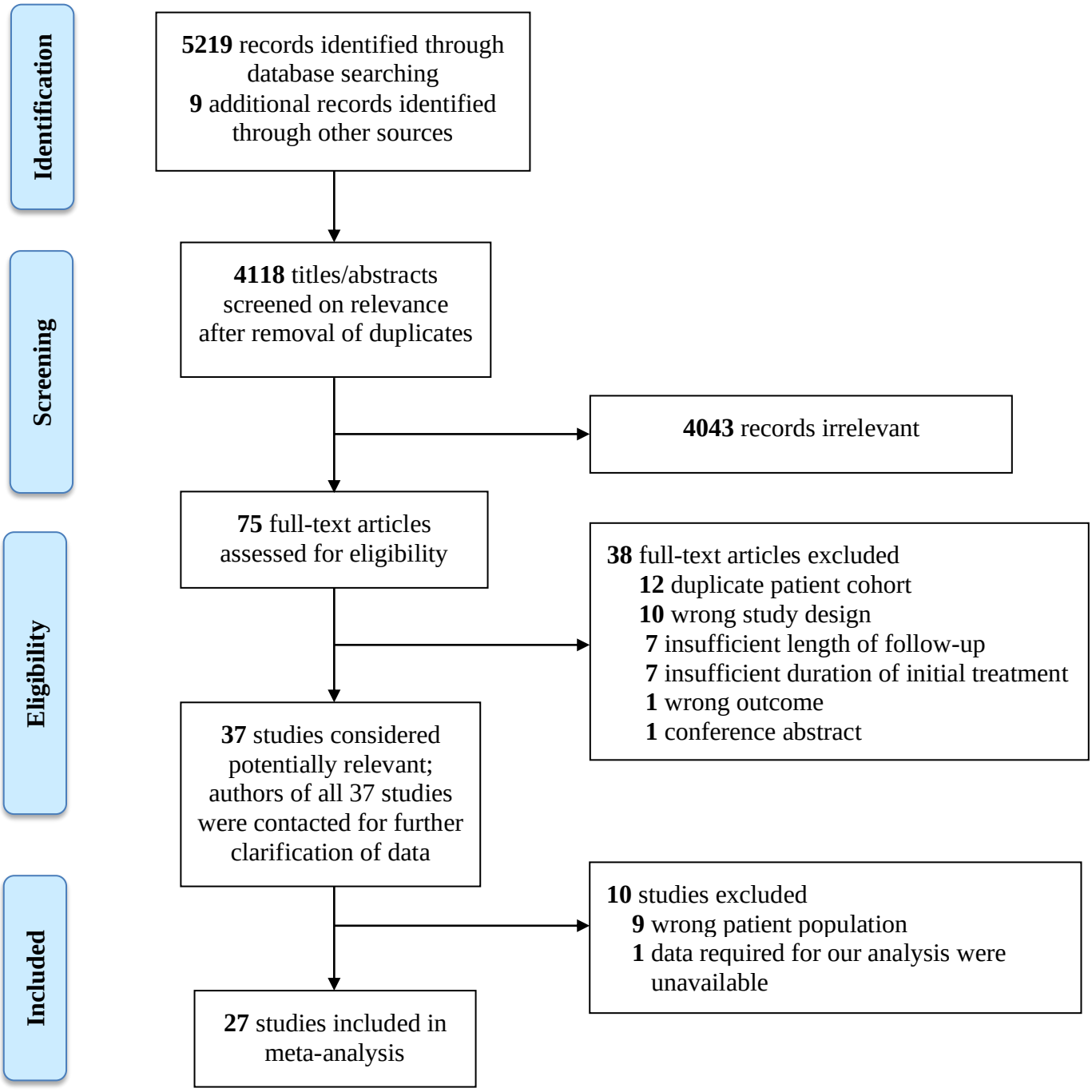
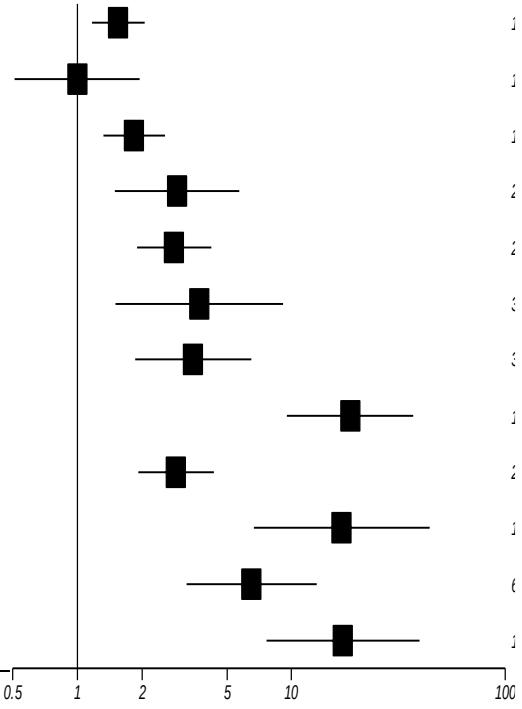


Figure 2: Incidence of major bleeding, according to presence and absence of risk factors for major bleeding.

Risk Factor	Study Cohorts, n	Major Bleeding Events/Person-Years, n / N		Incidence Rate per 100 Person-Years (95% CI)		IRR (95% CI)
		Risk Factor Present	Risk Factor Absent	Risk Factor Present	Risk Factor Absent	
Female sex						
VKA	23	94 / 4476	109 / 7685	2.02 (1.38-2.78)	1.55 (1.20-1.94)	1.55 (1.17-2.06)
DOAC	11	15 / 1483	26 / 2450	1.22 (0.67-1.93)	1.16 (0.70-1.72)	1.00 (0.51-1.95)
Age >65 years						
VKA	22	105 / 4964	74 / 6664	1.98 (1.41-2.64)	1.22 (0.87-1.63)	1.84 (1.32-2.57)
DOAC	11	25 / 1332	15 / 2606	2.01 (1.26-2.94)	0.66 (0.38-1.02)	2.92 (1.50-5.70)
Creatinine clearance <50 mL/min						
VKA	12	28 / 816	119 / 7853	2.89 (1.53-4.67)	1.58 (1.12-2.12)	2.83 (1.90-4.22)
DOAC	7	2 / 227	27 / 2642	1.41 (0.30-3.32)	1.13 (0.57-1.87)	3.71 (1.51-9.13)
History of bleeding						
VKA	10	8 / 230	119 / 6546	4.08 (1.97-6.91)	1.75 (1.23-2.35)	3.47 (1.86-6.50)
DOAC	10	9 / 102	27 / 3497	9.19 (4.13-16.0)	0.85 (0.55-1.21)	18.81 (9.54-37.07)
Concomitant antiplatelet therapy						
VKA	15	31 / 806	145 / 8689	3.98 (2.52-5.76)	1.61 (1.19-2.08)	2.89 (1.93-4.34)
DOAC	10	3 / 144	33 / 3385	3.45 (1.16-6.90)	1.05 (0.56-1.70)	17.18 (6.68-44.18)
Hemoglobin <100 g/L						
VKA	12	7 / 333	139 / 8578	2.73 (1.13-4.98)	1.45 (0.92-2.10)	6.51 (3.23-13.13)
DOAC	9	2 / 80	29 / 3235	4.03 (0.96-9.07)	1.00 (0.59-1.52)	17.41 (7.67-39.55)



I^2 = 0% for all IRRs. DOAC = direct oral anticoagulant; IRR = incidence rate ratio; VKA = vitamin K antagonist.

APPENDIX

Table S1: Categorization of Provoked or Unprovoked Venous Thromboembolism, According to the International Society on Thrombosis and Haemostasis.[62]

Persistent Provoking Risk Factors

- Active cancer, defined as:
  - cancer that has not received potentially curative treatment, or;
  - treatment is ongoing, or;
  - evidence that treatment has not been curative.

Major Transient Provoking Risk Factors

- Surgery with general anesthesia for > 30 minutes
- Confined to bed (only 'bathroom privileges') for at least 3 days with an acute illness.
- Cesarean section

Minor Transient Provoking Risk Factors

- Surgery with general anesthesia for < 30 minutes
- Admission to hospital for < 3 days with an acute illness
- Estrogen therapy
- Pregnancy or puerperium
- Confined to bed out of hospital for at least 3 days with an acute illness.
- Leg injury associated with reduced mobility for at least 3 days

Unprovoked

- No transient or persistent (major or minor) provoking risk factors.

Table S2: Literature Search Strategy for EMBASE.

No.	Searches
1	Venous Thrombosis/
2	(ven* adj2 thrombos*).ti,ab.
3	Deep Vein Thrombosis/
4	(deep adj3 thrombos*).ti,ab.
5	Pulmonary Embolism/
6	(pulmonary adj2 embolism*).ti,ab.
7	Venous Thromboembolism/
8	(ven* adj2 thromboembolism*).ti,ab.
9	Recurrent Venous Thromboembolism/
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	secondary prevention/
12	secondary prevention*.ti,ab.
13	(relapse adj2 prevention*).ti,ab.
14	(extended adj2 therap*).ti,ab.
15	11 or 12 or 13 or 14
16	Hemorrhage/
17	(hemorrhag* or haemorrhag*).ti,ab.
18	16 or 17
19	Anticoagulants/
20	Antithrombins/
21	(anticoagulant* or anti-coagulant* or antithrombin* or anti-thrombin*).tw.
22	(thrombin adj3 inhibit*).tw.
23	(Factor Xa adj2 (antagonist? or inhibit* or block*)).tw.
24	heparin/ or exp heparin, low-molecular-weight/
25	(heparin* or beparine or clarin or contusol or disebrin or eleparon or elheparin or elheparon or epiheparin or gag 98 or helberina or hepaflex or hepalean or heparitin* or hepcon or hepsal or inhepar or inviclot or lipo-hepin or lipohepin or liquemin or liquemine or menaven or monoparin or mucoitin or multiparin or nevparin or noparin or panheparin or panhepin or panheprin or parinix or praecivenin or pularin or thromb*or niparin or vetren or vaster).tw.
26	liquaemin.tw.
27	dalteparin*.tw.
28	fragmin*.tw.
29	enoxaparin*.tw.
30	clexane.tw.
31	lovenox.tw.
32	fraxiparin*.tw.
33	nadroparin*.tw.
34	Warfarin/
35	(warfarin or warfant or tedicumar or savaysa or endoxaban or befarin or adoisine or carfin or circuvit or coumadan or coumafene or coumaphene or dagonal or tintorane or uniwarfin or waran or warfar or warnerin or farin or

	jantoven or kumatox or maforan or orfarin or panwarfarin or panwarfin or prothromadin or warfil* or sofarin).tw.
36	coumadin*.tw.
37	aldocumar.tw.
38	marevan.tw.
39	(Vitamin K adj2 (antagonist? or inhibit* or block*)).tw.
40	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
42	RETRACTED ARTICLE/
43	or/41-42
44	(animal$ not human$).sh,hw.
45	(book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/
46	(random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/
47	43 not (44 or 45 or 46)
48	exp cohort analysis/
49	exp longitudinal study/
50	exp prospective study/
51	exp follow up/
52	cohort$.tw.
53	or/48-52
54	47 or 53
55	10 and 15 and 18 and 40 and 54
56	10 and 18 and 40 and 54

Table S3: Studies Excluded from Meta-Analysis.

Study Author and Year of Publication	Study Title	Reason for Exclusion
Agnelli 2013	Apixaban for extended treatment of venous thromboembolism	Wrong study population:1,653 patients with any VTE (including those with cancer and other provoking risk factors) received extended anticoagulation. Data among patients with a first unprovoked VTE were unavailable.
Kearon 1999	A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism	79 patients with a first unprovoked VTE received extended anticoagulation. Detailed information required for our analysis was unavailable.
Kearon 2003	Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism	Wrong study population; 509/738 (69%) of included unprovoked VTE patients had >1 previous episode of VTE with an average of 2 previous episodes of VTE.
Kurtoglu 2010	Long-term efficacy and safety of once-daily enoxaparin plus warfarin for the outpatient ambulatory treatment of lower-limb deep vein thrombosis in the TROMBOTEK trial	Wrong study population: 227/246 included patients had VTE associated with either cancer or major transient risk factors including major trauma, surgery, and prolonged immobilization
Palareti 1996	Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy	Wrong study population: 892 patients (including those with cancer) with any VTE (no classification of VTE as provoked or unprovoked).
Poli 2013	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	Wrong study population: Among 1078 included patients, 865 were those with first episode of any VTE (no classification of VTE as provoked or unprovoked), of which 187 had a prior episode of VTE. The remaining patients were those with atrial fibrillation.
Ridker 2003	Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism	Wrong study population: 102/255 (40%) of included unprovoked VTE patients had 2 or more prior episodes of VTE.
Rief 2018	Calculation of HAS-BLED Score Is Useful for Early Identification of Venous Thromboembolism Patients at High Risk for Major Bleeding Events: A Prospective Outpatients Cohort Study	Wrong study population: 11/111 included patients with any VTE (no classification of VTE as provoked or unprovoked) had cancer.
Schulman 2013	Extended use of dabigatran, warfarin, or placebo in venous thromboembolism	Wrong study population: 3,537 patients (including those with cancer) received extended anticoagulation for any VTE. VTE events were not classified as provoked or unprovoked.
Zentati 2017	Anaemia as an independent key risk factor for major haemorrhage in patients treated with vitamin K antagonists: Results of the SCORE prospective cohort	Wrong study population: 27/470 included patients with any VTE had cancer, and there was no classification of VTE as provoked or unprovoked.

Table S4: Characteristics of Included Studies.

Source	Study Design	Duration of Initial Anticoagulation	Duration of Follow-up and Regimen During Extended Anticoagulation[a]	Definition of Unprovoked VTE[b]	Definition of Major Bleeding	Overall Risk of Bias
WODIT-DVT Agnelli et al. 2001 (29)	RCT	3 months	9 months; VKA (target INR 2.0-3.0)	ISTH	Overt bleeding and associated with a fall in hemoglobin of ≥2 g/dL; transfusion of ≥2 units of red cells; retroperitoneal or intracranial; warranting permanent discontinuation of study drug	Low
WODIT-PE Agnelli et al. 2003 (30)	RCT	3 months	9 months; VKA (target INR 2.0-3.0)	ISTH	Overt bleeding and associated with a fall in hemoglobin of ≥2 g/dL; transfusion of ≥2 units of red cells; retroperitoneal or intracranial; warranting permanent discontinuation of study drug or re-hospitalization.	Low
PROLONG Palareti et al. 2006 (31, 63)	RCT	At least 3 months	24 months; VKA (target INR 2.0-3.0)	ISTH	Overt bleeding and associated with a fall in hemoglobin of ≥2 g/dL; transfusion of ≥2 units of blood; retroperitoneal or intracranial; requiring surgery or invasive procedures to stop bleeding	Low

AESOPUS Prandoni et al. 2009 (32)	RCT	3 months	33 months; VKA (target INR 2.0-3.0)	ISTH	Overt bleeding and associated with a fall in hemoglobin of ≥20 g/L; transfusion of ≥2 units of red blood cells; retroperitoneal or intracranial	Low
AUREC-FVIII Eischer et al. 2009 (33)	RCT	6 months	24 months; VKA (target INR 2.0-3.0)	ISTH	Bleeding that resulted in death, hospitalization, chronic sequelae, or transfusion of blood, plasma, or coagulation factors.	Low
Palla et al. 2010 (34)	Cohort	3 months	9 months; VKA (target INR 2.0-3.0)	ISTH	Bleeding that was either fatal; associated with a fall in hemoglobin of ≥2 g/dL; intra-abdominal or intracranial; requiring surgery or angiographic intervention ; requiring transfusion	Low
PROLONG II Cosmi et al. 2010 (35)	Cohort	At least 6 months	24 months; VKA (target INR 2.0-3.0)	ISTH	Overt bleeding and associated with a fall in hemoglobin of ≥2 g/dL; transfusion of ≥2 units of blood; retroperitoneal or intracranial; requiring surgery or invasive procedures to stop bleeding	Low
EINSTEIN-DVT Bauersachs et al. 2010 (36)	RCT	3 months	9 months; Rivaroxaban (20mg) or VKA (target INR 2.0-3.0)	ISTH	ISTH	Low
EINSTEIN-Extension Bauersachs et al. 2010 (36)	RCT	6-12 months	12 months; Rivaroxaban (20 mg)	ISTH	ISTH	Low

DACUS Siragusa et al. 2011 (37)	Cohort	3 months	21 months; VKA (target INR 2.0-3.0)	ISTH	Bleeding associated with a fall in hemoglobin of ≥2 g/dL; intracranial or retroperitoneal; requiring surgical intervention or blood transfusion	Low
EINSTEIN-PE Büller et al. 2012 (38)	RCT	3 months	9 months; Rivaroxaban (20 mg) or VKA (target INR 2.0-3.0)	ISTH	ISTH	Low
DULCIS Palareti et al. 2014 (39)	Cohort	At least 3 months	24 months; VKA (target INR 2.0-3.0)	ISTH (minor general surgery, pregnancy, puerperium, estrogen treatment, travel >6 hours, minor trauma, hospitalization for medical illness, reduced mobility)	ISTH	Low
DODS Kearon et al. 2015 (40, 64)	Cohort	3-7 months	60 months; VKA (target INR 2.0-3.0)	ISTH (estrogen treatment)	ISTH	Low
PADIS-PE Couturaud et al. 2015 (11)	RCT	6 months	18 months; VKA (target INR 2.0-3.0)	ISTH (estrogen treatment)	ISTH	Low
PISA-PEET Marconi et al. 2016 (41)	Cohort	12 months	60 months; VKA (target INR 2.0-3.0)	ISTH	Bleeding that was either fatal; associated with a fall in hemoglobin of ≥2 g/dL; intra-abdominal or intracranial; requiring surgery or angiographic intervention ; requiring transfusion	Low
SWITCO65+ Hofmann et al. 2016 (42)	Cohort	3 months	33 months; VKA (target INR 2.0-3.0)	ISTH	ISTH	Low

XALIA Ageno et al. 2016 (43)	Cohort	3 months	13 months; Rivaroxaban or VKA	ISTH	ISTH	Low
HOKUSAI-VTE Raskob et al. 2016 (44)	RCT	3 months	9 months; Edoxaban (60 mg) or VKA (target INR 2.0-3.0)	ISTH	ISTH	Low
MORGAGNI Prandoni et al. 2017 (45)	Cohort	At least 3 months	60 months; VKA (target INR 2.0-3.0)	ISTH	ISTH	Low
REVERSE II Rodger et al. 2017 (46)	Cohort	5-12 months	12 months; VKA (target INR 2.0-3.0) or DOAC	ISTH (estrogen treatment)	ISTH	Low
EINSTEIN-Choice Weitz et al. 2017 (47)	RCT	6-12 months	12 months; Rivaroxaban (10mg or 20mg)	ISTH	ISTH	Low
XALIA-LEA Kreutz et al. 2019 (48)	Cohort	3 months	13 months; Rivaroxaban or VKA	ISTH	ISTH	Low
PADIS-DVT Couturaud et al. 2019 (49)	RCT	6 months	18 months; VKA (target INR 2.0-3.0)	ISTH (estrogen treatment)	ISTH	Low
ExACT Bradbury et al. 2020 (50)	RCT	At least 3 months	24 months; VKA (target INR 2.0-3.0)	ISTH	ISTH	Low
VISTA Geersing et al. 2020 (51)	RCT	At least 3 months	24 months; VKA (target INR 2.0-3.0)	ISTH	Bleeding accompanied by a fall in hemoglobin of ≥20 g/L; transfusion of ≥2 units of blood; retroperitoneal or intracranial; requiring surgery or invasive procedures to stop bleeding	Low
Vedovati et al. 2020 (52)	Cohort	3 months	9 months; DOAC	ISTH	ISTH	Low

Wells et al. (53)	Cohort	At least 3 months	60 months; VKA (target INR 2.0-3.0) or DOAC	ISTH (hospitalization for medical illness, travel >8 hours, pregnancy, puerperium, or lower limb trauma with transient impairment of mobility)	ISTH	Low

Abbreviations: DOAC, direct oral anticoagulant; INR, international normalized ratio; ISTH, International Society on Thrombosis and Haemostasis; RCT, randomized controlled trial; VKA, vitamin K antagonist

[a] Maximum duration of follow-up, as applicable to the studied intervals.

[b] "ISTH" is listed for studies judged to have defined unprovoked VTE, as closely as possible, as VTE occurring in the absence of ISTH defined persistent or major transient provoking risk factors (Box). The minor transient risk factors included in the definition of unprovoked VTE are listed in brackets after "ISTH".

Table S5: Characteristics of Included Patients with First Unprovoked Venous Thromboembolism.

Source	Patients with First Unprovoked VTE	Men	Age >65 years	Initial Isolated Proximal DVT	Initial Isolated PE	Initial Concomitant PE and DVT	Creatinine Clearance <50 mL/min	History of Bleeding	Concomitant Antiplatelet Therapy	Hemoglobin <100 g/L
	No.	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
WODIT-DVT Agnelli et al. 2001	134	---	---	134 (100)	0 (0)	0 (0)	---	---	---	---
WODIT-PE Agnelli et al. 2003	90	42 (47)	62 (69)	0 (0)	30 (33)	60 (67)	---	---	---	---
PROLONG Palareti et al. 2006	103	55 (53)	76 (74)	16 (15)	20 (19)	67 (65)	---	---	---	---
AESOPUS Prandoni et al. 2009	120	80 (67)	70 (58)	105 (88)	0 (0)	15 (12)	---	---	---	---
AUREC-FVIII Eischer et al. 2009	17	5 (29)	7 (41)	---	---	---	---	---	---	---
Palla et al. 2010	156	72 (46)	117 (75)	0 (0)	87 (56)	69 (44)	37 (24)	12 (8)	42 (27)	21 (13)
PROLONG II Cosmi et al. 2010	104	51 (49)	77 (74)	74 (71)	18 (17)	12 (12)	---	---	4 (4)	---
EINSTEIN-DVT Bauersachs et al. 2010	1474	973 (66)	500 (34)	1469 (99)	---	---	89 (6)	57 (4)	123 (8)	39 (3)
Rivaroxaban	718	476 (66)	244 (34)	715 (99)	---	---	44 (6)	28 (4)	66 (9)	23 (3)
VKA	756	497 (66)	256 (34)	754 (99)	---	---	45 (6)	29 (4)	57 (8)	16 (2)
EINSTEIN-Extension Bauersachs et al. 2010	198	136 (69)	85 (43)	129 (65)	---	---	0 (0)	12 (6)	26 (13)	6 (3)

DACUS Siragusa et al. 2011	273	141 (52)	64 (23)	273 (100)	0 (0)	0 (0)	8 (3)	9 (3)	17 (6)	4 (2)
EINSTEIN-PE Buller et al. 2012	2160	1232 (57)	863 (40)	---	---	---	195 (9)	156 (7)	252 (12)	41 (2)
Rivaroxaban	1092	624 (57)	457 (42)	---	---	---	107 (10)	82 (8)	152 (14)	25 (2)
VKA	1068	608 (57)	406 (38)	---	---	---	88 (8)	74 (7)	100 (9)	16 (1)
DULCIS Palareti et al. 2014	311	189 (61)	214 (69)	165 (53)	75 (24)	71 (23)	---	---	---	---
DODS Kearon et al. 2015	67	38 (57)	23 (34)	33 (49)	---	---	---	---	8 (12)	---
PADIS-PE Couturaud et al. 2015	184	78 (42)	74 (40)	0 (0)	124 (67)	60 (33)	16 (9)	11 (6)	16 (9)	1 (1)
PISA-PEET Marconi et al. 2016	225	105 (47)	160 (71)	0 (0)	149 (66)	76 (34)	47 (21)	---	38 (17)	33 (15)
SWITCO65+ Hofmann et al. 2016	343	195 (57)	343 (100)	97 (28)	199 (58)	47 (14)	90 (26)	26 (8)	107 (31)	18 (5)
XALIA Ageno et al. 2016	1702	1022 (60)	747 (44)	1522 (89)	0 (0)	180 (11)	105 (6)	18 (1)	93 (5)	16 (1)
Rivaroxaban	1025	634 (62)	386 (38)	923 (90)	0 (0)	102 (10)	36 (4)	8 (1)	43 (4)	6 (1)
VKA	677	388 (57)	361 (53)	599 (88)	0 (0)	78 (12)	69 (10)	10 (1)	50 (7)	10 (1)
HOKUSAI-VTE Raskob et al. 2016	3956	2400 (61)	1204 (30)	2453 (62)	987 (25)	516 (13)	387 (10)	26 (1)	50 (1)	147 (4)
Edoxaban	1993	1205 (60)	604 (30)	1244 (62)	483 (24)	266 (13)	191 (10)	13 (1)	27 (1)	72 (4)
VKA	1963	1195 (61)	600 (31)	1209 (62)	504 26)	250 (13)	196 (10)	13 (1)	23 (1)	75 (4)
MORGAGNI Prandoni et al. 2017	103	69 (67)	64 (62)	73 (71)	0 (0)	30 (29)	---	---	---	---
REVERSE II Rodger et al. 2017	1705	1254 (74)	662 (39)	797 (47)	539 (32)	369 (22)	---	---	---	---
DOAC	342	254 (72)	127 (37)	125 (37)	122 (36)	95 (28)	---	---	---	---

VKA	1363	991 (73)	535 (39)	672 (49)	417 (31)	274 (20)	---	---	---	---
EINSTEIN-Choice Weitz et al. 2017	770	480 (62)	302 (39)	406 (53)	---	---	0 (0)	27 (4)	20 (3)	9 (1)
Rivaroxaban 10 mg	407	245 (62)	165 (41)	212 (52)	---	---	0 (0)	17 (4)	12 (3)	7 (2)
Rivaroxaban 20 mg	363	235 (64)	137 (38)	194 (53)	---	---	0 (0)	10 (3)	8 (2)	2 (1)
XALIA-LEA Kreutz et al. 2019	654	337 (52)	279 (43)	433 (66)	74 (11)	147 (22)	63 (10)	7 (1)	72 (11)	23 (4)
Rivaroxaban	544	278 (51)	234 (43)	362 (67)	58 (11)	124 (23)	52 (10)	6 (1)	56 (10)	19 (3)
VKA	110	59 (54)	45 (41)	71 (65)	16 (15)	23 (21)	11 (10)	1 (1)	16 (15)	4 (4)
PADIS-DVT Couturaud et al. 2019	50	31 (62)	19 (38)	50 (100)	0 (0)	0 (0)	6 (12)	1 (2)	2 (4)	0 (0)
ExACT Bradbury et al. 2020	139	94 (67)	67 (48)	70 (50)	69 (50)	0 (0)	---	---	---	---
VISTA Geersing et al. 2020	183	130 (71)	66 (36)	68 (37)	81 (44)	30 (16)	0 (0)	---	---	50 (27)
Vedovati et al. 2020	382	210 (55)	236 (62)	178 (47)	62 (16)	142 (37)	47 (12)	16 (4)	2 (1)	15 (4)
Wells et al. 2020	1599	1059 (66)	599 (36)	161 (10)	507 (32)	931 (58)	105 (7)	47 (3)	87 (5)	17 (1)
DOAC	156	107 (69)	39 (25)	5 (3)	43 (28)	108 (69)	5 (3)	7 (4)	6 (4)	0 (0)
VKA	1443	952 (66)	560 (39)	156 (11)	464 (32)	823 (57)	100 (7)	40 (3)	81 (6)	17 (1)
TOTAL	**17 202**	**10 478**	**6980**	**8706**	**3021**	**2822**	**1195**	**425**	**959**	**440**
DOAC	**7220**	**4404**	**2714**	**4087**	**768**	**837**	**482**	**199**	**398**	**175**
VKA	**9982**	**6065**	**4266**	**4619**	**2253**	**1994**	**713**	**226**	**561**	**265**

---, not available; DVT, deep vein thrombosis; DOAC, direct oral anticoagulant; PE, pulmonary embolism; VKA, vitamin K antagonist.

Table S6: Risk of Bias Assessment Using Modified Newcastle-Ottawa Scale.

Scoring Guide:

+ indicates that study satisfied the criteria
- indicates that study did not satisfy the criteria
Total score ≥4 indicates low risk of bias.

Study	Selection			Outcome			Total Score (out of 6)
	Was there a representative and well-defined sample of patients with a first unprovoked VTE?	Did patients complete a minimum of 3 months of anticoagulant treatment before start of follow-up?	Was there demonstration that no patient had major bleeding at start of follow-up?	Were objective and unbiased criteria used to assess major bleeding?	Was patient follow-up sufficiently long? (≥6 months)	Was patient follow-up sufficiently complete?	
Agnelli et al. 2001	+	+	+	+	+	+	**6**
Agnelli et al. 2003	+	+	+	+	+	+	**6**
Palareti et al. 2006	+	+	+	+	+	+	**6**
Prandoni et al. 2009	+	+	+	+	+	+	**6**
Eischer et al. 2009	+	+	+	+	+	+	**6**
Palla et al. 2010	+	+	+	-	+	+	**5**
Cosmi et al. 2010	+	+	+	+	+	+	**6**
Bauersachs et al. 2010	+	+	+	+	+	+	**6**
Bauersachs et al. 2010	+	+	+	+	+	+	**6**
Siragusa et al. 2011	+	+	+	+	+	+	**6**
Buller et al. 2012	+	+	+	+	+	+	**6**
Palareti et al. 2014	+	+	+	+	+	+	**6**
Kearon et al. 2015	+	+	+	+	+	+	**6**
Couturaud et al. 2015	+	+	+	+	+	+	**6**
Marconi et al. 2016	+	+	+	-	+	+	**5**
Hofmann et al. 2016	+	+	+	+	+	+	**6**
Ageno et al. 2016	+	+	+	+	+	+	**6**
Raskob et al. 2016	+	+	+	+	+	+	**6**
Prandoni et al. 2017	+	+	+	+	+	+	**6**
Rodger et al. 2017	+	+	+	+	+	+	**6**
Weitz et al. 2017	+	+	+	+	+	+	**6**
Kreutz et al. 2019	+	+	+	+	+	+	**6**
Couturaud et al. 2019	+	+	+	+	+	+	**6**
Vedovati et al. 2020	+	+	+	-	+	+	**5**
Bradbury et al. 2020	+	+	+	+	+	+	**6**
Geersing et al. 2020	+	+	+	-	+	+	**5**
Wells et al.	+	+	+	+	+	+	**6**

VTE, venous thromboembolism.

Table S7: Risk of Major Bleeding with Vitamin K Antagonists.

