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PERIPHERAL VASCULAR DISEASE (CHRISTOPHER J. COOPER AND RAJESH GUPTA, SECTION EDITORS)

Risk of Recurrent Venous Thromboembolism After an Initial Episode: Risk Stratification and Implications for Long-term Treatment

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Abstract

Purpose of Review Venous thromboembolism (VTE) is a common condition with significant associated morbidity and mortality. Recurrent VTE after an initial episode is a preventable medical condition. The following review discusses data supporting recurrence risk estimates after an initial VTE episode as well as treatment strategies to mitigate risk of recurrent VTE.

Recent Findings This review particularly highlights methods for stratifying the risk of recurrent VTE and recent studies that have evaluated direct oral anticoagulants for the prevention of recurrent VTE.

Summary Risk assessment for VTE recurrence should guide anticoagulation duration. In patients who present with unprovoked VTE events, there remains a high risk of recurrence that is significantly mitigated with extended duration anticoagulation with either a vitamin K antagonist or direct oral anticoagulant.

Keywords Venous thromboembolic disease · Deep venous thrombosis · Pulmonary embolism · Anticoagulation · Risk assessment · Recurrence

Introduction

Deep vein thrombosis (DVT) and pulmonary embolisms (PE), collectively referred to as venous thromboembolisms (VTE), comprise a common condition with significant morbidity and mortality. VTE is the third leading cause of death in the USA, accounting for nearly 100,000 deaths per year [1]. Throughout their lifetime, 5% of all patients will have experience at least one VTE [2–4]. Recurrent VTE after an initial episode is common [5] and represents a preventable condition that can significantly reduce patient morbidity, mortality, and health care costs [6]. The following review discusses strategies for evaluating risk of recurrent VTE after an initial episode and reviews the evidence supporting anticoagulation strategies to limit or prevent recurrent VTE.

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Risk Factors for Recurrent VTE

Provoked vs Unprovoked

The most significant determinant of risk for recurrent VTE is whether the VTE occurred in the setting of a provoked or unprovoked condition. Previous observational studies have identified a number of risk factors, termed transient or persistent provoking factors, that are associated with a greater risk of recurrent VTE [7–9]. Due to wide variability in the categorization of these factors in the literature, the International Society on Thrombosis and Haemostasis (ISTH) has recently published a guideline more specifically defining subgroups of VTE risk factors [10••]. Transient major risk factors include patients who recently underwent surgery with general anesthesia > 30 min or C-section. Transient minor provoking factors include patients with shorter surgeries (< 30 min), leg injury with immobility, hormonal therapy, and pregnancy. Persistent provoking factors are further characterized as malignant or non-malignant (i.e., inflammatory bowel disease or nephrotic syndrome or predisposing hypercoagulability). In

the absence of a potentially provoking risk factor, VTEs are characterized as "unprovoked."

A previous systematic review of 15 prospective cohort studies of patients with a first symptomatic VTE by Iorios et al. has shown that patients who present with a major transient risk factor are at lower risk for recurrent VTE after initial treatment, with an annualized rate of 0.7% recurrence [11]. Patients with minor provoking factors carried a 4–7-fold higher incidence of recurrent VTE. The risk of recurrent VTE is greatest in patients who present with VTE either in the setting of malignancy or no clear provoking factor, i.e., unprovoked VTE. Patients who present with an unprovoked VTE carry a 1-year recurrence risk of ~ 10%, 5-year recurrence risk of ~ 30%, and 10-year risk of nearly 40% [12••, 13, 14]. Patients with malignancy-associated VTE carry a 15% yearly risk of recurrent VTE [12••].

Demographic and Clinical Risk Factors

Many clinical risk factors have been identified. Male gender has consistently been associated with a higher risk of recurrent VTE [2, 15], with multiple meta-analyses and large population studies suggesting an overall 1.5–2-fold increase risk of recurrent VTE in males vs females even after accounting for gender-specific risk factors such as pregnancy and hormonal therapy [16–19]. Height is also associated with risk of recurrent VTE, with a 3.8-fold increase risk of recurrent VTE in patients > 200 cm in height [20]. Increased body mass index (BMI) [21, 22], ethnic background [23, 24], and lower socioeconomic status [25] are also thought to be demographic factors that associate with an increased risk of recurrent VTE.

Other clinical factors such as underlying thrombophilia, concurrent use of hormonal therapy, pregnancy, cancer, and location of VTE have also been studied as risk factors for recurrence. Thrombophilia has classically been thought to be a risk for an initial VTE event, but the risk of recurrent VTE in the setting of an underlying thrombophilia is less clear. Initial studies evaluating risk of recurrent VTE in this population consisted of prospective observational studies of families with a known mutation [26–31] and suffered from limited generalizability due to decreased genetic variability in the study populations. Large population studies that have tested patients for various inherited thrombophilias such as Factor V Leiden (FVL), prothrombin G20210 mutation (PGM), anti-thrombin deficiency (AT), protein C deficiency (PC), and protein S deficiency (PS) have suggested variable risk of recurrent VTE [7, 32, 33]. Other studies, however, have suggested a nearly 2-fold increase risk of recurrent VTE in patients with thrombophilic mutations [13, 34]. Subgroup analyses have suggested that anti-phospholipid antibody testing, which was present in studies suggesting increased risk, may have been the primary driver of increased risk of recurrent VTE [13, 34].

Pregnancy and hormonal therapy are also known risk factors of recurrent VTE. It is well known that there is a risk for venous thromboembolism in patients who take exogenous estrogen or progesterone therapy. This risk is dependent on the formulation, dose, and method of administration of the hormone therapy [35]. Hormone therapies have been demonstrated to affect multiple pathways in the coagulation cascade including both levels of both pro- and anticoagulant factors as well as intrinsic fibrinolytic activity [36]. Of note, multiple studies suggest that the effect of hormonal therapy upon recurrent VTE is potentially reversible. In the MEGA and PREVENT cohort of patients, the rate of recurrent VTE after an initial hormone therapy-related VTE was 3-fold lower than in patients where initial VTE was not hormone therapy-related [32, 37]. Patient-level meta-analyses have further confirmed a nearly 50% reduction in recurrent VTE rate in patients with hormone therapy-related VTE, but also note that the risk reduction is dependent on discontinuation of therapy [16].

