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Duration of anticoagulant therapy in pediatric venous thromboembolism: Current approaches and updates from randomized controlled trials

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Abstract

Introduction—Compared with the incidence of venous thromboembolism in the adult population, pediatric VTE is rare. Yet, recent data suggest that the incidence of VTE in children is increasing, and little is known about the optimal duration of anticoagulation in pediatrics.

Areas covered—This review summarizes current evidence-based adult recommendations and associated clinical trials from which current guidelines on the duration of anticoagulation in children have been extrapolated. It also discusses pediatric expert consensus-based guidelines and current pediatric clinical trials on duration of therapy in pediatric VTE.

Expert commentary—The vast majority of pediatric VTE are provoked, and evidence on duration of anticoagulation for pediatric VTE is highly limited, but suggests that a maximum duration of 3 months is reasonable for most patients with provoked VTE, whereas longer duration is likely appropriate for unprovoked VTE. Whether shorter duration than 3 months is optimal for pediatric provoked VTE is as yet unclear. Results from the multinational randomized controlled trial studying the duration of anticoagulant therapy for provoked VTE in patients <21 years old (Kids-DOTT) will be critical to inform the future standard of care in pediatric VTE treatment.

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Keywords

Duration of anticoagulation; pediatrics; venous thromboembolism; guidelines; randomized trial

1. Introduction

The incidence of venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism, is much lower in children than in the adult population. Pediatric VTE has been estimated to occur in less than 1 in 10,000 children per year [1,2]. In the last decade, however, the incidence of VTE in children of all age groups has shown a marked increase, from 34 to 58 cases per 10,000 hospital admissions in the United States [3]. This increase is presumed to be due to the increased use of invasive procedures and venous catheterization in children, easier access to (and more sensitive) imaging modalities, and improved survival of chronically ill children. It is estimated that 95% of VTEs in children are provoked events with the presence of central venous catheters being the most common risk factor [4]. Congenital heart disease, major infection, critical illness and mechanical ventilation, and malignancy are also common risk factors for pediatric VTE. The presence of heritable thrombophilia such as protein S deficiency, protein C deficiency, antithrombin deficiency, and the polymorphisms in factor V (G1691A), and prothrombin (G20210A) can add to the risk of both provoked and unprovoked thrombosis in children [5]. Factor V Leiden, however, has not been shown to increase the risk of recurrent thrombosis in children [5]. Pediatric VTE results in increased morbidity and mortality. Mortality directly related to VTE in children has been reported to be 0–3.7% [6–8]. Post-thrombotic syndrome (PTS), a chronic complication that can follow DVT in the extremities, has been reported with a frequency of 9.5–70% [8,9].

The mainstay of treatment of acute pediatric thrombosis is anticoagulation with heparins and/or vitamin K antagonists. The immediate goals of anticoagulation are to prevent propagation of acute thrombosis, prevent embolization, and prevent secondary VTE. Duration of therapy is therefore predicated on time-dependent risk of recurrent VTE. Unfortunately, there are limited data by which to accurately define the frequency of VTE recurrence and anticoagulation-associated adverse events in pediatric VTE. Recurrent VTE is estimated to occur in 7.5% of children with a mean follow-up of 2 years, based on sparse pediatric registries [4]. This is lower than the 30% (after 8 years of follow-up) risk in adults [10]. Bleeding in children on unfractionated heparin (UFH) therapy has ranged from 1.5% to 24% [11,12], with the higher incidence seen in critically ill children. The incidence of major bleeding was 3% in a review of over 300 children treated with low-molecular-weight heparin (LMWH) [13]. Major bleeding incidence reported with vitamin K antagonists has a range of 0.05–3.2% per patient year [4]. Only two international, randomized controlled trials of anticoagulation for VTE treatment have been published in children. The REVIVE trial was performed to compare UFH with transition to vitamin K antagonists to LMWH in the treatment of VTE in children aged 60 days to 18 years [6]. The study was closed early due to slow accrual with 76 patients enrolled, but this study showed that overall, 9% of subjects had major bleeding and 9% had recurrent thrombosis. The pilot-feasibility phase of the Kids-DOTT trial enrolled a prespecified 100 children with VTE, of which 69 were randomized to

6 weeks versus 3 months of anticoagulant of choice [14]. Rates of symptomatic recurrent VTE and clinically relevant bleeding were 3.3% and 1.4%, respectively. The rest-of-trial phase of Kids-DOTT is ongoing, with nearly 400 children enrolled as of the time of publication of this review (see also Section 4).