Source	Person-years	Events, n			Rate per 100 person-years (95% CI)			% Weight
		Major Bleeding	Intracranial Bleeding	Fatal Bleeding	Major Bleeding	Intracranial Bleeding	Fatal Bleeding	
Year 1								
WODIT-DVT Agnelli et al. 2001	87.0	4	0	0	4.60 (1.27 – 11.36)	0.00 (0.00 – 4.15)	0.00 (0.00 – 4.15)	2.2
WODIT-PE Agnelli et al. 2003	43.5	2	0	0	4.60 (0.56 – 15.64)	0.00 (0.00 – 8.13)	0.00 (0.00 – 8.13)	1.2
PROLONG Palareti et al. 2006	95.1	1	0	0	1.05 (0.03 – 5.72)	0.00 (0.00 – 3.80)	0.00 (0.00 – 3.80)	2.4
AESOPUS Prandoni et al. 2009	100.6	1	0	0	0.99 (0.03 – 5.41)	0.00 (0.00 – 3.60)	0.00 (0.00 – 3.60)	2.5
AUREC-FVIII Eischer et al. 2009	15.8	1	0	0	6.33 (1.60 – 30.56)	0.00 (0.00 – 20.82)	0.00 (0.00 – 20.82)	0.5
Palla et al. 2010	75.5	0	0	0	0.00 (0.00 – 4.77)	0.00 (0.00 – 4.77)	0.00 (0.00 – 4.77)	2.0
PROLONG II Cosmi et al. 2010	89.0	3	0	0	3.37 (0.70 – 9.54)	0.00 (0.00 – 4.06)	0.00 (0.00 – 4.06)	2.4
EINSTEIN-DVT Bauersachs et al. 2010								
VKA	243.0	4	1	1	1.65 (0.45 – 4.16)	0.41 (0.01 – 2.27)	0.41 (0.01 – 2.27)	4.9
DACUS Siragusa et al. 2011	267.0	2	---	0	0.75 (0.09 – 2.69)	---	0.00 (0.00 – 1.38)	5.2

EINSTEIN-PE Buller et al. 2012 VKA	417.0	12	8	2	2.88 (1.50 – 4.97)	1.92 (0.83 – 3.75)	0.48 (0.06 – 1.72)	6.7
DULCIS Palareti et al. 2014	293.0	7	3	1	2.39 (0.97 – 4.86)	1.02 (0.21 – 2.96)	0.34 (0.01 – 1.89)	5.5
DODS Kearon et al. 2015	64.0	3	0	0	4.69 (0.98 – 13.09)	0.00 (0.00 – 5.60)	0.00 (0.00 – 5.60)	1.7
PADIS-PE Couturaud et al. 2015	183.8	2	0	0	1.09 (0.13 – 3.88)	0.00 (0.00 – 1.99)	0.00 (0.00 – 1.99)	4.0
PISA-PEET Marconi et al. 2016	205.5	1	0	1	0.49 (0.01 – 2.68)	0.00 (0.00 – 1.78)	0.49 (0.01 – 2.68)	4.3
SWITCO65+ Hofmann et al. 2016	307.2	13	2	0	4.23 (2.27 – 7.13)	0.65 (0.08 – 2.33)	0.00 (0.00 – 1.19)	5.7
XALIA Ageno et al. 2016 VKA	322.0	6	0	0	1.86 (0.69 – 4.01)	0.00 (0.00 – 1.14)	0.00 (0.00 – 1.14)	5.8
HOKUSAI-VTE Raskob et al. 2016 VKA	982.0	14	6	3	1.43 (0.78 – 2.38)	0.61 (0.22 – 1.33)	0.31 (0.06 – 0.89)	9.8
MORGAGNI Prandoni et al. 2017	102.8	1	1	0	0.97 (0.02 – 5.30)	0.97 (0.02 – 5.30)	0.00 (0.00 – 3.52)	2.5
REVERSE II Rodger et al. 2017 VKA	1328	17	---	1	1.28 (0.75 – 2.04)	---	0.08 (0.00 – 0.42)	10.8
XALIA-LEA Kreutz et al. 2019 VKA	37.0	1	0	0	2.70 (0.07 – 14.16)	0.00 (0.00 – 9.49)	0.00 (0.00 – 9.49)	1.0

PADIS-DVT Couturaud et al. 2019	50.0	0	0	0	0.00 (0.00 – 7.11)	0.00 (0.00 – 7.11)	0.00 (0.00 – 7.11)	1.4
ExACT Bradbury et al. 2020	131.0	6	1	0	4.58 (1.70 – 9.70)	0.76 (0.02 – 4.18)	0.00 (0.00 – 2.78)	3.1
VISTA Geersing et al. 2020	170.0	2	0	0	1.18 (0.14 – 4.19)	0.00 (0.00 – 2.15)	0.00 (0.00 – 2.15)	3.8
Wells et al. 2020 VKA	1380	25	4	0	1.81 (0.09 – 2.69)	0.29 (0.08 – 0.74)	0.00 (0.00 – 0.27)	11.0
POOLED	**6988.8**	**128**	**26**	**9**	**2.00 (1.56-2.50)** I^2=35%	**0.53 (0.35-0.74)** I^2=0%	**0.18 (0.10-0.30)** I^2=0%	**100.0**
Cohorts with duration of initial anticoagulant treatment of exclusively 3 months	3086.3	60	17	7	2.04 (1.34 – 2.89) I^2=48%	0.59 (0.29– 0.98) I^2=21%	0.31 (0.15 – 0.54) I^2=0%	
Cohorts using ISTH definition of major bleeding	5840.8	111	26	8	2.11 (1.60 – 2.69) I^2=39%	0.64 (0.38 – 0.98) I^2=27%	0.17 (0.08 – 0.29) I^2=0%	
Year 2								
PROLONG Palareti et al. 2006	49.5	0	0	0	0.00 (0.00 – 7.18)	0.00 (0.00 – 7.18)	0.00 (0.00 – 7.18)	3.7
AESOPUS Prandoni et al. 2009	59.1	1	0	0	1.69 (0.04 – 9.07)	0.00 (0.00 – 6.05)	0.00 (0.00 – 6.05)	4.2
AUREC-FVIII Eischer et al. 2009	11.2	0	0	0	0.00 (0.00 – 28.06)	0.00 (0.00 – 28.06)	0.00 (0.00 – 28.06)	1.0
DACUS Siragusa et al. 2011	259.5	1	---	0	0.39 (0.01 – 2.13)	---	0.00 (0.00 – 1.41)	10.6
DULCIS Palareti et al. 2014	203.7	6	2	0	2.95 (1.09 – 6.30)	0.98 (0.12 – 3.50)	0.00 (0.00 – 1.79)	9.4

DODS Kearon et al. 2015	61.3	1	0	0	1.63 (0.04 – 8.76)	0.00 (0.00 – 5.84)	0.00 (0.00 – 5.84)	4.3
PADIS-PE Couturaud et al. 2015	90.8	2	0	0	2.20 (0.27 – 7.73)	0.00 (0.00 – 3.98)	0.00 (0.00 – 3.98)	5.8
PISA-PEET Marconi et al. 2016	184.4	0	0	0	0.00 (0.00 – 1.98)	0.00 (0.00 – 1.98)	0.00 (0.00 – 1.98)	9.0
SWITCO65+ Hofmann et al. 2016	224.4	8	1	0	3.57 (1.55 – 6.90)	0.45 (0.01 – 2.46)	0.00 (0.00 – 1.63)	9.9
XALIA Ageno et al. 2016								
VKA	28	1	0	0	3.57 (0.09 – 18.35)	0.00 (0.00 – 1.14)	0.00 (0.00 – 1.14)	2.3
MORGAGNI Prandoni et al. 2017	100.6	1	0	0	0.99 (0.03 – 5.41)	0.00 (0.00 – 3.60)	0.00 (0.00 – 3.60)	6.2
XALIA-LEA Kreutz et al. 2019								
VKA	2.0	0	0	0	0.00 (0.00 – 84.19)	0.00 (0.00 – 84.19)	0.00 (0.00 – 84.19)	0.2
PADIS-DVT Couturaud et al. 2019	25.0	0	0	0	0.00 (0.00 – 13.72)	0.00 (0.00 – 13.72)	0.00 (0.00 – 13.72)	2.1
ExACT Bradbury et al. 2020	125.0	3	0	0	2.40 (0.50 – 6.85)	0.00 (0.00 – 2.91)	0.00 (0.00 – 2.91)	7.1
VISTA Geersing et al. 2020	146.0	0	0	0	0.00 (0.00 – 2.50)	0.00 (0.00 – 2.50)	0.00 (0.00 – 2.50)	7.9
Wells et al. 2020								
VKA	1136	24	4	2	2.11 (1.36 – 3.13)	0.35 (0.10 – 90)	0.18 (0.02 – 0.63)	16.3
POOLED	**2706.5**	**48**	**7**	**2**	**1.65 (0.99 – 2.48)** I^2=40%	**0.42 (0.20 – 0.72)** I^2=0%	**0.21 (0.07 – 0.41)** I^2=0%	**100.0**

Years 3 - 5								
DODS Kearon et al. 2015	152.2	0	0	0	0.00 (0.00 – 2.40)	0.00 (0.00 – 2.40)	0.00 (0.00 – 2.40)	15.0
PISA-PEET Marconi et al. 2016	449.0	4	1	2	0.89 (0.24 – 2.27)	0.22 (0.01 – 1.23)	0.45 (0.05 – 1.60)	25.8
SWITCO65+ Hofmann et al. 2016	68.9	2	0	0	2.90 (0.35 – 10.10)	0.00 (0.00 – 5.21)	0.00 (0.00 – 5.21)	8.5
MORGAGNI Prandoni et al. 2017	153.3	0	0	0	0.00 (0.00 – 2.38)	0.00 (0.00 – 2.38)	0.00 (0.00 – 2.38)	15.0
Wells et al. 2020 VKA	1732.0	25	3	2	1.44 (0.94 – 2.12)	0.17 (0.03 – 0.49)	0.11 (0.01 – 0.41)	35.7
POOLED	**2555.4**	**31**	**4**	**4**	**0.95 (0.35-1.83)** I^2=55%	**0.28 (0.02-0.83)** I^2=55%	**0.42 (0.07-1.05)** I^2=55%	**100.0**

VKA, vitamin K antagonist.

Table S8: Risk of Major Bleeding with Direct Oral Anticoagulants.

Source	Person-years	Events, n			Incidence Rate per 100 person-years (95% CI)			% Weight
		Major Bleeding	Intracranial Bleeding	Fatal Bleeding	Major Bleeding	Intracranial Bleeding	Fatal Bleeding	
Year 1								
EINSTEIN-DVT Bauersachs et al. 2010 Rivaroxaban	233.0	2	1	0	0.86 (0.10 – 3.07)	0.43 (0.01 – 2.37)	0.00 (0.00 – 1.57)	8.0
EINSTEIN-Extension Bauersachs et al. 2010	103.0	2	0	0	1.94 (0.24 -6.84)	0.00 (0.00 – 3.52)	0.00 (0.00 – 3.52)	4.6
EINSTEIN-PE Buller et al. 2012 Rivaroxaban	431.0	4	1	1	0.93 (0.25 – 2.36)	0.23 (0.01 – 1.29)	0.23 (0.01 – 1.29)	11.0
XALIA Ageno et al. 2016 Rivaroxaban	388.0	1	1	0	0.26 (0.01 – 1.43)	0.26 (0.01 – 1.43)	0.00 (0.00 – 0.95)	10.5
HOKUSAI-VTE Raskob et al. 2016 Edoxaban	996.0	6	1	0	0.60 (0.22 – 1.31)	0.10 (0.08 – 0.56)	0.00 (0.00 – 0.37)	14.5
REVERSE II Rodger et al. 2017 DOAC	336.0	4	---	0	1.19 (0.33 – 3.02)	---	0.00 (0.00 – 1.09)	9.8
EINSTEIN-Choice Weitz et al. 2017 Rivaroxaban 10mg	325.0	2	0	0	0.62 (0.07 – 2.21)	0.00 (0.00 – 1.13)	0.00 (0.00 – 1.13)	9.6

Rivaroxaban 20 mg	294.0	3	2	0	1.02 (0.21 – 2.95)	0.68 (0.08 – 2.44)	0.00 (0.00 – 1.25)	9.1
XALIA-LEA								
Kreutz et al. 2019								
Rivaroxaban	209.0	1	0	0	0.48 (0.01 – 2.64)	0.00 (0.00 – 1.75)	0.00 (0.00 – 1.75)	7.5
Vedovati et al. 2020	303.0	10	3	1	3.30 (1.59 – 5.99)	0.99 (0.21 – 2.87)	0.33 (0.01 – 1.83)	9.3
Wells et al. 2020								
DOAC	150.0	5	0	0	3.33 (1.09 – 7.61)	0.00 (0.00 – 2.43)	0.00 (0.00 – 2.43)	6.1
POOLED	**3768.0**	**40**	**9**	**2**	**1.20 (0.74 – 1.77)** I^2=50%	**0.31 (0.15-0.53)** I^2=0%	**0.11 (0.03-0.24)** I^2=0%	**100.0**
Cohorts with duration of initial anticoagulant treatment of exclusively 3 months	2560.0	24	7	2	1.02 (0.46 – 1.80) I^2=50%	0.33 (0.14 – 0.60) I^2=7%	0.11 (0.02 – 0.28) I^2=0%	
Year 2								
XALIA								
Ageno et al. 2016								
Rivaroxaban	24.0.	0	0	0	0.00 (0.00 – 15.37)	0.26 (0.01 – 1.43)	0.00 (0.00 – 0.95)	21.2
XALIA-LEA								
Kreutz et al. 2019								
Rivaroxaban	9.0	0	0	0	0.00 (0.00 – 33.63)	0.00 (0.00 – 33.63)	0.00 (0.00 – 33.63)	8.2
Wells et al. 2020								
DOAC	81.0	0	0	0	0.00 (0.00-4.45)	0.00 (0.00-4.45)	0.00 (0.00-4.45)	70.6
POOLED	---	---	---	---	---	---	---	---
Years 3 - 5								
Wells et al. 2020								
DOAC	52.1	0	0	0	0.0 (0.0 – 7.09)	0.0 (0.0 – 7.09)	0.0 (0.0 – 7.09)	

---, insufficient data to estimate pooled incidence; DOAC, direct oral anticoagulant.

Table S9: Risk of Major Bleeding According to Sex.

Interval of Follow-up During Extended Anticoagulation	Major Bleeding Events / Person-Years		Incidence Rate per 100 Person-Years (95% CI)	
	Women	Men	Women	Men
Year 1				
VKA	58 / 2565	66 / 4337	2.38 (1.76 – 3.08) ; I^2= 11%	1.78 (1.30 – 2.33) ; I^2= 23%
DOAC	15 / 1422	26 / 2345	1.29 (0.70 – 2.06) ; I^2= 20%	1.22 (0.70 – 1.87) ; I^2= 37%
Year 2				
VKA	21 / 1017	27 / 1690	2.06 (1.11 – 3.29) ; I^2= 19%	1.78 (1.21 – 2.47) ; I^2= 0%
DOAC	---	---	---	---
Years 3-5				
VKA	15 / 892	16 / 1663	1.44 (0.38 – 3.19) ; I^2= 53%	1.02 (0.60 – 1.57) ; I^2= 0%
DOAC	---	---	---	---
			Cumulative Incidence, % (95% CI)	
After 2 years				
VKA			4.4% (2.9% – 6.3%)	3.5% (2.5% – 4.7%)
DOAC			---	---
After 5 years				
VKA			8.5% (4.0% – 15.0%)	6.5% (4.2% – 9.2%)
DOAC			---	---

---, insufficient data to estimate incidence; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

Table S10: Risk of Major Bleeding According to Age.

Interval of Follow-up During Extended Anticoagulation	Major Bleeding Events / Person-Years		Incidence Rate per 100 Person-Years (95% CI)	
	Age >65 years	Age ≤65 years	Age >65 years	Age ≤65 years
Year 1				
VKA	58 / 2776	53 / 3825	2.16 (1.49 – 2.95) ; I^2= 31%	1.50 (1.14 – 1.91) ; I^2= 0%
DOAC	25 / 1277	15 / 2494	2.09 (1.27 – 3.11) ; I^2= 25%	0.72 (0.39 – 1.16) ; I^2= 17%
Year 2				
VKA	26 / 1103	13 / 1433	2.17 (1.20 – 3.40) ; I^2= 21%	1.04 (0.58 – 1.63); I^2= 0%
DOAC	---	---	---	---
Years 3-5				
VKA	21 / 1080	8 / 1406	1.43 (0.45 – 2.96) ; I^2= 56%	0.63 (0.28 – 1.11) ; I^2= 0%
DOAC	---	---	---	---
			Cumulative Incidence, % (95% CI)	
After 2 years				
VKA			4.3% (2.7% – 6.2%)	2.5% (1.7% – 3.5%)
DOAC			---	---
After 5 years				
VKA			8.3% (4.0% – 14.3%)	4.4% (2.5% – 6.7%)
DOAC			---	---

---, insufficient data to estimate incidence; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

Table S11: Risk of Major Bleeding According to Site of Initial Venous Thromboembolism.

Interval of Follow-up During Extended Anticoagulation	Major Bleeding Events / Person-Years			Incidence Rate per 100 Person-Years (95% CI)		
	Isolated Proximal DVT	Isolated PE	Concomitant PE and DVT	Isolated Proximal DVT	Isolated PE	Concomitant PE and DVT
Overall						
VKA	68 / 4556	69 / 3547	54 / 3535	1.49 (1.16 – 1.89)	1.95 (1.51 – 2.46)	1.53 (1.15 – 1.99)
DOAC	20 / 2040	3 / 504	8 / 652	0.98 (0.60– 1.51)	0.60 (0.12 – 1.74)	1.23 (0.53– 2.42)
Year 1						
VKA	47 / 3054	41 / 1846	25 / 1639	1.68 (1.25 – 2.16) ; I^2= 0%	2.27 (1.20 – 3.66) ; I^2= 58%	1.73 (1.16 – 2.41) ; I^2= 0%
DOAC	20 / 1997	3 / 456	8 / 578	1.17 (0.45 – 2.24) ; I^2= 66%	0.97 (0.28 – 2.08) ; I^2= 0%	1.45 (0.30 – 3.11) ; I^2= 54%
Year 2						
VKA	12 / 907	19 / 847	16 / 865	1.61 (0.89 – 2.52) ; I^2= 0%	2.14 (1.03 – 3.62) ; I^2= 29%	2.24 (0.76 – 4.47) ; I^2= 30%
DOAC	---	---	---	---	---	---
Years 3-5						
VKA	9 / 595	9 / 854	13 / 1031	1.22 (0.13 – 3.39) ; I^2= 55%	1.13 (0.38 – 2.28) ; I^2= 30%	1.38 (0.76 – 2.18) ; I^2= 0%
DOAC	---	---	---	---	---	---
				Cumulative Incidence, % (95% CI)		
After 2 years						
VKA				3.3% (2.1% – 4.6%)	4.4% (2.2% – 7.1%)	3.9% (1.9% – 6.8%)
DOAC				---	---	---
After 5 years						
VKA				6.8% (2.5% – 14.0%)	7.6% (3.3% – 13.3%)	7.9% (4.1% – 12.7%)
DOAC				---	---	---

---, insufficient data to estimate incidence; DOAC, direct oral anticoagulant, DVT, deep vein thrombosis, PE, pulmonary embolism; VKA, vitamin K antagonist.

Table S12: Risk of Major Bleeding According to Creatinine Clearance.

Interval of Follow-up During Extended Anticoagulation	Major Bleeding Events / Person-Years		Incidence Rate per 100 Person-Years (95% CI)	
	Creatinine clearance <50 mL/min	Creatinine clearance ≥50 mL/min	Creatinine clearance <50 mL/min	Creatinine clearance ≥50 mL/min
Year 1				
VKA	10 / 437	70 / 4030	2.74 (1.42 – 4.46) ; I^2= 0%	1.80 (1.36 – 2.31) ; I^2= 14%
DOAC	2 / 224	32 / 3216	1.54 (0.36 – 3.54) ; I^2= 0%	1.13 (0.63 – 1.77) ; I^2= 54%
Year 2				
VKA	9 / 187	27 / 1761	5.33 (2.60 – 8.96) ; I^2= 0%	1.04 (0.58 – 1.63); I^2= 0%
DOAC	---	---	---	---
Years 3-5				
VKA	9 / 192	22 / 2059	5.33 (1.35 – 11.75) ; I^2= 55%	1.12 (0.71 – 1.62) ; I^2= 0%
DOAC	---	---	---	---
			Cumulative Incidence, % (95% CI)	
After 2 years				
VKA			7.9% (4.0% – 13.0%)	2.8% (1.9% – 3.9%)
DOAC			---	---
After 5 years				
VKA			21.9% (7.8% – 40.2%)	6.0% (4.0% – 8.5%)
DOAC			---	---

---, insufficient data to estimate incidence; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

Table S13: Risk of Major Bleeding According to History of Bleeding.

Interval of Follow-up During Extended Anticoagulation	Major Bleeding Events / Person-Years		Incidence Rate per 100 Person-Years (95% CI)	
	History of Bleeding	No History of Bleeding	History of Bleeding	No History of Bleeding
Year 1				
VKA	4 / 138	74 / 4090	3.97 (1.40 – 7.77) ; I^2= 0%	1.84 (1.35 – 2.41) ; I^2= 27%
DOAC	9 / 96	27 / 3336	9.75 (4.31 – 17.09) ; I^2= 0%	0.91 (0.56 – 1.36) ; I^2= 28%
Year 2				
VKA	9 / 187	27 / 1761	6.79 (1.85 – 14.50) ; I^2= 0%	1.87 (1.02 – 2.97); I^2= 32%
DOAC	---	---	---	---
Years 3-5				
VKA	1 / 40	26 / 1724	4.04 (0.25 – 12.09) ; I^2= 0%	3.23 (0.05 – 11.08) ; I^2= 70%
DOAC	---	---	---	---
			Cumulative Incidence, % (95% CI)	
After 2 years				
VKA			10.5% (3.2% – 21.1%)	3.7% (2.4% – 5.3%)
DOAC			---	---
After 5 years				
VKA			20.9% (3.9% – 46.4%)	12.7% (2.5% – 33.4%)
DOAC			---	---

---, insufficient data to estimate incidence; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

Table S14: Risk of Major Bleeding According to Concomitant Use of Antiplatelet Therapy.

Interval of Follow-up During Extended Anticoagulation	Major Bleeding Events / Person-Years		Incidence Rate per 100 Person-Years (95% CI)	
	Concomitant Antiplatelet Therapy	No Concomitant Antiplatelet Therapy	Concomitant Antiplatelet Therapy	No Concomitant Antiplatelet Therapy
Year 1				
VKA	14 / 3820	79 / 4536	4.31 (2.52 – 6.55) ; I^2= 0%	1.78 (1.34 – 2.28) ; I^2= 20%
DOAC	3 / 137	33 / 3225	3.53 (1.13 – 7.19) ; I^2= 0%	1.37 (0.58 – 1.88) ; I^2= 64%
Year 2				
VKA	14 / 232	29 / 1981	5.58 (2.46 – 9.87) ; I^2= 26%	1.34 (0.57 – 2.44); I^2= 53%
DOAC	---	---	---	---
Years 3-5				
VKA	4 / 198	27 / 2204	2.24 (0.32 – 5.81) ; I^2= 36%	1.21 (0.69 – 1.87) ; I^2= 15%
DOAC	---	---	---	---
			Cumulative Incidence, % (95% CI)	
After 2 years				
VKA			9.6% (4.9% – 15.8%)	3.1% (1.9% – 4.7%)
DOAC			---	---
After 5 years				
VKA			15.6% (5.8% – 29.6%)	6.6% (3.9% – 9.9%)
DOAC			---	---

---, insufficient data to estimate incidence; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

Table S15: Risk of Major Bleeding According to Hemoglobin Concentration.

Interval of Follow-up During Extended Anticoagulation	Major Bleeding Events / Person-Years		Incidence Rate per 100 Person-Years (95% CI)	
	Hemoglobin <100 g/L	Hemoglobin ≥100 g/L	Hemoglobin <100 g/L	Hemoglobin ≥100 g/L
Year 1				
VKA	6 / 171	74 / 4420	4.64 (2.04 – 8.22) ; I^2= 0%	1.63 (1.08 – 2.28) ; I^2= 50%
DOAC	2 / 80	29 / 3202	3.91 (0.85 – 9.05) ; I^2= 0%	1.01 (0.60 – 1.53) ; I^2= 39%
Year 2				
VKA	0 / 79	36 / 1989	0.0 (0.0 – 4.67) ; I^2= 26%	1.46 (0.53 – 2.83); I^2= 68%
DOAC	---	---	---	---
Years 3-5				
VKA	1 / 85	30 / 2168	3.98 (0.59 – 21.23) ; I^2= 61%	1.44 (0.98 – 1.99) ; I^2= 0%
DOAC	---	---	---	---
			Cumulative Incidence, % (95% CI)	
After 2 years				
VKA			4.6% (2.0% – 12.5%)	3.1% (1.6% – 5.0%)
DOAC			---	---
After 5 years				
VKA			15.6% (3.8% – 57.2%)	7.2% (4.5% – 10.6%)
DOAC			---	---

---, insufficient data to estimate incidence; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

Table S16: Incidence of Major Bleeding According to Study Design.

Interval of Follow-up During Extended Anticoagulation	Study Cohorts No.		Major Bleeding Events / Person-Years		Incidence Rate per 100 Person-Years (95% CI)	
	RCT	Cohort	RCT	Cohort	RCT	Cohort
Overall						
VKA	12	12	55 / 3025	152 / 9225	1.95 (1.31 – 2.71) ; I^2= 39%	1.61 (1.09 – 2.30); I^2= 69%
DOAC	6	5	19 / 2382	21 / 1553	0.89 (0.55 – 1.30) ; I^2= 0%	1.34 (0.50 – 2.58) ; I^2= 69%
Year 1						
VKA	12	12	49 / 2519	79 / 4470	2.16 (1.47 – 2.97) ; I^2= 26%	1.90 (1.31 – 2.60) ; I^2= 46%
DOAC	6	5	19 / 2382	21 / 1386	0.89 (0.55 – 1.30) ; I^2= 0%	1.56 (0.53 – 3.11) ; I^2= 73%
Year 2						
VKA	7	9	6 / 506	42 / 2200	1.35 (0.51 – 2.59) ; I^2= 5%	1.79 (0.90 – 2.97); I^2= 55%
DOAC	---	---	---	---	---	---
Years 3-5						
VKA	0	5	---	31 / 2555	---	0.95 (0.35-1.83) ; I^2= 55%
DOAC	---	---	---	---	---	---
					Cumulative Incidence, % (95% CI)	
After 2 years						
VKA					3.5% (2.0% – 5.5%)	3.7% (2.2% – 5.5%)
DOAC					---	---
After 5 years						
VKA					---	6.4% (3.2% – 10.6%)
DOAC					---	---

---, insufficient data to estimate incidence; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

Table S17: Case-Fatality Rate of Major Bleeding.

Source	**Fatal Bleeding**	**Major Bleeding**	**Case-Fatality Rate, %** (95% CI)	**% Weight**
WODIT-DVT	0	4	0.0 (0.0 – 60.2)	1.7
WODIT-PE	0	2	0.0 (0.0 – 84.2)	0.9
PROLONG	0	1	0.0 (0.0 – 97.5)	0.6
AESOPUS	0	2	0.0 (0.0 – 84.2)	0.9
AUREC-FVIII	0	1	0.0 (0.0 – 97.5)	0.6
PROLONG II	0	3	0.0 (0.0 – 70.8)	1.3
EINSTEIN-DVT (Rivaroxaban)	0	2	0.0 (0.0 – 84.2)	0.9
EINSTEIN-DVT (VKA)	1	4	25.0 (0.60 – 80.6)	1.7
EINSTEIN-Extension	0	2	0.0 (0.0 – 84.2)	0.9
DACUS	0	3	0.0 (0.0 – 70.8)	1.3
EINSTEIN-PE (Rivaroxaban)	1	4	25.0 (0.60 – 80.6)	1.7
EINSTEIN-PE (VKA)	2	12	16.7 (2.1 – 48.4)	4.7
DULCIS	1	13	7.7 (0.2 – 36.0)	5.1
DODS	0	4	0.0 (0.0 – 60.2)	1.7
PADIS-PE	0	4	0.0 (0.0 – 60.2)	1.7
PISA-PEET	3	5	60.0 (14.7 – 94.7)	2.1
SWITCO65+	0	23	0.0 (0.0 – 14.8)	8.9
XALIA (Rivaroxaban)	0	1	0.0 (0.0 – 97.5)	0.6
XALIA (VKA)	0	7	0.0 (0.0 – 41.0)	2.8
HOKUSAI-VTE (Edoxaban)	0	6	0.0 (0.0 – 45.9)	2.5
HOKUSAI-VTE (VKA)	3	14	21.4 (4.7 – 50.8)	5.5
MORGAGNI	0	2	0.0 (0.0 – 84.2)	0.9
REVERSE II (DOAC)	1	4	0.0 (0.0 – 60.2)	1.7
REVERSE II (VKA)	1	17	5.9 (0.1 – 28.7)	6.6
EINSTEIN-Choice (Rivaroxaban 10mg)	0	2	0.0 (0.0 – 84.2)	0.9
EINSTEIN-Choice (Rivaroxaban 20mg)	0	3	0.0 (0.0 – 70.8)	1.3
XALIA-LEA (Rivaroxaban)	0	1	0.0 (0.0 – 97.5)	0.6
XALIA-LEA (VKA)	0	1	0.0 (0.0 – 97.5)	0.6
Vedovati et al.	1	10	10.0 (0.3 – 44.5)	4.0
ExACT	0	9	0.0 (0.0 – 33.6)	3.6
VISTA	0	2	0.0 (0.0 – 84.2)	0.9
Wells et al. (DOAC)	0	5	0.0 (0.0 – 52.2)	2.1
Wells et al. (VKA)	4	74	5.4 (1.5 – 13.3)	28.2
POOLED	**17**	**247**	**8.4 (5.4 – 12.1) ;** I^2 = 0%	**100.0**

DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

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CHAPTER 5

Long-term Risk of Recurrent Venous Thromboembolism Among Patients Receiving Extended Oral Anticoagulant Therapy for First Unprovoked Venous Thromboembolism

A Systematic Review and Meta-Analysis

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Preface to Chapter 5

The aim of the systematic review and meta-analysis, presented in this Chapter, was to determine the incidence of recurrent venous thromboembolism (including fatal pulmonary embolism) among patients with a first unprovoked VTE that are receiving extended anticoagulation (up to 5 years) with direct oral anticoagulants or vitamin K antagonists. The author contributions are outlined on page 157 and the study appendix starts on page 172.

ABSTRACT

Background: The long-term risk for recurrent venous thromboembolism (VTE) during extended anticoagulation for a first unprovoked VTE is uncertain.

Objectives: To determine the incidence of recurrent VTE during extended anticoagulation up to 5 years in patients with a first unprovoked VTE.

Methods: MEDLINE, EMBASE, and the Cochrane CENTRAL were searched to identify randomized trials and prospective cohort studies reporting recurrent VTE among patients with a first unprovoked VTE who were to receive anticoagulation for a minimum of 6 additional months after completing ≥3 months of initial treatment. Unpublished data on number of recurrent VTE and person-years, obtained from authors of included studies, were used to calculate study-level incidence rate, and random-effects meta-analysis was used to pool results.

Results: Twenty-six studies and 15, 603 patients were included in the analysis. During 11, 631 person-years of follow-up, the incidence of recurrent VTE and fatal pulmonary embolism per 100 person-years was 1.41 (95% CI, 1.03-1.84) and 0.09 (0.04-0.16), with 5-year cumulative incidences of 7.1% (3.0%-13.2%) and 1.2% (0.4%-4.6%), respectively. The incidence of recurrent VTE was 1.08 (95% CI, 0.77-1.44) with direct oral anticoagulants and 1.55 (1.01-2.20) with vitamin K antagonists. The case-fatality rate of recurrent VTE was 4.9% (95% CI, 2.2%-8.7%).

Conclusions: In patients with a first unprovoked VTE, the long-term risk of recurrent VTE during extended anticoagulation is low but not negligible. Thus, clinicians and patients should be aware of this risk and take appropriate and timely action in case of suspicion of recurrent VTE. Estimates from this study can be used to advise patients on what to expect while receiving

extended anticoagulation, and estimate the net clinical benefit of extended treatment to guide long-term management of unprovoked VTE.

ESSENTIALS

- Long-term risk of recurrent VTE during extended anticoagulation for unprovoked VTE is uncertain.
- We examined this risk in a systematic review and meta-analysis of 26 studies and 15,603 patients.
- Incidence of recurrent VTE was 1.4 per 100 person-years, with a cumulative 5-year risk of 7%.
- This information can help advise patients on what to expect while receiving extended anticoagulation.

INTRODUCTION

Anticoagulant therapy is the mainstay of treatment for venous thromboembolism (VTE), and should be continued for at least 3 to 6 months.[1-3] Continuing anticoagulation beyond the initial 3-6 months of treatment (termed extended anticoagulation) is often considered for patients at high risk of recurrent VTE after discontinuing anticoagulation,[1-3] such as those with a first unprovoked or weakly provoked (i.e., associated with minor transient risk factors) VTE.4 When deciding whether to extend anticoagulation, knowledge of the long-term risk for recurrent VTE while receiving treatment is an important prognostic consideration which, depending upon the comfort level of clinicians and patients about an acceptably low risk of recurrent VTE, may influence decisions about continuing anticoagulation. Also, estimates for the absolute reduction in recurrent VTE and increase in major bleeding with continuing anticoagulation, as well as their combined effect on mortality are required for balancing the benefits and harms of extended anticoagulation to guide treatment duration.[5] In a recent meta-analysis, we determined that the overall incidence of major bleeding during extended anticoagulation for a first unprovoked or weakly provoked VTE was 1.74 events per 100 person-years (95% CI, 1.34-2.20) with vitamin K antagonists (VKA) and 1.12 events per 100 person-years (95% CI, 0.72-1.62) with direct oral anticoagulants (DOACs), with case-fatality rates of 8.3% and 9.7% with VKAs and DOACs, respectively.[6] In contrast, precise estimates for the incidence of recurrent VTE during extended anticoagulation are lacking, and as a result, advising patients on what to expect while receiving extended anticoagulation and estimating the net clinical benefit of extended treatment to guide long-term management remain difficult.

