REVIEW ARTICLE

Should D-dimer testing be used to predict the risk of recurrence after discontinuation of anticoagulant therapy for a first unprovoked episode of venous thromboembolism?

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KEY WORDS

anticoagulant duration, D-dimer, recurrence, venous thromboembolism

ABSTRACT

Recurrent venous thromboembolism carries significant risks of morbidity and mortality. Although recurrence can be prevented by ongoing anticoagulant therapy, treatment is inconvenient and associated with risks of major bleeding. As a consequence, the decision as to whether or not to continue anticoagulants after the first three months of treatment must take into account both potential benefits and potential risks. For patients who have developed unprovoked venous thromboembolism, these are often closely balanced and the optimal duration of anticoagulant therapy remains controversial. Recent publications suggest that D-dimer testing may be helpful in stratifying these individuals into higher and lower risks groups for recurrence after anticoagulant discontinuation. This paper reviews recent data surrounding the use of D-dimer to predict the risk of recurrent venous thromboembolism and how this test may help streamline decisions regarding duration of therapy.

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INTRODUCTION Venous thromboembolism (VTE) is frequently encountered, with an estimated annual incidence of 117 per 100,000 in the general population.[1] Over the years, we have gained substantial insight into the prevention and treatment of VTE and this evolving knowledge has lead to continual refinement of existing practice guidelines. However, despite our growing understanding of this disease, the appropriate duration of treatment, particularly after a first unprovoked event, remains controversial. Although recurrent events can be prevented by ongoing anticoagulation, this intervention can be costly and inconvenient, and is associated with risks of major bleeding. Thus, in making a decision about optimal duration of anticoagulant therapy, the benefits of treatment in preventing recurrent VTE must be considered against the associated risks of major bleeding. Because multiple factors can contribute to the risk of recurrence of treatment and to the risk of significant bleeding on therapy, the decision as to duration of anticoagulation is difficult and often subjective. Thus, clinicians would be greatly helped by the development of a simple objective test or set of tests that can accurately risk stratify patients who are considering discontinuation of anticoagulant therapy after adequate initial treatment for a first episode of VTE. Focusing on idiopathic or unprovoked VTE, this review will outline the risk of recurrence after treatment discontinuation and of bleeding while on anticoagulation, the consequences of both of these outcomes and the existing guidelines for treatment duration. We will also examine the recent data surrounding the use of D-dimer testing to predict the risk of recurrent VTE and how this may assist clinicians and patients in their decision making process.

Unprovoked VTE, the risk of recurrence and its consequences Treatment of VTE is targeted in the acute phase to the prevention of embolism, thrombus extension, and early recurrence, as well as to symptom control; while the goal of longer-term therapy is the prevention of late recurrence.[2] Anticoagulant therapy is associated

with an 80% reduction in the risk of recurrence, with the largest benefit seen during the first 3 months of treatment[3]; the annual risk of recurrence while on adequate warfarin therapy has been estimated at approximately 1%.[4] Several studies have examined the risk of recurrence after discontinuation of anticoagulation. Overall incidences of recurrent VTE have been reported as 10 to 15% at 6 months to 2 years of follow-up, 18.1% to 40.8% at 5 years, and up to 52.8% in 1 study that followed patients out to a maximum of 10 years.[5-7] The risk of recurrence is higher following an unprovoked (idiopathic) event (that is, one not recently preceded by a known clinical risk factor such as major surgery, hospitalization or prolonged immobilization) than after 1 associated with a major transient provoking risk factor (7 to 10% in the first year after stopping treatment versus 3% over the same time interval, respectively).[7,8] Patients who present initially with pulmonary embolism (PE) have the same overall risk of recurrence as patients who present with proximal deep vein thrombosis (DVT); however, their risk of recurrent PE is approximately three-fold higher.[9] PE is associated with a higher 1 month mortality than DVT[10] and approximately 15% of symptomatic pulmonary emboli are fatal versus 2% or less of acute DVT.[9] Thus, although the overall case-fatality rate of recurrent VTE is about 5%[11], the risk of fatal PE is 2 to 3 fold higher after initial PE than initial DVT[9]. Unfortunately, there is evidence that the risk of recurrence, though delayed, does not dissipate with longer treatment duration. Continuing therapy beyond 3 months appears to provide little benefit in reducing the risk of recurrence after anticoagulant cessation but does expose patients to the ongoing risks, costs and inconvenience associated with this intervention.[2,12]