With limited high-quality outcomes data to date in children, pediatric VTE management has largely been based on adult data and guidelines. In this review, we will discuss the evidence from adult trials that has informed pediatric VTE management. We will also review pediatric expert consensus guidelines and the ongoing Kids-DOTT trial, which is investigating a shortened versus conventional duration of anticoagulation in children with provoked VTE.

2. Duration of anticoagulation in adult VTE: evidence and current guidelines

The optimal length of anticoagulant therapy for secondary VTE prophylaxis in adults and children is still a matter of debate. The American College of Chest Physicians' (ACCP's) adult and pediatric guidelines have recommended 3 months of therapy for provoked VTE, with extended or indefinite therapy for unprovoked or recurrent VTE, depending upon careful assessment of risk of bleeding [4,15]. The likelihood of recurrent VTE in adults has been associated with the nature and chronicity of provoking factors for VTE, and is modulated by the duration of anticoagulant therapy [16]. Analysis of multiple studies has suggested that the risk of recurrent VTE in adults after a nonsurgical reversible risk factor is 5% at 1 year and 15% at 5 years, while corresponding recurrence risks in unprovoked VTE are 10% and 30%, respectively. Postsurgical VTE has the lowest risk of recurrence, at 1% after 1 year and 3% after 5 years [16].

Since the early 1970s, several randomized studies have examined the optimal length of oral anticoagulation as secondary thromboprophylaxis in adults, with durations ranging from 4 weeks to 12 months. Early studies were small and did not consistently use objective measures for the diagnosis of VTE, but suggested that a shorter course of therapy ranging from 4 to 6 weeks might be as effective as 6–12 months of therapy [17–20], whereas several subsequent studies with stronger methodology concluded that at least 3 months and potentially 6 months was the optimal anticoagulant therapy duration for VTE [21,22]. Notably, however, the latter studies included a mix of adult patients with provoked and unprovoked index VTEs. Table 1 provides a summary of some of the most relevant trials.

One of the most robust of these later trials was the multicenter randomized Duration of Anticoagulation (DURAC) trial. This trial enrolled 905 patients (mean age: 60 years) with a first episode of VTE as diagnosed by venography. The DURAC trial found that 6 months of anticoagulation resulted in a 50% reduction in the risk of recurrent VTE at 2 years relative to 6 weeks of anticoagulation [21]. There were no significant differences in major bleeding or death between the two duration-of-therapy groups. Interestingly, there was a sharp increase in the risk of recurrent VTE immediately after cessation of anticoagulation in the 6-week group, and the risk of recurrent VTE was similar between groups from 6 to 24 months post-diagnosis of index VTE. Of note, approximately 60% of patients in this study had either unprovoked index VTE or chronic VTE risk factors, although cancer and the heritable

thrombophilia of protein C, protein S, or antithrombin deficiency were excluded. In a 10-year follow-up study to DURAC, there was no significant difference in long-term outcomes, specifically PTS, between treatment arms [27].

Another randomized open-label study, the *Durée Optimale du Traitement Anti-Vitamine K* (DOTAVK) trial, was the first randomized trial to compare 3 versus 6 months of oral anticoagulant therapy in proximal DVT in adults [22]. This trial also investigated duration of therapy in distal DVT, via separate randomization of these patients to 6 weeks versus 3 months of oral anticoagulation. The DOTAVK trial enrolled 736 patients, and unfortunately was closed early due to slow accrual. Although underpowered to demonstrate non-inferiority, no difference in recurrent VTE or major bleeding risks were detected between the two duration-of-therapy arms in proximal DVT, by both the intention-to-treat and the per-protocol analysis. The overall VTE recurrence rate was 8.4%. Similar to the DURAC trial, nearly half of the study population had either an unprovoked index VTE or chronic VTE risk factors.