In a previous Cochrane systematic review of randomized controlled trials (RCTs) comparing different duration of anticoagulant therapy, Middeldorp and colleagues reported that

30 of 1771 (1.6%) patients from 10 RCTs receiving extended anticoagulation with VKAs experienced recurrent VTE.[7] However, that meta-analysis did not examine the risk of recurrent VTE over time, or measure the clinical impact of recurrent VTE (i.e., risk of fatal pulmonary embolism [PE] and case-fatality rate of recurrent VTE), and only included RCTs published up to May 2009. Since then, several prospective studies assessing extended treatment for unprovoked VTE, including studies of DOACs, have been published. Synthesis of this contemporary evidence to obtain precise estimates for the absolute effects of extended anticoagulation on recurrent VTE (and VTE-related mortality) can help inform prognosis and decision making about treatment duration for this group of patients.

Thus, in this systematic review and meta-analysis, we aimed to determine the incidence and clinical impact of recurrent VTE among patients with a first unprovoked or weakly provoked VTE receiving extended anticoagulation up to 5 years.

METHODS

This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.[8] The study protocol is registered in PROSPERO (CRD42019128597) and provided in **Appendix 1**.

Search Strategy and Study Selection

MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched from inception to July 23, 2021, without language restrictions. The search strategy used for EMBASE is presented in **Table S1** in **Appendix 2**. We also consulted content experts to identify other potentially eligible studies.

Two authors independently screened titles, abstracts, and full text publications to select studies which met the following eligibility criteria: (1) RCT or a prospective cohort study including patients with a first, objectively confirmed, symptomatic VTE categorized as either unprovoked or provoked by minor transient risk factors according to the International Society on Thrombosis and Haemostasis (ISTH) definition;[9] (2) patients were to receive oral anticoagulant therapy with an approved regimen for a minimum of 6 additional months after completing at least 3 months of initial anticoagulation; and (3) recurrent VTE (as defined by the study authors) was reported during extended anticoagulation. In the case of multiple articles reporting on duplicate patient populations, we included the publication with the longest duration of follow-up. Disagreements were resolved through discussion or by consulting a third author.

Data Extraction

Two authors independently extracted data. Disagreements were resolved through discussion or by consulting a third author. The following data were extracted: study design, duration of initial anticoagulant treatment; number of patients with first unprovoked VTE who had completed at least 3 months of initial anticoagulant treatment, maximum duration of follow-up, patient characteristics at baseline (including sex and location of initial VTE), anticoagulant regimen used during extended treatment, definition of unprovoked VTE, and definition of recurrent VTE and fatal PE. We contacted the principal investigators of each potentially relevant study to request aggregate data on the number of recurrent VTE (and fatal PE) events, and the number of person-years (to appropriately censor deaths, and patients lost to follow-up or withdrawn from the study) during extended anticoagulation among patients with a first unprovoked VTE. Our request to study authors also ensured that these aggregate data excluded recurrent VTE events

occurring off anticoagulant treatment, as well as patients with cancer, a history of VTE, or those who had not completed at least 3 months of initial anticoagulant treatment.

Risk of Bias Assessment

We assessed all studies, including each arm of a RCT, as an independent observational cohort given our study aim of calculating the incidence of recurrent VTE during follow-up of patients receiving extended anticoagulation. As such, two authors independently appraised risk of bias among the included studies using a modified version of the Newcastle-Ottawa Scale,[10] with clarifications requested from the study's authors when necessary. Studies that scored ≥4 points on the Newcastle-Ottawa Scale were considered at low risk of bias.[4]

Data Synthesis and Analysis

We determined the incidence of a first recurrent VTE per 100 person-years for each study cohort using the number of events and person-years of follow-up obtained from the authors of included studies. Data across studies were pooled using random effects meta-analysis weighting studies according to their inverse variance.[11]

We categorized the incidence of recurrent VTE into three intervals of follow-up: year 1, year 2, and years 3-5. We estimated the cumulative incidence of recurrent VTE after 2 and 5 years of extended anticoagulation using our calculated incidence rates (based on person-time at risk during each of the studied intervals) as follows[4]:

if the incidence of recurrent VTE (per 100 person-years) was 4.0 events in *year 1*, 3.5 events in *year 2*, and 3.0 events in *years 3-5*, then the proportion of patients who *did not* experience recurrent VTE in *years 1-5* was estimated as $(96.0\%_{year\ 1}) \times (96.5\%_{year\ 2}) \times$

$([97.0\%]^{3}_{years\ 3\text{-}5}) = 84.6\%$. The cumulative incidence of recurrent VTE in *years 1-5* was then estimated as $100\% - 84.6\% = 15.4\%$.

Similarly, the lower and upper bounds of the 95% confidence intervals (CIs) associated with the incidence rates were used to estimate the lower and upper bounds of the 95% CI for the cumulative incidences.

To measure the clinical impact of recurrent VTE, we determined the incidence of fatal PE and calculated case-fatality rate of recurrent VTE from the total number of fatal PE events divided by the total of recurrent VTE events. We excluded one study[12] from our calculations of the pooled incidence of fatal PE and the pooled case-fatality rate of recurrent VTE because fatal PE was not prospectively adjudicated but rather ascertained using ICD 9-CM classification.

The I^2 statistic was used to quantify between-study heterogeneity with I^2 values of 25%, 50%, and 75% defined as low, moderate, and high heterogeneity, respectively.[13] StatsDirect Version 3.3.5 (Merseyside, United Kingdom)) was used to perform all meta-analyses.[14]

Subgroup and Sensitivity Analyses

We conducted subgroup analyses based on the type of anticoagulant used during extended anticoagulation (VKA vs. DOACs) and study design (RCT vs. prospective cohort), and computed the incidence rate ratio [IRR] to statistically compare incidence of recurrent VTE between subgroups. We also performed sensitivity analyses restricted to studies in which the duration of initial anticoagulant treatment was exclusively 3 months, and excluding study cohorts whose recurrent VTE rates were outliers (defined as studies whose 95% CI did not overlap with the 95% CI of the pooled estimate).

RESULTS

A total of 5219 citations were identified from systematic literature search. Screening of titles and abstracts identified 75 records deemed eligible for full-text screening. Twenty-eight studies (supplemented with 9 additional studies identified from other sources) were considered potentially relevant for inclusion after review of full-texts (**Figure 1**). After contacting the authors of these 37 potentially relevant studies for further clarification of data in our target patient population, 10 studies[15-24] were deemed ineligible and were excluded (9 due to wrong patient population, 1 due to primary outcome not reported) (**Table S2 in Appendix 2**). Among the remaining 27 studies deemed eligible for inclusion in the meta-analysis, data required for our analysis were obtained from 26 studies while 1 study[25] was excluded because information required for our analysis was unavailable (**Figure 1** and **Table S2 in Appendix 2**).

Characteristics of Included Studies and Patients

Of the 26 included studies,[12,26-49] 14 were RCTs and 12 were prospective cohort studies with a total of 15, 603 patients with a first unprovoked or weakly provoked VTE who, after having completed at least 3 months of initial anticoagulant treatment, received extended anticoagulation (**Table 1**). The duration of initial anticoagulant treatment was exclusively 3 months in 12 studies (**Table 1**). All 26 studies (33 independent study cohorts) contributed to the 'year 1' interval, 15 studies (17 cohorts) contributed to the 'year 2' interval, and 4 studies (4 cohorts) contributed to the 'years 3-5' interval of follow-up during extended anticoagulation (**Table 1**). All included studies used common criteria[43] for the definition of recurrent VTE – individual study definitions are provided in **Table S3** in **Appendix 2**.

The overall risk of bias in individual studies was considered to be low (**Table 1**) – scores for the individual Newcastle-Ottawa Scale components are provided in **Table S4** in **Appendix 2**.

Risk of Recurrent VTE and Fatal PE

During 11, 631 person-years of follow-up, there were a total of 171 recurrent VTE events (1.41 per 100-person years; 95% CI, 1.03-1.84), and 3 fatal PE (0.09 per 100-person years; 95% CI, 0.04-0.16) (**Table 2**). Incidences in individual study cohorts during each of the studied intervals are provided in **Table S5** in **Appendix 2**.

The pooled incidence of recurrent VTE per 100 person-years was 1.46 (95% CI, 1.11-1.86) in year 1, 1.90 (95% CI, 0.89-3.28) in year 2, and 1.32 (95% CI, 0.34-2.92) in years 3-5. The pooled incidence of fatal PE per 100-person years was 0.10 events (95% CI, 0.04-0.17) in year 1, 0.0 events (95% CI, 0.0-0.23) in year 2, and 0.38 events (95% CI, 0.0-1.41) in years 3-5 (**Table 2**).

The cumulative incidence of recurrent VTE and fatal PE was 3.3% (95% CI, 2.0%-5.1%) and 0.1% (95% CI, 0.1%-0.4%) after 2 years, and 7.1% (95% CI, 3.0%-13.2%) and 1.2% (95% CI, 0.4%-4.6%) after 5 years, respectively (**Table 2**).

There was evidence of moderate heterogeneity for recurrent VTE (I^2 range, 47%-61%) – estimates for the overall incidence of recurrent VTE in individual studies ranged from 0.0 (95% CI, 0.0-4.06) to 7.03 (95% CI, 4.22-10.88), and low heterogeneity for fatal PE (I^2 range, 0%-20%) (**Table S5** in **Appendix 2).**

Subgroup Analyses

Type of Anticoagulant. There were 10 study cohorts (7064 patients) that received extended anticoagulation with DOACs and 23 study cohorts (8539 patients) that received extended treatment with VKAs (**Table 1**). The incidence of recurrent VTE per 100 person-years was 1.08

(95% CI, 0.77-1.44) with DOACs and 1.55 (95% CI, 1.01-2.20) with VKAs (IRR, 0.59; 95% CI, 0.39-0.85) (**Table 3**). The incidence of fatal PE per 100 person-years was 0.09 (95% CI, 0.02-0.21) with DOACs and 0.10 (95% CI, 0.03-0.18) with VKAs (**Table 3**). There were insufficient data to estimate incidence of recurrent VTE and fatal PE beyond 1 year of extended anticoagulation with DOACs (**Table 3**). The cumulative incidence of recurrent VTE and fatal PE with VKAs was 7.4% (95% CI, 3.0%-14.1%) and 1.2% 95% CI, 0.1%-4.6%) after 5 years, respectively (**Table 3**).

Study Design. There were 18 study cohorts (9578 patients) from 14 RCTs and 15 study cohorts (6025 patients) from 12 prospective cohort studies (**Table 2**). The incidence of recurrent VTE per 100 person-years was 1.40 (95% CI, 0.78-2.21) among study cohorts derived from RCTs and 1.46 (95% CI, 1.09-1.87) among those derived from prospective cohort studies (IRR, 0.99; 95% CI, 0.73-1.36) (**Table S6** in **Appendix 2**). The cumulative incidence of recurrent VTE among cohorts derived from RCTs was 3.6% (95% CI, 1.5%-8.0%) after 2 years (**Table S6** in **Appendix 2**) - there were no RCTs with follow-up beyond 2 years of extended anticoagulation with VKAs. The cumulative incidence of recurrent VTE among cohorts derived from prospective cohort studies was 3.1% (95% CI, 2.1%-4.4%) after 2 years, and 6.9% (95% CI, 3.0%-12.6%) after 5 years (**Table S6** in **Appendix 2**).

Case-Fatality Rate of Recurrent VTE

The pooled case-fatality rate of recurrent VTE was 4.9% (95% CI, 2.1%-8.7%) (**Table 4** and **Table S7** in **Appendix 2**) with any anticoagulant, 4.2% (95% CI, 1.3%-8.4%) with VKAs, and 7.3% (95% CI, 1.4%-17.1%) with DOACs (**Table 4**).

Sensitivity Analyses

Incidences of recurrent VTE in the primary analysis were similar when analyses were restricted to studies in which the duration of initial anticoagulant treatment was exclusively 3 months, or excluding 3 study cohorts (n=1390) whose recurrent VTE event rates were outliers (**Table S5** in **Appendix 2**).

DISCUSSION

Our comprehensive systematic review and meta-analysis demonstrates the considerable long-term risk and clinical impact of recurrent VTE while receiving extended anticoagulant therapy, with a 5-year cumulative incidence of 7% and a case-fatality rate of 5%. This information has important implications for clinical practice. Firstly, the diagnosis and management of recurrent VTE in patients receiving anticoagulation therapy remain difficult.[50,51] Suspected recurrent VTE is common[52] but given the high efficacy established for oral anticoagulants in the secondary prevention of VTE, clinicians and patients assume that anticoagulant therapy offers near-total protection against recurrent VTE. However, the possibility of a recurrent VTE during anticoagulant therapy should not be dismissed. In our study, we showed that recurrent VTE during extended anticoagulation represents a considerable long-term burden – 1 in every 14 patients receiving anticoagulant therapy would be expected to experience a recurrent VTE within 5 years. Thus, while our results may reassure patients that their prognosis while receiving extended anticoagulation is good, with a low (less than 2% per year) risk of recurrent VTE, the risk is not zero and clinicians ought to keep a low threshold for suspicion of recurrent VTE in patients receiving extended anticoagulant therapy for unprovoked VTE, and perform thorough diagnostic investigations for suspected recurrent VTE.[51] Similarly, patients should be aware of

the risk of recurrent VTE while receiving extended anticoagulation and seek medical attention if they experience signs and symptoms of recurrent VTE.

Also, knowledge of the time course of recurrent VTE during extended anticoagulation may aid clinicians decide about the frequency of clinical surveillance of patients with VTE in whom indefinite anticoagulation is to be considered. Unlike the risk of recurrent VTE after discontinuing anticoagulation which varies considerably over time[4], the annual incidence of recurrent VTE in our analysis appeared to be similar in each of the studied time intervals of extended anticoagulation – a finding that supports current guideline recommendations that patients receiving indefinite anticoagulation for VTE should be reviewed regularly to ensure that persistence with the therapeutic strategy remains appropriate.[3]

Secondly, guideline recommendations for the secondary prevention of VTE need to be based on robust absolute risks of both recurrent VTE and major bleeding during extended anticoagulant therapy, as these risks are the key determinants of the magnitude of treatment benefits and harms. The American College of Chest Physicians 2016 guidelines and the American Society of Hematology 2020 guidelines suggest indefinite anticoagulation over discontinuing anticoagulation in patients with a first unprovoked proximal DVT and/or PE who have completed at least 3-6 months of initial treatment, unless the risk of major bleeding is deemed high.[2, 3] These guidelines also acknowledge that there is a paucity of data on the absolute risk of recurrent VTE during extended anticoagulation – our meta-analysis is the largest study, to our knowledge, that provides precise estimates for the risk of recurrent VTE among patients with a first unprovoked or weakly provoked VTE receiving extended anticoagulant treatment. Using the 1-year risk of recurrent VTE after discontinuing anticoagulation of 10.3 per 100 persons (95% CI, 8.6-12.1)[4], and the 1-year estimates for the risk of recurrent VTE during extended

anticoagulation determined in this meta-analysis, the anticipated *absolute* reductions in recurrent VTE would be 8.6 (95% CI, 9.7-7.4) fewer events per 100 persons receiving extended anticoagulation with VKAs and 9.2 (95% CI, 10.6-7.8) fewer events per 100 persons receiving extended anticoagulation with DOACs, which are in line with the *relative* risk reductions documented in RCTs evaluating extended anticoagulation versus placebo.[53]

Strengths of this systematic review include a comprehensive search with inclusion of unpublished data from studies with an overall low risk of bias. Moreover, while many of the studies included in our analysis also included patients with VTE provoked by major transient or persistent risk factors, as well as patients with a history of VTE, we extracted (with help from study authors) and combined data on >15,000 patients specifically with a first unprovoked or weakly provoked VTE who were prospectively followed for recurrent VTE during extended anticoagulant therapy. We also standardized different durations of follow-up across study cohorts and used exact person-time at risk during each of the studied intervals to assess recurrent VTE risk over time. Limitations of this study include limited data (from insufficient number of studies) to compare recurrent VTE risk between reduced vs. therapeutic dose DOACs, and lack of long-term (beyond 1 year) data on patients receiving extended anticoagulation with DOACs. Also, owing to resource and time constraints as well as access to individual patient-level data specifically from the industry-sponsored studies included in our analysis, we did not elect to perform a meta-analysis of individual patient data which would have allowed us to compute direct estimates for the cumulative incidence of recurrent VTE over time, account for death from causes other than PE as a competing event for recurrent VTE, explore potential sources to explain the moderate-level heterogeneity observed between studies, and investigate clinical risk factors or reasons (e.g., non-adherence to drug dosing) for the occurrence of recurrent VTE

during anticoagulation. Finally, 11 studies did not provide a definition for fatal PE, whereas 13 of the 15 studies that provided a definition for fatal PE classified unexplained deaths as PE-related – the latter may have led to an overestimation of our estimates for the incidence of fatal PE and case-fatality rate of recurrent VTE.[54, 54]

In conclusion, the long-term risk of recurrent VTE in patients with a first unprovoked or weakly provoked VTE receiving extended oral anticoagulation is low but not negligible. Contemporary estimates for the risk of recurrent VTE and fatal PE along with the case-fatality rate of recurrent VTE, synthesized in this systematic review and meta-analysis, can be used by clinicians to advise patients on what to expect while receiving extended anticoagulation. Furthermore, when combined with current best estimates for the risk of recurrent VTE after discontinuing anticoagulation and the risk major bleeding during extended anticoagulation, estimates from this study could be used to determine the net clinical benefit of extended treatment to guide long-term management of unprovoked VTE.

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Author Contributions

Study concept and design: **FK**, T Tritschler, MK, BH, GLG, MR, DF. *Data acquisition:* All authors. *Statistical analysis:* **FK**. *Drafting of the manuscript:* **FK**, T Tritschler, MR, DF. *Critical revision of the manuscript for important intellectual content:* All authors. *Final approval of the manuscript:* All authors.

Conflict of Interest

PW reports receiving honoraria for advisory board meetings from Bayer Healthcare, Sanofi, and Daiichi Sankyo, and Research Funding from BMS/Pfizer. JW reports serving as a consultant for which he has received honoraria from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb,

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Table 1: Characteristics of Studies and Patients Included in Meta-Analysis

Source	Study Characteristics				Patients with First Unprovoked VTE			Overall Risk of Bias
	Design	Duration of Initial Anticoagulation	Duration and Regimen During Extended Anticoagulation[a]	Definition of Unprovoked VTE[b]	Total No.	Men No. (%)	Site of initial VTE No. (%)	
WODIT-DVT Agnelli et al. 2001[26]	RCT	3 months	9 months; VKA (target INR 2.0-3.0)	ISTH	134	---	134 (100) isolated proximal DVT	Low
WODIT-PE Agnelli et al. 2003[27]	RCT	3 months	9 months; VKA (target INR 2.0-3.0)	ISTH	90	42 (47)	30 (33) isolated PE 60 (67) concomitant PE and DVT	Low
PROLONG Palareti et al. 2006[28,56]	RCT	At least 3 months	24 months; VKA (target INR 2.0-3.0)	ISTH	103	55 (53)	16 (15) isolated proximal DVT 20 (19) isolated PE 67 (65) concomitant PE and DVT	Low
AESOPUS Prandoni et al. 2009[29]	RCT	3 months	33 months; VKA (target INR 2.0-3.0)	ISTH	120	80 (67)	105 (88) isolated proximal DVT 15 (12) concomitant PE and DVT	Low
AUREC-FVIII Eischer et al. 2009[30]	RCT	6 months	24 months; VKA (target INR 2.0-3.0)	ISTH	17	5 (29)	---	Low
Palla et al. 2010[31]	Cohort	3 months	9 months; VKA (target INR 2.0-3.0)	ISTH	156	72 (46)	87 (56) isolated PE 69 (44) concomitant PE and DVT	Low
PROLONG II Cosmi et al. 2010[31]	Cohort	At least 6 months	24 months; VKA (target INR 2.0-3.0)	ISTH	104	51 (49)	74 (74) isolated proximal DVT 18 (17) isolated PE 12 (12) concomitant PE and DVT	Low
EINSTEIN-DVT Bauersachs et al. 2010[32]	RCT	3 months	9 months; Rivaroxaban (20mg) or VKA (target INR 2.0-3.0)	ISTH	1474	973 (66)	1469 (99) isolated proximal DVT	Low
EINSTEIN-Extension Bauersachs et al. 2010[33]	RCT	6-12 months	12 months; Rivaroxaban (20 mg)	ISTH	198	136 (69)	129 (65) isolated proximal DVT	Low
DACUS Siragusa et al. 2011[34]	Cohort	3 months	21 months; VKA (target INR 2.0-3.0)	ISTH	273	141 (52)	273 (100) isolated proximal DVT	Low

EINSTEIN-PE Buller et al. 2012[35]	RCT	3 months	9 months; Rivaroxaban (20 mg) or VKA (target INR 2.0-3.0)	ISTH	2160	1232 (57)	---	Low
DULCIS Palareti et al. 2014[36]	Cohort	At least 3 months	24 months; VKA (target INR 2.0-3.0)	ISTH (minor general surgery, pregnancy, puerperium, estrogen treatment, travel >6 hours, minor trauma, hospitalization for medical illness, reduced mobility)	311	189 (61)	165 (53) isolated proximal DVT 75 (24) isolated PE 71 (23) concomitant PE and DVT	Low
DODS Kearon et al. 2015[37,57]	Cohort	3-7 months	60 months; VKA (target INR 2.0-3.0)	ISTH (estrogen treatment)	67	38 (57)	33 (49) isolated proximal DVT	Low
PADIS-PE Couturaud et al. 2015[38]	RCT	6 months	18 months; VKA (target INR 2.0-3.0)	ISTH (estrogen treatment)	184	78 (42)	124 (67) isolated PE 60 (33) concomitant PE and DVT	Low
PISA-PEET Marconi et al. 2016[12]	Cohort	12 months	60 months; VKA (target INR 2.0-3.0)	ISTH	225	105 (47)	149 (66) isolated PE 76 (34) concomitant PE and DVT	Low
SWITCO65+ Hofmann et al. 2016[39]	Cohort	3 months	33 months; VKA (target INR 2.0-3.0)	ISTH	343	195 (57)	97 (28) isolated proximal DVT 199 (58) isolated PE 47 (14) concomitant PE and DVT	Low
XALIA Ageno et al. 2016[40]	Cohort	3 months	13 months; Rivaroxaban or VKA	ISTH	1702	1022 (60)	1522 (89) isolated proximal DVT 180 (11) concomitant PE and DVT	Low
HOKUSAI-VTE Raskob et al. 2016[41]	RCT	3 months	9 months; Edoxaban (60 mg) or VKA (target INR 2.0-3.0)	ISTH	3956	2400 (61)	2453 (62) isolated proximal DVT 987 (25) isolated PE 516 (13) concomitant PE and DVT	Low
MORGAGNI Prandoni et al. 2017[42]	Cohort	At least 3 months	60 months; VKA (target INR 2.0-3.0)	ISTH	103	69 (67)	73 (71) isolated proximal DVT 30 (29) concomitant PE and DVT	Low
REVERSE II Rodger et al. 2017[43]	Cohort	5-12 months	12 months; VKA (target INR 2.0-3.0) or DOAC	ISTH (estrogen treatment)	1705	1254 (74)	797 (47) isolated proximal DVT 539 (32) isolated PE 369 (22) concomitant PE and DVT	Low
EINSTEIN-Choice Weitz et al. 2017[44]	RCT	6-12 months	12 months; Rivaroxaban (10mg or 20mg)	ISTH	770	480 (62)	406 (53) isolated proximal DVT	Low
XALIA-LEA Kreutz et al. 2019[45]	Cohort	3 months	13 months; Rivaroxaban or VKA	ISTH	654	337 (52)	433 (66) isolated proximal DVT 74 (11) isolated PE 147 (22) concomitant PE and DVT	Low

PADIS-DVT Couturaud et al. 2019[46]	RCT	6 months	18 months; VKA (target INR 2.0-3.0)	ISTH (estrogen treatment)	50	31 (62)	50 (100) isolated proximal DVT	Low
Vedovati et al. 2020[47]	Cohort	3 months	9 months; DOAC	ISTH	382	210 (55)	178 (47) isolated proximal DVT 62 (16) isolated PE 142 (37) concomitant PE and DVT	Low
ExACT Bradbury et al. 2020[48]	RCT	At least 3 months	24 months; VKA (target INR 2.0-3.0)	ISTH	139	94 (67)	70 (50) isolated proximal DVT 69 (50) isolated PE	Low
VISTA Geersing et al. 2020[49]	RCT	At least 3 months	24 months; VKA (target INR 2.0-3.0)	ISTH	183	130 (71)	68 (36) isolated proximal DVT 81 (44) isolated PE 30 (16) concomitant PE and DVT	Low

Abbreviations: DOAC, direct oral anticoagulant; INR, international normalized ratio; ISTH, International Society on Thrombosis and Haemostasis; RCT, randomized controlled trial; VKA, vitamin K antagonist

[a] Maximum duration of follow-up, as applicable to the studied intervals.

[b] "ISTH" is listed for studies judged to have defined unprovoked VTE, as closely as possible, as VTE occurring in the absence of persistent or major transient provoking risk factors as defined by the ISTH. The minor transient risk factors included in the definition of unprovoked VTE are listed in brackets after "ISTH".

Table 2: Incidence of Recurrent Venous Thromboembolism.

Intervals of Follow-up During Extended Anticoagulation	Events, n		Person-Years	Event Rate per 100 Person-Years (95% CI)	
	Recurrent VTE	Fatal PE[a]		Recurrent VTE	Fatal PE[a]
Overall (entire follow-up)	171	3	11 631	1.41 (1.03 – 1.84)	0.09 (0.04 – 0.16)
Year 1	124	2	9204	1.46 (1.11 – 1.86)	0.10 (0.04 – 0.17)
Year 2	35	0	1604	1.90 (0.89 – 3.28)	0.0 (0.0 – 0.23)
2-year Cumulative Incidence, (95% CI)				3.3% (2.0% – 5.1%)	0.1% (0.1% – 0.4%)
Years 3 – 5	12	1	823	1.32 (0.34 – 2.92)	0.38 (0.0 – 1.41)
5-year Cumulative Incidence, (95% CI)				7.1% (3.0% – 13.2%)	1.2% (0.4% – 4.6%)

Abbreviations: PE, pulmonary embolism; VTE, venous thromboembolism.

[a] We excluded one study[12] (n=225) from our calculation for the incidence of fatal PE because fatal PE was not prospectively adjudicated but rather ascertained using ICD 9-CM classification.

Table 3: Incidence of Recurrent Venous Thromboembolism According to Type of Anticoagulant.

Intervals of Follow-up During Extended Anticoagulation	Events, n		Person-Years	Event Rate per 100 Person-Years (95% CI)	
	Recurrent VTE	Fatal PE		Recurrent VTE	Fatal PE
Vitamin K Antagonists[a, b]					
Overall (entire follow-up)	135	2	7995	1.55 (1.01 – 2.20)	0.10 (0.03 – 0.18)
Year 1	88	1	5600	1.73 (1.19 – 2.38)	0.11 (0.04 – 0.21)
Year 2	35	0	1571	1.92 (0.85 – 3.80)	0.0 (0.0 – 0.23)
2-year Cumulative Incidence, (95% CI)				3.6% (2.0% – 6.1%)	0.1% (0.0% – 0.4%)
Years 3 – 5	12	1	823	1.32 (0.34 – 2.92)	0.38 (0.0 – 1.41)
5-year Cumulative Incidence, (95% CI)				7.4% (3.0% – 14.1%)	1.2% (0.1% – 4.6%)
Direct Oral Anticoagulants[a]					
Overall (entire follow-up)	36	1	3636	1.08 (0.77 – 1.44)	0.09 (0.02 – 0.21)
Year 1	36	1	3603	1.09 (0.77 – 1.45)	0.09 (0.02 – 0.21)
Year 2	---	---	---	---	---
2-year Cumulative Incidence, (95% CI)				---	---
Years 3 – 5	---	---	---	---	---
5-year Cumulative Incidence, (95% CI)				---	---

Abbreviations: PE, pulmonary embolism; VTE, venous thromboembolism

[a] Among a total of 33 independent study cohorts included in the analysis, there were 23 study cohorts (n=8539) that received extended anticoagulation with vitamin K antagonists and 10 study cohorts (n=7064) that received extended anticoagulation with direct oral anticoagulants.

[b] We excluded one study[12] (n=225) from our calculation of the incidence of fatal PE because fatal PE was not prospectively adjudicated but rather ascertained using ICD 9- CM classification.

---, insufficient data to estimate incidence.

Table 4. Case-Fatality Rate of Recurrent Venous Thromboembolism.

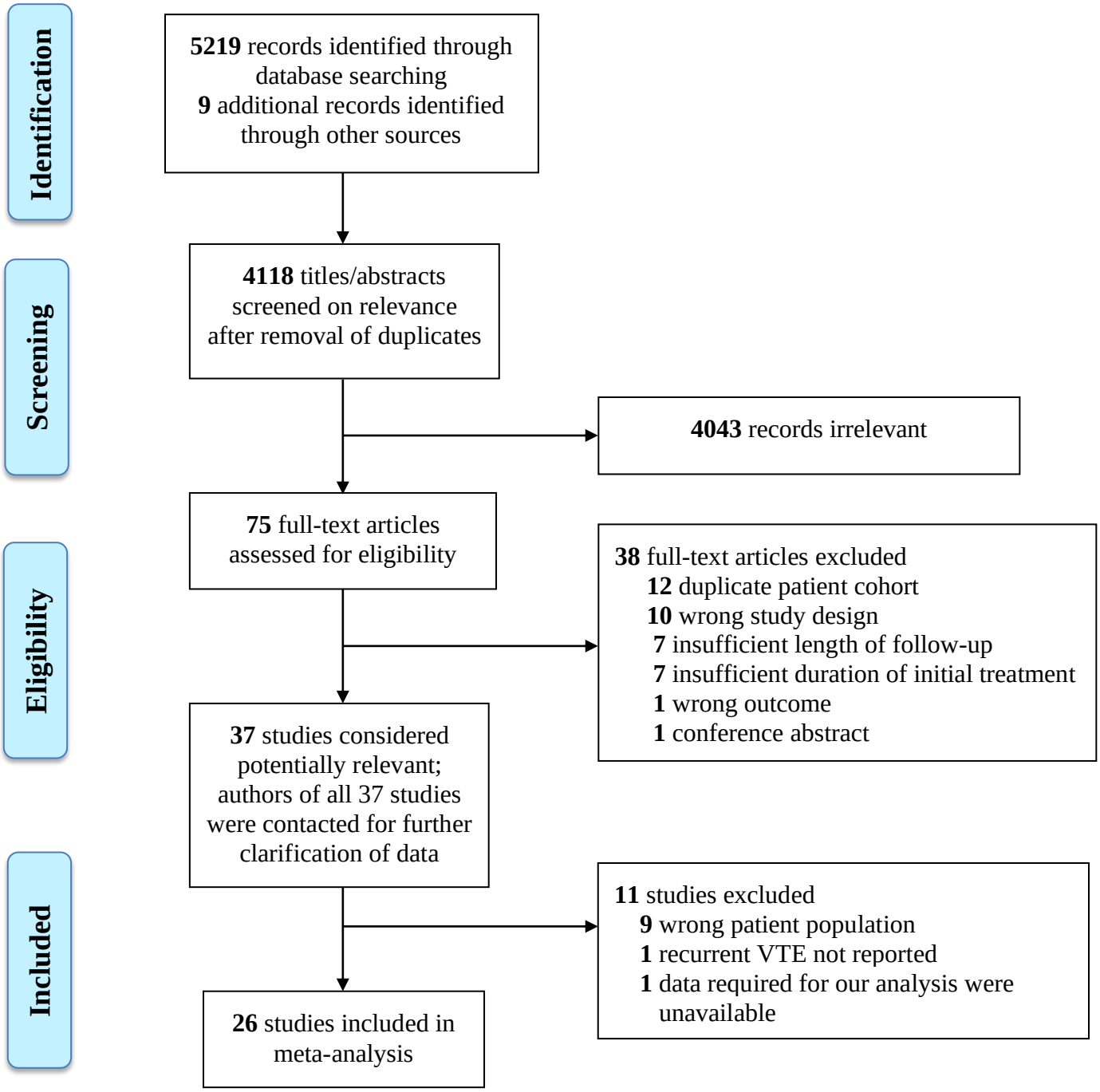
	Fatal PE, n	Recurrent VTE, n	Case-Fatality Rate, % (95% CI)
Any anticoagulant	3	149	4.9% (2.1% – 8.7%)
Vitamin K antagonists [a, b]	2	113	4.2% (1.3% – 8.4%)
Direct oral anticoagulants[a]	1	36	7.3% (1.4% – 17.1%)

Abbreviations: PE, pulmonary embolism; VTE, venous thromboembolism

[a] We excluded one study[12] (n=225) from our calculations of case-fatality rate of recurrent VTE because fatal PE was not prospectively adjudicated but rather ascertained using ICD 9- CM classification.

