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Current Treatment of Venous Thromboembolism

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Abstract

Venous thromboembolism (VTE), comprising deep vein thrombosis and pulmonary embolism, is a common disorder with at least 250,000 new events occurring each year in the United States alone. Treatment of VTE entails anticoagulation, which is achieved initially with the use of a parenterally administered anticoagulant followed by a more prolonged course of treatment with an oral vitamin K antagonist. The duration of anticoagulation depends on the clinical assessment of the benefit-risk ratio of prolonged anticoagulation versus the risk of recurrent events. In this review, we discuss some of the issues that we believe are among the most critical unanswered questions in the management of VTE in the present era.

Venous thromboembolism (VTE) is a term that encompasses both deep vein thrombosis (DVT) and pulmonary embolus (PE). VTE is a common disorder, and although there are remaining uncertainties about its precise incidence, it accounts for at least 250,000 -- and as many as 900,000 -- incident cases per annum in the United States [1]. When compared to the other major cardiovascular thrombotic disorders, the incidence of VTE is very similar to the incidence of fatal or non-fatal stroke or myocardial infarction [2, 3]. The diagnosis of VTE can be challenging, requiring an algorithmic approach combining the degree of clinical suspicion, and objective appropriately validated laboratory markers (such as plasma D-dimer) and radiologic studies [4]. The clinical presentation of about two thirds of patients is with DVT, while the remaining one third present with PE. However, since occult PE is common in patients presenting with DVT (and vice versa), DVT and PE are currently considered to be complementary manifestations of the same pathophysiologic process. Little is known about why some DVT embolize, while others apparently do not. Finally, although not the primary focus of this article, it has become clear that the opportunity to prevent much of the burden of VTE, particularly among hospitalized patients, has not been realized [5]. Thus, implementing appropriate VTE prophylaxis guidelines remains a universal high priority topic for health systems [6, 7].

On the face of it, the initial treatment of VTE, combining 5–7 days of a rapid-acting parenterally administered unfractionated heparin, low molecular weight heparin, or Fondaparinux™ and a more prolonged course of an oral vitamin K antagonist, is a straightforward intervention supported by several decades of irrefutable evidence from clinical trials [8]. In the first 3 months of therapy, the primary goals of DVT treatment are to prevent extension and embolization of the thrombus (thereby facilitating the action of endogenous thrombolysis), whereas in PE the primary goal is to prevent potentially fatal recurrence events. Beyond the 3 month time point, the use of continued anticoagulation is considered to be ‘secondary prophylaxis’, aimed at prevention of late recurrence. Using standard modern day regimens, the rates of early (within 3 months) recurrence or death are quite low overall, generally in the order of 3%, or less [9]. In

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its most extreme forms, massive PE may present with sudden death, or with hypotension (systolic arterial pressure <90 mm Hg) and/or circulatory collapse, which are generally considered to be an indication for thrombolytic therapy [10]. Anticoagulation therapy for the more than 90% of patients presenting with non-massive PE is administered in a manner analogous to that for DVT, but there remains some controversy about the role of adjunctive therapies in a sub-set of these patients (discussed later in this article).

An important concept to emerge from a number of studies evaluating the risks and benefits of longer term (>3 month) secondary prophylaxis with oral vitamin K antagonists is the fact that acute VTE unprovoked by recognized triggers such as surgery or trauma is in fact a chronic disorder that is associated with a significant risk of late recurrence – up to 50% after 10 years following the cessation of anticoagulation [11, 12]. However, the prevention of late recurrence has to be weighed against the risks of bleeding associated with the long-term use of warfarin. Balancing these considerations, analysis of the evidence by an expert panel has led to the recommendation that long-term secondary prophylaxis is indicated for those patients with a low risk of bleeding and access to high quality anticoagulant monitoring. This recommendation was also qualified by a statement to the effect that patient preference should be taken into account [8].

Given this accumulated wealth of experience, what are some of the remaining knowledge gaps and unmet needs in the management of patients with VTE? We have selected four topics for brief discussion that we believe to be among the most critical questions in the current era.