Campbell et al. led a randomized study of 749 patients that, similar to other trials, included patients with both provoked and unprovoked VTE assigned to either 3- or 6-month duration of anticoagulation. Eight percent of patients had recurrence in each of the two arms, and 8% had nonfatal major bleeding. This study suggested that in those patients without known risk factors for recurrence, there is no benefit to 6 months over 3 months of anticoagulation [23].

Potential weaknesses of these trials are the lack of patient selection based on risk factors for thrombosis such as unprovoked/ idiopathic thrombosis or permanent risk factors, the use of vitamin K antagonists (which requires close laboratory monitoring and adjustments to achieve and maintain within therapeutic range), and lack of assessment of other long-term clinical outcomes such as PTS in most trials. Along this line, several trials addressed the duration of anticoagulation in patients with unprovoked thrombosis. Kearon et al. conducted a double-blind, randomized controlled trial comparing 3 months versus 2 years of anticoagulation with warfarin after a first episode of unprovoked VTE in 162 adults [28]. Testing for factor V Leiden, prothrombin G20210A, lupus anticoagulant, and anticardiolipin antibodies were also performed in order to evaluate putative relationships between these genetic and acquired thrombophilias and outcomes. The study was stopped early due to interim analysis showing that extended anticoagulation resulted in a 95% reduction in the risk of recurrent VTE. Major bleeding occurred in three patients (3.8% per patient year; 95% confidence interval [CI] 0.0–8.1) in the extended therapy group, two of whom had supra-therapeutic international normalized ratios. Secondary analyses found that the presence of a lupus anticoagulant was significantly associated with recurrent VTE.

Similarly, the Warfarin Optimal Duration Italian Trial (WODIT) randomized 267 adults with a first episode of unprovoked DVT to 3 months versus 12 months duration of anticoagulation and assessed for recurrent VTE during 2 years of follow-up [24]. The risk of recurrent VTE was similar between the shorter and longer duration-of-therapy groups, at 15.8% and 15.7%, respectively, and the average times to recurrence were 11.2 and 16 months, respectively. Notably, following cessation of anticoagulation, the risk of recurrent VTE was 15% in each arm. Four patients in the longer duration-of-therapy group had

nonfatal major bleeding while on treatment (3%) with anticoagulation in therapeutic range. There were two fatal major bleeding episodes in the shorter duration-of-therapy group (1.5%) that occurred after the discontinuation of anticoagulation. These findings from the WODIT trial suggested that the clinical benefit of extended duration anticoagulation with regard to reduction in VTE recurrence risk is principally realized during active treatment.

In adults with unprovoked VTE, D-dimer levels following an initial course of anticoagulation have been used to stratify randomization to stop versus continue therapy for an extended duration. The PROLONG study assessed the risk of recurrent VTE if patients had an abnormal D-dimer drawn 1 month after cessation of at least 3 months of anticoagulation; those with a positive D-dimer were randomized to either restart or continue off anticoagulation [25]. Among patients with an abnormal D-dimer 1 month after stopping anticoagulation, 15% of those who remained off anticoagulation developed recurrent VTE (10.9 events per 100 patient years), compared with a 2.9% (2% patient years) combined rate of recurrent VTE or major bleeding (2 events per 100 patient years) among those patients who resumed anticoagulation. Patients with negative D-dimer at 1 month off anticoagulation had a low risk of recurrent VTE (4 events per 100 patient years). In PROLONG-II, patients with abnormal D-dimer levels at the end of a course of anticoagulation were continued on anticoagulation, while D-dimer levels were obtained every 2 months for 1 year in those patient with initially negative D-dimer testing at the end of a course of anticoagulation, and anticoagulation restarted if/when the D-dimer became elevated [29]. This study suggests that continued monitoring of D-dimer after suspension of anticoagulation could help tailor the duration of anticoagulation in adults with unprovoked VTE.