[b] Among a total of 33 independent study cohorts included in the analysis, there were 23 study cohorts (n=8539) that received extended anticoagulation with vitamin K antagonists and 10 study cohorts (n=7064) that received extended anticoagulation with direct oral anticoagulants.

Figure 1: Flow Diagram of Study Identification and Selection.



APPENDIX 1 – Study Protocol

Objective
The aim of this systematic review and meta-analysis will be to estimate the rate of recurrent VTE events during extended oral anticoagulation for up to 5 years in patients with a first unprovoked VTE, who have completed at least 3 months of initial treatment.

Eligibility Criteria
Studies meeting the following criteria will be included in the systematic review.

Population
The targeted group of participants will be adults with a first episode of objectively confirmed, symptomatic major VTE (proximal DVT or PE) that is either unprovoked or provoked by minor transient risk factors, according to the ISTH definition [**1**]. Patients will be eligible if they have received treatment with an approved oral anticoagulant therapy, continued for a minimum of 6 additional months beyond completion of 3 months of anticoagulation with either 1) intravenous heparin or LMWH for 3 months; or 2) intravenous heparin or LMWH for at least 5 days followed by dabigatran, edoxaban, or a vitamin K antagonist; or 3) apixaban or rivaroxaban. Studies will be excluded if they only include patients with VTE associated with major transient and/or persistent provoking risk factors according to the ISTH definition [**1**].

Interventions and Comparators
The review will include studies wherein participants have received treatment with an approved oral anticoagulant therapy, continued for a minimum of 6 additional months beyond completion of 3 months of anticoagulation. As the study objective is to establish the rate of recurrent VTE during extended anticoagulation, studies will not be required to include a comparator group. As such, all studies, including each arm of a randomized controlled trial (RCT), will be evaluated as an independent observational cohort, with follow-up starting at the time that oral anticoagulants are continued for secondary prevention (i.e., beyond completion of at least 3 months of *initial* treatment).

Outcomes
The primary outcome will be the rate of first symptomatic recurrent VTE in patients on extended oral anticoagulation.

Study Design
Studies eligible for this systematic review will consist of both RCTs and prospective cohort studies. Case reports, case series, case-control or cross sectional studies, as well as retrospective cohort and registry-based studies will be excluded.

Search Strategy
In conjunction with an information specialist, electronic databases including MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials will be systematically searched with no language restrictions. Search terms will be related to VTE, anticoagulants, and study design. We will use medical subject heading (MeSH) terms and supplement the search with

keywords and adjust vocabulary and syntax across databases. Reference lists of retrieved articles will be hand-searched to identify additional relevant studies, while grey literature will not be considered.

Data Management and Selection Process

Results from the literature search will be uploaded to Covidence [**2**]. Screening of titles/abstracts as well as full-text articles will be performed by at least 2 independent investigators of the review team. Discrepancies will be resolved by consensus discussion or by a third person if needed. The process of study selection will be presented using the PRISMA flow diagram [**3**]. In the case of published reports including duplicate patients, only the publication with the longest follow-up of patients will be included.

Data Collection

Data from included studies will be collected using a standardized data extraction form implemented in Microsoft Excel. Data extraction will be conducted by at least 2 reviewers independently, with clarifications requested from the study's authors when necessary. A third person will verify a subset of the studies to ensure accurate data collection. The standardized data extraction form will be piloted by 2 reviewers independently for the first 5 full-text articles. After comparing the results of the pilot phase for data extraction, further changes will be made to the standardized data extraction form, if needed. Disagreements between reviewers will be resolved by consensus or by a third person if required.

The following information will be collected from included studies:

d) Study information: year of study publication, author and journal information
e) Study characteristics: design, period, country(ies), funding source, and criteria used to define VTE and its etiology.
f) Participant characteristics: number of eligible patients, number of eligible male patients, age, site of initial VTE, type and dose of anticoagulant used during the initial treatment period, person-years of follow-up, and number of patients lost to follow-up.
f) Intervention characteristics: type and dose of anticoagulant agent used during the extended treatment period.
g) Outcomes: number of recurrent VTE, and fatal PE.

Outcomes and Prioritization

The primary outcome will be the rate of first symptomatic recurrent VTE during extended oral anticoagulation. Recurrent VTE is a patient-relevant outcome and the primary efficacy outcome of all recent phase III anticoagulation trials. The secondary outcome will be the rate of fatal PE during extended oral anticoagulation. The case-fatality rate of recurrent VTE during extending anticoagulation will also be calculated, from the total number of fatal PE events divided by the total number of recurrent VTE events.

Risk of Bias Assessment

At least two reviewers will independently assess the risk of bias at the individual study level. For a subset of studies, a third reviewer will verify the accuracy of the risk of bias assessment done by the first two reviewers. Conflicts will be resolved by consensus or by a third reviewer if needed. Given each arm of a RCT will be evaluated as an independent observational cohort, the

risk of bias for each study will be assessed using the Newcastle-Ottawa scale for prospective cohort studies [**4**].

Data Synthesis

The incidence rate (expressed as events per 100 person-years) of the primary and secondary outcomes will be calculated from each observational cohort from the number of events and person-years of follow-up. If feasible from the available data, these rates will be calculated and reported at standardized time intervals during extended anticoagulation (e.g., at 12, 24, 60, and 120 months following completion of the *initial* 3-6-month period of anticoagulation) to account for the different lengths of follow up from each study. To assess clinical and statistical heterogeneity, we will compare study design, patients' characteristics, and studied interventions of included studies prior to pooling results. Statistical heterogeneity will be measured using the I^2 statistic (>75% considered to represent high heterogeneity).

If meta-analysis is deemed appropriate, we will combine the total number of events and person-years of follow up across all included study cohorts to calculate an estimate of the absolute rate of recurrent VTE per 100 person-years of follow up, with cohorts weighted according to their inverse variance [**5**]. Furthermore, the cumulative incidence of recurrent VTE events at each of the standardized time intervals will be estimated from the incidence rate of recurrent VTE events at each time period.

For example, if we are able to obtain the exact person-time at risk accounting for deaths and other patient losses to follow-up, from the authors of the included studies, during each of the standardized time intervals, we will calculate the cumulative incidence of recurrent VTE using calculations described previously [**6**]. We will first determine the proportion of patients who *do not* experience recurrent VTE based on event rates during each of the abovementioned time intervals; we will then determine the proportion of patients who *do* experience recurrent VTE by multiplying the proportion of patients, in each interval of consideration, who *do not* experience recurrent VTE. For example, the cumulative incidence of recurrent VTE after 5 years of extended of oral anticoagulation will be calculated as follows:

> If the rate of recurrent VTE (per 100 person-years) is 10.0 events in *Year 1*, 5.0 events in *Year 2*, and 4.0 events in *Year 3-5*, then the proportion of patients who *do not* experience a recurrent VTE within 5 years = 90.0% (year 1) × 95.0% (year 2) × $(96.0\%)^3$ (years 3, 4, and 5) = 75.6%, resulting in a cumulative incidence for recurrent VTE of 24.4% after 5 years of extended treatment.

We will determine the upper and lower limits of the 95% confidence interval for cumulative incidence by performing the calculations described above, on the upper and lower limits of the 95% confidence interval of the event rates, respectively. These analyses will be repeated for the secondary outcome of fatal PE. A random effects model will be used for data synthesis due to the expected diversity of the studied interventions. All meta-analyses will be performed using StatsDirect version 3 (Cheshire, United Kingdom) software [**7**].

Planned sensitivity analyses

Sensitivity analyses will be undertaken to establish the robustness of primary findings. We will perform sensitivity analyses excluding study cohorts whose event rates are outliers, as well as excluding studies judged to be at high risk of bias. Estimates from overall and sensitivity analyses will be compared to gauge the impact of potential heterogeneity and biases on the primary results.

Planned subgroup analyses

If feasible from the available data, subgroup analyses will be performed based on the study design (i.e., cohorts derived from RCTs versus prospective observational studies), and the type of anticoagulation used for extended treatment. Findings from all analyses will be presented in the final report which will be reported in accordance with PRISMA guidelines [**4**].

References:

1. Kearon C, Ageno W, Cannegieter SC, et al. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. ***J Thromb Haemost***. 2016;14(7):1480-1483.
2. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org.
3. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. ***BMJ***. 2009;339:b2535.
4. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
5. DerSimonian R, Laird N. Meta-analysis in clinical trials. ***Control Clin Trials***. 1986;7(3):177-188.
6. Khan F, Rahman A, Carrier M, et al. Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: systematic review and meta-analysis. ***BMJ*** 2019; 366: l4363.
7. StatsDirect Ltd. StatsDirect statistical software. http://www.statsdirect.com. England: StatsDirect Ltd. 2013.

APPENDIX 2 - Additional Tables

Table S1: Literature Search Strategy for EMBASE

No.	Searches
1	Venous Thrombosis/
2	(ven* adj2 thrombos*).ti,ab.
3	Deep Vein Thrombosis/
4	(deep adj3 thrombos*).ti,ab.
5	Pulmonary Embolism/
6	(pulmonary adj2 embolism*).ti,ab.
7	Venous Thromboembolism/
8	(ven* adj2 thromboembolism*).ti,ab.
9	Recurrent Venous Thromboembolism/
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	secondary prevention/
12	secondary prevention*.ti,ab.
13	(relapse adj2 prevention*).ti,ab.
14	(extended adj2 therap*).ti,ab.
15	11 or 12 or 13 or 14
16	Hemorrhage/
17	(hemorrhag* or haemorrhag*).ti,ab.
18	16 or 17
19	Anticoagulants/
20	Antithrombins/
21	(anticoagulant* or anti-coagulant* or antithrombin* or anti-thrombin*).tw.
22	(thrombin adj3 inhibit*).tw.
23	(Factor Xa adj2 (antagonist? or inhibit* or block*)).tw.
24	heparin/ or exp heparin, low-molecular-weight/
25	(heparin* or beparine or clarin or contusol or disebrin or eleparon or elheparin or elheparon or epiheparin or gag 98 or helberina or hepaflex or hepalean or heparitin* or hepcon or hepsal or inhepar or inviclot or lipo-hepin or lipohepin or liquemin or liquemine or menaven or monoparin or mucoitin or multiparin or nevparin or noparin or panheparin or panhepin or panheprin or parinix or praecivenin or pularin or thromb*or niparin or vetren or vaster).tw.
26	liquaemin.tw.
27	dalteparin*.tw.
28	fragmin*.tw.
29	enoxaparin*.tw.
30	clexane.tw.
31	lovenox.tw.
32	fraxiparin*.tw.
33	nadroparin*.tw.
34	Warfarin/

35	(warfarin or warfant or tedicumar or savaysa or endoxaban or befarin or adoisine or carfin or circuvit or coumadan or coumafene or coumaphene or dagonal or tintorane or uniwarfin or waran or warfar or warnerin or farin or jantoven or kumatox or maforan or orfarin or panwarfarin or panwarfin or prothromadin or warfil* or sofarin).tw.
36	coumadin*.tw.
37	aldocumar.tw.
38	marevan.tw.
39	(Vitamin K adj2 (antagonist? or inhibit* or block*)).tw.
40	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
42	RETRACTED ARTICLE/
43	or/41-42
44	(animal$ not human$).sh,hw.
45	(book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/
46	(random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/
47	43 not (44 or 45 or 46)
48	exp cohort analysis/
49	exp longitudinal study/
50	exp prospective study/
51	exp follow up/
52	cohort$.tw.
53	or/48-52
54	47 or 53
55	10 and 15 and 18 and 40 and 54
56	10 and 18 and 40 and 54

Table S2: Studies Excluded from Meta-Analysis.

Study Author and Year of Publication	Study Title	Reason for Exclusion
Agnelli 2013	Apixaban for extended treatment of venous thromboembolism	Wrong study population:1,653 patients with any VTE (including those with cancer and other provoking risk factors) received extended anticoagulation. Data among patients with a first unprovoked VTE were unavailable.
Kearon 1999	A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism	79 patients with a first unprovoked VTE received extended anticoagulation. Detailed information required for our analysis was unavailable.
Kearon 2003	Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism	Wrong study population; 509/738 (69%) of included unprovoked VTE patients had >1 previous episode of VTE with an average of 2 previous episodes of VTE.
Kurtoglu 2010	Long-term efficacy and safety of once-daily enoxaparin plus warfarin for the outpatient ambulatory treatment of lower-limb deep vein thrombosis in the TROMBOTEK trial	Wrong study population: 227/246 included patients had VTE associated with either cancer or major transient risk factors including major trauma, surgery, and prolonged immobilization
Palareti 1996	Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy	Wrong study population: 892 patients (including those with cancer) with any VTE (no classification of VTE as provoked or unprovoked).
Poli 2013	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	Wrong study population: Among 1078 included patients, 865 were those with first episode of any VTE (no classification of VTE as provoked or unprovoked), of which 187 had a prior episode of VTE. The remaining patients were those with atrial fibrillation.
Ridker 2003	Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism	Wrong study population: 102/255 (40%) of included unprovoked VTE patients had 2 or more prior episodes of VTE.
Rief 2018	Calculation of HAS-BLED Score Is Useful for Early Identification of Venous Thromboembolism Patients at High Risk for Major Bleeding Events: A Prospective Outpatients Cohort Study	Wrong study population: 11/111 included patients with any VTE (no classification of VTE as provoked or unprovoked) had cancer.
Schulman 2013	Extended use of dabigatran, warfarin, or placebo in venous thromboembolism	Wrong study population: 3,537 patients (including those with cancer) received extended anticoagulation for any VTE. VTE events were not classified as provoked or unprovoked.
Zentati 2017	Anaemia as an independent key risk factor for major haemorrhage in patients treated with vitamin K antagonists: Results of the SCORE prospective cohort	Wrong study population: 27/470 included patients with any VTE had cancer, and there was no classification of VTE as provoked or unprovoked.
Wells 2016	Prediction of bleeding risk in patients on extended oral anticoagulation for venous thromboembolism	Outcome not reported: Recurrent VTE events during extended anticoagulation were not recorded.

Table S3: Definition and Adjudication of Recurrent Venous Thromboembolism.

Study	Definition of Recurrent VTE	Definition of Fatal PE	Independent, Blinded Adjudication of Outcomes
Agnelli et al. 2001	The criteria for the diagnosis of recurrent DVT were positive results on CUS or venography in the contralateral leg; an intraluminal filling defect in the ipsilateral leg that was visible on a venogram; or the finding on ultrasonography of a newly non-compressible venous segment in the ipsilateral leg. The criteria for the diagnosis of PE were a diagnostic pulmonary angiogram, a ventilation-perfusion lung scan indicating a high probability of PE, or an indeterminate lung scan with a high degree of clinical suspicion of PE in a patient with an objectively diagnosed asymptomatic recurrence of DVT.	Not reported.	Yes
Agnelli et al. 2003	The criteria for the diagnosis of recurrence of PE were a new filling defect revealed by pulmonary angiography or spiral CT or a new high-probability perfusion defect revealed by ventilation-perfusion lung scan. Sudden, otherwise unexplained death was also considered a recurrence of PE. The criteria for the diagnosis of DVT as an outcome for recurrence of VTE in patients without DVT at baseline were the presence of a non-compressible proximal vein on ultrasonography or an intraluminal filling defect on venography. In patients with DVT at baseline, the criteria for the diagnosis of recurrent DVT were abnormal results on CUS (proximal veins) or venography in the contralateral leg or, in the ipsilateral leg, an extension of an intraluminal filling defect on venography; a newly non-compressible venous segment; or an increase of 4 mm or more in the diameter of the thrombus (proximal veins) on ultrasonography.	Death due to pulmonary embolism (not further specified) or sudden, otherwise unexplained death was also considered a recurrence of PE.	Yes
Palareti et al. 2006	In cases of a suspected recurrence of DVT, the results of CUS were compared with those of the last available previous examination. A recurrent DVT was diagnosed if a previously fully compressible segment (contralateral or ipsilateral) was no longer compressible or if an increase of at least 4 mm in the diameter of the residual thrombus during compression was detected. When the diameter of the thrombus changed by 1.1 to 3.9mm, or in cases of high or moderate clinical probability and normal findings on proximal compression ultrasonography, the examination was repeated 5 to 7 days later. In patients with suspected PE, the diagnosis of recurrence was based on objective algorithms with the use of clinical probability, ventilation–perfusion lung scanning or helical CT, and CUS, D-dimer testing, or both if indicated.	Not reported.	Yes
Prandoni et al. 2009	Recurrent thromboembolism was diagnosed by CUS, ventilation–perfusion lung scanning, or helical tomography, as appropriate. If recurrent thrombosis was suspected in a previously unaffected leg, the sole diagnostic criterion was incompressibility of a proximal vein. Ultrasonographic criteria for recurrent ipsilateral thrombosis were incompressibility of a proximal vein segment initially free of thrombi or incompressibility of a proximal vein that had completely recanalized. Non-fatal PE was defined by a segmental or subsegmental ventilation–perfusion mismatch on lung scanning or an intraluminal filling defect on spiral CT of the chest.	Fatal PE was diagnosed if it was confirmed at autopsy, preceded immediately before death by objectively confirmed PE or VTE, or was a sudden death that could not be explained by a disease or condition other than PE.	Yes

Eischer et al. 2009	Recurrent VTE was established by venography, color duplex sonography, ventilation-perfusion scanning, and/or spiral CT. DVT was considered to have recurred if the patient had a thrombus in the leg not affected by the previous event; a thrombus in another deep vein in the leg affected by the previous event; or a thrombus in the same venous system affected in the previous event with proximal extension of at least 5 cm if the upper limit of the original thrombus had been visualized or a constant filling defect surrounded by contrast medium (if the original thrombus had not been visible).	Not reported.	Yes
Palla et al. 2010	Suspected recurrences were confirmed by objective tests (a new intraluminal filling defects on spiral CT or one or more new segmental defects on lung scan).	Death was considered to be as a result of PE if it was confirmed by autopsy, if it was anteceded by non-fatal manifestations of recurrent thromboembolism, or if death occurred suddenly and no alternative explanations could be found.	No
Cosmi et al. 2010	In cases of suspected DVT recurrence, the results of CUS were compared with those of the last available previous examination. A recurrent DVT was diagnosed if a previously fully compressible segment (contralateral or ipsilateral) was no longer compressible or if an increase of at least 4mm in the diameter of the residual thrombus during compression was detected. When thrombus diameter changed between 1.1mm and 3.9mm, or in cases of high/moderate clinical probability and normal proximal CUS, the examination was repeated 5 to 7 days later. In patients with suspected PE, diagnosis of recurrence was based on objective algorithms using clinical probability, ventilation-perfusion lung scanning or helical CT, CUS, and/or D-dimer if indicated.	Not reported.	Yes
Bauersachs et al. 2010 (EINSTEIN-DVT)	The criteria for the diagnosis of DVT were a new non-compressible venous segment or a substantial increase (4 mm or more) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography or a new intraluminal filling defect on venography. The criteria for diagnosis of PE were a new intraluminal filling defect on spiral CT or pulmonary angiography, a cutoff of a vessel of more than 2.5mm in diameter on pulmonary angiography, a new perfusion defect of at least 75% of a segment with corresponding normal ventilation (high probability), a new non– high-probability perfusion defect associated with DVT, as documented by ultrasonography or venography.	PE was considered the cause of death if there was objective documentation or if death could not be attributed to a documented cause and PE could not be confidently ruled out.	Yes
Bauersachs et al. 2010 (EINSTEIN-Extension)	The criteria for the diagnosis of DVT were a new non-compressible venous segment or a substantial increase (4 mm or more) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography or a new intraluminal filling defect on venography. The criteria for diagnosis of PE were a new intraluminal filling defect on spiral CT or pulmonary angiography, a cutoff of a vessel of more than 2.5mm in diameter on pulmonary angiography, a new perfusion defect of at least 75% of a segment with corresponding normal ventilation (high probability), a new non– high-probability perfusion defect associated with DVT, as documented by ultrasonography or venography.	PE was considered the cause of death if there was objective documentation or if death could not be attributed to a documented cause and PE could not be confidently ruled out.	Yes

Siragusa et al. 2011	Diagnosis of recurrent proximal DVT was based on CUS findings only; recurrent events were confirmed if a previously fully compressible segment (contralateral or ipsilateral) was no longer compressible or if an increase of 4 mm or more in the diameter of the residual thrombus during compression was detected; in unclear cases, repetition of the test (after 5-7 days) or contrast venography was performed. In patients with suspected PE, diagnosis of recurrent VTE was based on objective algorithms, accordingly to the protocol of the center.	Not reported.	Yes
Buller et al. 2012	The criteria for the objective diagnosis of recurrent PE were a new intraluminal filling defect on spiral CT or pulmonary angiography, a cutoff of a vessel of more than 2.5 mm in diameter on pulmonary angiography, a new perfusion defect of at least 75% of a segment with corresponding normal ventilation (high probability), a new non–high-probability perfusion defect associated with DVT documented on ultrasonography or venography, or a new PE confirmed at autopsy. The criteria for the objective diagnosis of a new DVT were a new, non-compressible venous segment or a substantial increase (4mm or more) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography or a new intraluminal filling defect on venography.	PE was considered the cause of death if there was objective documentation of the condition or if death could not be attributed to a documented cause and PE could not be confidently ruled out.	Yes
Palareti et al. 2014	Any recurrent DVT was adjudicated if a previously fully compressible segment (contralateral or ipsilateral) was no longer compressible or if an increase of at least 4mm in the diameter of the residual thrombus during compression was detected. In patients with suspected PE, recurrence was diagnosed on the basis of objective algorithms, incorporating clinical probability; ventilation-perfusion lung scanning; or CTPA, CUS, and/or D-dimer testing as appropriate.	Not reported.	Yes
Kearon et al. 2015	Criteria for ultrasonographic diagnosis of recurrent proximal DVT were a new non-compressible common femoral or popliteal vein site, an increase of at least 4 mm in compressed thrombus diameter at the common femoral or popliteal site, or clear extension of a thrombus margin (extension of thrombus position by ≥10 cm or, if this measurement was not available, by at least one third of the length of the thigh as drawn on a leg vein diagram). The criterion for venographic diagnosis of recurrent proximal DVT was a new intraluminal filling defect in the proximal veins. Criteria for diagnosis of recurrent segmental or more proximal PE were a new intraluminal filling defect involving a segmental or more proximal pulmonary artery on CTPA, a new high-probability perfusion defect on a ventilation-perfusion scan, or having a non-diagnostic CTPA or ventilation-perfusion scan but meeting criteria for diagnosis of recurrent proximal DVT.	Deaths adjudicated as due to PE including sudden death without a history of cardiac disease or another more likely cause of death.	Yes
Couturaud et al. 2015	Symptomatic recurrent DVT or PE was diagnosed if clinical suspicion was objectively confirmed by ultrasonography, ventilation-perfusion lung scanning, spiral computerized tomographic angiography, pulmonary angiography, or autopsy, in the event of a sudden death for which no other cause could be identified.	Objectively confirmed PE before death, autopsy-confirmed PE or sudden death for which no other cause could be identified.	Yes
Marconi et al. 2016	The diagnosis of PE recurrence was made by perfusion lung scintigraphy according to previously published criteria; briefly, the diagnosis of recurrence was made when 1 or more new segmental defects were detected on lung scan. The diagnosis of DVT recurrence was made according to standard criteria; briefly, the criteria were represented by abnormal results on compression ultrasonography (proximal veins) in the contralateral leg or, in the ipsilateral leg, a newly non-compressible venous segment or an increase of 4 mm or more in the diameter of the thrombus (proximal veins) on ultrasonography.	Based on mortality register (ICD-9 codes).	No

Hofmann et al. 2016	The objective criterion for the diagnosis of recurrent PE was a new intraluminal filling defect on spiral CT or pulmonary angiography; cutoff of contrast material in a vessel more than 2.5 mm in diameter on pulmonary angiography; a new perfusion defect involving at least 75% of a segment, with corresponding normal ventilation (i.e., a high-probability lung scan); a new non-diagnostic lung scan accompanied by documentation of DVT by ultrasonography or venography; or confirmation of a new PE at autopsy. The objective criterion for the diagnosis of new DVT was a new, non-compressible venous segment or a substantial increase (≥4 mm) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography or a new intraluminal filling defect on venography.	Death confirmed by autopsy, death followed a clinically severe PE or death in a patient who died suddenly or unexpectedly.	Yes
Ageno et al. 2016	Recurrent VTE was defined as the new onset of symptoms confirmed by diagnostic testing.	Not reported.	Yes
Raskob et al. 2016	In the absence of previous DVT investigations at baseline, diagnosis of recurrent DVT required one or both of the following: a non-compressible venous segment on ultrasonography; An intraluminal filling defect on venography, CT scan or MR venography. If there were previous DVT investigations at baseline, diagnosis of recurrent DVT required one or both of the following: abnormal CUS where compression had been normal or, if non-compressible during screening, a substantial increase (≥4 mm) in diameter of the thrombus during full compression; an extension of an intraluminal filling defect, or a new intraluminal filling defect, or an extension of non-visualization of veins in the presence of a sudden cut-off on venography CT scan or MR-venography. Diagnosis of recurrent PE required one of the following findings: a (new) intraluminal filling defect in (sub) segmental or more proximal branches on spiral CT scan; a (new) intraluminal filling defect or an extension of an existing defect or a new sudden cutoff of vessels more than 2.5mm in diameter on the pulmonary angiogram; a (new) perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scintigraphy; a non-diagnostic lung scan accompanied by documentation of new DVT by ultrasonography or venography.	PE was considered the cause of death if there was objective documentation, or if death could not be attributed to a documented cause and PE could not be excluded.	Yes
Prandoni et al. 2017	Non-fatal PE was defined in the presence of (sub)segmental ventilation-perfusion mismatch or an intraluminal filling defect on computed tomography. If recurrent thrombosis was suspected in a previously unaffected extremity, the sole diagnostic criterion was vein incompressibility. Ultrasound criteria for recurrent ipsilateral thrombosis were incompressibility of a proximal vein segment initially free from thrombi and/or incompressibility of a vein that had completely recanalized.	Fatal PE was diagnosed if it was confirmed at autopsy or was preceded in the immediate period before death by objectively confirmed VTE.	Yes
Rodger et al. 2017	Ultrasonography was performed with a high-resolution 5- or 7.5-MHz linear-array transducer. The deep veins were evaluated for compressibility at 1-cm intervals from the common femoral vein to the point where the popliteal vein joins the calf veins. In patients with no history of DVT, DVT was diagnosed if the vein was non-compressible. In patients with a history of DVT, DVT was diagnosed if there was a new non-compressible site or if the diameter of a clot had increased by at least 4 mm from a previous measurement. If the change in clot diameter was 1 mm or less, recurrence was ruled out. If the clot diameter had increased by 1.1 to 3.9 mm, the ultrasound examination was repeated one week later or venography was performed. All patients with a suspected PE had a ventilation–perfusion scan. If results of the scan were normal, unchanged or better than those from the baseline exam, the diagnosis of PE was excluded. If the ventilation–perfusion scan showed a new mismatched segmental defect or a greater	Not reported.	Yes

	perfusion defect compared with baseline, a PE was diagnosed. If a new matched or subsegmental perfusion defect was found, a spiral CT scan was performed. If this scan showed an intraluminal filling defect in a segmental or larger artery in an area that had normal perfusion in the baseline ventilation–perfusion scan, a PE was diagnosed. All other patients were required to undergo pulmonary angiography to diagnose or exclude suspected recurrent PE. PE found at autopsy was considered to be diagnostic of recurrent VTE.		
Weitz et al. 2017	Symptoms of PE with one of the following findings: a (new) intraluminal filling defect in (sub)segmental or more proximal branches on spiral computed tomography (CT) scan; a (new) intraluminal filling defect or an extension of an existing defect or a new sudden cut-off of vessels more than 2.5mm in diameter on the pulmonary angiogram; a (new) perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scintigraphy; Inconclusive spiral CT, pulmonary angiography or lung scintigraphy with demonstration of DVT in the lower extremities by CUS or venography. Symptoms of DVT with one of the following findings: abnormal CUS where compression had been normal or, if non-compressible at screening or baseline, a substantial increase (≥4mm) in diameter of the thrombus during full compression; an extension of an intraluminal filling defect, or a new intraluminal filling defect or an extension of non-visualization of veins in the presence of a sudden cut-off on venography.	Fatal PE based on autopsy or objective diagnostic testing prior to death; death that could not be attributed to a documented cause and for which PE/DVT could not be ruled out (unexplained death).	Yes
Kreutz et al. 2019	Recurrent VTE was defined as the new onset of symptoms confirmed by diagnostic or fatal PE or unexplained death where PE cannot be ruled out.	Fatal PE (not further specified) or unexplained death where PE cannot be ruled out.	Yes
Couturaud et al. 2019	Symptomatic recurrent DVT or PE was objectively confirmed by ultrasonography, ventilation/perfusion lung scanning, spiral CT angiography, or autopsy, or in the event of sudden death for which no cause other than PE could be identified.	Objectively confirmed PE before death, autopsy-confirmed PE or sudden death for which no cause other than PE could be identified.	Yes
Vedovati et al. 2020	Not reported.	Not reported.	No
Bradbury et al. 2020	Radiological criteria for recurrent DVT were a new non-compressible venous segment compared to the examination at baseline; an increase of 4 mm or more in thrombus diameter with compression; or a convincing extension in length.	Not reported.	Yes
Geersing et al. 2020	Recurrent VTE was defined as proximal DVT or fatal or nonfatal PE, as confirmed by CUS for DVT and by CTPA for PE, accompanied by management with anticoagulation treatment.	Not reported.	No

Abbreviations: CT, computed tomography; CTPA, computed tomography pulmonary angiography; CUS, compression ultrasonography; DVT, deep vein thrombosis; MR, magnetic resonance; PE, pulmonary embolism, VTE, venous thromboembolism.

Table S4: Risk of Bias Assessment Using Modified Newcastle-Ottawa Scale

Scoring Guide:

+ indicates that study satisfied the criteria
- indicates that study did not satisfy the criteria
Total score ≥4 indicates low risk of bias.