Pregnancy is similarly associated with a significant increase in risk of recurrent VTE in patients who have previously suffered a VTE prior to pregnancy, with the greatest risk occurring in the postpartum period up to 12 weeks after delivery [38, 39]. Studies report a widely variable estimate of recurrence risk of VTE in pregnant patients with a prior VTE, with estimates ranging from 2 to 6% antepartum and upwards of 10% postpartum [40]. Many of these studies are limited by incomplete testing in all patients, non-consecutive evaluation of patients, incomplete assessment of associated risk factors (i.e., antecedent oral contraceptive therapy use, thrombophilia testing, situational assessment), and lack of power in assessing response to thromboprophylaxis to truly assess modifiability of recurrence risk [40]. Large database studies and consensus expert guidelines have suggested that patients with prior VTE during pregnancy are at risk for recurrent VTE with estimates of risk of recurrent VTE during a subsequent pregnancy of nearly 2-fold compared to those without a prior VTE [12••, 41].

Location of VTE

The location of the VTE has previously been associated with risk of recurrence. In DVTs, the proximity of the DVT has been shown to affect risk of recurrence. A distal DVT is defined as a DVT confined to the infra-popliteal veins in lower limbs. Proximal DVT, on the other hand, include any DVTs that extend proximally into the popliteal, femoral, and iliac veins.

In a study by Prandoni et al. of 1626 patients with unprovoked proximal DVT or PE, there was a 22.3% at a median of 50 months of follow-up [13]. Galanaud et al. prospectively evaluated 749 patients for 3 years after an index VTE event. In patients with isolated distal DVT vs proximal DVT, the annualized recurrence risk was 2.7% vs 5.2% for a recurrent DVT and 0.9% vs 1.0% for recurrent PE [42]. In a meta-analysis by Baglin et al., there was a 4.8-fold higher

cumulative recurrence rate for patients with a proximal DVT vs isolated distal DVT [43]. Studies also suggest that the location of recurrent VTE may also be affected by the location of the initial VTE, with a greater risk of recurrent VTE manifesting as a PE in patients who initially presented with PE as opposed to DVT (HR 3.1, 95% CI 1.9–5.1) [43].

Residual Vein Obstruction as a Predictor of Recurrent VTE

Residual vein obstruction at the time of completion of initial duration of anticoagulation is associated with an increased risk of recurrent VTE. Defined by the presence of thrombus comprising 40% or more of the lumen at the time of completion of therapy, it is thought that residual vein thrombosis reflects the extent of original thrombus burden as well as the individual patient's predilection to thrombus formation. Multiple meta-analyses have demonstrated a modest effect of residual vein obstruction (RVO) on the risk of recurrent VTE with hazard ratio ranging from 1.3–1.5 [44, 45]. However, current ACCP guidelines do not routinely recommend repeat imaging in patients who are treated for a symptomatic VTE [12••].

Malignancy

Patients with active malignancy are thought to have an especially high risk of recurrent VTE, with yearly recurrence risk as high as 15% after an initial VTE episode [12••, 22, 46]. Risk assessment for recurrent VTE in patients with active cancer was further refined with the development of a risk model developed using a retrospective cohort study at the Ottawa Hospital [47]. In 543 patients with mean age of 63 and 44% male gender, 89% of the patients presented with a solid tumor malignancy, whereas only 11% had hematologic malignancies. After diagnosis of the VTE, 36.8% (200) patients were treated with warfarin and 63.2% (343) treated with low molecular weight heparin. Based on multivariate analysis, the study identified three factors that significantly associated with increased risk of recurrence: (1) female gender, (2) lung cancer, and (3) prior VTE. Additionally, the presence of breast cancer or low-stage cancer (TNM stage 1) was associated with a significantly lower risk of recurrence. Based on these findings, a risk score was developed. The presence of a score ≥ 1 was associated with a high frequency of recurrence (16.2%) throughout the study period of 200 weeks, whereas a score < 0 was associated with a lower frequency (1.8%). This score was further validated in a set of patients derived from the CLOT and CANTHANOX trials, and it has subsequently been verified in a separate multicenter observational trial [48]. Other retrospective studies have also stratified recurrent VTE risk by type of malignancy, with the greatest risk being attributed to (1) pancreatic cancer (HR 6.38), (2) brain cancer (HR 4.57), (3) myelodysplastic syndromes (HR 3.49), (4) ovarian cancer (HR 3.22), and (5) lung cancer (HR 2.73) [49•].

The significant association between malignancy and VTE has led to the suggestion that patients who present with a VTE should be screened for an undiagnosed malignancy, with meta-analyses suggesting a ~10% occult malignancy detection rate [50]. Beyond a detailed history, physical examination, and age appropriate cancer screening, a more extensive screening strategy using computed tomography (CT) of the abdomen and pelvis increased detection rate from 49.4 to 69.7% [50]. However, subsequent randomized controlled trials have shown increased health care costs with no change in time-to-detection of malignancy or cancer-related mortality with extensive screening [51–53]. As such, the most current guidelines from the ISTH published in 2017 recommend limited screening in patients with unprovoked VTEs in the form of a thorough history and physical examination, laboratory investigations (complete blood count, urinalysis, calcium level, and liver function tests), radiographic testing in the form of a chest x-ray, and age appropriate cancer screening in accordance with national recommendations [54••]. In select situations of "unusual" locations of VTEs such as splanchnic vein thrombosis, cerebral vein thrombosis, and upper extremity VTE that are more often associated with underlying conditions such as occult cancer, myeloproliferative disorder, and paroxysmal nocturnal dyspnea, "limited" screening for the known associated conditions should be completed [54••].