As an alternative to oral vitamin K antagonists, studies have been performed to assess the potential of aspirin as extended secondary VTE prevention after a standard course of anticoagulation in adults. The Aspirin for the Prevention of Recurrent Venous Thromboembolism (the Warfarin and Aspirin [WARFASA]) trial aimed to assess the benefit of aspirin as secondary VTE prevention after a treatment course of anticoagulation in adults with unprovoked VTE [26]. This study randomized 403 patients to aspirin 100 mg or placebo for 2 years after completion of 6–18 months of anticoagulation. Recurrent VTE occurred in 5.9% per year in the aspirin group versus 11% per year in the placebo group (hazard ratio 0.55; 95% CI 0.33–0.92; $P=0.02$). There were two episodes of nonfatal bleeding, one in each of the two groups. The Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) trial was also a randomized, double-blind, placebo-controlled trial of aspirin for secondary prevention of thromboembolism after a course of anticoagulation in adults with unprovoked VTE [30]. ASPIRE enrolled 822 patients, and the rate of recurrent VTE in the aspirin group was 4.8% per year versus 6.5% per year in the placebo group. While this difference was not statistically significant, it was a reduction of VTE by 26%, and there was a significant decrease in vascular events such as myocardial infarction and stroke in the aspirin group. These studies suggest that aspirin after standard-duration anticoagulation can reduce the risk of VTE recurrence in adults with unprovoked VTE [31].

In the last decade, VTE treatment trials with the non-vitamin K direct oral anticoagulants (DOACs), which include oral direct thrombin inhibitors and Xa inhibitors, have

demonstrated efficacy of these agents in secondary VTE prevention, with similar or better safety profiles than warfarin [32–35]. DOACs have also been studied for extended secondary thromboprophylaxis after an initial 6–12 months course of anticoagulation, and have shown reductions in recurrent VTE risk without a substantively increased risk of major bleeding [33,36]. These studies generally included a broad population of mixed provoked and unprovoked VTE patients, and first- or second-or-more episode of VTE.

In the most recent iteration of the ACCP guidelines of antithrombotic treatment for VTE in adults [15], extended therapy (defined as anticoagulation with no defined stop date) is suggested for first unprovoked thrombosis or recurrent thrombosis when the bleeding risk is low to moderate. DOACs are now suggested as first-line therapy over vitamin K antagonists for treatment of thrombosis in individuals without cancer. New recommendations also include suggestion of aspirin over no aspirin for secondary prevention in patients with unprovoked VTE who have no contraindication to aspirin and who desire to stop anticoagulation.

3. Duration of anticoagulation in pediatric VTE: current consensus-based guidelines

Since 1995, when the first ACCP expert guideline for the treatment of pediatric thrombosis was published [37], substantive advances have been made in the understanding of pediatric thrombosis, its management, and outcomes. Yet, the problem remains that many of the current pediatric recommendations are based on adult data. This is suboptimal, as there are several important differences between pediatric and adult VTE patients [16] including: types of comorbidities; distribution of common anatomic locations of VTE; profile of provoked versus unprovoked VTE (and number of provoking factors); and rates of mortality and morbidities associated with VTE [1,2]. In addition, the hemostatic system in children changes from birth to adulthood [38], and anticoagulant pharmacokinetics are age-dependent. Three anticoagulant drugs are most commonly used in pediatrics: UFH given as an intravenous infusion, used in inpatient settings particularly among critically ill children whose lability in clinical status warrant the use of a short-acting agent; LMWH by twice-daily subcutaneous injection, used as subacute therapy in the majority of children, given that >90% of VTE in children are provoked [4]; and oral vitamin K antagonists, used particularly in children who have unprovoked VTE or significant chronic risk factors for recurrent VTE. The volume of distribution, clearance, and peak serum levels of UFH can vary greatly in children, with neonates having the greatest differences in these variables compared with adults [39,40]. Similarly, doses of LMWH are age-dependent, and doses are higher in neonates compared with older children to achieve the same anti-Xa activity [41]. Vitamin K antagonists, which are currently the oral anticoagulants commonly used in children, can be difficult to manage in children due to the tablet-only formulation, diet variability in pediatrics, the need for frequent laboratory monitoring, and the higher doses required in neonates [42]. Presently, several DOACs are undergoing evaluation in pediatric development programs [43].