Study	Selection			Outcome			Total Score (out of 6)
	Was there a representative and well-defined sample of patients with a first unprovoked VTE?	Did patients complete a minimum of 3 months of anticoagulant treatment before start of follow-up?	Was there demonstration that no patient had recurrent VTE at start of follow-up?	Were objective and unbiased criteria used to assess recurrent VTE?	Was patient follow-up sufficiently long? (≥6 months)	Was patient follow-up sufficiently complete?	
Agnelli et al. 2001	+	+	+	+	+	+	**6**
Agnelli et al. 2003	+	+	+	+	+	+	**6**
Palareti et al. 2006	+	+	+	+	+	+	**6**
Prandoni et al. 2009	+	+	+	+	+	+	**6**
Eischer et al. 2009	+	+	+	+	+	+	**6**
Palla et al. 2010	+	+	+	-	+	+	**5**
Cosmi et al. 2010	+	+	+	+	+	+	**6**
Bauersachs et al. 2010	+	+	+	+	+	+	**6**
Bauersachs et al. 2010	+	+	+	+	+	+	**6**
Siragusa et al. 2011	+	+	+	+	+	+	**6**
Buller et al. 2012	+	+	+	+	+	+	**6**
Palareti et al. 2014	+	+	+	+	+	+	**6**
Kearon et al. 2015	+	+	+	+	+	+	**6**
Couturaud et al. 2015	+	+	+	+	+	+	**6**
Marconi et al. 2016	+	+	+	-	+	+	**5**
Hofmann et al. 2016	+	+	+	+	+	+	**6**
Ageno et al. 2016	+	+	+	+	+	+	**6**
Raskob et al. 2016	+	+	+	+	+	+	**6**
Prandoni et al. 2017	+	+	+	+	+	+	**6**
Rodger et al. 2017	+	+	+	+	+	+	**6**
Weitz et al. 2017	+	+	+	+	+	+	**6**
Kreutz et al. 2017	+	+	+	+	+	+	**6**
Couturaud et al. 2019	+	+	+	+	+	+	**6**
Vedovati et al. 2020	+	+	+	-	+	+	**5**
Bradbury et al. 2020	+	+	+	+	+	+	**6**
Geersing et al. 2020	+	+	+	-	+	+	**5**

Abbreviations: VTE, venous thromboembolism.

Table S5: Risk of Recurrent Venous Thromboembolism During Extended Anticoagulation.

Source	Person-years	Events, n		Rate per 100 person-years (95% CI)		% Weight
		Recurrent Venous Thromboembolism	Fatal Pulmonary Embolism	Recurrent Venous Thromboembolism	Fatal Pulmonary Embolism	
Year 1						
WODIT-DVT Agnelli et al. 2001	87.0	4	0	4.60 (1.27 – 11.36)	0.00 (0.00 – 4.15)	1.8
WODIT-PE Agnelli et al. 2003	43.5	0	0	0.00 (0.00 – 8.13)	0.00 (0.00 – 8.13)	1.0
PROLONG Palareti et al. 2006	95.1	2	0	2.10 (0.26 – 7.39)	0.00 (0.00 – 3.80)	1.9
AESOPUS Prandoni et al. 2009	100.6	1	0	0.99 (0.03 – 5.41)	0.00 (0.00 – 3.60)	2.0
AUREC-FVIII Eischer et al. 2009	15.8	0	0	0.00 (0.00 – 20.82)	0.00 (0.00 – 20.82)	0.4
Palla et al. 2010	75.5	2	0	2.65 (0.32 – 9.24)	0.00 (0.00 – 4.77)	1.6
PROLONG II Cosmi et al. 2010	89.0	0	0	0.00 (0.00 – 4.06)	0.00 (0.00 – 4.06)	1.8
EINSTEIN-DVT Bauersachs et al. 2010						
Rivaroxaban	230.0	1	0	0.43 (0.01 – 2.40)	0.00 (0.00 – 1.59)	3.4
VKA	240.0	2	0	0.83 (0.10 – 2.98)	0.00 (0.00 – 1.53)	3.5
EINSTEIN-Extension	103.0	1	0	0.97 (0.02 – 5.29)	0.00 (0.00 – 3.52)	2.1

Bauersachs et al. 2010						
DACUS Siragusa et al. 2011	266.0	9	0	3.38 (1.56 – 6.33)	0.00 (0.00 – 1.38)	3.7
EINSTEIN-PE Buller et al. 2012						
Rivaroxaban	428.0	5	1	1.17 (0.38 – 2.71)	0.23 (0.01 – 1.29)	4.6
VKA	415.0	1	0	0.24 (0.01 – 1.34)	0.00 (0.00 – 0.88)	4.6
DULCIS Palareti et al. 2014	293.0	3	0	1.02 (0.21 – 2.96)	0.00 (0.00 – 1.25)	3.9
DODS Kearon et al. 2015	64.0	2	0	3.13 (0.38 – 10.84)	0.00 (0.00 – 5.60)	1.4
PADIS-PE Couturaud et al. 2015	183.8	0	0	0.00 (0.00 – 1.99)	0.00 (0.00 – 1.99)	3.0
PISA-PEET Marconi et al. 2016	205.5	8	---	3.89 (1.70 – 7.53)	---	3.2
SWITCO65+ Hofmann et al. 2016	307.2	4	0	1.30 (0.36 – 3.30)	0.00 (0.00 – 1.19)	4.0
XALIA Ageno et al. 2016						
Rivaroxaban	384.0	4	0	1.04 (0.28 – 2.65)	0.00 (0.00 – 0.96)	4.4
VKA	319.0	5	0	1.57 (0.51 – 3.62)	0.00 (0.00 – 1.14)	4.1
HOKUSAI-VTE Raskob et al. 2016						
Edoxaban	996.0	8	0	0.80 (0.35 – 1.58)	0.00 (0.00 – 0.37)	6.0
VKA	982.0	10	0	1.02 (0.49 – 1.86)	0.00 (0.00 – 0.37)	6.0

MORGAGNI Prandoni et al. 2017	102.8	1	0	0.97 (0.02 – 5.30)	0.00 (0.00 – 3.52)	2.0
REVERSE II Rodger et al. 2017						
Rivaroxaban	336.0	6	0	1.78 (0.66 – 3.85)	0.00 (0.00 – 1.09)	4.0
VKA	1328.0	18	1	1.36 (0.81– 2.13)	0.08 (0.00 – 0.42)	6.2
EINSTEIN-Choice Weitz et al. 2017						
Rivaroxaban 10mg	323.0	4	0	1.24 (0.34 – 3.14)	0.00 (0.00 – 1.13)	4.1
Rivaroxaban 20 mg	291.0	2	0	0.69 (0.08 – 2.46)	0.00 (0.00 – 1.26)	3.9
XALIA-LEA Kreutz et al. 2019						
Rivaroxaban	209.0	4	0	1.91 (0.52 – 4.83)	0.00 (0.00 – 1.75)	3.3
VKA	37.0	0	0	0.00 (0.00 – 9.49)	0.00 (0.00 – 9.49)	0.9
PADIS-DVT Couturaud et al. 2019	50.0	0	0	0.00 (0.00 – 7.11)	0.00 (0.00 – 7.11)	1.2
ExACT Bradbury et al. 2020	131.0	7	0	5.34 (2.18 – 10.70)	0.00 (0.00 – 2.78)	2.4
VISTA Geersing et al. 2020	170.0	9	0	5.29 (2.45 – 9.81)	0.00 (0.00 – 2.15)	2.9
Vedovati et al. 2020	303.0	1	0	0.33 (0.01 – 1.83)	0.00 (0.00 – 1.21)	4.0
POOLED	**9204**	**124**	**2**	**1.46 (1.11 – 1.86)**	**0.10 (0.04 – 0.17)**	**100.0**
	Test for Heterogeneity, I^2			47%	0%	

Cohorts with duration of initial anticoagulant treatment of exclusively 3 months	5422.8	61	1	1.23 (0.87 – 1.65)	0.08 (0.02 – 0.17)	
	Test for Heterogeneity, I^2			33%	0%	
Year 2						
PROLONG Palareti et al. 2006	49.5	0	0	0.00 (0.00 – 7.18)	0.00 (0.00 – 7.18)	5.4
AESOPUS Prandoni et al. 2009	59.1	1	0	1.69 (0.04 – 9.07)	0.00 (0.00 – 6.05)	3.8
AUREC-FVIII Eischer et al. 2009	11.2	0	0	0.00 (0.00 – 28.06)	0.00 (0.00 – 28.06)	2.0
DACUS Siragusa et al. 2011	259.5	4	0	1.54 (0.42 – 3.90)	0.00 (0.00 – 1.41)	9.5
DULCIS Palareti et al. 2014	203.7	1	0	0.49 (0.01 – 2.70)	0.00 (0.00 – 1.79)	9.1
DODS Kearon et al. 2015	61.3	0	0	0.00 (0.00 – 5.84)	0.00 (0.00 – 5.84)	6.0
PADIS-PE Couturaud et al. 2015	90.8	0	0	0.00 (0.00 – 3.98)	0.00 (0.00 – 3.98)	7.1
PISA-PEET Marconi et al. 2016	184.4	5	---	2.71 (0.89 – 6.21)	---	8.8
SWITCO65+ Hofmann et al. 2016	224.4	1	0	0.45 (0.01 – 2.46)	0.00 (0.00 – 1.63)	9.2
XALIA Ageno et al. 2016 Rivaroxaban	24	0	0	0.00 (0.00 – 14.25)	0.00 (0.00 – 14.25)	3.5

VKA	28	1	0	3.57 (0.09 – 18.35)	0.00 (0.00 – 12.34)	3.9
MORGAGNI Prandoni et al. 2017	100.6	1	0	0.99 (0.03 – 5.41)	0.00 (0.00 – 3.60)	7.4
XALIA-LEA Kreutz et al. 2019						
Rivaroxaban	9.0	0	0	0.00 (0.00 – 33.63)	0.00 (0.00 – 33.63)	1.7
VKA	2.0	0	0	0.00 (0.00 – 84.19)	0.00 (0.00 – 84.19)	0.6
PADIS-DVT Couturaud et al. 2019	25.0	0	0	0.00 (0.00 – 13.72)	0.00 (0.00 – 13.72)	3.6
ExACT Bradbury et al. 2020	125.0	11	0	8.80 (4.48 – 15.20)	0.00 (0.00 – 2.91)	8.0
VISTA Geersing et al. 2020	146.0	11	0	7.53 (3.82 – 13.08)	0.00 (0.00 – 2.50)	8.3
POOLED	**1603.5**	**35**	**0**	**1.90 (0.89 – 3.28)**	**0.00 (0.00 – 0.23)**	**100.0**
Test for Heterogeneity, I^2				61%	0%	
Cohorts with duration of initial anticoagulant treatment of exclusively 3 months	606	6	0	1.22 (0.51 – 2.24)	0.00 (0.00 – 0.61)	
Test for Heterogeneity, I^2				0%	0%	
Excluding outliers	1333	13	0	1.17 (0.67 – 1.81)	---	
Test for Heterogeneity, I^2				0%	0%	
Years 3 - 5						
DODS Kearon et al. 2015	152.2	1	0	0.66 (0.02 – 3.61)	0.00 (0.00 – 2.40)	24.4

PISA-PEET Marconi et al. 2016	449.0	9	---	2.00 (0.92 – 3.77)	---	35.5
SWITCO65+ Hofmann et al. 2016	68.9	2	1	2.90 (0.35 – 10.10)	1.45 (0.04 – 7.82)	15.6
MORGAGNI Prandoni et al. 2017	153.3	0	0	0.00 (0.00 – 2.38)	0.00 (0.00 – 2.38)	24.5
POOLED	**823**	**12**	**1**	**1.32 (0.34 – 2.92)**	**0.38 (0.00 – 1.41)**	**100.0**
	Test for Heterogeneity, I^2			56%	20%	

Table S6: Risk of Recurrent Venous Thromboembolism During Extended Anticoagulation According to Study Design.

Interval of Follow-up During Extended Anticoagulation	**Recurrent Venous Thromboembolism**		**Person-Years**		**Event Rate per 100 Person-Years** (95% CI)	
	RCT	**Cohort**	**RCT**	**Cohort**	**RCT**	**Cohort**
Overall	79	92	5391	6239	1.40 (0.78 – 2.21)	1.46 (1.09 – 1.87)
Year 1	57	71	4885	4425	1.31 (0.83 – 1.90) ; I^2= 55%	1.78 (1.29 – 2.36) ; I^2= 38%
Year 2	22	13	507	1097	2.36 (0.31 – 6.24) ; I^2= 77%	1.36 (0.77 – 2.13) ; I^2= 0%
2-Year Cumulative Incidence, (95% CI)					3.6% (1.5% – 8.0%)	3.1% (2.1% – 4.4%)
Years 3 – 5	---	12	---	823	---	1.32 (0.34 – 2.92) ; I^2= 56%
5-Year Cumulative Incidence, (95% CI)					---	6.9% (3.0% – 12.6%)

Abbreviations: RCT, randomized controlled trial.
---, insufficient data to estimate incidence.

Table S7: Case-Fatality Rate of Recurrent Venous Thromboembolism During Extended Anticoagulation.

Source	**Fatal PE**	**Recurrent VTE**	**Case-Fatality Rate, %** (95% CI)	**% Weight**
WODIT-DVT	0	4	0.0 (0.0 – 60.2)	2.8
PROLONG	0	2	0.0 (0.0 – 84.2)	1.7
AESOPUS	0	1	0.0 (0.0 – 97.5)	1.1
Palla et al.	0	2	0.0 (0.0 – 84.2)	1.7
EINSTEIN-DVT (rivaroxaban)	0	1	0.0 (0.0 – 97.5)	1.1
EINSTEIN-DVT (vitamin K antagonist)	0	2	0.0 (0.0 – 84.2)	1.7
EINSTEIN-Extension	0	1	0.0 (0.0 – 97.5)	1.1
DACUS	0	13	0.0 (0.0 – 24.7)	7.9
EINSTEIN-PE (rivaroxaban)	1	5	20.0 (0.5 – 71.6)	3.4
EINSTEIN-PE (vitamin K antagonist)	0	1	0.0 (0.0 – 97.5)	1.1
DULCIS	0	4	0.0 (0.0 – 60.2)	2.8
DODS	0	3	0.0 (0.0 – 70.8)	2.2
SWITCO65+	1	7	14.3 (0.4 – 57.9)	4.5
XALIA (rivaroxaban)	0	4	0.0 (0.0 – 60.2)	2.8
XALIA (vitamin K antagonist)	0	6	0.0 (0.0 – 45.9)	3.9
HOKUSAI-VTE (edoxaban)	0	8	0.0 (0.0 – 36.9)	5.1
HOKUSAI-VTE (vitamin K antagonist)	0	10	0.0 (0.0 – 30.9)	6.2
MORGAGNI	0	2	0.0 (0.0 – 84.2)	1.7
REVERSE II (direct oral anticoagulant)	0	6	0.0 (0.0 – 45.9)	4.0
REVERSE II (vitamin K antagonist	1	24	5.6 (0.1 – 27.3)	11.4
EINSTEIN-Choice (rivaroxaban 10mg)	0	4	0.0 (0.0 – 60.2)	2.8
EINSTEIN-Choice (rivaroxaban 20mg)	0	2	0.0 (0.0 – 84.2)	1.7
XALIA-LEA (rivaroxaban)	0	4	0.0 (0.0 – 60.2)	2.8
Vedovati et al.	0	1	0.0 (0.0 – 97.5)	1.1
ExACT	0	18	0.0 (0.0 – 18.5)	8.4
VISTA	0	20	0.0 (0.0 – 16.8)	11.8
POOLED	**3**	**153**	**4.9 (2.1 – 8.7) ;** I^2 = 0%	**100.0**

Abbreviations: PE, pulmonary embolism; VTE, venous thromboembolism.

CHAPTER 6

Long-Term Risk of Major Bleeding After Discontinuing Anticoagulation for Unprovoked Venous Thromboembolism

A Systematic Review and Meta-Analysis

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Preface to Chapter 6

The aim of this systematic review and meta-analysis was to determine the incidence of major bleeding (including fatal bleeding) up to 5 years after discontinuing anticoagulant therapy for a first unprovoked venous thromboembolism. Differences in bleeding risk based on sex and study design were also examined. The author contributions are outlined on page 207 and the study appendix starts on page 222.

What is known about this topic?

- In order to estimate the net clinical benefit of extended anticoagulant therapy and counsel patients with a first unprovoked venous thromboembolism (VTE) about the duration of treatment, clinicians require precise estimates for the long-term risks of recurrent VTE and major bleeding both with and without anticoagulation.
- Estimates of the long-term risk of major bleeding after discontinuing anticoagulation in patients with first unprovoked VTE are uncertain.

What does this paper add?

- In this meta-analysis of 20 studies and 8740 patients with a first unprovoked VTE, the overall risk of major bleeding after discontinuing anticoagulation was 0.4% per patient-year with a 5-year cumulative incidence of 1%.
- This information can help inform patient prognosis and estimate the incremental risk of major bleeding with extended anticoagulation to guide decision making about treatment duration for unprovoked VTE.

ABSTRACT

Background: The long-term risk of major bleeding after discontinuing anticoagulant therapy for a first unprovoked venous thromboembolism (VTE) is uncertain.

Objectives: To determine the incidence of major bleeding up to 5 years after discontinuing anticoagulation for a first unprovoked VTE.

Methods: We searched MEDLINE, EMBASE, and Cochrane CENTRAL (from inception to January 2021) to identify relevant randomized controlled trials (RCTs) and prospective cohort studies reporting major bleeding after discontinuing anticoagulation in patients with a first unprovoked or weakly provoked VTE who had completed ≥3 months of initial treatment. Unpublished data on major bleeding events and person-years were obtained from authors of included studies to calculate study-level incidence rates. Random-effects meta-analysis was used to pool results across studies.

Results: Of 1123 records identified by the search, 20 studies (17 RCTs) and 8740 patients were included in the analysis. During 13 011 person-years of follow-up after discontinuing anticoagulation, the pooled incidence of major bleeding (n=41) and fatal bleeding (n=7) per 100 person-years was 0.35 (95% confidence interval [CI], 0.20-0.54) and 0.09 (95% CI, 0.05-0.15). The 5-year cumulative incidence of major bleeding was of 1.0% (95% CI, 0.4%-2.4%). The case-fatality rate of major bleeding after discontinuing anticoagulation was 19.9% (95% CI, 10.6%-31.1%).

Conclusions: The risk of major bleeding once anticoagulants are discontinued in patients with a first unprovoked VTE in not zero. Estimates from this study can help clinicians counsel patients about the incremental risk of major bleeding with extended anticoagulation to guide decision making about treatment duration for unprovoked VTE.

INTRODUCTION

Venous thromboembolism (VTE) should be treated with anticoagulant therapy for at least 3 to 6 months.[1-3] Deciding whether to stop or continue anticoagulation beyond the initial 3 to 6 months of treatment (termed *extended anticoagulation*) remains a challenge particularly for patients with a first unprovoked VTE or VTE associated with minor transient risk factors (i.e., weakly provoked). To counsel these patients, clinicians require precise estimates for the *long-term* risks of recurrent VTE and major bleeding both with and without anticoagulation in order to estimate the net clinical benefit of extended treatment.

In three recent systematic reviews and meta-analyses, we determined the long-term risk of: 1) major bleeding during extended anticoagulation;[4] , 2) recurrent VTE during extended anticoagulation;[5], and 3) recurrent VTE after discontinuing anticoagulation[6] among patients with a first unprovoked or weakly provoked VTE. However, estimates for the long-term risk of major bleeding after discontinuing anticoagulation in this patient population are not well-established. Quantifying this risk is important to accurately estimate the incremental risk of major bleeding with extended anticoagulation, that is over and above the risk of major bleeding with no anticoagulant therapy (i.e. establish a baseline risk of major bleeding in patients with unprovoked/weakly provoked VTE).

A previous systematic review and meta-analysis of 11 randomized controlled trials (RCTs) reported a major bleeding incidence of 0.45 events per 100 person-years (95% confidence interval [CI], 0.29-0.64) after discontinuing anticoagulation in 3965 patients with VTE who did not receive extended treatment.[7] However, approximately 20% of all VTE patients included in this meta-analysis either had cancer, a history of prior VTE (i.e., not first event), or VTE associated with strong provoking risk factors. Moreover, this meta-analysis did not examine

the risk of major bleeding in men and women separately, or assess bleeding risk over time, and only included RCTs which were published up to February 2013.[7]

We performed a systematic review and meta-analysis of RCTs and prospective cohort studies to determine the annual and cumulative incidence of major bleeding up to 5 years after discontinuing anticoagulation in patients with a first episode of unprovoked or weakly provoked VTE that completed at least 3 months of initial treatment.

METHODS

The protocol for this study is registered in PROSPERO (CRD42017056309). This systematic review and meta-analysis is reported according to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[8]

Search Strategy and Study Selection

An information specialist performed an electronic search in MEDLINE, EMBASE, and the Cochrane CENTRAL databases from inception to 1 January 2021, without language restrictions. Electronic searches were supplemented by hand searching bibliographies of relevant review articles to identify other potentially eligible studies. The systematic search strategy used for MEDLINE is provided in **Appendix Table S1**.

Two reviewers (F.K. and A.R.) independently screened titles, abstracts, and full-text publications using Covidence[9] (an online systematic review software program). Any disagreements were resolved through discussion or by consulting a third reviewer. Published RCTs and prospective cohort studies were eligible if they satisfied the following criteria: 1) included patients with a first episode of objectively confirmed, symptomatic VTE that was either

unprovoked or provoked by minor transient risk factors (as defined per International Society on Thrombosis and Haemostasis [ISTH] guidance on categorization of VTE[10] or per individual studies), 2) completed at least 3 months of initial anticoagulation before discontinuing treatment in eligible patients, and 3) reported major bleeding (as defined per ISTH criteria[11] or by individual studies) events during a minimum follow-up duration of 9 months after discontinuing anticoagulation. We included the publication with the longest follow-up when more than one article analyzed the same patients.

Data Extraction and Quality Assessment

For each eligible study, two reviewers (F.K. and A.R) independently extracted the following data: study design; number of eligible patients; mean age, % men, definitions of unprovoked VTE and major bleeding, and duration of follow-up after discontinuing anticoagulation. For calculating incidence, we requested the following information from authors of every eligible study: aggregate data on the number of first major bleeding and fatal bleeding events, and person-years of follow-up (to ensure appropriate censoring of deaths, and patient losses to follow-up or withdrawals) after stopping anticoagulation among patients with a first unprovoked or weakly provoked VTE. To assess bleeding risk over time, we requested study authors to categorize these aggregate data into the following time intervals after discontinuing anticoagulation, as applicable to the duration of study follow-up: year 1, year 2, and years 3-5. Our request to study authors also ensured that major bleeding events during anticoagulant treatment, as well as patients with active cancer (as defined by the individual studies), a history of prior VTE, or strongly provoked VTE were excluded from those aggregate data.

Two reviewers (F.K. and A.R.) independently appraised risk of bias among the included

studies using a modified version of the Newcastle-Ottawa Scale[12] based on 3 selection criteria and 3 outcome criteria – criteria assessing comparability were considered irrelevant in the context of our meta-analysis as we sought to determine the incidence of major bleeding during patient follow-up after discontinuing anticoagulation. Thus, we assessed all studies, including each arm of a RCT, as an independent observational cohort. Studies with ≥4 Newcastle-Ottawa Scale points were judged as having low risk of bias.[6]

Data Synthesis and Analysis

Incidence rate of major bleeding events per 100 person-years was calculated within each study cohort using the total number of first major bleeding events divided by the total person-years of follow-up. Results across study cohorts were pooled using DerSimonian–Laird random-effects meta-analysis, with cohorts weighted by the inverse of their variance.[13] Since we calculated the annual incidence rate using exact person-time at risk, we calculated the cumulative incidence of major bleeding at 2 and 5 years after discontinuing anticoagulation by 1) estimating the cumulative proportion of patients who *did not* experience major bleeding as the product of the proportion of patients who *did not* experience major bleeding during each of the specified time intervals, and then 2) estimating the cumulative proportion of patients that experienced major bleeding as the complement of the cumulative proportion of patients that *did not* experience major bleeding.[6] For example, the cumulative incidence of major bleeding at 5 years after discontinuing anticoagulation was calculated as follows:

If the incidence rate of major bleeding events per 100 person-years was 1.0 in *year 1*, 0.8 in *year 2*, and 0.6 in *years 3-5*, then the cumulative proportion of patients that *did not* experience major bleeding between years 1-5 was calculated as $(99.0\%_{year\ 1}) \times (99.2\%_{year\ 2}) \times ([99.4\%]^{3}{}_{years}$

$_{3\text{-}5}$) =96.5%. The cumulative proportion of patients that experienced major bleeding between *years 1-5* was then estimated as 100%−96.5% =3.5%.

The calculation described above was repeated using the lower and upper limits of the 95% confidence intervals (CIs) associated with the incidence rates in order to estimate the lower and upper limits of the 95% CI for the cumulative incidences.

We also determined the case-fatality rate of major bleeding from the total number of fatal bleeding events divided by the total number of major bleeding events.

Subgroup analyses based on patient's sex and study design (RCTs vs. cohort studies) were performed to investigate potential sources of between-study heterogeneity. Incidence rate ratio [IRR] was computed to statistically compare major bleeding rates among subgroups. We also performed sensitivity analyses restricted to 1) studies that used the ISTH definition of major bleeding; and 2) excluding cohorts among included RCTs that were randomized to receive aspirin after completing initial anticoagulant therapy.

Between-study heterogeneity was quantified using the I^2 statistic with values of 25% defined as low, 50% as moderate, and 75% as high heterogeneity. All meta-analyses were performed using StatsDirect Version 3.3.5 (Merseyside, United Kingdom).[14]

RESULTS

Literature Search and Study Characteristics

The systematic literature search identified a total of 1115 citations. After screening of titles and abstracts, 92 records were deemed eligible for full-text screening. After full-text screening, 18 studies (supplemented with 8 additional studies identified from other sources) were considered eligible for inclusion in meta-analysis (**Figure 1**). After contacting the authors of these 26 studies

for data clarifications in our target population, we acquired the requested data from 20 studies[15-34], while the remaining 6 studies[35-40] were excluded because information required for our analysis was unavailable or not provided.

A total of 17 RCTs[15-25, 28, 29, 31-34] and 3 prospective cohort studies[26, 27, 30] with 8740 patients with a first unprovoked or weakly provoked VTE were included in the analysis (**Table 1**). All 20 studies (27 independent study cohorts) contributed to the 'year 1' interval, 13 studies (19 cohorts) contributed to the 'year 2' interval, and 4 studies (6 cohorts) contributed to the 'years 3-5' interval of follow-up after discontinuing anticoagulation (**Table 1**). Eleven studies met the ISTH criteria for definition of major bleeding (**Table 1**). The overall risk of bias in individual studies was judged to be low (**Table 1**) – individual study scores for each Newcastle-Ottawa Scale criterion are provided in **Appendix Table S2**.

Major Bleeding after Discontinuing Anticoagulation

During 13, 011 person-years of follow-up after discontinuing anticoagulation, there were a total of 41 major bleeding events (0.35 events per 100-person years; 95% CI, 0.20-0.54) and 7 fatal bleeding events (0.09 events per 100-person years; 95% CI, 0.05-0.15) (**Table 2**). Incidences of major and fatal bleeding events in individual study cohorts during each of the studied intervals of follow-up are provided in **Appendix Table S3**.

After discontinuing anticoagulation, the pooled incidence of major bleeding per 100 person-years was 0.44 (95% CI, 0.25-0.70) in year 1, 0.28 (95% CI, 0.14-0.48) in year 2, and 0.10 (95% CI, 0.0-0.42) in years 3-5, with a 5-year cumulative incidence of 1.0% (95% CI, 0.4%-2.4%) (**Table 2**). The pooled incidence of fatal bleeding per 100-person years was 0.15

(95% CI, 0.07-0.25) in year 1, and 0.13 (95% CI, 0.07-0.24) in year 2 – there were insufficient data to estimate the incidence of fatal bleeding beyond 2 years of follow-up (**Table 2**).

Based on 7 fatal bleeding and 41 major bleeding events, the pooled case-fatality rate of major bleeding after discontinuing anticoagulation was 19.9% (95% CI, 10.6%-31.1%) **(Figure 2).**

Subgroup Analyses

Patient's sex. Information on major bleeding events after discontinuing anticoagulation in men and women separately was available from 17 studies (n=7775). The pooled incidence of major bleeding events per 100 person-years was 0.43 (95% CI, 0.21-0.74) in women and 0.28 (95% CI, 0.15-0.44) in men (IRR, 1.34; 95% CI, 0.75-2.47) (**Table 3**). The pooled incidence of fatal bleeding events per 100 person-years was 0.14 (95% CI, 0.06-0.26) in women and 0.12 (95% CI, 0.05-0.22) in men (**Table 3**).

Study design. There were 24 study cohorts (n=6697) from the 17 RCTs and 3 cohorts (n=2043) from the 3 prospective cohort studies included in this analysis (**Table 4**). Among study cohorts derived from RCTs, the pooled incidence of major and fatal bleeding events per 100 person-years was 0.39 (95% CI, 0.21-0.63) and 0.09 (95% CI, 0.04-0.16), respectively (**Table 4**). Among cohorts derived from prospective cohort studies, the pooled incidence of major and fatal bleeding events per 100 person-years was 0.19 (95% CI, 0.03-0.50) and 0.09% (95% CI, 0.02-0.22). The IRR for major bleeding among patients derived from RCTs vs. prospective cohort studies was 1.87 (95% CI, 0.78-5.47).

Sensitivity Analyses

Estimates for the incidence of major bleeding in the primary analyses were similar in analyses restricted to 11 studies (n=5378) using the ISTH definition of major bleeding, and analyses excluding 3 study cohorts (n=1496) randomized to receive aspirin after completing initial anticoagulation (**Appendix Table S3**).

DISCUSSION

This large systematic review and meta-analysis establishes that the annual risk of major bleeding once anticoagulants are discontinued in patients with a first unprovoked or weakly provoked VTE who have competed at least 3 months of initial anticoagulant therapy is 0.4% (95% CI, 0.20 – 0.54), with a 5-year cumulative incidence of 1.0% (95% CI, 0.4%-2.4%).

The clinical implications of our findings are two-fold. First, our results can be used to advise patients about their prognosis after discontinuing anticoagulation for a first unprovoked or weakly provoked VTE. Estimates for the incidence rate of major and fatal bleeding synthesized in our study may inform patients that their prognosis after discontinuing anticoagulation is good, with a less than 0.5% risk for a future major or fatal bleeding event per year. At the same time, our results underscore that the risk of major bleeding after discontinuing anticoagulation is not zero and thus, clinicians and patients should be aware of this baseline bleeding risk when making treatment decision.

Second, estimates from our study can assist clinicians in more accurately estimating the incremental risk of major bleeding with extended anticoagulation required to determine the net clinical benefit of extended anticoagulation and guide treatment duration. In a recent systematic review and meta-analysis, we determined that the overall incidence of major bleeding events per 100 person-years among patients with first unprovoked or weakly provoked VTE receiving extended anticoagulation was 1.74 events per 100 person-years (95% CI, 1.34-2.20) with vitamin

K antagonists (VKA) and 1.12 events per 100 person-years (95% CI, 0.72-1.62) with direct oral anticoagulants (DOACs).[4] Using the overall incidence for major bleeding of 0.35 events (95% CI, 0.20-0.54) in patients with first unprovoked or weakly provoked VTE *not* receiving extended anticoagulation, determined in this meta-analysis, the incremental risk (per patient-year) of major bleeding during extended anticoagulant therapy would be estimated at 1.39% (95% CI, 0.99-1.85; number needed to harm, 72) with VKAs and 0.77% (95% CI, 0.37-1.27; number needed to harm, 130) with DOACs. When combined with incidences for recurrent VTE of 1.55 events per 100 person-years (95% CI, 1.01 – 2.20) with VKAs[5], 1.08 events per 100 person-years (95% CI, 0.77 – 1.44) with DOACs,[5] and 10.3 events per 100 person-years (95% CI, 8.6 – 12.1) without extended anticoagulation,[6] estimates from this meta-analysis could be used to balance the absolute VTE reduction benefits of extended anticoagulant therapy in shared decision making regarding long-term management of patients with a first unprovoked or weakly provoked VTE.