Biomarker Risk Factors: D-dimer

Biomarker-based assessment has also been shown to be useful in predicting recurrence of VTE. The most well-studied biomarker is D-dimer, a byproduct of fibrinolysis. The PROLONG study evaluated the usefulness of D-dimer to predict the risk of recurrent VTE after completion of initial anticoagulation for an unprovoked VTE event. Subjects completed at least 3 months of anticoagulation, then anticoagulation was discontinued, and 1 month later, the D-dimer was assessed. Subjects with normal D-dimer levels remained off of anticoagulation. Subjects with elevated D-dimer values were randomized to resume anticoagulation or no anticoagulation [55]. Among subjects that did not resume anticoagulation, an abnormal D-dimer was associated with a 2.27-fold increased incidence of recurrent VTE (95% CI 1.15–4.46) compared to those with a normal D-dimer level. Among subjects with elevated D-dimer, the risk of recurrent VTE among subjects without anticoagulation was 15.0% vs 2.9% for subjects randomized to resuming anticoagulation, for a hazard ratio of 4.26. Further studies in the form of systemic review and meta-analyses have confirmed an approximate 2–3-fold increased risk for recurrent VTE in the setting of an abnormal D-dimer [16, 56, 57]. A multicenter cohort study of 410 patients with a first unprovoked VTE who completed

initial treatment for VTE (3–7 months in duration) showed that the risk of recurrent VTE with negative D-dimer in men was 9.7% per patient-year (95% CI 6.7–13.7%), as opposed to 5.4% (95% CI 2.5–10.2%) in non-estrogen-associated VTE in women and 0% (95% CI 0.0–3.0%) in estrogen-associated VTE in women [58]. Given the uncertainty about how to use D-dimer testing and the interaction of D-dimer testing outcome with patient sex, the CHEST guidelines for venous thromboembolism do not make recommendations for making decisions about duration of extended therapy based on D-dimer levels [12••].

Risk Assessment Scores for Recurrent Venous Thromboembolic Disease

The multitude of risk factors discussed above has been combined into a number of multivariate risk scores developed to assess the risk of recurrent VTE. The first of these models was the HERDOO2 score [59], developed to identify patients at low risk of recurrent VTE. In a multicenter prospective study of 646 patients with an unprovoked VTE that all received 5–7 months of anticoagulation, analysis of demographic, clinical, and laboratory identified a subset of patients who were at low risk of recurrence (1.6%) in the mean follow-up period of 18 months. These patients were female and ≤ 1 of the following associated factors: (1) post-thrombotic syndrome signs, (2) D-dimer ≥ 250 μg/L while on anticoagulation, (3) BMI ≥ 30, and (4) age ≥ 65 years. Men were excluded from the scoring system due to a higher recurrence rate of 13.3% compared to 5.5% in women in the study, with a particularly high rate of recurrence of 24% in patients with findings of post-thrombotic syndrome.

This risk model was followed by a more detailed Vienna prediction model [60]. In this longitudinal study of 929 individuals enrolled after their first episode of an unprovoked VTE, the study evaluated clinical and demographic factors again that would predict recurrent VTE risk. They additionally collected blood work for both thrombophilia (factor V Leiden and prothrombin 20210 A/G mutation) testing and biomarker (D-dimer, thrombin generation assay)-based assessment. Ultimately, a nomogram was created based on the following risk factors: (1) gender (male = higher risk, female = lower risk), (2) type of thromboembolism (PE > proximal DVT > distal DVT in risk of recurrence), and (3) D-dimer (higher value associated with higher risk).

In 2012, an additional scoring system was validated based on a patient-level meta-analysis of 1818 patients with unprovoked VTE [61]. Studies were included in which patients received at least 3 months of anticoagulation with a vitamin K antagonist. In a median follow-up of 22.4 months, three factors were found to be significantly associated with recurrent VTE: (1) abnormal D-dimer after completion of anticoagulation, (2) age < 50 years, and (3) male gender. The use of hormone therapy at the time of VTE diagnosis was found to be a protective factor. After application of a score to each of these factors (Table 1), an annualized incidence of recurrence was found to be greater than 5% if the DASH score was greater than 1.

While promising as tools to better risk stratify patients at low or high risk for recurrent VTE, one criticism of these multivariate models has been the lack of external validation [62]. The Vienna prediction model has been retrospectively

Table 1 Published scoring systems for estimation of risk of recurrent venous thromboembolism (VTE)

Scoring system	Risk factor/criteria	Interpretation/outcome
HERDOO2 scoring system	1. Female gender (pre-requisite) 2. Post-thrombotic syndrome—1 a. Hyperpigmentation b. Edema c. Redness of leg 3. D-dimer ≥ 250 μg/ml on anticoagulation—1 4. Obesity BMI ≥ 30–1 5. Old age (age ≥ 65)—1	Identify low-risk females with score of 0 or 1 that may discontinue anticoagulation after 6 months
Vienna prediction model	1. Gender (male—higher risk) 2. Type of VTE (PE > proximal DVT > distal DVT—risk of recurrence) 3. D-dimer after discontinuation of AC (higher value = higher risk)	Nomogram calculator—https://cemsiis.meduniwien.ac.at/en/kb/science-research/software/clinical-software/recurrent-vte/
DASH score	1. D-dimer abnormal—2 2. Age < 50–1 3. Sex/gender—male 1 4. Hormone-associated—(− 2)	Quantitative risk assessment based on score—< 5% recurrence risk for scores ≤ 1

VTE venous thromboembolism, *DVT* deep vein thrombosis, *PE* pulmonary embolus

externally validated in a previous study with similar performance of discriminating patients at low risk for recurrent VTE [63], but a prospective study of 156 patients aged 65 years or older suggested that the Vienna risk model did not accurately distinguish high- vs low-risk patients (AUC 0.39 at 12 months and AUC 0.43 at 24 months for predicting VTE recurrence) [64]. The DASH score has also been evaluated externally in a retrospective cohort study of 827 patients. While the cohort was enriched for low-risk patients compared to the original study (66.3% vs 51.6%, $p < 0.001$), the DASH score did correlate well with recurrence rates in patients aged < 65 years of age (c-statistic 0.72). Similar to studies using the Vienna prediction model, it performed poorly in patients ≥ 65 years of age (c-statistic 0.54). Finally, the HERDOO2 score has most recently been externally validated in a multinational prospective cohort of 2785 patients [65]. In low-risk women as defined by the HERDOO2 scoring system, there was an overall 3% rate of recurrent VTE (95% CI 1.8–4.8%), with higher rates of recurrence in the high-risk groups who discontinued anticoagulation compared to those who did not.

