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REVIEW

Unprovoked Venous Thromboembolism: Short term or Indefinite Anticoagulation? Balancing Long-Term Risk and Benefit

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ABSTRACT

Whether to continue oral anticoagulant therapy indefinitely after completing 3 to 6 months of oral anticoagulant therapy for "unprovoked" venous thromboembolism (VTE), is one of the most important unanswered questions in VTE management. This long-term decision should be based on balancing the long-term mortality risk from recurrent VTE, largely preventable with oral anticoagulant therapy, against the long-term mortality risk of major bleeding, the principle complication of oral anticoagulant therapy. There exist important knowledge gaps in estimating the long-term mortality risk of recurrent VTE in patients with unprovoked VTE who discontinue therapy and the long-term mortality risk from major bleeding in those who continue oral anticoagulant therapy. These knowledge gaps, reviewed herein, are the source of uncertainty for patients and health care providers wrestling with this important question. One promising solution is recurrent VTE risk stratification where unprovoked VTE patients are categorised as low or high risk for recurrent VTE and clinical decision making is less ambiguous and ultimately will likely lead to better outcomes.

Clinical scenario: A 30 year old male football player presents to your clinic after completing 6 months of anticoagulation therapy for an unprovoked proximal DVT. He is eager to discontinue anticoagulants and return to play. His physical examination shows a: BMI 21, hyper pigmentation and edema in the affected limb. An ultrasound of his leg shows a residual non-occlusive popliteal vein thrombus and the laboratory testing reveals a D-Dimer of 200 ng/mL while on anticoagulants and 350 ng/mL off of anticoagulants 1 month later. He also has Factor V Leiden. Should you discontinue anticoagulants or consider indefinite anticoagulation?

1. Introduction

Venous thromboembolism (VTE), manifested as deep vein thrombosis (DVT) or pulmonary embolism (PE), is a common, potentially fatal yet preventable and treatable medical problem. VTE is the third leading cause of cardiovascular mortality with 1 in 20 experiencing VTE in their lifetime.[1–7] VTE is associated with acute morbidity as well as with long-term consequences such as post-thrombotic syndrome (PTS)[8]and recurrent VTE.[9] The acute and short-term therapy of VTE involves anticoagulants (parenteral then oral) which may be complicated by major bleeding and death from major bleeding, but, as reviewed below, are effective at preventing recurrent VTE and death from recurrent VTE while on therapy. VTE can be etiologically classified based on the presence or absence of clinical precipitating (or provoking) factors as: provoked (due to a transient reversible risk factor e.g. cast, surgery, immobilization, recent trauma), malignancy-associated or unprovoked.[10] Malignancy-associated VTE is now most often treated with at least 6 months of low molecular weight heparin[11] and anticoagulant treatment is generally indicated as long as the malignancy is active. Patients with VTE provoked by a transient reversible risk factor (e.g. surgery or recent trauma) have a very low risk of recurrent VTE after 3–6 months of oral anticoagulant therapy (OAT) and can safely discontinue OAT[12–16] because the major bleeding risk of ongoing anticoagulants clearly exceeds the risk of recurrent VTE after completing short-term therapy. The remaining group of patients with unprovoked VTE will form the focus of this review.

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The optimal duration of anticoagulation for unprovoked VTE has been described as the *most important unanswered question* in VTE management.[17,18] The clinical dilemma is whether patients with unprovoked VTE should remain on anticoagulants indefinitely (i.e. life long) or stop after a short initial period of therapy (3 to 6 months). To answer this important clinical question we clearly must 1) focus on the trade-off between suppressing recurrent VTE with anticoagulants and bleeding caused by these anticoagulants; and 2) consider long-term events given the indefinite time horizon of this clinical question. Over the last decade, dozens of major trials and cohort studies addressing the question of how long to anticoagulate patients with "unprovoked" VTE have been published in the highest impact journals[9,19–22] and largely focused on short-term (<2 years) differences in recurrent VTE event rates. Unfortunately, despite important findings from these studies, clinicians remain vexed with indecision when faced with the question of who should remain on anticoagulants after an initial 3–6 months of therapy. This is highlighted by the lack of change in the most widely used practice guidelines.[23,24] Nine years ago these guidelines stated: "…Patients with a first unprovoked VTE should be treated for at least 6 months"[23] and the most recent version states "…For patients with unprovoked DVT (PE), we recommend treatment with a VKA for at least 3 months…for patients with a first unprovoked VTE…in whom risk factors for bleeding are absent…we recommend long-term treatment."[24] Effectively, we have gone from "no less than 6 months but maybe longer" to "no less than 3 months but maybe forever."