The 2012 ACCP (Chest) guidelines for antithrombotic therapy in children address duration of anticoagulation in pediatric VTE [4]. These recommendations largely echo those of the adult VTE treatment recommendations; namely, an anticoagulant duration of 3 months is recommended for provoked VTE (including cerebral sinovenous thrombosis) in which the provoking factors have resolved, of 6–12 months for a first unprovoked VTE, and of indefinite duration for recurrent unprovoked VTE. Notably, however, the pediatric guidelines include consideration in *neonates* of a shorter duration of anticoagulation than recommended in adults, as part of a recommended range of “6 weeks–3 months”.

4. NHLBI-sponsored Kids-DOTT trial: design, published findings, and current status

Kids-DOTT is an ongoing, multicenter, multinational randomized trial investigating the duration of anticoagulation in patients less than 21 years of age with first episode, provoked VTE (NCT00687882). As noted previously, the primary aim of this study is to evaluate the efficacy and safety of shortened-duration (6 weeks) versus conventional-duration (3 months) among young patients in whom some blood flow is evident in the originally involved venous segment(s) after the initial 6 weeks of anticoagulant therapy. The primary efficacy outcome is symptomatic recurrent VTE and the primary safety outcome is clinically relevant bleeding. The analysis employs a bivariate end point approach, evaluating net clinical benefit as the trade-off between the primary efficacy and safety end points (i.e. risks of recurrent VTE and bleeding). The trial also employs parallel cohorts (nonrandomized) for patients with persistently positive antiphospholipid antibody (APA) profiles and those with persistently occlusive thrombosis [14]. Inclusion criteria include radiologically confirmed VTE (including right atrial thrombosis) within 30 days of enrollment and identification of a provoking factor at the time of diagnosis of VTE (e.g. venous catheterization, infection, recent surgery, use of estrogen-containing oral contraception). Exclusion criteria include history of prior VTE, congenital heart disease with single ventricle physiology or intracardiac shunt procedure for which chronic anticoagulation is being given, active cancer, proximal pulmonary embolism, and moderate-to-severe deficiencies of antithrombin, protein C or protein S defined as follows: antithrombin less than 30 IU/dL for patients 3 months or older or below the level of detection in subjects less than 3 months of age, protein C less than 20 IU/dL for patients 3 months or older or below the level of detection in subjects less than 3 months, and protein S activity or free protein S less than 20 IU/dL. Anticoagulation is prescribed clinically, and monitored in accordance with current ACCP guidelines. At 6 weeks post-diagnosis of index VTE, eligible patients are randomized to stop anticoagulation versus to continue for an additional 6 weeks (hence, total duration of 3 months) of anticoagulation. With a targeted total sample size of approximately 800 participants, and a projected completion date of 2021, the Kids-DOTT trial is expected to provide definitive evidence to inform the future standard of care on duration of anticoagulation in patients <21 years old with provoked VTE.

5. Conclusions

Present guidelines for duration of anticoagulation in pediatric VTE are based largely upon evidence from adult trials and corresponding treatment recommendations in adult VTE. The duration of anticoagulation in pediatric VTE needs to reflect a balance between risks of recurrent VTE and anticoagulant-associated bleeding, as well as quality of life and cost of care. Given the state of current knowledge, many of these factors are as yet unclear and difficult to estimate despite their importance in informing clinical decision-making. It is hoped that the ongoing NHLBI-funded multinational Kids-DOTT trial will provide high-quality evidence by which to inform the future standard of care in pediatric VTE treatment.