1. The need for better oral anticoagulants for the treatment of VTE

The introduction of low molecular weight heparins and related inhibitors of factor Xa (such as the pentasaccharide Fondaparinux™) have arguably addressed the clinical need for better parenteral anticoagulants. These agents have superior bioavailability and reduced need for monitoring compared to unfractionated heparin. However, the need for orally available anticoagulants to replace warfarin and other vitamin K antagonists in the secondary prophylaxis of VTE persists. Warfarin was introduced into clinical practice in 1954, and to this day it remains the only licensed oral agent for the treatment of VTE. The limitations of the oral vitamin K antagonists include their slow onset of action, the variability of dosing between individuals resulting in part from genetic polymorphisms in warfarin's metabolic pathways, and the fact that frequent monitoring is required to manage food and drug interactions, which are often unpredictable. In addition, like many anticoagulants, warfarin suffers from a relatively narrow therapeutic window that necessitates careful monitoring. Thus, major bleeding events were twice as common in studies targeting an INR >3.0 compared to those targeting the most commonly used target range of 2.0–3.0 [13], and an INR >4.5 is a strong independent risk factor for bleeding, with an odds ratio of almost 6 [14]. More importantly, major bleeding associated with anticoagulant therapy is frequently associated with poor clinical outcomes. For example, in the RIETE Registry, the all cause mortality in the 2–3% of patients developing major bleeding during treatment for VTE was 33%, of whom about half died as a direct result of the hemorrhagic event [15]. While these numbers may appear high relative to the published clinical trials, their validity is supported by community-based studies that likely are more representative of the 'real world' experience with warfarin-induced bleeding [16]. Many of the patients who would have been ineligible for the trials that have formed the basis for current evidence-based recommendations, including elderly subjects, may account for the excess community-based mortality and morbidity with warfarin [17, 18].

Although several oral anticoagulants have been approved outside the United States for prophylaxis of VTE, including the Xa inhibitors rivaroxaban and apixaban and the thrombin inhibitor dabigatran etexilate, none has yet been approved for the treatment of VTE. The

pharmacology and development of these agents, as well as a detailed description of their performance in prospective randomized clinical trials, has been reviewed elsewhere [19]. The first phase III VTE treatment study comparing dabigataran etexilate to warfarin in the treatment of acute VTE was recently published [20]. In the RECOVER Study, patients were randomized to dose-adjusted warfarin (at a standard INR target of 2.0–3.0) or fixed dose dabigatran after receiving unfractionated or low molecular weight heparin for 5–11 days. Non-inferiority of dabigatran etexilate compared to warfarin for the primary endpoint of recurrent VTE or VTE-related death within 6 months of therapy was demonstrated. Similarly, dabigatran etexilate was as safe as warfarin, with rates of bleeding and liver function abnormalities that did not differ. A theoretical advantage of the new oral anticoagulants over warfarin is their rapid onset of action, which could obviate the need for initial parenteral anticoagulation. As yet however, no trial has demonstrated that this strategy is safe and efficacious. Conversely however, a potential limitation of the new anticoagulants is the absence of a specific antidote to reverse their anticoagulant effect in the event of bleeding. The potential impact of this limitation in clinical practice remains to be seen.

2. The uncertainty whether all forms of VTE require treatment

With the advent of increasingly sensitive radiologic methods of detection, venous thrombosis may be revealed in an anatomic location and/or clinical scenario in which the benefit-risk profile of active treatment has not been clearly defined. This uncertainty inevitably leads to disparities in management among different centers and even between physicians within the same practice.

In the lower extremities, clots detected below the popliteal vein (i.e within the calf veins) typically present with symptoms that overlap with those seen in patients with more proximal DVT. The diagnosis of isolated distal DVT is common in clinical practice, where it may account for about one half of DVT diagnoses in the outpatient setting. Since distal clots that remain confined to the calf veins are considered to be at very low risk (<1%) of embolization on 3-month follow-up [21], it has been recommended by some authors that these patients not receive systemic anticoagulation [22]. This opinion is supported by the lack of convincing data in favor of anticoagulation, since patients with symptomatic isolated distal DVT have generally been excluded from clinical trials focusing on the treatment of VTE. Furthermore, existing registries agree that the clinical profile of patients with isolated symptomatic distal DVT fundamentally differs from those with symptomatic proximal DVT, with distal DVT occurring more often in patients with transient risk factors [23, 24]. On follow up, isolated distal DVT (when treated with anticoagulant therapy) appears to be associated with a lower risk of death compared to proximal DVT [23, 24], but there remains some uncertainty about the relative rates of recurrence and major bleeding. Thus, it is probably inappropriate to extrapolate treatment outcomes of studies that only included patients with proximal DVT, and the existing clinical equipoise calls for a definitive answer through prospective randomized clinical trials focusing on the treatment of patients with isolated distal DVT. Clinically relevant endpoints in these trials might reasonably include the relief of acute symptoms, in addition to the prevention of proximal extension, embolization, and recurrence.