Strengths of our study include a comprehensive literature search and pooling of unpublished data from studies with an overall low risk of bias. With help from investigators of original studies, we combined data on more than 8500 patients specifically with a first unprovoked or weakly provoked VTE (as well as subgroups of men and women) who were prospectively followed for major bleeding after discontinuing anticoagulant therapy. Limitation of our study is that we did not perform an individual patient-level meta-analysis (owing to resource and time constraints as well as access to such data) which would have allowed us to calculate direct estimates for the cumulative incidence of major bleeding over time, and adjust estimates by various risk factors (and potential interactions between risk factors [e.g., age and sex]). Also, in the three prospective cohort studies included in our analysis[26, 27, 30], decisions about discontinuing anticoagulant therapy were influenced by stratification of the risk of

recurrent VTE (i.e., negative D dimer test result or a clinical decision rule). Consequently, certain patient factors (e.g., younger age) may have contributed to the potential lower risk of major bleeding observed among the prospective cohort studies included in our analysis. However, the overall point estimates for bleeding rates did not meaningfully change after exclusion of the three cohort studies.

CONCLUSION

The risk of major bleeding once anticoagulants are discontinued in patients with a first unprovoked VTE in not zero. Estimates from this study can help clinicians counsel patients on the incremental risk of major bleeding with extended anticoagulation to guide decision making about treatment duration for unprovoked VTE.

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Table 1: Characteristics of included studies.

Source (year)	**Study Design**	**No. of patients with first unprovoked VTE**	**Men** (%)	**Age, years** (Range or SD)	**Unprovoked VTE Definition[a]** (minor transient risk factors included)	**Major Bleeding Definition**	***Follow-up Duration, years**	**Overall Risk of Bias**
LAFIT Kearon et al. (1999)[15]	RCT	83	53.0	58 (16)	ISTH	Overt bleeding and associated with a fall in hemoglobin of ≥2 g/dL; transfusion of ≥2 units of red cells; retroperitoneal or intracranial; warranting permanent discontinuation of study drug	2	Low
WODIT-DVT Agnelli et al. (2001)[16]	RCT	133	61.2	67.7 (7.3)	ISTH	Overt bleeding and associated with a fall in hemoglobin of ≥2 g/dL; transfusion of ≥2 units of red cells; retroperitoneal or intracranial; warranting permanent discontinuation of study drug	1	Low
DOTAVK Pinede et al. (2001)[17]	RCT	308			ISTH	Requiring hospitalization, transfusion, or treatment with blood products or vitamin K; when intracranial, intraocular, intraarticular, retroperitoneal; and/or when hemoglobin level fell by ≥2 g/dL.		Low
Arm 1		161	47.6	58.2 (1.0)			1	
Arm 2		147	47.0	58.9 (0.9)			1	
WODIT-PE Agnelli et al. (2003)[18]	RCT	181			ISTH	Overt bleeding and associated with a fall in hemoglobin of ≥2 g/dL; transfusion of ≥2 units of red cells; retroperitoneal or intracranial;		Low

						warranting permanent discontinuation of study drug or re-hospitalization.		
Arm 1		91	41.6	61.0 (15.5)			2	
Arm 2		90	39.4	62.9 (16.3)			2	
DURAC I Schulman et al. (2006)[19]	RCT	272	61.4	60.6 (15.4)	ISTH	Conditions requiring hospitalization, treatment with blood products or vitamin K, or both hospitalization and treatment.	5	Low
PROLONG Palareti et al. (2006)[20]	Cohort	505	41.7	68.2 (12.5)	ISTH	Overt bleeding and associated with a fall in hemoglobin of ≥2 g/dL; transfusion of ≥2 units of blood; retroperitoneal or intracranial; requiring surgery or invasive procedures to stop bleeding.	1	Low
AESOPUS Prandoni et al. (2009)[21]	RCT	151	57.6	69.0 (21-89)	ISTH	Overt bleeding and associated with a fall in hemoglobin of ≥20 g/L; transfusion of ≥2 units of red blood cells; retroperitoneal or intracranial.	2	Low
EINSTEIN-Extension Bauersachs et al. (2010)[22]	RCT	465	58.5	57.6 (16.2)	ISTH	ISTH	1	Low
WARFASA Becattini et al. (2012)[23]	RCT	402			ISTH	ISTH		Low
Arm 1		197	61.9	62.1 (15.1)			2	
Arm 2		205	65.8	61.9 (15.3)			2	
ASPIRE Brighton et al. (2012)[24]	RCT	822			ISTH	ISTH		Low
Arm 1		411	54	54 (15.8)			2	

Arm 2		411	55	55 (16)			2	
RE-SONATE Schulman et al. (2013)[25]	RCT	651	42.4	56.1 (15.5)	All patients were initially treated for >290 days	ISTH	1	Low
DULCIS Palareti et al. (2014)[26]	Cohort	637	54.5	63 (45-75)	ISTH (minor general surgery, pregnancy, puerperium, estrogen treatment, travel >6 hours, minor trauma, hospitalization for medical illness, reduced mobility)	ISTH	2	Low
DODS Kearon et al. (2015)[27]	Cohort	391	56.3	51 (14)	ISTH (exogenous estrogen)	ISTH	5	Low
PADIS-PE Couturaud et al. (2015)[28]	RCT	371			ISTH (exogenous estrogen)	ISTH		Low
Arm 1		187	55.1	57.3 (17.4)			3	
Arm 2		184	42.5	58.7 (16)			3	
SURVET Andreozzi et al. (2015)[29]	RCT	615			ISTH	Overt bleeding which was fatal, or occurred in a critical location, or required a transfusion of 2 or more units of whole blood or red cells.		Low
Arm 1		308	55.1	57.3 (17.4)			2	
Arm 2		307	42.5	58.7 (16)			2	
REVERSE II Rodger et al. (2017)[30]	Cohort	1015	51.4	53.2 (18-95)	ISTH (exogenous estrogen)	ISTH	1	6
EINSTEIN-Choice Weitz et al. (2017)[31]	RCT	880	56.7	58.4 (15.0)	ISTH	ISTH	1	6

PADIS-DVT Couturaud et al. (2019)[32]	RCT	104			ISTH (exogenous estrogen)	ISTH		
Arm 1		54	72.2	61.5 (14.5)			3	
Arm 2		50	62.0	59.0 (17.2)			3	
ExACT Bradbury et al. (2020)[33]	RCT	134	67.2	63.3 (12.7)	ISTH	ISTH	2	Low
VISTA Geersing et al. (2020)[34]	RCT	620	57.0	55.0 (14)	ISTH	Bleeding accompanied by a fall in hemoglobin of ≥20 g/L; transfusion of ≥2 units of blood; retroperitoneal or intracranial; requiring surgery or invasive procedures to stop bleeding	2	Low

ISTH, International Society on Thrombosis and Haemostasis; RCT, randomized controlled trial; SD, standard deviation; y, years.

[a] "ISTH" is listed for studies judged to have defined unprovoked VTE, as closely as possible, as VTE occurring in the absence of ISTH defined persistent or major transient provoking risk factors.[10] The minor transient risk factors included in the definition of unprovoked VTE are listed in brackets after "ISTH".

[b] As applicable to the studied intervals of year 1, year 2, and years 3-5.

Table 2: Risk of major bleeding after discontinuing anticoagulation.

Interval After Discontinuing Anticoagulation	**Person-Years of Follow-up**	**Total Events, n**		**Rate per 100 person-years** (95% CI)	
		Major Bleeding	**Fatal Bleeding**	**Major Bleeding**	**Fatal Bleeding**
Overall	13 011	41	7	0.35 (0.20 – 0.54); I^2 = 59%	0.09 (0.05 – 0.15); I^2 = 0%
Year 1	7715	32	6	0.44 (0.25 – 0.70); I^2 = 49%	0.15 (0.07 – 0.24); I^2 = 0%
Year 2	3776	8	1	0.28 (0.14 – 0.48); I^2 = 0%	0.13 (0.04 – 0.27); I^2 = 0%
2-Year Cumulative Incidence, (95% CI)				0.7% (0.4% – 1.2%)	0.3% (0.1% – 0.5%)
Years 3-5	1520	1	---	0.10 (0.0 – 0.42); I^2 = 24%	---
5-Year Cumulative Incidence, (95% CI)				1.0% (0.4% – 2.4%)	---

---, data were insufficient to estimate incidence.

Table 3: Risk of major bleeding after discontinuing anticoagulation according to sex.

Interval After Discontinuing Anticoagulation	Person-Years of Follow-up	Total Events, n		Event Rate per 100 person-years (95% CI)	
		Major Bleeding	Fatal Bleeding	Major Bleeding	Fatal Bleeding
Men					
Overall	6355	16	3	0.28 (0.15 – 0.44); I^2 = 16%	0.12 (0.05 – 0.22); I^2 = 0%
Year 1	3529	14	3	0.44 (0.23 – 0.72); I^2 = 13%	0.21 (0.09 – 0.39); I^2 = 0%
Year 2	1992	2	0	0.26 (0.09 – 0.53); I^2 = 0%	0.0 (0.0 – 0.19); I^2 = 0%
2-Year Cumulative Incidence, (95% CI)				0.7% (0.3% – 1.3%)	0.2% (0.1% – 0.6%)
Years 3-5	---	---	---	---	---
5-Year Cumulative Incidence, (95% CI)				---	---
Women					
Overall	5577	22	4	0.43 (0.21 – 0.74); I^2 = 51%	0.14 (0.06 – 0.26); I^2 = 0%
Year 1	3304	17	3	0.59 (0.16 – 0.97); I^2 = 38%	0.22 (0.09 – 0.40); I^2 = 0%
Year 2	1642	5	1	0.45 (0.18 – 0.83); I^2 = 0%	0.27 (0.08 – 0.57); I^2 = 0%
2-Year Cumulative Incidence, (95% CI)				1.0% (0.3% – 1.8%)	0.7% (0.2% – 1.0%)
Years 3-5	---	---	---	---	---
5-Year Cumulative Incidence, (95% CI)				---	---

---, data were insufficient to estimate incidence.
Information in men and women separately was available from 17 studies and 7775 patients.

Interval After Discontinuing Anticoagulation	Person-Years of Follow-up	Total Events, n		Event Rate per 100 person-years (95% CI)	
		Major Bleeding	Fatal Bleeding	Major Bleeding	Fatal Bleeding
Randomized Controlled Trials					
Overall	9840	35	5	0.39 (0.21 – 0.63); I^2 = 60%	0.09 (0.04 – 0.16); I^2 = 0%
Year 1	5941	27	4	0.48 (0.25 – 0.79); I^2 = 50%	0.14 (0.06 – 0.25); I^2 = 0%
Year 2	3067	7	1	0.31 (0.14 – 0.54); I^2 = 0%	0.15 (0.04 – 0.32); I^2 = 0%
2-Year Cumulative Incidence, (95% CI)				0.8% (0.4% – 1.3%)	0.3% (0.1% – 0.6%)
Years 3-5	832	1	---	0.26 (0.01 – 1.27); I^2 = 41%	---
5-Year Cumulative Incidence, (95% CI)				1.6% (0.4% – 5.0%)	---
Prospective Cohort Studies					
Overall	3171	6	2	0.19 (0.03 – 0.50); I^2 = 58%	0.09 (0.02– 0.22); I^2 = 0%
Year 1	1774	5	2	0.30 (0.04 – 0.82); I^2 = 55%	0.15 (0.02 – 0.39); I^2 = 0%
Year 2	709	1	0	0.20 (0.0 – 0.80); I^2 = 0%	0.0 (0.0 – 0.52); I^2 = 0%
2-Year Cumulative Incidence, (95% CI)				0.5% (0.0% – 1.7%)	0.2% (0.0% – 0.9%)
Years 3-5	---	---	---	---	---
5-Year Cumulative Incidence, (95% CI)				---	---

Table 4: Risk of major bleeding after discontinuing anticoagulation according to study design.

---, data were insufficient to estimate incidence.
There were 24 study cohorts (n=6697) from the 17 RCTs and 3 cohorts (n=2043) from the 3 prospective cohort studies included in this analysis.

Figure 1: Flow diagram of study identification and selection.

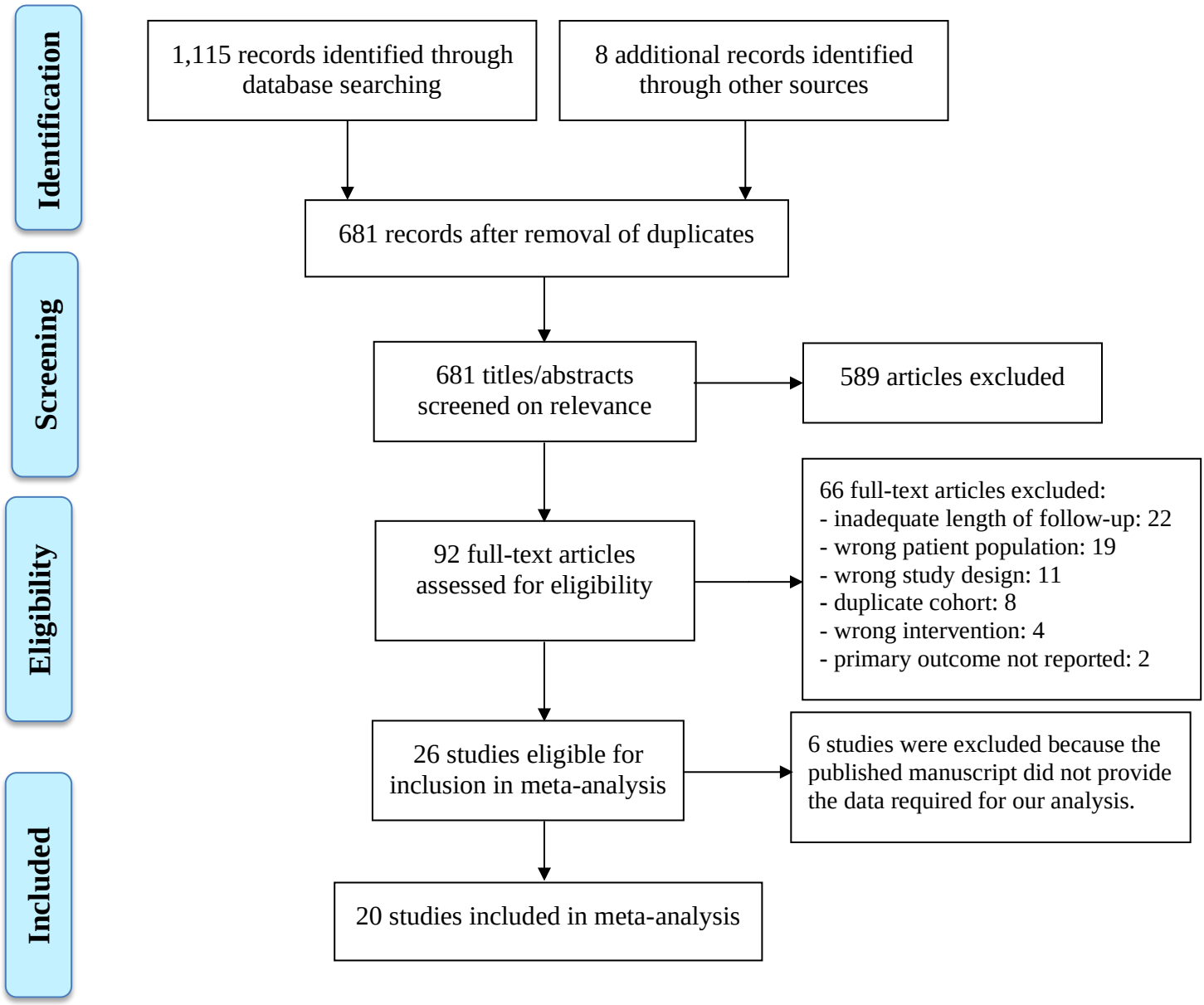
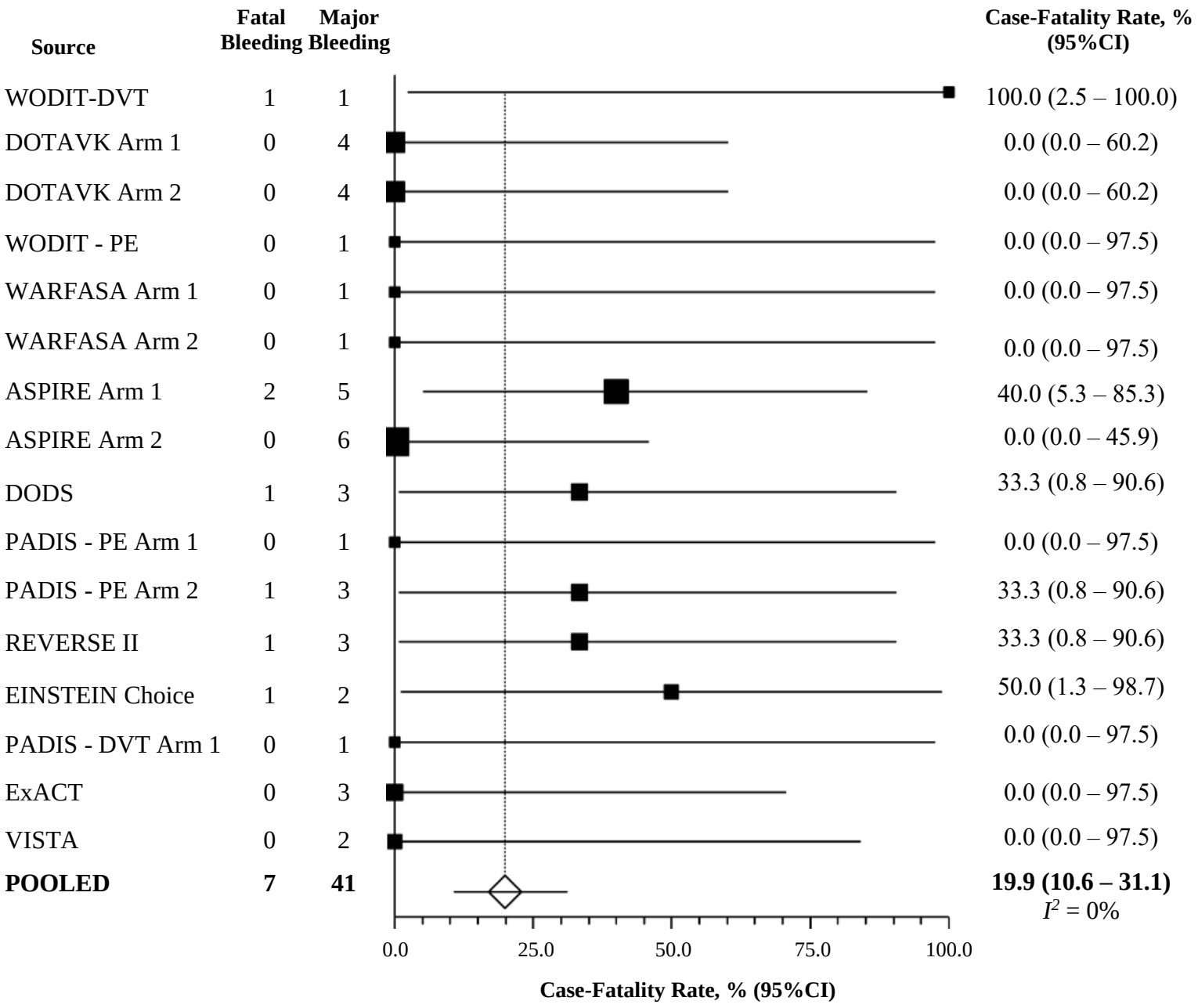


Figure 2: Case-fatality rate of major bleeding after discontinuing anticoagulation.



APPENDIX

Table S1: Literature Search Strategy for EMBASE

1. Venous Thromboembolism/
2. Venous Thrombosis/
3. Pulmonary Embolism/
4. ven* thrombos*.tw
5. ven* thromboe*.tw
6. pulmonary embol*.tw
7. DVP.mp
8. or/1-7
9. Anticoagulants/
10. Warfarin/
11. Rivaroxaban/
12. Dabigatran/
13. Heparin/
14. Heparin, Low-Molecular Weight/15. Factor Xa Inhibitors/
16. vitamin k antagonist.tw
17. VKA.tw
18. Aspirin/
19. ASA.tw
20. or/9-19
21. 8 and 20
22. Secondary Prevention/
23. Recurrence/
24. Randomized Controlled Trial/
25. Cohort Studies/
26. 24 or 25
27. 22 or 23
28. 21 and 27
29. 26 and 28
30. 21 and 26 and 27

Table S2: Modified Newcastle-Ottawa Scale Risk of Bias Assessment.

Scoring Guide:
+ indicates that the study satisfied the criteria
- indicates that the study did not satisfy the criteria
Total score ≥4 indicates an overall low risk of bias.

Study	Selection			Outcome			Total Score (out of 6)
	Was there a representative and well-defined sample of patients with a first unprovoked VTE?	Did patients complete a minimum of 3 months of anticoagulant treatment before start of follow-up?	Was there demonstration that no patient had major bleeding at start of follow-up?	Were objective and unbiased criteria used to assess major bleeding?	Was patient follow-up sufficiently long? (≥ 9 months)	Was patient follow-up sufficiently complete?	
Kearon et al. 1999	+	+	+	+	+	+	**6**
Agnelli et al. 2001	+	+	+	+	+	+	**6**
Pinede et al. 2001	+	+	+	+	+	+	**6**
Agnelli et al. 2003	+	+	+	+	+	+	**6**
Palareti et al. 2006	+	+	+	+	+	+	**6**
Schulman et al. 2006	+	+	+	+	+	+	**6**
Prandoni et al. 2009	+	+	+	+	+	+	**6**
Bauersachs et al. 2010	+	+	+	+	+	+	**6**
Becattini et al.2012	+	+	+	+	+	+	**6**
Brighton et al. 2012	+	+	+	+	+	+	**6**
Schulman et al. 2013	+	+	+	+	+	+	**6**
Palareti et al. 2014	+	+	+	+	+	+	**6**
Kearon et al. 2015	+	+	+	+	+	+	**6**
Couturaud et al. 2015	+	+	+	+	+	+	**6**
Andreozzi et al. 2015	+	+	+	+	+	+	**6**
Rodger et al. 2017	+	+	+	+	+	+	**6**
Weitz et al. 2017	+	+	+	+	+	+	**6**
Couturaud et al. 2019	+	+	+	+	+	+	**6**
Bradbury et al. 2020	+	+	+	+	+	+	**6**
Geersing et al. 2020	+	+	+	-	+	+	**5**

Table S3: Risk of Major Bleeding After Discontinuing Anticoagulation.

Source	Person-Years	Number of Events		Event Rate per 100 person-years (95% CI)	
		Major Bleeding	Fatal Bleeding	Major Bleeding	Fatal Bleeding
Year 1					
Kearon et al. 1999	43.1	0	0	0.0 (0.0 – 8.2)	0.0 (0.0 – 8.2)
Agnelli et al. 2001	89.4	1	1	1.1 (0.0 – 6.1)	1.1 (0.0 – 6.1)
Pinede et al. 2001					
Arm 1	153.1	4	0	2.6 (0.7 – 6.6)	0.0 (0.0 – 2.4)
Arm 2	106.1	4	0	3.8 (1.0 – 9.4)	0.0 (0.0 – 3.4)
Agnelli et al. 2003					
Arm 1	83.4	0	0	0.0 (0.0 – 4.3)	0.0 (0.0 – 4.3)
Arm 2	76.1	0	0	0.0 (0.0 – 4.7)	0.0 (0.0 – 4.7)
Schulman et al. 2006	256.0	0	0	0.0 (0.0 – 1.4)	0.0 (0.0 – 1.4)
Palareti et al. 2006	471.4	0	0	0.0 (0.0 – 0.8)	0.0 (0.0 – 0.8)
Prandoni et al. 2009	139.2	0	0	0.0 (0.0 – 2.6)	0.0 (0.0 – 2.6)
Bauersachs et al. 2010	261.5	0	0	0.0 (0.0 – 1.4)	0.0 (0.0 – 1.4)
Becattini et al. 2012					
Arm 1	169.2	1	0	0.6 (0.0 – 3.2)	0.0 (0.0 – 2.2)
Arm 2	181.9	0	0	0.0 (0.0 – 2.0)	0.0 (0.0 – 2.0)
Brighton et al. 2012					
Arm 1	376.5	4	1	1.1 (0.3 – 2.7)	0.3 (0.0 – 1.5)
Arm 2	393.6	4	0	1.0 (0.3 – 2.6)	0.0 (0.0 – 1.0)
Schulman et al. 2013	625.7	0	0	0.0 (0.0 – 0.6)	0.0 (0.0 – 0.6)
Palareti et al. 2014	585.5	0	0	0.0 (0.0 – 0.6)	0.0 (0.0 – 0.6)
Kearon et al. 2015	314.0	2	1	0.6 (0.08 – 2.3)	0.3 (0.0 – 1.8)
Couturaud et al. 2015					
Arm 1	184.8	0	0	0.0 (0.0 – 2.0)	0.0 (0.0 – 2.0)
Arm 2	180.5	2	1	1.1 (0.1 – 4.0)	0.3 (0.0 – 3.0)
Andreozzi et al. 2015					
Arm 1	287.4	0	0	0.0 (0.0 – 1.3)	0.0 (0.0 – 1.3)
Arm 2	287.1	0	0	0.0 (0.0 – 1.3)	0.0 (0.0 – 1.3)
Rodger et al. 2017	874.0	3	1	0.3 (0.1 – 1.0)	0.1 (0.0 – 0.6)
Weitz et al. 2017	733.9	2	1	0.3 (0.0 – 1.0)	0.1 (0.0 – 0.7)
Couturaud et al. 2019					
Arm 1	53.5	0	0	0.0 (0.0 – 6.7)	0.0 (0.0 – 6.7)
Arm 2	49.0	0	0	0.0 (0.0 – 7.3)	0.0 (0.0 – 7.3)
Bradbury et al. 2020	125	3	0	2.4 (0.5 – 6.9)	0.0 (0.0 – 2.9)
Geersing et al. 2020	614	2	0	0.3 (0.04 – 1.2)	0.0 (0.0 – 0.6)
Pooled					
Overall	**7714.7**	**32**	**6**	**0. 44 (0.25 – 0.70)**	**0.15 (0.07 – 0.24)**
Heterogeneity (I^2)				49%	0%
Excluding Aspirin/Sulodexide	**6118.1**	**26**	**5**	**0. 47 (0.24– 0.78)**	**0.15 (0.07 – 0.26)**
Heterogeneity (I^2)				51%	0%
Year 2					
Kearon et al. 1999	18.91	0	0	0.0 (0.0 – 17.7)	0.0 (0.0 – 17.7)
Agnelli et al. 2003					
Arm 1	67.1	1	0	1.5 (0.0 – 8.0)	0.0 (0.0 – 5.3)
Arm 2	57.6	0	0	0.0 (0.0 – 6.2)	0.0 (0.0 – 6.2)

Schulman et al. 2006	227.5	0	0	0.0 (0.0 – 1.6)	0.0 (0.0 – 1.6)
Prandoni et al. 2009	196.2	0	0	0.0 (0.0 – 1.9)	0.0 (0.0 – 1.9)
Becattini et al. 2012					
Arm 1	128.0	0	0	0.0 (0.0 – 2.8)	0.0 (0.0 – 2.8)
Arm 2	141.0	1	0	0.7 (0.0 – 3.9)	0.0 (0.0 – 2.6)
Brighton et al. 2012					
Arm 1	309.2	1	1	0.3 (0.0 – 1.8)	0.3 (0.0 – 1.8)
Arm 2	332.9	2	0	0.6 (0.1 – 2.2)	0.0 (0.0 – 1.1)
Palareti et al. 2014	414.4	0	0	0.0 (0.0 – 0.9)	0.0 (0.0 – 0.9)
Kearon et al. 2015	294.0	1	0	0.3 (0.0 – 1.9)	0.0 (0.0 – 1.2)
Couturaud et al. 2015					
Arm 1	183.0	1	0	0.6 (0.0 – 3.0)	0.0 (0.0 – 2.0)
Arm 2	149.6	1	0	0.7 (0.0 – 3.7)	0.0 (0.0 – 2.4)
Andreozzi et al. 2015					
Arm 1	204.4	0	0	0.0 (0.0 – 1.8)	0.0 (0.0 – 1.8)
Arm 2	230.1	0	0	0.0 (0.0 – 1.6)	0.0 (0.0 – 1.6)
Couturaud et al. 2019					
Arm 1	51.5	0	0	0.0 (0.0 – 6.9)	0.0 (0.0 – 6.9)
Arm 2	46.8	0	0	0.0 (0.0 – 7.6)	0.0 (0.0 – 7.6)
Bradbury et al. 2020	105	0	0	2.4 (0.5 – 6.9)	0.0 (0.0 – 2.9)
Geersing et al. 2020	619	0	0	0.3 (0.04 – 1.2)	0.0 (0.0 – 0.6)
Pooled					
Overall	**3776.0**	**8**	**1**	***0.28 (0.14– 0.48)***	***0.13 (0.04– 0.27)***
Heterogeneity (I^2)				0%	0%
Excluding Aspirin/Sulodexide	**3071.9**	**5**	**1**	**0.24 (0.09 – 0.44)**	**0.14 (0.04 – 0.30)**
Heterogeneity (I^2)				0%	0%
Years 3-5					
Schulman et al. 2006	581	0	0	0.0 (0.0 – 0.6)	0.0 (0.0 – 0.6)
Kearon et al. 2015	690.0	0	0	0.0 (0.0 – 0.5)	0.0 (0.0 – 0.5)
Couturaud et al. 2015					
Arm 1	173.0	0	0	0.0 (0.0 – 2.1)	0.0 (0.0 – 2.1)
Arm 2	20.4	0	0	0.0 (0.0 – 16.5)	0.0 (0.0 – 16.5)
Couturaud et al. 2019					
Arm 1	51.0	0	0	0.0 (0.0 – 7.0)	0.0 (0.0 – 7.0)
Arm 2	5.0	1	0	0.2 (0.5 – 71.6)	0.0 (0.0 – 52.1)
Pooled					
Overall	**1520**	**1**	**---**	***0.10 (0.0 – 0.42)***	**---**
Heterogeneity (I^2)				24%	0%

---, data were insufficient to estimate incidence.

CHAPTER 7

Protocol for a Modelling Study to Assess the Clinical and Cost-Effectiveness of Indefinite Anticoagulant Therapy for First Unprovoked Venous Thromboembolism

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Preface to Chapter 7

This Chapter details the rationale and planned methodology for a decision-analytic modelling study aimed to assess the differences in clinical benefits, harms, and costs of discontinuing versus continuing anticoagulant therapy indefinitely for a first unprovoked venous thromboembolism. The author contributions are outlined on page 242.

ABSTRACT

Introduction: Deciding whether to stop or extend anticoagulant therapy indefinitely after completing at least 3 months of initial treatment for a first unprovoked venous thromboembolism (VTE) remains a challenge for clinicians, patients, and policy makers. Guidelines suggest an indefinite duration of anticoagulant therapy in these patients, yet its benefits, harms, and costs have not been formally assessed. The aim of this proposed modelling study is to assess the differences in clinical benefits, harms, and costs of stopping versus continuing anticoagulant therapy indefinitely for a first unprovoked VTE.

Methods and analysis: We will develop a probabilistic Markov model, adopting a one-month cycle length and a lifetime horizon, to estimate life-years, quality-adjusted life-years, costs, and the incremental cost-effectiveness ratios for a simulated population of patients with a first unprovoked VTE who will receive indefinite duration of anticoagulant therapy versus a population who will not receive extended treatment after completing 3 months of initial anticoagulant therapy. The economic evaluation will adopt a third-party payer perspective relating to a Canadian publicly-funded healthcare system. Estimates for the probability of relevant clinical events will be informed by systematic reviews and meta-analyses, while costs and utility values will be obtained from published Canadian sources. Stratified analyses based on sex, age, and site of initial VTE will also be performed to identify subgroups of patients with a first unprovoked VTE in whom continuing anticoagulant therapy indefinitely might prove to be clinically beneficial and cost-effective over stopping treatment. We will also conduct sensitivity and scenario analyses to assess robustness of study findings to changes in individual or groups of key parameters.

Ethics and dissemination: Ethical approval is not applicable for this study. The results will be disseminated through presentations at relevant conferences and in a manuscript that will be submitted to a peer-reviewed journal.