2. Knowledge gaps in the important outcome: long-term mortality

To answer this crucial question one could envisage that the ideal study design would be to examine the long-term mortality trade-off of indefinite anticoagulation versus short-term anticoagulation for patients with unprovoked VTE. This hypothetical study could randomize patients with unprovoked VTE who had completed short-term anticoagulant therapy to 1) continuing anticoagulants indefinitely or 2) discontinuing anticoagulants. Ideally the time horizon of the study would include following patients until death and the ideal outcome would be all-cause mortality (see Box 1). An all-cause mortality outcome would provide net mortality benefit estimates that incorporate reductions in death from recurrent VTE and increases in death from major bleeding events. An alternative outcome, perhaps as valid, could examine a composite outcome combining major VTE related mortality and major bleed related mortality. However, this hypothetical study is unlikely to be feasible due to 1) the large sample size that would be required to detect what are likely small mortality differences between the groups and 2) the long-term follow-up, likely >10 years, required to capture the long-term trade-off of risks.

To feasibly answer this question we must turn to surrogates of mortality and more realistic follow-up time horizons. In the context of VTE management trials, the most valid surrogates appear to be symptomatic major VTE (proximal DVT and PE) and major bleeding. The clinical relevance of asymptomatic DVT, distal DVT and non-major bleeding are controversial and will not be further considered in this review. However, as outlined below, the surrogate events are not equally likely to be related to mortality and hence we must differentially weigh these surrogate outcomes of death by using case-fatality rates to estimate what mortality differences may exist between competing anticoagulant treatment strategies (see Box 1). A "case-fatality rate for disease X" is defined as the proportion of patients who die from disease/complication X in the population of patients who develop disease/complication X. The answer to this important indefinite treatment question will not come from 1) only examining short-term event rates, as elaborated below or 2) only focusing on one side of the counterbalancing benefit and effects of short or long-term treatment (e.g. only looking at recurrent VTE event rates).

Box 1
Methodological ranking of outcomes in long-term VTE management

Best
Long-term all-cause mortality
Long-term composite outcome of VTE related mortality

Good
Long-term recurrent major VTE rates and long-term major bleeding rates weighted by their respective case-fatality rates-
Long-term recurrent major VTE rates and long-term major bleeding rates non-weighted

Poor
Long-term recurrent major VTE rates alone
Short-term major VTE rates and major bleeding rates

An alternative approach to conducting the aforementioned trial to determine the optimal balance of the benefits (reduced VTE recurrence risk) and risks (major bleeding) of continuing anticoagulant therapy, could be to simply tally all-cause fatalities (major bleeding and recurrent VTE) in long-term treatment studies and all-cause fatalities (major bleeding and recurrent VTE) in short-term treatment studies. In reality, the answer would remain elusive because studies to date, even after meta-analysis, have insufficient numbers to permit mortality to be examined as the primary outcome. When we turn to the appropriate surrogates of mortality for this therapeutic question, that is recurrent VTE and major bleeding, the answer remains unclear due to the apparent diminishing risk for recurrent VTE over time off of anticoagulants, uncertainty in the estimates of major bleeding over time, uncertainty in the estimates for case-fatality rate of recurrent VTE and major bleeding and, importantly, the short time horizon of the majority of studies in this area (<3 years). The latter does not permit existing literature to guide us on the inherent trade-off of short-term benefit of avoiding VTE recurrence versus cumulative long-term risk of major bleeding and quality of life that could only be gleaned by long-term studies (e.g. >5 years).

Herein we will consider an approach that incorporates and focuses on current knowledge of 1) the risks of recurrent VTE after short-term anticoagulant therapy for unprovoked VTE, 2) the risks of major bleeding with ongoing long-term anticoagulant therapy for VTE and 3) weighing the latter 2 surrogate events of mortality using case-fatality rates to determine if anticoagulants should be continued in unselected patients with unprovoked VTE. We hope that this information can be used to accurately counsel patients with a first unprovoked VTE and set a research agenda to address important these knowledge gaps.

2.1. What are the risks of recurrent VTE in unprovoked VTE patients who have completed short-term therapy?

In the common group of patients with an unprovoked VTE the risk of recurrence has been consistently found to be higher than provoked VTE after discontinuing anticoagulants, especially over the medium term (1–2 years), but this risk declines with time[22,25–27] (see Table 1 and Fig. 1). The risk of recurrent VTE in patients with unprovoked VTE after 3 to 6 months of OAT varies from 5% to 15% in the year following discontinuation of OAT (i.e. at Time point B or C to Time point D — 1 year after discontinuing anticoagulants in Fig. 1)[19,21,25,27] (one study found a 27% per year risk of recurrence [20]). This risk appears to then