Therapeutic Options in Mitigating Recurrent VTE Risk

The mainstay of therapy in the prevention of recurrent VTE in patients is anticoagulation. Multiple studies have previously investigated various regimens and types of anticoagulation for optimally balancing recurrent VTE risk and ongoing bleeding risk with anticoagulation therapy.

Prior randomized controlled clinical trials have evaluated the role of anticoagulation in preventing recurrent VTE in patients with unprovoked VTE (Table 2). Kearon et al. prospectively enrolled 162 patients with idiopathic unprovoked VTE to short-term anticoagulation for 3 months vs 2 full years prior to withdrawal [66]. Due to the symptomatic VTE recurrence rate of 27.4% patient-years vs 1.3% patient-years in the short vs long duration of anticoagulation arms, the trial was terminated early at 10 months. Agnelli et al. confirmed the importance of extended anticoagulation in idiopathic DVT [67]. Agnelli et al. enrolled 267 patients to anticoagulation for 3 months vs 1 year. With a mean follow-up of 37 months, there was a 12.3% patient-year incidence of recurrent VTE in the short-term anticoagulation arm, compared to 1.2% in the long-term arm. Two-thirds of these recurrences occurred during the first year after discontinuation of anticoagulation. Interestingly, at the completion of 1 year of treatment when all arms were taken off of anticoagulation, the overall incidence of recurrent VTE was collectively 5%. Couturaud et al. studied 371 patients who presented with PE as their manifestation of symptomatic VTE to anticoagulation or placebo, and they also found a significant reduction in recurrent VTE with anticoagulation (HR 0.15, 95% CI 0.05–0.43) [68].

Low-dose anticoagulation has also been studied as a means to simultaneously reduce recurrent VTE risk while mitigating concurrent bleeding risk. Ridker et al. prospectively evaluated the efficacy of a lower INR goal of warfarin (1.5–1.9) in 508 patients to either low-dose warfarin (INR goal 1.5–1.9) or placebo after completing a mean of 6.5 months of therapy with full-dose anticoagulation [69]. The study was terminated early after a mean follow-up of 2.1 years due to a significant decrease in recurrent VTE with low-dose warfarin (HR 0.36, 95% CI 0.19–0.67) as compared to placebo. To address whether low-dose anticoagulation would be non-inferior or superior to full-dose anticoagulation for prevention of recurrent VTE, Kearon et al. studied low-dose warfarin (INR goal 1.5–1.9) to full-dose warfarin (INR goal 2.0–3.0) in a prospective randomized controlled trial of 738 patients who completed at least 3 months of treatment for a first VTE [70]. In a mean follow-up of 25.2 months, there was a significantly higher rate of recurrent VTE in patients who received low-dose vs full-dose anticoagulation (HR 2.8, 95% CI 1.1–7.0) with no significant change in major bleeding (HR 1.2, 95% CI 0.4–3.0) or overall bleeding (HR 1.3, 95% CI 0.8–2.1), suggesting no clear benefit to low-dose anticoagulation in the prevention of recurrent VTE when compared to full dose.

These findings highlight the importance of extended duration of anticoagulation in patients with unprovoked VTEs and suggest that the benefit of anticoagulation is not maintained after discontinuation of therapy. This is now reflected in the CHEST guidelines of 2016 that now recommend extended duration anticoagulation in patients with unprovoked proximal DVT or PE with a concomitant low risk of bleeding (grade 2B), with qualification that patient gender and D-dimer levels be used to guide the decision of extended therapy or discontinuation [12••]. These guidelines are based on studies utilizing vitamin K antagonist therapy for treatment. Since these initial studies, other treatments such as low-dose aspirin therapy and direct oral anticoagulant therapy have also been investigated.

Pharmacologic Therapies to Prevent Recurrent Venous Thromboembolic Disease

Aspirin Therapy

A number of studies have investigated continued prophylaxis with antiplatelet agents as opposed to anticoagulant therapy. These include the WARFASA and ASPIRE trials [71]. The WARFASA trial was a multicenter randomized controlled trial comparing aspirin (100 mg daily) vs placebo in patients who had completed 6–18 months of oral anticoagulation for a first episode of unprovoked VTE. In this cohort of patients, there was a statistically significant decrease in recurrent VTE events at 2 years in patients who received aspirin therapy as opposed

Table 2 Studies evaluating risk reduction of recurrent venous thromboembolism (VTE) with treatment with a vitamin K antagonist

Study	No. of patients	Drug/circumstance	Follow-up	Recurrence
Kearon et al. NEJM 1999	162	• Warfarin (INR 2–3) • RCT • 3 months AC and then randomized to continued AC for 2 years vs withdrawal	Early termination after 10 months	• Symptomatic VTE recurrence • Withdrawal arm 27.4% per pt-yr vs 1.3% per pt-yr cont a/c arm • 95% reduction in recurrence risk
Agnelli et al. NEJM 2001	267 (DVT only)	Warfarin INR 2.0–3.0 RCT 3 months AC then randomized to continue AC to 1 year or withdraw AC	Mean 37 months	• Symptomatic VTE recurrence • Withdrawal arm, 1st 9 months: 12.3% per pt-yr vs 1.2% per pt-yr A/C (RR 0.09, 95% CI 0.02–0.69) • After d/c all tx: incidence ~ 5.0% per pt-yr • 91% reduction in recurrence risk
Couturaud et al. JAMA 2015 (PADIS-PE)	371 (PE only)	Warfarin INR 2.0–3.0 RCT 6 months AC then randomized to continue AC vs placebo	18 months active tx 24 months follow-up after stopping tx	• 1.6% vs 13.4% (HR, 0.15; 95% CI, 0.05–0.43) • 85% reduction in recurrence risk
Ridker et al. NEJM 2003 (PREVENT)	508	Warfarin INR 1.5–2.0 RCT Full AC (median 6.5 months) then either low-dose warfarin or placebo	Early termination after mean 2.1 years	• Placebo 7.2% per 100 pt-yrs vs 2.6 per 100 pt-yrs warfarin (HR 0.36, 95% CI 0.19–0.67) • 63% reduction in recurrence risk
Kearon et al. NEJM 2003 (ELATE)	738	Warfarin INR 1.5–1.9 RCT Full AC for > 3 months, then either full-dose AC (INR 2–3) or low dose (INR 1.5–1.9)	Mean 25.2 months follow-up	• Low intensity 1.9 per 100 pt-yrs vs 0.7 per 100 pt-yrs full (HR 2.8, 95% CI 1.1–7.0)

INR international normalized ratio, *RCT* randomized controlled trial, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *yr* year

to placebo treatment without an increase in bleeding (HR for recurrent VTE 0.58, 95% CI 0.36–0.93) [71]. The ASPIRE trial was similarly a randomized controlled trial of 822 patients who received aspirin (100 mg daily) or placebo for up to 4 years after completing treatment for an unprovoked VTE. Unlike the WARFASA trial, the ASPIRE trial did not show a statistically significant reduction in recurrent VTE (HR 0.74, 95% CI 0.52–1.05) without any increase in bleeding rates.