6. Expert commentary

As noted above, the greatest weakness in the current management of pediatric thrombosis is the lack of randomized controlled trials in children to help guide providers on both the choices of anticoagulants and the optimal duration of anticoagulation in children. Studies to assess potential factors that could stratify children with VTE as having either high risk, low risk, or intermediate risk for recurrent thrombosis are needed. While assessment of D-dimer and factor VIII activity levels may be helpful in determining children with VTE who are at increased risk of poor outcomes [44], D-dimer has not been shown to be very specific for DVT in children [45], particularly in children with chronic systemic disease. Further investigation of sensitive and specific prognostic factors such as laboratory-based functional and molecular determinants is needed. This gap in knowledge is being addressed in a secondary aim of the Kids-DOTT trial, and should continue to be investigated in future studies.

The impact of duration of anticoagulation on PTS in pediatric VTE may be clearer with the completion of the Kids-DOTT trial, as it is being investigated as a secondary end point in the trial. In adults, the impact of anticoagulant duration on PTS risk remains largely unknown; only one trial to date has evaluated long-term outcomes in relation to initial duration of anticoagulation [27]. The utility of endovascular thrombolysis in improving long-term outcomes such as PTS in children also needs further investigation.

Several other areas in pediatric VTE warrant investigation. While antiphospholipid syndrome (APS) in children is relatively uncommon, the risk of recurrent VTE has historically been believed to be elevated irrespective of the presence of provoking factors with the index VTE episode. Currently, little is known regarding the optimal duration of anticoagulation for VTE associated with APS, whether among adults or children. Via its parallel nonrandomized cohort of children with provoked VTE with persistent APAs, Kids-DOTT has the potential to provide important data by which to power a future randomized controlled trial to evaluate the optimal duration of therapy in pediatric VTE patients who meet criteria for APS. Another key question that lacks sufficient pediatric data on safety and efficacy is the use of anticoagulation or aspirin for extended secondary thromboprophylaxis in children with unprovoked VTE. In future studies on this issue, continued emphasis will need to be placed on net clinical benefit – i.e. the trade-off between decreased recurrent VTE risk and increased risk of clinically relevant bleeding with the extended use of

anticoagulation or aspirin when compared to conventional-duration anticoagulation. Given the rarity of unprovoked VTE, a randomized controlled trial in this area would be quite challenging, but cooperative multicenter prospective cohort studies and registries could be quite helpful.

7. Five-year view

The Kids-DOTT trial and the ongoing trials of DOACs in children will have a great impact on our understanding of anticoagulant therapy options, prognostic factors, and optimal duration of anticoagulation for pediatric VTE treatment, with regard not only to the risks of recurrent VTE and clinically relevant bleeding but also to PTS. With growing interest in pediatric VTE, as well as the development of new tools for diagnosing PTS [46] and its impact upon quality of life in children, it is expected that clinical trials in pediatric VTE will increasingly address PTS and QOL among the key outcomes of clinical interest and importance to patients and parents. Through the ongoing emphasis in the pediatric VTE field on optimal duration, intensity, and modalities of antithrombotic therapy, and the continued study of prognostic factors and risk-stratified therapeutic paradigms, there is much reason for optimism that outcomes will be substantively improved among children with VTE in the future.

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Key issues

- The optimal duration of anticoagulation for VTE treatment in children remains unclear.
- Most adult studies suggest that there is no benefit to 6 months of anticoagulation over 3 months in provoked VTE and that indefinite anticoagulation should be considered for unprovoked or persistent-risk-associated VTE.
- The incidence of pediatric VTE is rare compared with adult VTE, and pediatric expert guidelines for the management of VTE are based on adult studies.
- The Kids-DOTT trial is a multicenter multinational randomized controlled trial in patients <21 years of age with provoked VTE, in which the primary objective is to evaluate non-inferiority of shortened-duration (6 weeks) versus standard-duration (3 months) anticoagulation
- New trials of DOACs in children will also offer insight on potentially new treatment options for pediatric VTE.