Strengths and limitations of this study

- To our knowledge, this is the first study designed to compare the clinical benefits, harms, and costs of stopping versus continuing anticoagulant therapy indefinitely for a first unprovoked VTE.
- Stratified analyses will address the influence of important patient characteristics (e.g., differences in sex, age, and site of initial VTE) on study outcomes to potentially help guide an individualized patient-centered approach to long-term management of first unprovoked VTE.
- This study, as with all modelling studies, will be based on necessary assumptions as well as data (associated with uncertainty) derived from various sources, some of which may be limited (e.g., outdated, low quality).

INTRODUCTION

Deep vein thrombosis (DVT) and pulmonary embolism (PE), jointly denoted as venous thromboembolism (VTE), represent a major global burden of disease.[1] Anticoagulant therapy is the mainstay of treatment for VTE,[1] and is highly effective in reducing the risk of recurrent VTE (i.e., secondary prevention) as long as treatment is continued.[2] Current clinical practice is to stop anticoagulant therapy after 3-6 months of initial treatment in patients with VTE provoked by major transient risk factors (e.g., major surgery), and to extend anticoagulant therapy indefinitely in patients with VTE provoked by a persistent risk factor (e.g., cancer).[3, 4] For patients with a first unprovoked or weakly provoked (i.e., associated with minor transient risk factors) VTE, deciding whether to stop or continue anticoagulant therapy indefinitely remains an important challenge for clinicians, patients, and policy makers. To justify indefinite duration of anticoagulant therapy, the long-term risk of mortality from recurrent VTE if treatment is stopped should be off-set by the long-term risk of mortality from major bleeding on extended (beyond the initial 3-6 months) therapy.[5, 6]

Numerous randomized controlled trials have assessed extended anticoagulation versus stopping anticoagulation after 3-6 months initial treatment for secondary prevention of VTE, but no trials have compared stopping anticoagulation with indefinite anticoagulation (maximum duration follow-up in the extended treatment arm was 4 years).[2, 7-15] Moreover, these trials were designed to evaluate the efficacy of extended therapy on reducing the risk of recurrent VTE; none were powered to detect a difference in reduction of VTE-related or all-cause mortality. Furthermore, a recent Cochrane systematic review and meta-analysis concluded that there is insufficient evidence to make definitive conclusions regarding effectiveness and safety of

extended anticoagulation for the prevention of recurrent VTE in unprovoked VTE patients who have completed initial treatment, and emphasized the need for high-quality randomized controlled trials.[16]

An ideal study design to capture the long-term mortality trade-offs between recurrent VTE and major bleeding in order to provide evidence for or against indefinite anticoagulant therapy, would involve randomizing unprovoked VTE patients who have completed short-term treatment, to either stop anticoagulation or continue anticoagulation indefinitely. Such a trial however, is unlikely to be conducted. Reasons for unfeasibility of this hypothetical study include long-term, ideally lifelong (i.e. until death) follow-up of patients, and the large sample size that would be required to detect the probable small differences in mortality between the two study arms.[6, 17] Additionally, inconveniences/burdens of medical treatment, patient preferences, and costs associated with VTE management may further influence decision about treatment duration at a patient or societal level.[6] Decision analytical modelling, which involves using a specific mathematical model based on best available evidence from the literature, offers an appealing and feasible alternative study design to compare the long-term benefits, harms, and costs of stopping versus continuing anticoagulant therapy indefinitely.

Finally, as fewer than half of patients with first unprovoked VTE are expected to have a recurrent VTE within 10 years of stopping anticoagulation,[18] identifying subgroups of patients having a recurrent VTE risk sufficiently low enough or a major bleeding risk sufficiently high enough to justify stopping treatment is a high priority. The International Society on Thrombosis and Haemostasis (ISTH) suggests that in patients with unprovoked VTE, a recurrent VTE risk of 5% (with an upper bound of the 95% confidence interval of 8%) in the first year after discontinuing treatment is low enough to justify stopping anticoagulant therapy.[19] Similarly,

given that the case-fatality rate of major bleeding is 2-3 fold higher than that of recurrent VTE,[1, 18] experts have proposed that patients with a major bleeding risk of ≥3% per year should be not be considered for indefinite anticoagulant therapy, regardless of their risk of recurrent VTE.[20-22] However, such thresholds lack systematic assessment of the difference in projected long-term risks of mortality. Thus, it is unclear whether these thresholds are reasonable.

OBJECTIVES

The objectives of this modelling study will be to estimate life-years, quality-adjusted life-years, costs, and the incremental cost-effectiveness ratios for a simulated population of patients with a first unprovoked VTE who will receive indefinite duration of anticoagulant therapy versus a population who will not receive extended treatment after completing 3 months of initial anticoagulant therapy. The economic evaluation will be conducted from a third-party payer perspective with a target audience of clinicians, patients, and policy makers.

METHODS

An overview of the decision model to be used in this study is described below.

Target Population

Patients with first unprovoked VTE aged 55 years (approximate average age in management of VTE trials) who are to be considered for extended anticoagulation beyond completion of 3 months of initial anticoagulant treatment.

Intervention and Comparators

The intervention will be anticoagulant therapy with direct oral anticoagulants (DOACs; apixaban, dabigatran, edoxaban, rivaroxaban) extended (beyond the initial 3 months of treatment) indefinitely,[1, 4] and the comparator will be no extended anticoagulant therapy.

Form of Analysis

A cost-utility analysis will be utilized, as the recommended approach by the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines for economic evaluations[23] of therapeutic interventions where meaningful differences in the health-related quality of life and health utility between the intervention and the comparator have been demonstrated.

Perspective

The economic evaluation will adopt a third-party payer perspective, relating to a Canadian publicly-funded healthcare system as suggested by CADTH guidelines for economic evaluation of health technologies in Canada.[23]

Time Horizon

The analysis will adopt a lifetime horizon (i.e., until death).

Outcome Measures

Results for life expectancy will be expressed as both life-years per 1000 persons and life-days per person. Results for quality-adjusted life expectancy will be expressed as both quality adjusted life-years (QALYs) per 1000 persons and quality adjusted life-days per person. QALYs

will be calculated by multiplying life-years by utility scores derived from the published literature. Cost-effectiveness will be expressed in terms of the incremental cost per life-years gained, incremental cost per QALYs gained, and costs per clinical events (e.g., recurrent VTE, major bleeding, or death) averted, as per CADTH guidelines for an economic evaluation.[23]

Model Structure

A Markov model[24] will be used for the analyses. The model is used to represent random processes which continue over time. Compare to other models (such a decision tree analysis), Markov models are advantageous when a clinical problem, such as deciding the treatment duration for VTE, involves risk that continues over time, when key events may occur more than once, and when the timing of events is important. Using a probabilistic Markov model, with a cycle length of one month, long-term outcomes will be assessed for two cohorts of identical patients with a first unprovoked VTE who have completed 3 months of initial anticoagulant therapy – one cohort assigned to stop anticoagulation (termed "no extended anticoagulation"), and another assigned to continue anticoagulation indefinitely (termed "indefinite anticoagulation").

The key health states associated with the two treatment strategies in the model will include recurrent DVT, recurrent PE, major bleeding, death as well as long-term outcomes of the post-thrombotic syndrome (PTS), chronic thromboembolic pulmonary hypertension (CTEPH), and post-ICH [**Figure 1**]. For both patient cohorts, patients will start and remain in the assigned treatment strategy of "no extended anticoagulation" or "indefinite anticoagulation" until the occurrence of any of the specified adverse clinical outcomes.

Probability of Adverse Outcomes

***Major Bleeding*.** The annual rate of major bleeding after stopping anticoagulant therapy will be defined as 0.4% per year based on a recent a systematic review and meta-analysis of 8740 patients with a first unprovoked VTE that had completed at least 3months of initial anticoagulant treatment.[25] The annual rate of major bleeding during extended anticoagulant therapy will be defined as 1.1% per year based on a recent systematic review and meta-analysis of 7220 patients with a first unprovoked VTE that had completed at least 3 months of initial anticoagulant treatment and received extended anticoagulation of up to 1 year with a DOAC.[26] Based on input from clinical experts, for the base case, patients assigned to the 'indefinite anticoagulation' arm that experience a major bleeding event at any point will temporarily interrupt anticoagulation (for 2 weeks)[4], and then restart treatment.

Recurrent VTE. Using data from a recent systematic review and meta-analysis of 7515 patients with a first unprovoked VTE that had completed at least 3 months of initial anticoagulant treatment, the risk of recurrent VTE after stopping anticoagulant therapy will be defined as 10% in the first year, 6% in the second year, 4% in years 3 to 5, and 3% in the subsequent years.[18] Based on input from clinical expertise, the base-case model will assume that patients in the 'no extended anticoagulation' arm that experience a recurrent VTE at any point, will initiate indefinite treatment and start in the first month of 'indefinite anticoagulation' arm for the subsequent cycle. The annual rate of recurrent VTE during extended anticoagulant therapy will be defined as 1.1% per year based on a recent systematic review and meta-analysis of 7064 patients with a first unprovoked VTE that had completed at least 3 months of initial anticoagulant treatment and received extended anticoagulation of up to 1 year with a DOAC.[27]

***Mortality*.** Age- and sex-adjusted all-cause death rate will be obtained from Statistics Canada.[28]

The case-fatality rate of recurrent VTE will be defined as 4% and the case-fatality rate associated with DOAC-related major bleeding will be defined 10%, as informed by recently published systematic review and meta-analysis.[18, 26] Additionally, we will incorporate and account for mortality risk for patients with clinical events other than recurrent VTE and major bleeding, including excess risk of death from CTEPH and ICH.

Costs

As we take a perspective of the publicly funded Canada's health care system, we will include costs borne to the government. Costs will be adjusted to 2022 Canadian dollars by using the Bank of Canada Inflation Calculator.[29] The annual costs of drugs to be included in the analysis (apixaban, edoxaban, dabigatran, rivaroxaban, and warfarin) will be obtained from the Ontario Drug Benefit formulary[30] or from the drug manufacturer. For each drug therapy, annual drug treatment costs will include a $7-15 prescription fee (every 3 months) and an 8% pharmacist's markup. An additional cost of International Normalized Ratio (INR) monitoring for warfarin will be added. Costs of drugs will be fixed. Since the cost of individual DOACs will vary, a weighted average cost (unit drug cost weighted by the prevalence of drug use obtained from Canadian sources) will be used in the analysis.

Costs associated with management of clinical events will include costs for hospitalization, laboratory testing, diagnostics, specialist consultation/follow-up visits, as well as the long-term management costs of ICH, PTS, and CTEPH. Estimates for costs including the utilization rate and unit costs for direct oral anticoagulants will be obtained from the most recently available Canadian sources, including recently published cost-effectiveness literature on anticoagulants for

VTE.[31-35]

Utilities

Utility scores will be assigned according to specific health states, in a given cycle. Utility values associated with non-fatal recurrent VTE and major bleeding events, PTS, and CTEPH will be derived directly from published data.[31-35] We will consider utility values that are recent, related to our target population of interest, and use appropriate methodology as per CADTH guidelines.[23]

Discounting

Future costs and events will be discounted at a rate of 1.5% per annum, according to the CADTH guidelines for economic evaluation. [23]

Stratified Analyses

Given that patient characteristics such as sex, age, and site of initial VTE influence the risk of recurrent VTE and the risk of bleeding, sub-group analyses will be conducted according to patient's sex, site of initial VTE (isolated proximal DVT, isolated PE, and concomitant PE and DVT), as well as age (i.e., 35, 50, 65, and 80 years). Results from this stratified analyses will be used to identify subgroups of patients with a first unprovoked VTE in whom continuing anticoagulant therapy indefinitely might be clinically beneficial and cost-effective over stopping treatment.

Sensitivity and Scenario Analysis

One-way sensitivity analyses will be performed on key parameters (e.g. rates of clinical events, costs of management of clinical events, utility associated with health states) included in the decision model over their plausible ranges to determine a 'threshold', that is, a value of a parameter that would result in neither treatment strategy being preferred over the other, and above or below which one treatment strategy provides a survival benefit or is cost-effective over the other. Ranges for adverse outcomes will be derived from either the 95% confidence intervals for event rates from the published literature or based on clinically reasonable values.

Since our base-case model will assume that patients who experience a major bleeding event while receiving anticoagulant therapy will temporarily interrupt anticoagulation (for 2 weeks) and then restart treatment, a scenario analysis will be performed assuming that patients who experience an anticoagulant-related major bleed will discontinue treatment permanently. Given that our base-case analysis will model continuing anticoagulant therapy indefinitely with DOACs, we will conduct a scenario analysis using warfarin (INR range of 2.0 – 3.0) as the choice of anticoagulant for extended treatment.[4]

A 2-way sensitivity analysis will also be performed in order to determine the effect of variation in the rates of recurrent VTE in the first year off anticoagulant therapy and annual rates of major bleeding during extended treatment, on net clinical benefit and cost-effectiveness of indefinite duration of anticoagulant therapy.

For all analyses, the expected values of costs, outcomes and cost effectiveness ratios will be obtained through second-order Monte Carlo simulations, randomly sampling a distribution of all variables 5,000 times. Uncertainty around parameters will be characterized by the following distributions: probabilities (beta); utilities (beta); costs of events (gamma); treatment effects (log

normal). In addition, uncertainty over cost effectiveness will be reported as a cost-effectiveness acceptability curve, which presents the probability that each treatment choice is optimal given different values of willingness to pay for an additional QALY. For our primary analysis, we will assume a willingness-to-pay value of $50,000 per QALY.

The model will be externally validated by comparing rates of clinical outcomes with those reported in the literature. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement will be followed in reporting this economic evaluation.[36] Model creation and analyses will be performed using Microsoft Excel.

Patient and Public Involvement

No patient partners were involved in the research process of our study protocol. We plan on involving patient partners in the CanVECTOR network (www.canvector.ca) along with our network of clinical colleagues in the dissemination and/or knowledge translation activities for final study results. These activities may include developing evidence summaries (concise summary of a published research study written in plain language), and presenting our findings at the annual CanVECTOR conference with patients, clinicians, and thrombosis researchers in the audience.

DISCUSSION

Clinicians, patients, and policy makers currently lack clear guidance on making decisions regarding the optimal duration of anticoagulant therapy for a first unprovoked VTE. Guidelines suggest considering an indefinite duration of anticoagulant therapy in these patients, but the clinical benefits, harms, and costs of this treatment strategy are uncertain. Findings from our

proposed modelling study will help inform the uncertainty about whether to stop or continue anticoagulant therapy indefinitely in patients with a first unprovoked VTE who have completed 3 months of initial treatment. Important information will particularly be obtained through our planned subgroup, sensitivity, and scenario analyses which will address the influence of important patient characteristics (e.g., differences in sex, age, and site of initial VTE) and other anticoagulant regimens (e.g., reduced-dose DOACs and warfarin) on study outcomes to potentially help guide an individualized patient-centered approach to long-term management of first unprovoked VTE. That is, identify patients in whom indefinite anticoagulation may not be worthwhile so that such patients can be spared the burdens, the costs, and harms of lifelong anticoagulation; and identify which patients should continue anticoagulation indefinitely, and with which anticoagulant, in order to maximize health benefits within the available healthcare resources.

Limitations

As with all modelling studies, our proposed study will be based on necessary assumptions, as well as data (associated with uncertainty) derived from various sources, some of which may be limited (e.g., outdated, low-quality). However, we will perform extensive scenario analyses, including alternate assumptions, to establish the robustness of study findings. We acknowledge the limitation regarding the lack of memory of Markov models – that is, the probability of transitioning between states in a given cycle does not depend on events occurred in the previous cycles. To overcome this limitation, we will utilize time-varying transition probabilities for certain clinical events (e.g., probability of death increases with age, probability of recurrent VTE decreases with time spent off anticoagulant therapy).

Ethics and Dissemination

Ethical approval and patient consent are not required since this is a modelling study based on the use of secondary data from the published literature and publicly available sources. The study findings will be submitted for presentation at relevant national and international conferences, and for publication in a peer-reviewed journal.

Author Contributions: FK, KT, DC, MAR, and DAF conceived the idea and design for this modelling study. **FK**, KT, and DC developed the methodology for this study protocol. The contents of this manuscript were drafted by **FK**, KT, DC, and DAF with input from SVK, TT, BH, GLG, and MAR. The manuscript was reviewed by **FK**, KT, DC, SVK, TT, BH, GLG, MAR, and DAF for important intellectual content. **FK**, KT, DC, SVK, TT, BH, GLG, MAR, and DAF read and approved the final manuscript.

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Disclosure of Conflicts of Interest: None declared**.**

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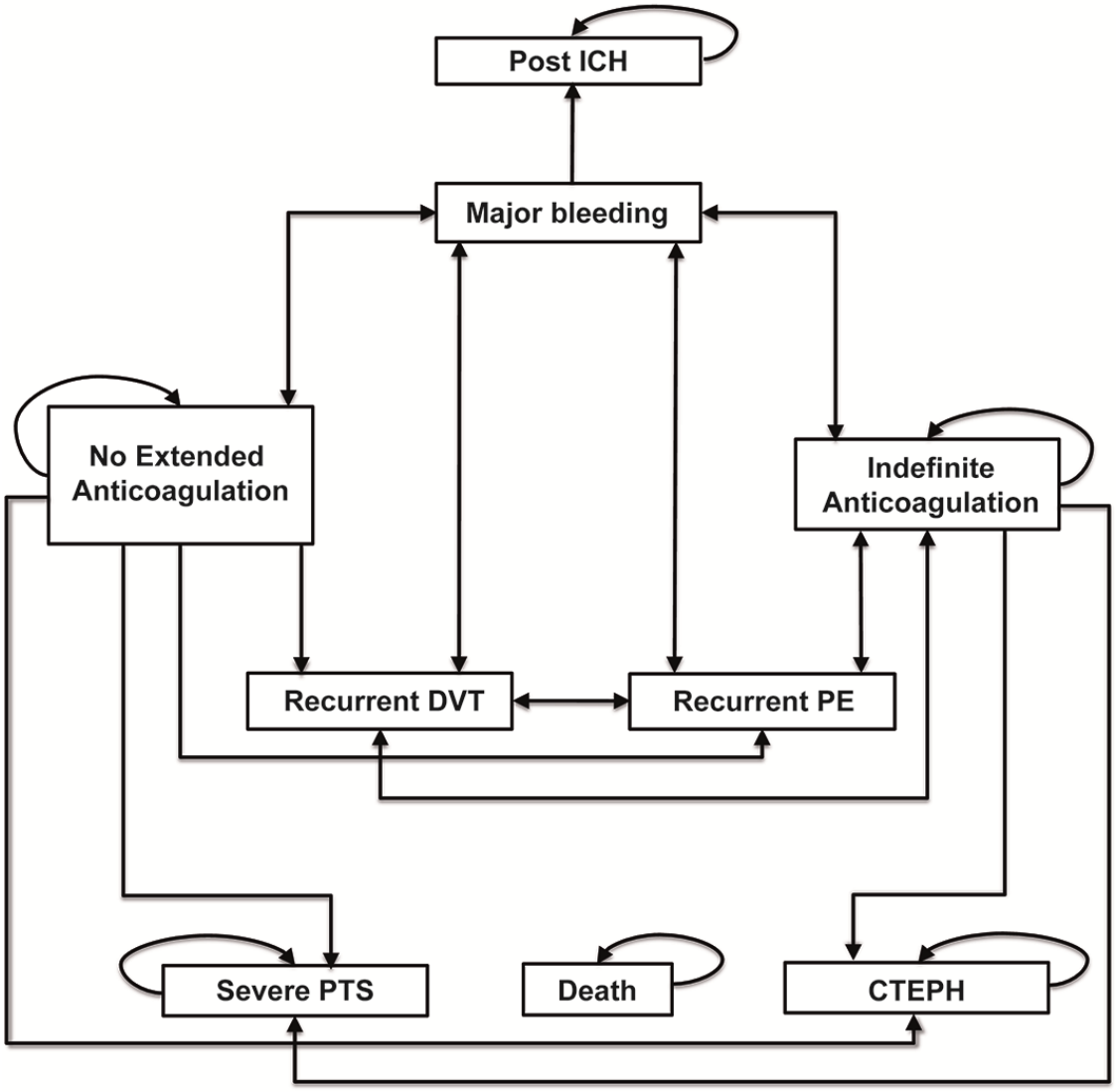
Figure 1: Markov model structure.



Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ICH, intracranial hemorrhage; PE, pulmonary embolism.

CHAPTER 8

Clinical Benefits, Harms, and Cost-Effectiveness of Indefinite Anticoagulant Therapy for First Unprovoked Venous Thromboembolism

A Modelling Study

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The article presented in this chapter is in preparation for submission to a journal.

Preface to Chapter 8

This Chapter presents the results of the modelling study designed in Chapter 7. The aim of this study was to compare the clinical benefits, harms, and cost-effectiveness of continuing versus discontinuing anticoagulant therapy indefinitely for a first unprovoked venous thromboembolism. The author contributions are outlined on page 259.

ABSTRACT

Background: Clinical practice guidelines suggest indefinite anticoagulation for a first unprovoked venous thromboembolism (VTE), yet its benefits, harms, and costs are uncertain.

Objective: To compare the clinical benefits, harms, and cost-effectiveness of continuing versus discontinuing anticoagulation indefinitely after completing initial treatment for a first unprovoked VTE.

Design: Markov cohort simulation model.

Data Sources: Long-term risks and case-fatality rates of recurrent VTE and major bleeding, with and without extended anticoagulation, were obtained from systematic reviews and meta-analyses. Additional clinical, quality of life, and economic data were sourced from published literature.

Target Population: Patients aged 55 years with a first unprovoked VTE who had completed 3-6 months of initial anticoagulant treatment.

Time Horizon: Lifetime.

Perspective: Canadian healthcare public payer.

Intervention: Indefinite anticoagulation with direct oral anticoagulants (DOACs) versus no extended anticoagulation beyond the initial 3-6 months of treatment.

Outcome Measures: Recurrent VTE, major bleeding, costs (in 2022 Canadian dollars), and quality-adjusted life years (QALYs).

Results of Base-Case Analysis: In a hypothetical cohort of 1000 patients, indefinite anticoagulation, compared to no extended anticoagulation, prevented 253 recurrent VTE events (number needed to treat = 4) but induced an additional 69 major bleeding events (number needed to harm = 15). Continuing anticoagulation indefinitely resulted in higher health system costs

($70 019.35 vs. $61 438.10 per person) and no improvement in QALYs (15.26 vs. 15.31 per person; incremental difference of -18.25 quality adjusted life-days).

Results of Sensitivity Analyses: Results were most sensitive to the annual risk of major bleeding and case-fatality rate of major bleeding during extended anticoagulation however, no value of the full and plausible ranges tested for these parameters led to cost savings or a net gain in QALYs.

Limitation: The model rests on several necessary assumption, and required lifetime extrapolation of one-year risks for recurrent VTE and major bleeding during extended anticoagulation with DOACs.

Conclusions: Indefinite anticoagulation for a first unprovoked VTE is unlikely to either result in a net clinical benefit or be cost-effective. With no net gain in QALYs (albeit a small net loss), there is no rationale for continuing anticoagulation indefinitely in all (i.e., unselected) patients with a first unprovoked VTE. However, the clinical and cost-effectiveness of indefinite anticoagulation in subgroups of patients at high risk of recurrent VTE and low risk of major bleeding requires investigation, and will be an important next step.

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INTRODUCTION

Venous thromboembolism, which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a chronic disease that often recurs and is associated with anticoagulant-related major bleeding, long-term disability, and death.[1] The estimated total annual healthcare costs of VTE and its complications range between US$7–10 billion in the USA and Can$600 million in Canada.[1]

Anticoagulant therapy for 3-6 months is the minimum required duration of treatment for patients with VTE.[1] Whether to extend treatment beyond the initial 3-6 months of anticoagulation in patients with a first unprovoked VTE has been debated.[2,3] The American Society of Hematology clinical practice guidelines suggest continuing anticoagulation indefinitely over discontinuing anticoagulation after completing 3-6 months of initial treatment for a first unprovoked proximal DVT and/or PE, except in patients who have a high risk for bleeding.[4] However, the lifetime clinical benefits, harms, as well as cost-effectiveness of indefinite anticoagulation have not been formally assessed.

While a randomized controlled trial (RCT) would be the optimal study design to provide evidence for or against continuing anticoagulation indefinitely in patients with a first unprovoked VTE, it is unlikely to be conducted due to the lifelong (i.e. until death) follow-up and extremely large sample size that would be required.[5,6] Decision-analytic modelling can provide evidence to inform guidelines under circumstances in which RCTs are unfeasible.[7,8] This first requires synthesizing contemporary and reliable estimates for parameters that can influence the clinical and cost-effectiveness of indefinite anticoagulation in patients with first unprovoked VTE. To that end, we recently published systematic reviews and meta-analyses that estimated the long-

term risks and case-fatality rates for recurrent VTE and major bleeding, with and without extended anticoagulation in this patient population.[9-12]

The aim of this study was to compare the clinical benefits, harms, and cost-effectiveness of continuing versus discontinuing anticoagulation indefinitely after completing initial treatment for a first unprovoked VTE.

METHODS

The rationale and design of this study are further detailed in a published protocol.[13] Our study is reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards statement.[14]

Study Design and Population

We conducted a decision-analytic modelling study to examine the differences in health system costs and clinically relevant outcomes between two hypothetical cohorts of patients with a first unprovoked VTE that had completed 3-6 months of initial anticoagulant therapy – one cohort assigned to continue anticoagulation indefinitely ("indefinite anticoagulation" model), and another assigned to discontinue anticoagulation indefinitely ("no extended anticoagulation" model).

Model Structure, Assumptions, and Input Parameters

We created a probabilistic Markov model to simulate costs (adjusted to 2022 Canadian dollars) and outcomes (recurrent VTE, major bleeding, and quality-adjusted life-years [QALYs]) for two cohorts of the patient population described above, over a lifetime horizon. The model had a cycle

length of 1 month based on the expected frequency of clinical events and the dosing schedules for the extended treatment of VTE. The economic analysis adopted a third-party payer perspective relating to the Canadian publicly-funded healthcare system.

For both model cohorts, patients started and remained in the assigned treatment strategy of "no extended anticoagulation" or "indefinite anticoagulation" until the occurrence of the following clinical events: recurrent DVT, recurrent PE, major bleeding, post-thrombotic syndrome (PTS), chronic thromboembolic pulmonary hypertension (CTEPH), and death [**Figure 1**].

Our base-case model was based on the following key assumptions chosen to best fit current clinical practice in the long-term management of VTE: Patients in the two cohorts started at an age of 55 years (average age across RCTs of direct oral anticoagulants [DOACs] for the extended treatment of VTE);[15,16] patients in the "indefinite anticoagulation" health state received therapeutic doses of DOACs (apixaban, dabigatran, edoxaban, or rivaroxaban);[1, 4]; patients in the 'indefinite anticoagulation' health state that experienced a recurrent VTE switched to low-molecular-weight heparin (dalteparin 200 units/kg) for 4 weeks;[1] patients in the 'indefinite anticoagulation' health state that experienced a major bleeding event at any point had their anticoagulation temporarily interrupted for 2 weeks[4], and then restarted treatment; the 'major bleeding' health state was further subclassified into major intracranial hemorrhage (ICH), minor ICH, and non-ICH – patients experiencing a major ICH transitioned to and remained in the 'post-ICH' health state [**Figure 1**] until death; and patients could transition to the 'death' health state from any other health state.

The description of model input parameters and additional assumptions are outlined in **Table 1**. The long-term risks and case-fatality rates of recurrent VTE and major bleeding, with

and without extended anticoagulation, were sourced from our recently published systematic reviews and meta-analyses.[9-12] Additional data related to transition probabilities, costs, and utility values were obtained from other published sources (e.g., Ontario Drug Benefit formulary, Canadian cost-effectiveness studies of anticoagulants for the treatment of VTE) identified through a targeted literature search [**Table 1**]. The model structure, input parameters, and assumptions were validated by clinical experts to ensure that they coincided with current clinical practice.

Future costs and QALYs were discounted at an annual rate of 1.5% as per guidelines for economic evaluation of health technologies from the Canadian Agency for Drugs and Technologies in Health.[17] Model creation and analyses were performed using Microsoft Excel (Version 16.60, 2022).

Outcomes Measures

To quantify the absolute benefit-harm trade-offs of indefinite anticoagulation, we calculated the number of recurrent VTE prevented and major bleeding induced, as well as the number needed to treat (inverse of total recurrent VTE prevented) and the number needed to harm (inverse of major bleeding induced) per 1000 patients. We defined the net clinical benefit of indefinite anticoagulation as the gain or loss in QALYs. Cost-effectiveness of indefinite anticoagulation was measured as the net monetary benefit, calculated as follows: [incremental net QALYs × $50 000 (willingness-to-pay threshold per QALY)] − incremental net costs.

Sensitivity Analyses

A deterministic one-way sensitivity analysis was performed for event rates of key clinical events,

costs, and utility values used in the model, and a probabilistic sensitivity analysis was performed for all parameters in the model using the Monte Carlo method with 5000 iterations. We also conducted scenario analyses assuming 1) patients that experience an anticoagulant-related major bleeding event permanently discontinue their anticoagulation, and 2) all patients received warfarin (international normalized ratio range of 2.0 – 3.0) for indefinite anticoagulation.

Role of the Funding Source

The funding sources had no role in the study design, analysis, interpretation of data, writing of the manuscript, or decision to submit the manuscript for publication.

RESULTS

In a hypothetical cohort of 1000 patients with a first unprovoked VTE that had completed at least 3-6 months of initial anticoagulant treatment, indefinite anticoagulation, as compared to no extended anticoagulation, resulted in fewer recurrent VTE events (139 vs. 392; number needed to treat = 4) and an increase in major bleeding events (144 vs. 75; number needed to harm = 15) over a lifetime horizon. From the perspective of Canada's healthcare system, continuing anticoagulation indefinitely was associated with higher costs (Can$70 019.35 vs. Can$61 438.10 per person) and no improvement in QALYs (15.26 vs. 15.31 per person; **Table 2)**, with an incremental net monetary benefit (NMB) of Can$-12 661.59 at a willingness-to-pay threshold of Can$50 000 per QALY.

Model results were most sensitive to the annual risk of major bleeding during extended anticoagulation and the case-fatality rate of major bleeding. That is, the NMB from indefinite anticoagulation varied the most when testing the full and plausible ranges for the annual risk of

major bleeding during extended anticoagulation of 0.72% to 1.62%, and the case-fatality rate of major bleeding of 3.2% to 19.2%. However, in all one-way sensitivity analyses, no extended anticoagulation remained economically dominant (i.e., lower costs and similar QALYs) over indefinite anticoagulation, at a willingness-to-pay threshold of Can$50 000 per QALY (**Figure 2)**.

Results from the probabilistic analyses showed that no iteration led to cost savings and 4% of the iterations led to an improvement in QALYs with indefinite anticoagulation. Moreover, at a willingness-to-pay threshold of Can$50 000 or Can$100 000 per QALY, the probability of indefinite anticoagulation being the cost-effective treatment strategy was a 0%. Results from scenario analyses assuming 1) patients who experience an anticoagulant-related major bleeding event discontinue treatment permanently, and 2) all patients received warfarin (INR range of 2.0 – 3.0) for indefinite treatment, were consistent with base-case results showing that indefinite anticoagulation increased health system costs and did not improve QALYs over a lifetime horizon.

DISCUSSION

In this modelling study of patients with a first unprovoked that completed 3-6 months of initial treatment, we found that compared to no extended anticoagulation, indefinite anticoagulation was not cost-effective as it increased health system costs by Can$8581.25 per person and no improvement in QALYs (incremental difference of 0.05 QALYs or 18.25 quality adjusted life-days per person). These results were largely driven by the annual risk of major bleeding during extended anticoagulation and the case-fatality rate associated with major bleeding. In terms of absolute benefit-harm trade-offs, we found that 253 recurrent VTE events are likely to be averted

while an additional 69 major bleeding events are likely to be induced for every 1000 patients continuing versus discontinuing anticoagulation indefinitely.