Since both studies were not individually powered to detect treatment effects for particular subgroups, pooled analysis of both studies evaluates risk of recurrent VTE, bleeding, major adverse vascular events (VTE, myocardial infarction, stroke, and cardiovascular disease death), and pre-specified subgroup analyses. In 1224 patients overall, 608 who received placebo and 616 who received aspirin, there was a significant decrease in recurrent VTE (HR 0.68, 95% CI 0.58–0.90), major vascular events (HR 0.66, 95% CI 0.50–0.86), and similarly low bleeding rates in both groups (0.4%/year vs 0.5%/year in aspirin vs placebo groups). As a result of these findings, low-dose aspirin therapy carries a grade 2B recommendation in the ACCP 2016 guidelines after completion of initial therapy with anticoagulation for recurrent VTE prevention [12••].

A recent study has compared oral anticoagulation directly to low-dose aspirin therapy. In a randomized controlled clinical trial of 3396 patients who received either a direct oral anticoagulant rivaroxaban (10 mg or 20 mg daily) or low-dose aspirin (100 mg daily), 12-month follow-up after the completion of an initial period of anticoagulation showed a significantly decreased risk of recurrent VTE in patients who received rivaroxaban as opposed to aspirin (20 mg HR 0.34, 95% CI 0.2–0.59; 10 mg HR 0.26, 95% CI 0.14–0.47). One criticism of this trial is that 58% of all patients were classified as having a provoked VTE event. However, subgroup analyses showed grossly similar reductions in recurrent VTE rates for rivaroxaban vs aspirin regardless of whether the index VTE event was provoked or not [72•].

Therefore, while aspirin is considered a better preventative therapy than no treatment, oral anticoagulation is currently considered a superior treatment for prevention of recurrent VTE.

Direct Oral Anticoagulants (DOACs)

With the advent of alternative oral anticoagulant agents that directly inhibit Factor Xa or thrombin directly, there has been a recent increase in the number of oral agents available for chronic management of recurrent VTE [73–75] (Table 3). While initially studied in the setting of stroke prevention for non-valvular atrial fibrillation, a number of these medications

Table 3 Summary of studies evaluating efficacy of direct oral anticoagulant medications in the prevention of recurrent venous thromboembolism (VTE) after an initial episode

Study	No. of Patients	Drug/circumstance	Follow-up	Recurrence
Bauersachs NEJM 2010 (EINSTEIN)	1196 DVT	• 6–12 months full a/c then • Rivaroxaban 20 mg vs • Placebo for 6 or 12 months	Event driven	• Rivaroxaban superior 1.3% vs 7.1% • HR 0.18; 95% CI 0.09–0.39
Agnelli NEJM 2013 (AMPLIFY-EXT)	2482 VTE	• 6–12 months a/c then • Apixaban 2.5 or 5 mg placebo for 12 months • ~ 90% unprovoked • Equipoise for cont a/c	1 year active study period	• Apixaban 5 mg, 1.7%; Apixaban 2.5 mg, 1.7% Placebo, 8.8% • HR A5 vs placebo, 0.2 (95% CI 0.11–0.34) • HR A2.5 vs placebo, 0.19 (95% CI 0.11–0.33) • HR A5 vs A2.5, 0.97 (95% CI 0.46–2.02)
Schulman NEJM 2013 (RE-SONATE)	1343 VTE	• 6–18 months a/c then • Dabigatran vs placebo	6 months	• Dabigatran 0.4%; placebo 5.6% • HR 0.08, 95% CI 0.02–0.25
Schulman NEJM 2013 (RE-MEDY)	2856 VTE	• 3–12 months a/c then • Dabigatran vs • Warfarin	18 months	• Dabigatran 1.8% • Warfarin 1.3% • HR 1.44; 95% CI 0.78–2.64
Weitz NEJM 2017 (EINSTEIN CHOICE)	3365 VTE	• 6–12 months full a/c then • Rivaroxaban 20 mg vs 10 mg • ASA 100 mg • 40% unprovoked • Equipoise for cont a/c	Median 351 days	• Rivaroxaban 20 mg, 1.8% • Rivaroxaban 10 mg, 1.5% • ASA 100 mg, 5.6% • HR R20 vs ASA, 0.34; 95% CI 0.20–0.59 • HR R10 vs ASA, 0.26; 95% CI 0.14–0.47

have subsequently been studied directly in the treatment and prevention of VTE.

The first trial evaluating direct oral anticoagulant therapies for the prevention of recurrent VTEs was the EINSTEIN trial [76•]. This double-blind randomized controlled trial enrolled and randomized 1196 patients to either rivaroxaban (20 mg daily) or placebo treatment for 6–12 months after an initial 6–12 months of full anticoagulation for treatment of a DVT. There was a statistically significant decrease in the primary outcome of recurrent symptomatic VTE in patients treated with rivaroxaban (HR 0.18, 95% CI 0.09–0.39) compared to placebo with no significant increase in the primary safety endpoint of bleeding (4 cases with rivaroxaban vs 0 cases with placebo, $p = 0.11$). The role of rivaroxaban in the prevention of recurrent VTE was further clarified with the EINSTEIN CHOICE trial [72•], a randomized controlled trial of 3365 patients that compared low-dose aspirin (100 mg daily) to two doses of rivaroxaban (10 mg or 20 mg) for the prevention of recurrent VTE. In a median follow-up of 351 days, both doses of rivaroxaban were superior to aspirin in the prevention of recurrent VTE (HR 0.34 for 20 mg, 95% CI 0.2–0.59; HR 0.26 for 10 mg, 95% CI 0.14–0.47). There was no difference in major bleeding between the three groups, and no difference in recurrent VTE or death between the two doses of rivaroxaban. As a result of this trial, the 10 mg daily dose of rivaroxaban is now approved for the prevention of recurrent VTE.