Table 1

Randomized studies examining optimal length of oral anticoagulation involving adults with unprovoked and provoked index VTEs.

Author Year	Study design (Location)	No. of patients (Mean age)	Type of Index VTE	Type and duration Anticoagulation therapy	Findings
Schulman S 1995 [21] (DURAC)	Multicenter randomized open-label (Sweden)	902 (60 years)	First episode of acute PE and/or leg/iliac DVT	6-weeks VKA vs. 6-months VKA (INR target = 2.0–2.85)	443 Patients randomized to 6 weeks, 454 randomized to 6 months of VKA. Approximately 60% of patients had chronic risk factors or unprovoked thrombosis Follow-up: 2 years Significant reduction in the risk of recurrent VTE with 6 months of oral anticoagulation therapy compared to 6 weeks: OR: 2.1 (1.4–3.1), $P < 0.001$ Lower risk of recurrent events seen from the second to the sixth month of therapy; thereafter, risk of recurrent VTE similar between groups No significant difference in mortality or incidence of major hemorrhage between the two treatment groups Findings suggests high level of prothrombotic activity for at least 6 months after a first VTE episode
Pinede L 2001 [22] (DOTAVK)	Multicenter randomized open-label (France)	736 (58.5 years)	First episode of isolated calf DTV (C-DVT), proximal DVT (P-DVT) or PE	C-DVT: 6-weeks VKA (short) vs. 12-weeks VKA (long) P-DVT/PE: 12-weeks VKA (short) vs. 24-weeks VKA (long)	55% of patients with chronic risk factors, 44.6% patients with unprovoked VTE Study terminated early due to slow enrollment No significant difference in risk of recurrent VTE between short and long treatment groups: RR 87 (95% CI 0.50–1.49) No significant difference in risk of major hemorrhage between short and long treatment groups
Campbell IA 2007 [23]	Multicenter randomized open-label (UK)	749 (58.7 years)	DVT, PE, or both	3 months warfarin vs. 6 months warfarin (INR target = 2.0–3.5)	369 Patients randomized to 3 months, 380 to 6 months of VKA. 45% of patients had unprovoked VTE Follow-up: 1 year No significant difference in risk of failure during treatment or VTE recurrence after treatment (8.4% in the 3-month group and 7.6% in the 6-month group; $P = 0.80$) Risk of major hemorrhage was significantly increased in the 6-month group when compared to the 3-month group (2% vs. 0%; $P = 0.008$) Findings suggest that for patients with DVT or PE in whom there are no persistent risk factors, 3 months of anticoagulation therapy is as effective as 6 months and is associated with a lower risk of major bleeding
Agnelli G 2001 [24] (WODIT)	Multicenter randomized open-label blinded end point (Italy)	267	First episode of idiopathic proximal DVT status post 3 months of warfarin therapy	Discontinuation of warfarin after 3 months vs. Continuation of warfarin for 9 additional months (INR target = 2.0–3.0)	134 Patients randomized to continue VKA (12 months total), 133 to discontinue VKA (3 months total) No significant difference in the risk of recurrent VTE overall between groups, at an average follow-up time of 3 years (RR = 0.99, 95% CI 0.57–1.73), nor specifically following discontinuation of VKA (at approx. 5% per year) However, the risk of recurrent VTE during the initial 9 months after randomization was significantly higher in the discontinuation group (8.3% vs. 0.7%, $P = 0.003$) These findings suggest that, for patients with idiopathic DVT, prolonging anticoagulant therapy beyond 3 months results in a delay – rather than an overall reduction in – the risk of recurrent VTE