A further example of a clinical dilemma with respect to the uncertainty of the risk-benefit of anticoagulant therapy may arise when unexpected venous thrombosis - often DVT or PE, but also thrombus in other locations such as in the portal vein - is detected in patients with cancer undergoing routine staging computed tomography (CT) scanning. Asymptomatic VTE may be quite prevalent, occurring in up to 10% of patients with cancer undergoing staging CT scans [25, 26]. These patients may have been truly asymptomatic, or the non-specific symptoms of thrombosis, such as fatigue or shortness of breath, may have erroneously been attributed to their underlying disease [27]. Either way, the natural history of these previously unsuspected

thrombi in terms of morbidity and mortality is not yet well defined, nor is the benefit-risk profile of standard anticoagulation therapy. Until these data are available, it has been recommended that these patients be managed in a similar fashion to those with symptomatic PE [8].

In both examples referenced in this section, the interpretation of clinical trials' data could potentially be complicated by imprecision in the diagnostic accuracy of imaging studies of distal DVTs or sub-segmental PEs, respectively.

3. The role of thrombolysis in the prevention of post-thrombotic syndrome after acute DVT

In up to one third of cases of DVT in the lower extremity, post-thrombotic syndrome (PTS) may ensue as a late onset chronic debilitating complication that imparts a significant negative effect on subjects' quality of life [28]. PTS is characterized by discomfort, hyper-pigmentation, and swelling in the affected limb, and in severe cases it may be accompanied by cutaneous ulceration. These symptoms result from some combination of persistent venous hypertension - usually due to residual intravascular obstruction – and/or venous valvular insufficiency [29]. While the prolonged use of fitted compression stockings has been demonstrated to reduce the incidence of PTS after DVT [30, 31], the role that the acute DVT treatment approach may play in modulating the subsequent risk has yet to be defined. For a number of years, a variety of circumstantial evidence has suggested that pharmacologic removal of the acute thrombus using fibrinolytic therapy (usually administered locally via an indwelling catheter, with or without mechanical clot disruption) may preserve the function of the adjacent venous valves and minimize residual clot, which in aggregate could reduce the risk of future PTS [32]. Recently, more robust prospective studies randomizing patients with acute proximal DVT to pharmacological thrombolysis (with or without mechanical thrombectomy) *vs*. standard anticoagulation are underway [33, 34]. In the recently initiated NIH-sponsored ATTRACT trial [34] participants will be assessed for PTS and quality of life at 24 months post intervention; if the results of this study demonstrate clinical benefit, cost-benefit, and acceptable safety of pharmacomechanical treatment, an entire paradigm shift in the treatment of acute DVT may need to be entertained.

4. The need to test acute intervention strategies for sub-massive PE

The management of patients with sub-massive PE, defined as the absence of hemodynamic compromise but with detectable right ventricular dysfunction, is controversial. Right ventricular dysfunction is generally defined by some combination of abnormalities on echocardiography, and serum levels of cardiac biomarkers (such as troponin and/or brain natriuretic peptide). Because these patients, especially if they are also hypoxemic at presentation, may be at greater risk of death [35–37], it has been argued that thrombolytic therapy is indicated as first line treatment. In addition, some retrospective studies have indicated that the prognosis may be improved by the use of adjunctive inferior vena cava filters [10]. However, both of these approaches remain controversial, since the studies that have attempted to address the issues have generally been underpowered and methodologically diverse or inadequate. It is to be hoped that a large prospective randomized study now underway in Europe, the PEITHO Pulmonary Embolism Thrombolysis Study [Comparison Trial Evaluating Efficacy and Safety of Single i.v. Bolus Tenecteplase Plus Standard Anticoagulation as Compared with Standard Anticoagulation in Normotensive Patients; ClinicalTrials.gov Identifier NCT00639743], will answer the question whether systemically administered thrombolytic therapy is superior to standard anticoagulation in patients with sub-massive PE. However, it remains unclear whether risk stratification of subjects using clinical, echocardiographic and laboratory criteria adds to the ability to predict outcomes [38].

In summary, the treatment of VTE, although supported by extensive high quality evidence, remains a challenging area with still many unmet needs and unanswered questions. Ultimately, the burden of disease will hopefully be reduced by more effective implementation of prophylactic guidelines, particularly among patients hospitalized for other indications.

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