The efficacy of dabigatran has also been studied in recurrent VTE prevention [77•]. The RE-MEDY trial was a double-blind non-inferiority study comparing warfarin to dabigatran in 2856 patients randomized to either warfarin or dabigatran after 3–12 months of initial anticoagulation for symptomatic VTE. In a mean follow-up of 18 months, there was no significant difference in recurrent VTE between the two treatments (HR 1.44, 95% CI 0.78–2.64) and no difference in major bleeding (HR 0.52, 95% CI 0.27–1.02). There, however, was a decrease in total bleeding episodes in patients receiving dabigatran (HR 0.54, 95% CI 0.41–0.71). The RE-SONATE trial compared dabigatran to placebo in 1343 patients with a mean follow-up of 6 months. There was a significant decrease in recurrent VTE in patients treated with dabigatran (HR 0.08, 95% CI 0.02–0.25) with an associated increase in major or clinically relevant bleeding as well (HR 2.92, 95% CI 1.52–5.60).

Finally, apixaban has also been evaluated for its ability to reduce recurrent VTE [78•]. The AMPLIFY-EXT trial randomized 2482 patients to placebo or apixaban at two different doses (2.5 mg twice daily or 5 mg twice daily) for 12 months after an initial 6–12 months of anticoagulation. Of note, 90% of the patients in this study were deemed to have an unprovoked VTE. In the 12-month active study period, there was a similar reduction in recurrent VTE events with both doses of apixaban when compared to placebo (HR 0.2 for 5 mg dose,

95% CI 0.11–0.34; HR 0.19 for 2.5 mg dose, 95% CI 0.11–0.33) with no significant difference in primary outcome between both apixaban doses. There was additionally no difference in major bleeding, clinically relevant bleeding, or death from any cause between all three treatment groups, although there were numerical less bleeding events with the apixaban 2.5 mg twice daily dose compared with the 5 mg twice daily dose. Apixaban is FDA-approved for the prevention of recurrent VTE and the recommended dose is 2.5 mg twice daily.

Conclusions

Venous thromboembolism (VTE) is a common condition with significant associated morbidity and mortality. In patients with unprovoked VTE events or malignancy-associated VTE, the recurrence risk is sufficiently high that extended therapy should be strongly considered based on current guidelines and evidence. Further risk stratification is possible based on clinical and biomarker data, and this can be used to further risk stratify patients who may have a moderate or high bleeding risk. In such patients who have an unfavorable risk to benefit ratio of anticoagulation, lower dose regimens with anticoagulation and therapies such as aspirin have been shown to reduce risk of recurrent VTE.

Compliance with Ethical Standards

Conflict of Interest Vineet Agrawal and Esther S.H. Kim declare that they have no conflicts of interest.

Human Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism. Am J Prev Med. 2010;38:S495–501.
2. Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S. The risk of recurrent venous thromboembolism in men and women. N Engl J Med. 2004;350:2558–63.
3. White RH. The epidemiology of venous thromboembolism. Circulation. 2003;107:4I–8.
4. Heit JA. The epidemiology of venous thromboembolism in the community: implications for prevention and management. J Thromb Thrombolysis. 2006;21:23–9.
5. Martinez C, Cohen AT, Bamber L, Rietbrock S. Epidemiology of first and recurrent venous thromboembolism: a population-based cohort study in patients without active cancer. Thromb Haemost. 2014;112:255–63.
6. Lefebvre P, Laliberté F, Nutescu EA, Duh M, LaMori J, Bookhart BK, et al. All-cause and disease-related health care costs associated with recurrent venous thromboembolism. Thromb Haemost. 2013;110:1288–97.
7. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet (London, England). 2003;362:523–6.
8. Anderson FA, Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003;107:I9–16.
9. White RH. Identifying risk factors for venous thromboembolism. Circulation. 2012;125:2051–3.
10. •• Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing G-J, Kyrle PA, et al. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. J Thromb Haemost. 2016;14:1480–3 **An important guideline statement from the ISTH that specifically defines provoked and unprovoked venous thromboembolism**.
11. Iorio A, Kearon C, Filippucci E, Marcucci M, Macura A, Pengo V, et al. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor. Arch Intern Med. 2010;170:1710–6.
12. •• Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease. Chest. 2016;149:315–52 **The most recent set of comprehensive guidelines that provide recommendations and literature review on the diagnosis, management, and prevention of venous thromboembolism**.
13. Prandoni P, Noventa F, Ghirarduzzi A, Pengo V, Bernardi E, Pesavento R, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica. 2007;92:199–205.
14. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. J Thromb Thrombolysis. 2016;41:3–14.
15. de Haan HG, van Hylckama Vlieg A, van der Gaag KJ, de Knijff P, Rosendaal FR. Male-specific risk of first and recurrent venous thrombosis: a phylogenetic analysis of the Y chromosome. J Thromb Haemost. 2016;14:1971–7.
16. Douketis J, Tosetto A, Marcucci M, Baglin T, Cushman M, Eichinger S, et al. Patient-level meta-analysis: effect of measurement timing, threshold, and patient age on ability of D-dimer testing to assess recurrence risk after unprovoked venous thromboembolism. Ann Intern Med. 2010;153:523–31.
17. Roach REJ, Lijfering WM, Rosendaal FR, Cannegieter SC, le Cessie S. Sex difference in risk of second but not of first venous thrombosis clinical perspective. Circulation. 2014;129:51–6.
18. Roach REJ, Lijfering WM, Tait RC, Baglin T, Kyrle PA, Cannegieter SC, et al. Sex difference in the risk of recurrent venous thrombosis: a detailed analysis in four European cohorts. J Thromb Haemost. 2015;13:1815–22.
19. McRae S, Tran H, Schulman S, Ginsberg J, Kearon C. Effect of patient's sex on risk of recurrent venous thromboembolism: a meta-analysis. Lancet (London, England). 2006;368:371–8.
20. Flinterman LE, van Hylckama Vlieg A, Rosendaal FR, Cannegieter SC. Body height, mobility, and risk of first and recurrent venous thrombosis. J Thromb Haemost. 2015;13:548–54.
21. Eichinger S, Hron G, Bialonczyk C, Hirschl M, Minar E, Wagner O, et al. Overweight, obesity, and the risk of recurrent venous thromboembolism. Arch Intern Med. 2008;168:1678–83.
22. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ. Predictors of recurrence after deep vein thrombosis and