Author Year	Study design (Location)	No. of patients (Mean age)	Type of Index VTE	Type and duration Anticoagulation therapy	Findings
Palaretti G 2006 [25] (PROLONG)	Multicenter randomized open-label (Italy)	619 (63 years)	First episode unprovoked VTE including proximal DVT of lower limbs and/or PE after 3 months of anticoagulation with VKA	Patients with elevated D-dimer: No further VKA vs. Resume VKA for 18 months (INR target = 2.0–3.0)	392 Patients with normal D-dimer (no further therapy) 227 with abnormal D-dimer: 105 randomized to resume VKA, 122 randomized to no further VKA Follow-up: maximum 18 months (average 1.4 years) <i>Patients with elevated D-dimer:</i> The risk of recurrent VTE was significantly increased in the no-further-VKA group compared to the resume-VKA group (15% vs. 2.3%; HR 4.26, 95% CI 1.23–14.6; $P=0.02$) <i>Patients with normal D-dimer:</i> VTE recurrence risk – at 6.2% (24 of 385 patients) – was significantly lower ($P=0.005$) than that in patients with an abnormal D-dimer who stopped anticoagulation (i.e. both groups received 3-month total course of VKA) Considering also bleeding risk (composite end point with recurrent VTE), the study found a benefit of prolonged VKA therapy in patients with unprovoked VTE who have persistently elevated D-dimer levels 1 month after discontinuation of a 3-month course of anticoagulation therapy
Beccattini C 2012 [26] (WARFASA)	Multicenter randomized double-blind placebo-controlled (Italy)	403 (62 years)	First episode unprovoked proximal DVT or PE after 6–18 months of anticoagulation with VKA	Aspirin 100 mg vs. Placebo for 2 years	205 Patients randomized to aspirin, 197 to placebo Median follow-up: approx. 2 years Risk of VTE recurrence was significantly lower in patients who received aspirin vs. placebo (6.6% vs. 11.2%; HR 0.58; 95% CI 0.36–0.93) One patient in each group had a major bleeding episode Results from this study indicate that, among patients with first episode, unprovoked VTE, aspirin therapy, begun after 6–18 months of oral anticoagulant treatment, reduces the rate of recurrent VTE when compared to placebo, with no apparent increase in the risk of major bleeding
Kearon C 1999 [28]		162 (59 years)	First episode unprovoked VTE after 3 months of anticoagulation with VKA	VKA (INR target = 2.0–3.0) vs. Placebo for 24 months	9 patients randomized to warfarin, 83 to placebo mean duration of follow-up: 10 months warfarin was associated with 95% risk reduction in recurrent VTE (95% CI = 63–99%) Risk of major bleeding was 0% per patient/year for placebo vs 4% per patient/year for warfarin Risk of recurrent VTE was 1% per patient/year for warfarin vs. 27% per patient/year for placebo. Trial was stopped early for efficacy
Goldenberg NA 2015 [14] (Kids DOTT Ongoing)	Multicenter, randomized, open-label, blinded end point (Multinational)	383 ^a (8 years ^b)	First episode provoked VTE	6 weeks anticoagulation vs. 3 months anticoagulation (agent as per clinical standard of care, mostly LMWH ^c)	Patients are randomized at 6 weeks post-diagnosis of index VTE to discontinue anticoagulation vs. to continue anticoagulation for an additional 6 weeks Primary end points: <ul style="list-style-type: none"> Efficacy: risk of symptomatic recurrent VTE at 1 year Safety: risk of clinically relevant bleeding Secondary efficacy end points: Risk of symptomatic recurrent VTE at 2 years; risk of PTS at 1 and 2 years

PE: pulmonary embolism; DVT: deep venous thrombosis; OR: odds ratio; VTE: venous thromboembolism; RR: relative risk; CI: confidence interval; VKA: vitamin K antagonist; HR: hazard ratio; PTS: post-thrombotic syndrome; DURAC: Duration of Anticoagulation; INR: international normalized ratio; LMWH: low-molecular-weight heparin.

^aAs of 1 December 2017. (Estimated total enrollment: approximately 800 participants.)

Projected completion date: 2021.

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