These findings have important implications for clinical practice and health policy. Contrary to current guideline recommendations, our results suggest that indefinite anticoagulation for a first unprovoked VTE is unlikely to result in a net clinical benefit even under most favourable assumptions including: annual risk for major bleeding during extended anticoagulation of as low as 0.72%, annual risk for intracranial bleeding during extended anticoagulation of as low as 0.14%, case-fatality rate of major bleeding of as low as 3.2%, risk for recurrent DVT at 1 year after discontinuing anticoagulation of as high as 7.7%, risk for recurrent PE at 1 year after discontinuing anticoagulation of as high as 4.2%, or a case-fatality rate of recurrent VTE of as high as 6.1%. In probabilistic analyses considering the uncertainty associated with all parameters used in the model, there was a 0% probability that indefinite anticoagulation would be cost-effective. Thus, there is no rationale for continuing anticoagulation indefinitely in all (i.e., unselected) patients with a first unprovoked VTE.

It is important to note that the absolute net loss in quality-adjusted life expectancy from indefinite anticoagulation is small, and as such, other individual factors such as patient preferences, may influence decisions about whether to continue or discontinue anticoagulation indefinitely. For instance, as per our base-case findings of an average net loss of 18 days per person from continuing anticoagulation indefinitely, some patients might prefer to accept lifelong anticoagulation to avoid the acute and chronic morbidities of recurrent VTE, even to live on average 2.6 less weeks. On the other hand, some patients might prefer to forego the burdens/inconveniences of taking anticoagulants for life, to live on average 2.6 more weeks. This closely balanced trade-off in quality-adjusted life expectancy from either treatment strategy also

accentuates the need to personalize long-term anticoagulation management for patients with unprovoked VTE. Individualized stratification of the risks for recurrent VTE (e.g., based on sex[9], site of initial VTE[9], HERDOO2 score[18]) and major bleeding (e.g., based on age, kidney function, history of bleeding, concomitant use of antiplatelet therapy, level of anemia)[12] is imperative, and may help identify patients in whom indefinite anticoagulation might result in a net clinical benefit or be cost-effective. Exploring the clinical and cost-effectiveness of indefinite anticoagulation in the abovementioned subgroups of patients with unprovoked VTE should therefore be the focus of future investigations.

Our study has limitations. First, as with all decision-analytic modelling studies, it is based on data from the literature, some of which are limited. In particular, the model required lifetime extrapolation of one-year risks for recurrent VTE and major bleeding during extended anticoagulation with DOACs. Second, we made a number of necessary assumptions, as well as incorporated estimates of probabilities (associated with uncertainty) from varied sources (sometimes outdated or of low-quality) in our model. However, we believe our input parameters were based on the best available evidence and we tested the robustness of our study findings by performing one-way sensitivity analyses, including alternate assumptions, which determined that our model results and conclusions were robust. Third, our model did not consider non-major VTE (distal DVT or subsegmental PE) and non-major bleeding. Lastly, our base case assumption is built on 55 year old patients, hence, the potential impact of age on the probability of adverse outcomes over time was not considered. Our conclusions may not apply to younger patients followed for longer time horizons or older patients for shorter time horizons. This is especially important given that the risks of recurrent VTE after discontinuing anticoagulants are highest in the first years and as such, the benefits of extended anticoagulation accrue early while the

bleeding harms accumulate over time.

In conclusion, we found that indefinite anticoagulation for a first unprovoked VTE is unlikely to result in a net clinical benefit or be cost-effective. With no net gain in QALYs (albeit a small net loss), there is no rationale for continuing anticoagulation indefinitely in all (i.e., unselected) patients with a first unprovoked VTE. However, the clinical and cost-effectiveness of indefinite anticoagulation in subgroups of patients with unprovoked VTE (e.g., high risk of recurrent VTE and low risk of major bleeding) requires further investigation, and will be an important next step.

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Table 1: Model input parameters.

Parameter	Base-Case Estimates and Range Used in Sensitivity Analyses	Distribution	Sources	Notes / Assumptions
No Extended Anticoagulation Model				
Rate of recurrent VTE (95% CI)				
in year 1				
recurrent DVT	0.062 (0.048 – 0.077)	Beta		
recurrent PE	0.033 (0.024 – 0.042)	Beta		
in year 2				
recurrent DVT	0.037 (0.028 – 0.047)	Beta		
recurrent PE	0.020 (0.014 – 0.026)	Beta	Khan et al.[9]	Incidence rates from a systematic review and meta-analysis of 7515 patients with a first unprovoked VTE that had completed at least three months of initial anticoagulant treatment.
in years 3-5				
recurrent DVT	0.025 (0.020 – 0.029)	Beta		
recurrent PE	0.010 (0.004 – 0.018)	Beta		
in subsequent years				
recurrent DVT	0.022 (0.010 – 0.038)	Beta		
recurrent PE	0.007 (0.014 – 0.026)	Beta		
Annual rate of major bleeding (95% CI)				
any major bleeding	0.0035 (0.0020 – 0.0054)	Beta	Khan et al.[10]	Incidence rate from a systematic review and meta-analysis of 8740 patients with a first unprovoked VTE that had completed at least three months of initial anticoagulant treatment.
ICH	0.0007 (0.0004 – 0.0011)	Beta	Khan et al.[10]	Calculated using the annual rate of any major bleeding after discontinuing anticoagulation,[10] and that ICH accounts for approximately 20% of all major bleeding events in patients with first unprovoked VTE.[12]
Indefinite Anticoagulation Model				
Annual rate of recurrent VTE (95% CI)	0.0108 (0.0077 – 0.0144)	Beta	Khan et al.[11]	Incidence rate from a systematic review and meta-analysis of 7064 patients with a first unprovoked VTE that had completed at least three months of initial anticoagulant treatment and received

				extended anticoagulation of up to one year with a DOAC.
proportion PE (range)	30% (20% – 40%)	Beta	Khan et al.[9]	
Annual rate of major bleeding (95% CI)				
any major bleeding	0.0112 (0.0072 – 0.0162)	Beta	Khan et al.[12]	Incidence rates from a systematic review and meta-analysis of 7220 patients with a first unprovoked VTE that had completed at least three months of initial anticoagulant treatment and received extended anticoagulation of up to one year with a DOAC.
ICH	0.0029 (0.0014 – 0.0050)	Beta	Khan et al.[12]	
proportion with poor functional outcomes (range)[a]	25% (20% – 30%)	Beta	Baharoglu et al.[19]	Estimate from a prospective follow-up study of 916 consecutive ICH patients enrolled in a Dutch registry. Poor functional outcome defined as modified Rankin Scale 4-5 at 90 days. This proportion of patients will transition to post-ICH state.
Long-Term Complications of VTE				
Annual severe PTS probability (range)	0.04 (0.02 – 0.06)	Beta	Kahn et al.[20] Schulman et al.[21]	
Two-year CTEPH incidence (95% CI)	0.028 (0.015 – 0.041)	Beta	Ende-Verhaar et al.[22]	Estimate from a systematic review and meta-analysis of 1775 survivors of acute PE without major comorbidities, with most patients followed for 2 years or longer.
Mortality				
Baseline age- and sex-adjusted mortality 1 – 10 years 11 – 30 years	 1.57 (1.55 – 1.59) 1.31 (1.28 – 1.33)	Beta	Soggard et al.[23]	Mortality rate ratios from a 30-year Danish population-based cohort study of 128,223 patients with a first VTE and a comparison cohort of 640,760 people from the general population.
Case-fatality rate of recurrent VTE (95% CI)	0.038 (0.02 – 0.061)	Beta	Khan et al.[9]	
Case-fatality rate of major bleeding (95% CI)	0.097 (0.032 – 0.192)	Beta	Khan et al.[12]	
Excess mortality from ICH, mean (95% CI)	2.60 (2.09 – 3.24)	Beta	Kimpton et al.[24] Gonzalez-Perez et al.[25]	
Excess mortality from CTEPH, mean (95% CI)	12.25 (10.27 – 14.31)	Beta	Kimpton et al. [24] Delcroix et al.[26]	
Costs[b]				

Treatment				
Medication				
DOAC (monthly)	$90.87	Fixed	MOHLTC (ODBF)[27]	Weighted average cost calculated using daily unit price and estimated proportion of use for each drug: rivaroxaban ($2.87; 45%), apixaban ($3.26; 45%), dabigatran ($2.50; 5%), edoxaban ($2.84; 5%)
LMWH	$1221.58	Fixed	Kimpton et al.[24] MOHLTC (ODBF)[27]	Dalteparin (200 units/kg) for 4 weeks – patients who experienced a recurrent VTE while on indefinite anticoagulation with a full-dose DOAC switch to LMWH for 4 weeks.
Recurrent DVT	$759	Fixed	Kimpton et al.[24] CADTH[28] MOHLTC (OSoB)[29] MOHLTC (OCCI)[30]	All recurrent DVT events managed as outpatients; outpatient cost including 1 Doppler ultrasound, 1 general physician visit, 1 specialist consultation, 2 specialist follow-up, and 2 complete blood counts.
Recurrent PE				
inpatient (per day), mean (95% CI)	$1665 ($1000 – $2653)	Gamma	Kimpton et al.[24] MOHLTC (OCCI) [30]	67% of patients with recurrent PE managed as inpatients[24] with a length of stay of 2 days [expert opinion].
outpatient	$1551	Fixed	Kimpton et al.[24] CADTH[28] MOHLTC (OSoB)[29] MOHLTC (OCCI) [30]	
Major bleeding				
Non-ICH	$5514 ± 25%	Gamma	CADTH[28]	Treatment cost for a non-ICH major bleeding corresponds to that of a major gastrointestinal bleeding.
ICH	$17,288 ± 25%	Gamma	CADTH[28] Goeree et al.[31]	
PTS	$8181 ± 25%	Gamma	Kimpton et al. [24] CADTH[28] Caprini et al.[32]	
CTEPH	$91,412 ± 25%	Gamma	Kimpton et al. [24] CADTH[28]	
Long-Term Management				

Indefinite anticoagulation	$7.60 ± 25%	Gamma	CADTH[28]	Weighted monthly cost of 1 annual follow-up visit, assuming 50% of follow-up by a general physician and 50% of follow-up by a specialist.
Post-PTS	$299 ± 25%	Gamma	Kimpton et al. [24] CADTH[28] Caprini et al.[32]	
Post-CTEPH	$140 ± 25%	Gamma	Kimpton et al. [24] CADTH[28]	
Post-ICH	$756 ± 25%	Gamma	Kimpton et al. [24] CADTH[28] Goeree et al.[31]	
Utility Values for Health States[c]				
No extended anticoagulation / indefinite anticoagulation	0.863 (0.861 – 0.865)	Normal	Guertin et al.[33]	
Recurrent DVT (1 month)	0.810 (0.550 – 0.940)	Normal	CADTH[28] Ikobaltzeta et al.[34] Hogg et al.[35]	
Recurrent PE (1 month)	0.750 (0.450 – 0.910)	Normal	CADTH[28] Ikobaltzeta et al.[34] Hogg et al.[35]	
Major bleeding				
Non-ICH (1 week)	0.650 (0.150 – 0.860)	Normal	CADTH[28] Ikobaltzeta et al.[34] Hogg et al.[35]	Utility value for non-ICH major bleeding state corresponds to that associated with major gastrointestinal bleeding.
Minor ICH (3 months)	0.750 (0.550 – 0.920)	Normal		
Major ICH (indefinite)	0.150 (0.000 – 0.650)	Normal		
Severe PTS (indefinite), mean (SE)	0.774 ± 0.045	Normal	Kimpton et al[24] Lenert et al.[36]	
CTEPH (indefinite)	0.560 (0.528 – 0.592)	Normal	CADTH[28] Meads et al.[37]	
Post-ICH (indefinite)	0.713 (0.702 – 0.724)	Normal	CADTH[28] Rivero-Arias et al.[38]	

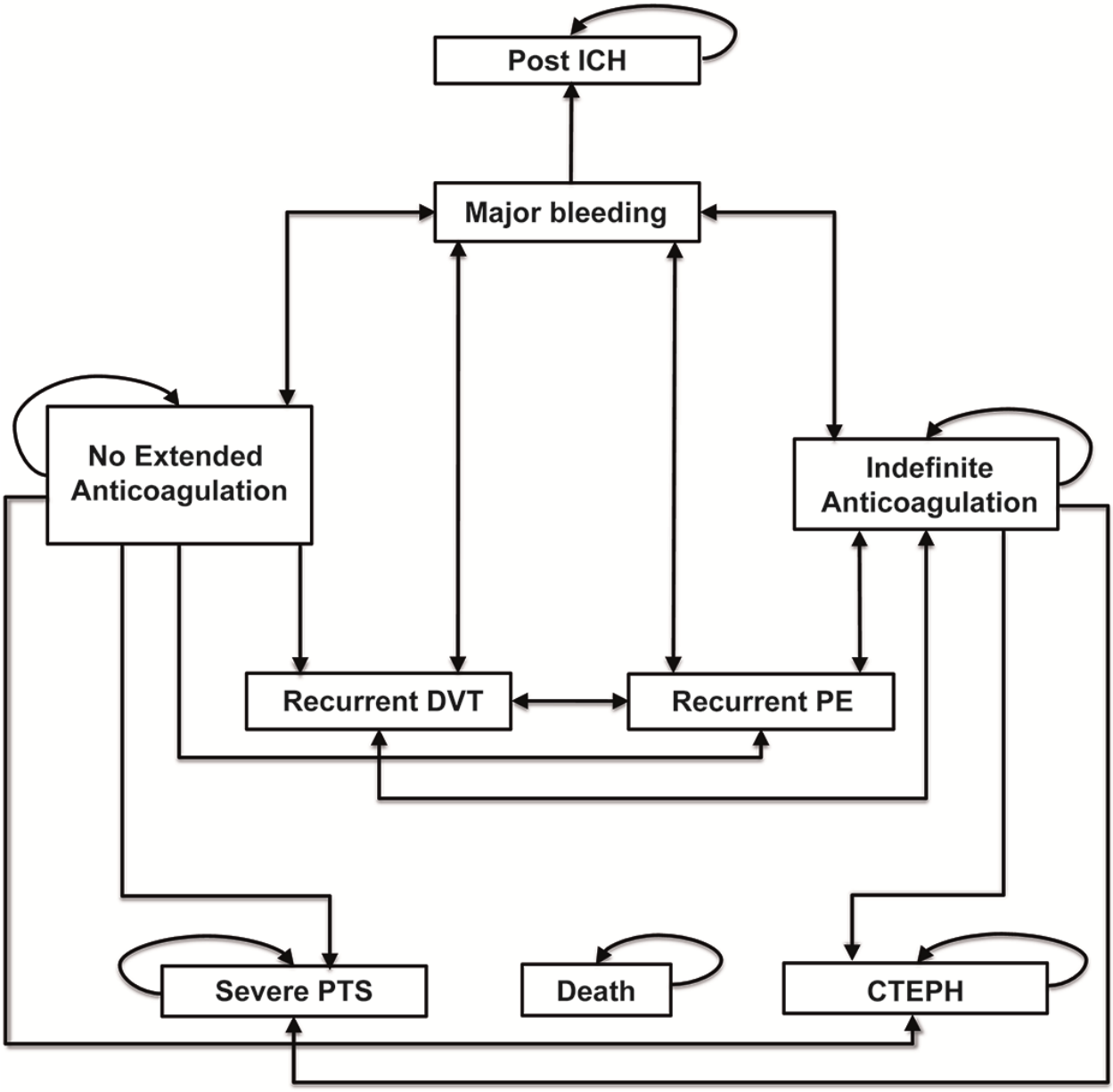
[a]applies to patients in both 'no extended anticoagulation' and 'indefinite anticoagulation 'models
[b]estimates are mean ± SE unless stated otherwise
[c]estimates are median (interquartile range) unless stated otherwise; duration of health state in indicated in parentheses.
Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ICH, intracranial hemorrhage; MOHLTC, Ministry of Health and Long-Term Care; OCCI, Ontario Case Costing Initiative; ODBF, Ontario Drug Benefit Formulary; OSoB, Ontario Schedule of Benefits; PE, pulmonary embolism; PTS, post-thrombotic syndrome.

Table 2: Results from base-case analysis.

	Mean Costs (95% CI), Can$	**Mean QALYs (95% CI)**
No extended anticoagulation	61 438.10 (43 950.49 – 83 019.50)	15.31 (14.27 – 16.37)
Indefinite anticoagulation	70 019.35 (52 015.60 – 91 162.60)	15.26 (14.22 – 16.30)
Incremental difference (indefinite anticoagulation vs. no extended anticoagulation)	8581.25 (4763.45 – 13520.49)	-0.05 (-0.13 – 0.01)

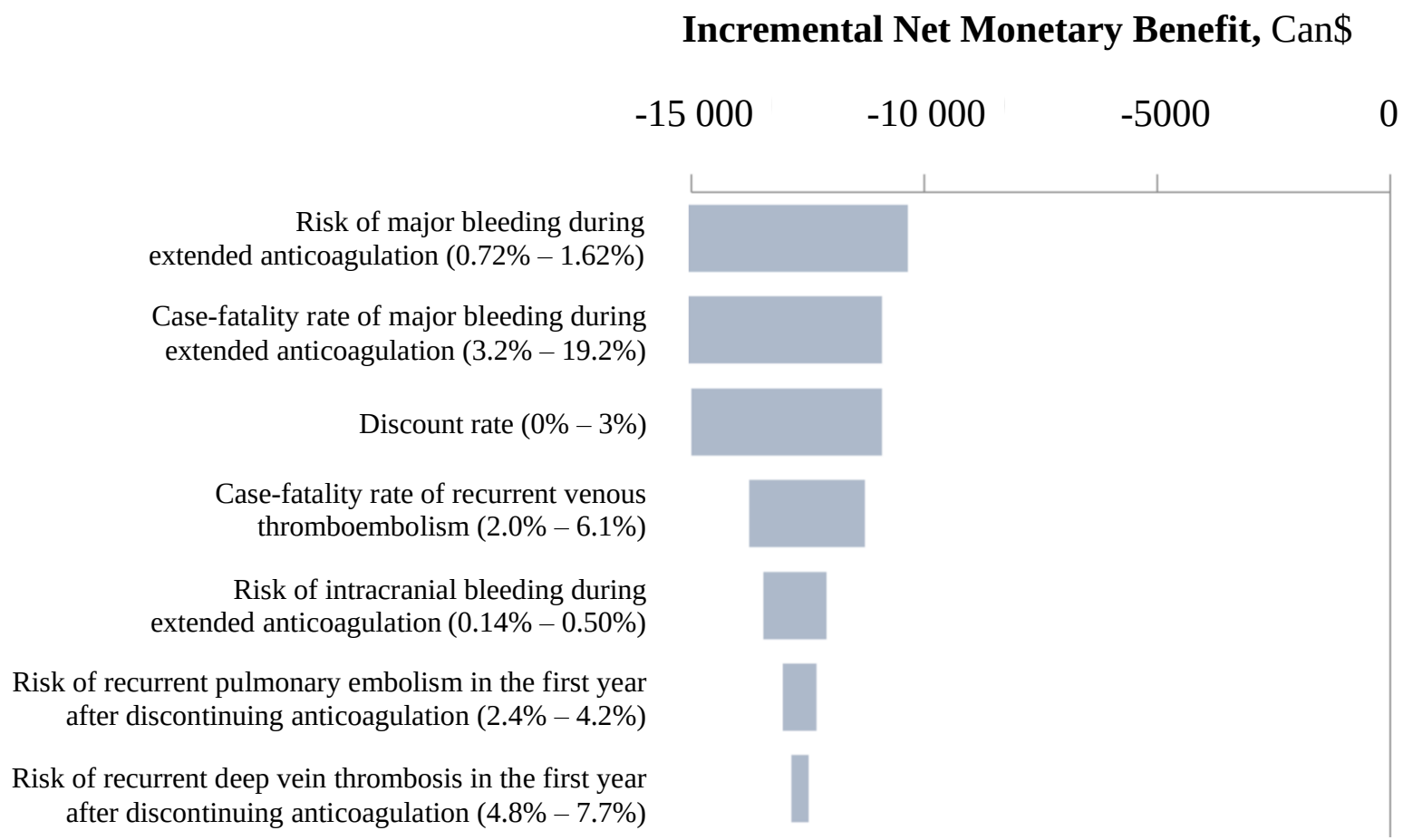
Abbreviations: QALYs, quality-adjusted life-years.

Figure 1: Markov model structure.



Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ICH, intracranial hemorrhage; PE, pulmonary embolism; PTS, post-thrombotic syndrome.

Figure 2: Deterministic one-way sensitivity analyses.



Ranges for parameters tested in sensitiviy analysis are shown in brackets. Incremental net monetary benefit (NMB) from indefinite anticoagualtion is

calculated as: [incremental net QALYs × 50 000] – incremental net costs. Base-case NMB is Can$-12 661.59 at a willingness-to-pay threshold of Can$50 000 per QALY.

CHAPTER 9

DISCUSSION

The central aim of this doctoral thesis was to address key evidence gaps that are pertinent to making decisions regarding the the duration of anticoagulation for patients with a first unprovoked venous thromboembolism (VTE). Chapter 1 of this thesis outlined the key evidence gaps, namely the uncertainty in estimates of the long-term benefits (i.e., reduction in recurrent VTE) and harms (i.e., increase in major bleeding) associated with extended duration of anticoagulation, and the trade-offs between them with respect to health system costs and life expectancy, and then presented four associated research questions which were assessed through four separate studies. In Chapter 2, we provided a comprehensive overview of VTE, in which an approach to deciding the duration of anticoagulation for patients with a first unprovoked VTE is highlighted. Chapter 4-6 present three separate studies (of four total) which synthesized contemporary and reliable estimates for parameters that can influence the clinical and cost-effectiveness of continuing versus discontinuing anticoagulation indefinitely. Results from these studies directly informed and were incorporated into the fourth study (Chapters 7 and 8) which evaluated the clinical and cost-effectiveness of considering indefinite anticoagulation for a first unprovoked VTE. Chapter 9, this chapter, summarizes the key findings from these studies and discuss the implications of this work for clinical practice/policy and future research.

9.1 SUMMARY OF KEY FINDINGS

Long-term risks of major bleeding with extended anticoagulation – The first study of this thesis presented in Chapter 4 aimed to examine the risk of major bleeding during extended

anticoagulation of up to 5 years in patients with a first unprovoked venous thromboembolism (VTE), overall and in clinically important subgroups.[2] We conducted a systematic review and meta-analysis of 27 studies reporting major bleeding among 17, 202 patients with a first unprovoked VTE receiving oral anticoagulation for a minimum of 6 additional months after completing at least 3 months of initial anticoagulant treatment. We found that the annual risk of major bleeding was 1.7% with vitamin K antagonists (VKAs) and 1.1% with direct oral anticoagulants (DOACs), while the 5-year cumulative risk of major bleeding with VKAs was 6% – there were insufficient data to estimate major bleeding risk beyond 1 year of extended anticoagulation with DOACs. In patients receiving either a VKA or a DOAC, the risk of major bleeding was higher among those who were older than 65 years or had creatinine clearance <50 mL/min, a history of bleeding, concomitant use of antiplatelet therapy, or a hemoglobin level <100 g/L. The case-fatality rate of major bleeding was 8.3% with VKAs and 9.7% with DOACs.

Long-term risk of recurrent VTE during extended anticoagulation – The second study of this thesis presented in Chapter 5 entitled aimed to examine the risk of recurrent VTE during extended anticoagulation of up to 5 years in patients with a first unprovoked VTE.[3] We conducted a systematic review and meta-analysis of 26 studies reporting recurrent VTE among 15, 603 patients with a first unprovoked VTE receiving oral anticoagulation for a minimum of 6 additional months after completing at least 3 months of initial anticoagulant treatment. We found that the annual risk of recurrent VTE was 1.6% with VKAs and 1.1% with DOACs. The 5-year cumulative risk of recurrent VTE with VKAs was 7% – there were insufficient data to estimate recurrent VTE risk beyond 1 year of extended anticoagulation with DOACs.

Long-term risk of major bleeding without extended anticoagulation – The third study of this thesis presented in Chapter 6 aimed to examine the risk of major bleeding up to 5 years after discontinuing anticoagulation for a first unprovoked VTE.[4] We conducted a systematic review and meta-analysis of 20 studies reporting major bleeding after discontinuing anticoagulation among 8, 740 patients with a first unprovoked VTE that had completed at least 3 months of initial anticoagulant treatment. We found that the risk of major bleeding after discontinuing anticoagulation is not zero and thus, should be factored in when estimating the net clinical benefit of indefinite anticoagulation. The annual risk of major bleeding was 0.35% with a 5-year cumulative risk of 1.0%.

Clinical benefits, harms, and cost-effectiveness of indefinite anticoagulation – The fourth and last component of this thesis presented in Chapter 8 aimed to compare the clinical benefits, harms, and cost-effectiveness of continuing versus discontinuing anticoagulation indefinitely for a first unprovoked VTE. We conducted a decision-analytic modelling study to examine the differences in health system costs and clinically relevant outcomes (recurrent VTE, major bleeding, quality-adjusted life-years [QALYs]) between two identical hypothetical cohorts of patients with a first unprovoked VTE that had completed 3 months of initial anticoagulant therapy – one cohort assigned to continue anticoagulation indefinitely and another assigned to discontinue anticoagulation indefinitely. We found that continuing anticoagulation in all (i.e., unselected) patients with a first unprovoked VTE is unlikely to either result in net clinical or monetary benefit. Compared to no extended anticoagulation, indefinite anticoagulation was not cost-effective from the perspective of Canada's publicly funded healthcare system as it increased costs and did not improve QALYs.

9.2 IMPLICATIONS FOR CLINICAL PRACTICE AND POLICY

For patients with a first episode of unprovoked VTE, clinical practice guidelines recommend a minimum of 3-6 months of initial treatment with direct oral anticoagulants (DOACs), and suggest extending anticoagulation indefinitely, except in those at high risk of bleeding.[5,6] The evidence underpinning these recommendations is largely derived from RCTs comparing 3-6 months of anticoagulation with extended treatment of a limited duration (i.e., 12 to 24 months), and not powered to detect mortality differences between treatment strategies.[7-10] To counsel patients, clinicians require precise estimates for the *long-term (beyond 1 to 2 years)* risks of recurrent VTE and major bleeding, with and without extended anticoagulation, to ensure that the *long-term* benefits afforded by extending anticoagulation indefinitely outweigh its associated *long-term* harms. To that end, the research work comprising this doctoral thesis contributes a large body of evidence to the existing literature and fills knowledge gaps relevant to decision making about the duration of anticoagulation for unprovoked VTE.

Contemporary and reliable estimates established in Chapters 4-6, in combination with our prior work that determined the long-term risk of recurrent VTE without extended anticoagulation,[11] provide clinicians, patients, and policy-makers with a management framework in which to consider the long-term risks and consequences of recurrent VTE and major bleeding if anticoagulation is continued indefinitely after the initial 3 to 6 months of treatment, and weigh them against the long-term risks and consequences of recurrent VTE and major bleeding if anticoagulation is discontinued in order to guide treatment duration. Chapter 8 used this management framework and simulated the long-term trade-offs of recurrent VTE and major bleeding to estimate the projected net clinical and monetary benefit of indefinite anticoagulation. Taken together, the key clinical/policy implication of findings from this thesis are that there is a tight balance between the competing risks of mortality from continuing anticoagulation

indefinitely versus discontinuing anticoagulation after completing 3 to 6 months of initial treatment for a first unprovoked VTE. Consequently, a one size fits all approach to long-term anticoagulation management of this group of VTE patients, as suggested by current guidelines, is unlikely to be optimal. This thesis work emphasizes the need for a personalized approach to deciding the duration of anticoagulation for a first unprovoked VTE with the goal of identifying subgroups of patients in whom indefinite anticoagulation might result in a net clinical benefit or be cost-effective.

In a previous meta-analysis, we showed that men have a higher long-term risk of recurrent VTE without extended anticoagulation than women with first unprovoked VTE – the risk of recurrent VTE at 1 year after discontinuing anticoagulation is about 12% in men and 9% in women, with cumulative 10-year risks of about 40% and 30% respectively.[11] The prospectively validated HERDOO2 (Hyperpigmentation, Edema, or Redness in either leg; D-dimer level ≥250 μg/L; Obesity with body mass index ≥30 kg/m^2; or Older age, ≥65 years) clinical decision rule identified all men and approximately 50% of all women (those with 2 or more HERDOO criteria) with a first unprovoked as having a high risk (>8% in the first year after discontinuing treatment) of recurrent VTE.[12] However, whether these thresholds for the risk of recurrent VTE are high enough to result in net clinical or monetary benefit from indefinite anticoagulation remains unclear.

On the other hand, no prospectively validated clinical score is available to identify patients with VTE who are at low risk of major bleeding during extended anticoagulation. Therefore, clinicians must rely on clinical judgment to determine a patient's bleeding risk. Findings from Chapter 4 of this thesis demonstrated that there is a clinically meaningful difference in the long-term risk for anticoagulant-related major bleeding among patients with a

first unprovoked VTE stratified according to presence or absence of the following risk factors: age older than 65 years, creatinine clearance less than 50 mL/min, history of bleeding, concomitant use of anti- platelet therapy, and hemoglobin level less than 100 g/L.[2] The absence of some of these risk factors was associated with an annual bleeding risk of <1% during extended anticoagulation with DOACs (e.g., age <65 years, no history of bleeding).[2] However, whether this threshold for the risk of major bleeding is low enough to result in net clinical or monetary benefit from indefinite anticoagulation, remains unclear.

9.3 IMPLICATIONS FOR FUTURE RESEARCH

The research work encompassing this thesis has highlighted additional evidence-practice gaps and areas of uncertainty, and in turn, lays the foundation for future research. To stimulate a personalized approach in deciding the duration of anticoagulation, we need to establish thresholds of the risk of recurrent VTE and major bleeding, above or below which indefinite anticoagulation provides a net clinical benefit or is cost-effective over discontinuing anticoagulation. The decision-analytic Markov model presented in Chapter 8 can serve to perform additional analyses (e.g., for men and women or younger and older patients, separately) and establish risk thresholds to determine which of the two durations of anticoagulation would be preferred (with respect to a net clinical or monetary benefit) for varying risks of recurrent VTE and major bleeding. Prospective cohort studies, such as those designed to develop and validate clinical decision rules, could then test the hypothesis that predefined subgroups of patients with unprovoked VTE have risks of recurrent VTE (after discontinuing anticoagulation) and major bleeding (during extended anticoagulation) that are similar to, lower, or higher than these established risk thresholds.

Additionally, our systematic reviews focused on examining the risk of major bleeding and recurrent VTE during extended anticoagulation, Chapters 4 and 5 respectively, found that there were: 1) limited data beyond one year of extended anticoagulation with DOACs, 2) insufficient number of studies (with limited data) to compare bleeding and recurrent VTE risk estimates between reduced- and therapeutic-dose DOACs, and 3) most DOAC cohorts included in our analyses received extended anticoagulation with rivaroxaban and thus, synthesized risk estimates for DOACs may not always be generalizable to all DOACs. These findings should inform future research aimed at examining the long-term (>2 years) efficacy and safety of different regimens of DOACs in patients with unprovoked VTE. Indeed, the ongoing RENOVE trial (NCT03285438), designed to specifically compare the long-term efficacy and safety of reduced-dose apixaban (2.5mg twice daily) and rivaroxaban (10mg once daily) with their respective therapeutic doses, is expected to inform the role of these regimens in the extended treatment of unprovoked VTE.

9.4 CONCLUSIONS

This doctoral thesis established current evidence-based estimates for the long-term risks and consequences of recurrent VTE and major bleeding, with and without extended anticoagulation in patients with a first unprovoked VTE. It also demonstrated that considering indefinite anticoagulation in all (i.e., unselected) patients with a first unprovoked VTE, as per current guideline recommendations, is unlikely to be either cost-effective or result in a net clinical benefit, and emphasized the need for a personalized approach to deciding the duration of anticoagulation. Findings from this doctoral thesis can serve to impact clinical practice and health policy by informing patient prognosis to guide shared decision-making regarding treatment duration, and informing future research aimed at identifying which patients should

receive anticoagulation indefinitely in order to maximize health benefits for the available healthcare resources.

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