pulmonary embolism: a population-based cohort study. Arch Intern Med. 2000;160:761–8.
23. White RH, Zhou H, Romano PS. Incidence of idiopathic deep venous thrombosis and secondary thromboembolism among ethnic groups in California. Ann Intern Med. 1998;128:737–40.
24. White RH, Zhou H, Murin S, Harvey D. Effect of ethnicity and gender on the incidence of venous thromboembolism in a diverse population in California in 1996. Thromb Haemost. 2005;93:298–305.
25. Kort D, van Rein N, van der Meer FJM, Vermaas HW, Wiersma N, Cannegieter SC, et al. Relationship between neighborhood socioeconomic status and venous thromboembolism: results from a population-based study. J Thromb Haemost. 2017;15:2352–60.
26. Segal JB, Brotman DJ, Necochea AJ, Emadi A, Samal L, Wilson LM, et al. Predictive value of factor V Leiden and prothrombin G20210A in adults with venous thromboembolism and in family members of those with a mutation. JAMA. 2009;301:2472.
27. Sokol J, Timp JF, le Cessie S, van Hylckama-Vlieg A, Rosendaal FR, Kubisz P, et al. Mild antithrombin deficiency and risk of recurrent venous thromboembolism: results from the MEGA follow-up study. J Thromb Haemost. 2018;16:680–8.
28. Ospina-Romero M, Cannegieter SC, den Heijer M, Doggen CJM, Rosendaal FR, Lijfering WM. Hyperhomocysteinemia and risk of first venous thrombosis: the influence of (unmeasured) confounding factors. Am J Epidemiol. 2018;187:1392–400. https://doi.org/10.1093/aje/kwy004.
29. Lijfering WM, Mulder R, ten Kate MK, Veeger NJGM, Mulder AB, van der Meer J. Clinical relevance of decreased free protein S levels: results from a retrospective family cohort study involving 1143 relatives. Blood. 2009;113:1225–30.
30. Lijfering WM, Christiansen SC, Rosendaal FR, Cannegieter SC. Contribution of high factor VIII, IX and XI to the risk of recurrent venous thrombosis in factor V Leiden carriers. J Thromb Haemost. 2009;7:1944–6.
31. Lijfering WM, Middeldorp S, Veeger NJGM, Hamulyak K, Prins MH, Buller HR, et al. Risk of recurrent venous thrombosis in homozygous carriers and double heterozygous carriers of factor V Leiden and prothrombin G20210A. Circulation. 2010;121:1706–12.
32. Christiansen SC, Cannegieter SC, Koster T, Vandenbroucke JP, Rosendaal FR. Thrombophilia, clinical factors, and recurrent venous thrombotic events. JAMA. 2005;293:2352–61.
33. Ribeiro DD, Lijfering WM, Barreto SM, Lopes FD, Pires G de S, Rosendaal FR, et al. The influence of prothrombotic laboratory abnormalities on the risk of recurrent venous thrombosis. Thromb Res. 2012;130:974–6.
34. Santamaria MG, Agnelli G, Taliani MR, Prandoni P, Moia M, Bazzan M, et al. Thrombophilic abnormalities and recurrence of venous thromboembolism in patients treated with standardized anticoagulant treatment. Thromb Res. 2005;116:301–6.
35. Jacobsen AF, Sandset PM. Venous thromboembolism associated with pregnancy and hormonal therapy. Best Pract Res Clin Haematol. 2012;25:319–32.
36. Reitsma PH, Versteeg HH, Middeldorp S. Mechanistic view of risk factors for venous thromboembolism. Arterioscler Thromb Vasc Biol. 2012;32:563–8.
37. Cushman M, Glynn RJ, Goldhaber SZ, Moll S, Bauer KA, Deitcher S, et al. Hormonal factors and risk of recurrent venous thrombosis: the prevention of recurrent venous thromboembolism trial. J Thromb Haemost. 2006;4:2199–203.
38. Pomp ER, Lenselink AM, Rosendaal FR, Doggen CJM. Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. J Thromb Haemost. 2008;6:632–7.
39. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med. 2005;143:697–706.
40. Bates SM. Pregnancy-associated venous thromboembolism: prevention and treatment. Semin Hematol. 2011;48:271–84.
41. White RH, Chan W-S, Zhou H, Ginsberg JS. Recurrent venous thromboembolism after pregnancy-associated versus unprovoked thromboembolism. Thromb Haemost. 2008;100:246–52.
42. Galanaud J-P, Sevestre M-A, Genty C, Kahn SR, Pernod G, Rolland C, et al. Incidence and predictors of venous thromboembolism recurrence after a first isolated distal deep vein thrombosis. J Thromb Haemost. 2014;12:436–43.
43. Baglin T, Douketis J, Tosetto A, Marcucci M, Cushman M, Kyrle P, et al. Does the clinical presentation and extent of venous thrombosis predict likelihood and type of recurrence? A patient-level meta-analysis. J Thromb Haemost. 2010;8:2436–42.
44. Carrier M, Rodger MA, Wells PS, Righini M, Le Gal G. Residual vein obstruction to predict the risk of recurrent venous thromboembolism in patients with deep vein thrombosis: a systematic review and meta-analysis. J Thromb Haemost. 2011;9:1119–25.
45. Donadini MP, Ageno W, Antonucci E, et al. Prognostic significance of residual venous obstruction in patients with treated unprovoked deep vein thrombosis. Thromb Haemost. 2013;111:172–9.
46. Prandoni P, Lensing AWA, Piccioli A, Bernardi E, Simioni P, Girolami B, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood. 2002;100:3484–8.
47. Louzada ML, Carrier M, Lazo-Langner A, Dao V, Kovacs MJ, Ramsay TO, et al. Development of a clinical prediction rule for risk stratification of recurrent venous thromboembolism in patients with cancer-associated venous thromboembolism. Circulation. 2012;126:448–54.
48. den Exter PL, Kooiman J, Huisman MV. Validation of the Ottawa prognostic score for the prediction of recurrent venous thromboembolism in patients with cancer-associated thrombosis. J Thromb Haemost. 2013;11:998–1000.
49.• Chee CE, Ashrani AA, Marks RS, Petterson TM, Bailey KR, Melton LJ, et al. Predictors of venous thromboembolism recurrence and bleeding among active cancer patients: a population-based cohort study. Blood. 2014;123:3972–8 **A detailed population-based cohort study looking at trends of venous thromboembolism recurrence by cancer type**.
50. Carrier M, Le Gal G, Wells PS, Fergusson D, Ramsay T, Rodger MA. Systematic review: the trousseau syndrome revisited: should we screen extensively for cancer in patients with venous thromboembolism? Ann Intern Med. 2008;149:323–33.
51. Carrier M, Lazo-Langner A, Shivakumar S, Tagalakis V, Zarychanski R, Solymoss S, et al. Screening for occult cancer in unprovoked venous thromboembolism. N Engl J Med. 2015;373:697–704.
52. Robin P, Le Roux P-Y, Le Moigne E, et al. Additional testing following screening strategies for occult malignancy diagnosis in patients with unprovoked venous thromboembolism. Thromb Res. 2017;155:6–9.
53. Coyle K, Carrier M, Lazo-Langner A, Shivakumar S, Zarychanski R, Tagalakis V, et al. Cost effectiveness of the addition of a comprehensive CT scan to the abdomen and pelvis for the detection of cancer after unprovoked venous thromboembolism. Thromb Res. 2017;151:67–71.
54.•• Delluc A, Antic D, Lecumberri R, Ay C, Meyer G, Carrier M. Occult cancer screening in patients with venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost. 2017;15:2076–9 **Recent guideline statement from the ISTH with specific recommendations on screening for occult malignancy in patients with venous thromboembolism**.
55. Palareti G, Cosmi B, Legnani C, Tosetto A, Brusi C, Iorio A, et al. D-dimer testing to determine the duration of anticoagulation therapy. N Engl J Med. 2006;355:1780–9.

56. Verhovsek M, Douketis JD, Yi Q, Shrivastava S, Tait RC, Baglin T, et al. Systematic review: D-dimer to predict recurrent disease after stopping anticoagulant therapy for unprovoked venous thromboembolism. Ann Intern Med. 2008;149(481–90):W94.
57. Bruinstroop E, Klok FA, Van De Ree MA, Oosterwijk FL, Huisman MV. Elevated d-dimer levels predict recurrence in patients with idiopathic venous thromboembolism: a meta-analysis. J Thromb Haemost. 2009;7:611–8.
58. Kearon C, Spencer FA, O'Keeffe D, et al. d-Dimer testing to select patients with a first unprovoked venous thromboembolism who can stop anticoagulant therapy. Ann Intern Med. 2015;162:27.
59. Rodger MA, Kahn SR, Wells PS, Anderson DA, Chagnon I, le Gal G, et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. Can Med Assoc J. 2008;179:417–26.
60. Eichinger S, Heinze G, Jandeck LM, Kyrle PA. Risk assessment of recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism: the Vienna prediction model. Circulation. 2010;121:1630–6.
61. Tosetto A, Iorio A, Marcucci M, Baglin T, Cushman M, Eichinger S, et al. Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: a proposed prediction score (DASH). J Thromb Haemost. 2012;10:1019–25.
62. Ensor J, Riley RD, Moore D, Snell KIE, Bayliss S, Fitzmaurice D. Systematic review of prognostic models for recurrent venous thromboembolism (VTE) post-treatment of first unprovoked VTE. BMJ Open. 2016;6:e011190.
63. Marcucci M, Iorio A, Douketis JD, Eichinger S, Tosetto A, Baglin T, et al. Risk of recurrence after a first unprovoked venous thromboembolism: external validation of the Vienna prediction model with pooled individual patient data. J Thromb Haemost. 2015;13:775–81.
64. Tritschler T, Méan M, Limacher A, Rodondi N, Aujesky D. Predicting recurrence after unprovoked venous thromboembolism: prospective validation of the updated Vienna prediction model. Blood. 2015;126:1949–51.
65. Rodger MA, Le Gal G, Anderson DR, et al. Validating the HERDOO2 rule to guide treatment duration for women with unprovoked venous thrombosis: multinational prospective cohort management study. BMJ. 2017;356:j1065.
66. Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, Anderson DR, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med. 1999;340:901–7.
67. Agnelli G, Prandoni P, Santamaria MG, Bagatella P, Iorio A, Bazzan M, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med. 2001;345:165–9.
68. Couturaud F, Sanchez O, Pernod G, Mismetti P, Jego P, Duhamel E, et al. Six months vs extended oral anticoagulation after a first episode of pulmonary embolism. JAMA. 2015;314:31–40.
69. Ridker PM, Goldhaber SZ, Danielson E, Rosenberg Y, Eby CS, Deitcher SR, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med. 2003;348:1425–34.
70. Kearon C, Ginsberg JS, Kovacs MJ, Anderson DR, Wells P, Julian JA, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med. 2003;349:631–9.
71. Becattini C, Agnelli G, Schenone A, Eichinger S, Bucherini E, Silingardi M, et al. Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med. 2012;366:1959–67.
72.• Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. N Engl J Med. 2017;376:1211–22 **Important reference that demonstrated the efficacy of a direct oral anticoagulant, rivaroxaban, in the extended treatment of venous thromboembolism**.
73. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–51.
74. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91.
75. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92.
76.• EINSTEIN Investigators, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363:2499–510 **Important reference that demonstrated the efficacy of a direct oral anticoagulant, rivaroxaban, in treatment of venous thromboembolism**.
77.• Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361:2342–52 **Important reference that demonstrated the efficacy of a direct oral anticoagulant, dabigatran, in treatment of venous thromboembolism**.
78.• Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2013;368:699–708 **Important reference that demonstrated the efficacy of a direct oral anticoagulant, apixiban, in extended treatment of venous thromboembolism.**