Anticoagulation, the risk of major bleeding and its consequences A multitude of studies carried out in patients receiving long term oral anticoagulant therapy report an annual incidence of major bleeding of approximately 3%.[6,12-17] An older review looking at studies published between 1986 and 1991, found an overall case-fatality rate from major bleeding while on therapeutic anticoagulation of about 20% and that the risk of bleeding was 10-fold higher in the first month of anticoagulation compared with that after the first year. Other patient-specific risk factors for major anticoagulant-related bleeding included serious comorbid illness, age and intensity of warfarin therapy.[17] A more recent meta-analysis, specifically looking at oral anticoagulation in patients treated for VTE, that included studies published between 1989 and 2003, calculated an overall case-fatality rate from major bleeding of 13.4%. This study also confirmed that major bleeding occurred more frequently at the beginning of treatment (2.06% in the first 3 months alone vs. 2.74 per 100 patient-years after the first 3 months). Although this study found a lower percentage of intracranial hemorrhage among those who died from major bleeding than that recorded in the previous meta-analysis (30% vs. 70%), the case-fatality rate of these events was, as expected, quite high (11 out of 24 cases).[18]

Given the case-fatality of recurrent VTE of approximately 5% and the case-fatality of major bleeding while on anticoagulation for VTE of approximately 15%, it would seem logical that the minimum requirement for tipping the balance in favor of longer duration anticoagulation would be a risk of recurrent DVT 3 fold higher than the 3% annual risk of major bleeding. For those presenting initially with PE, a lower threshold for extending anticoagulation may need to be considered.

Current guidelines for duration of anticoagulation after a first unprovoked event In the 2008 8th Edition of the American College of Chest Physicians (ACCP) guidelines on antithrombotic and thrombolytic therapy,[2] a grade 1A recommendation for at least 3 months of treatment for an unprovoked DVT or PE is given. A further grade 1C recommendation is made for reassessment of the risks and benefits of continued anticoagulation after the first 3 months and, in the absence of risk factors for bleeding or suboptimally-controlled anticoagulation, a grade 1A recommendation is made for long-term treatment. The guideline authors also recommend that this decision should be reassessed periodically to ensure that nothing has shifted the risk-to-benefit ratio (grade 1C).

However, given that the overall risks of fatal recurrent VTE after initial therapy for an unprovoked event appear to be closely balanced with the risks of fatal bleeding on treatment, it would be helpful to know if there is a subset of patients at lower risk of recurrence and thus not warranting indefinite exposure to a potentially life-threatening and inconvenient intervention. Some clinical risk factors can be used to predict a higher (e.g. male gender)[19] and lower (e.g. isolated calf DVT)[20] risk of recurrence. Although screening for a series of risk factors might be useful, ultimately, one would like a single test to help make decisions. Recent prospective studies have evaluated the D-dimer, a candidate blood test that may allow physicians to better determine which patients may be considered at low enough risk to safely discontinue anticoagulation after a defined period of treatment.

What is the D-dimer? The last step in thrombus formation is the covalent cross-linking of fibrin monomer D-domains *via* activated factor XIII. When plasmin degrades cross-linked fibrin, it is unable to cleave these covalent bonds and ultimately produces 180 kDa fragments known as D-dimer that consist of 2 such linked D-domains. D-dimers are cleared through the kidneys and the reticulo-endothelial system, and have a plasma half life of 8 hours. Although plasma D-dimer levels are elevated in individuals with

VTE, low levels can be found circulating under normal physiologic conditions and pathologically elevated levels can be found in any condition associated with enhanced fibrin formation and fibrinolysis.[21]

Diagnostic utility of D-dimer in the diagnosis of VTE

Many different D-dimer assays have been developed and marketed. All rely on the use of monoclonal antibodies to detect D-dimer molecules. A variety of assay techniques are available, including enzyme-linked immunosorbent assays, latex agglutination and immunoturbidimetric tests, and whole blood agglutination methods. Generally, all are characterized by an intermediate to high sensitivity and a low to intermediate specificity. Due to the wide variety of techniques, it is difficult to standardize D-dimer testing and, at present, results of each should be considered method-specific.[21]

D-dimer tests have been used in the evaluation of suspected DVT and, subsequently, suspected PE, for the last 20 years[22-25] and their incorporation into diagnostic algorithms has been refined over time. Because D-dimer tests are generally more sensitive than specific for VTE, they are used largely for their negative predictive value to aid in ruling out the disease in patients with a low (or moderate, depending on the sensitivity of the assay in question) pre-test probability of VTE. Multiple studies and a recent systematic review have confirmed the reliability of combining D-dimer testing and a clinical probability tool to rule out DVT and PE.[26-32]

Using the D-dimer to predict recurrent VTE Following publication of a series of post-hoc analyses of prospective studies suggesting that a low or negative D-dimer about 1 month after anticoagulant discontinuation was associated with a lower risk of recurrent VTE, interest developed in expanding the clinical utility of these assays to help predict the risk of recurrence after stopping anticoagulant therapy for a first unprovoked VTE. However, concerns about the inadequate power of individual studies, the variety of assays investigated, and the heterogeneity of patients included in these trials fueled ongoing debate over the validity of these results. In the hopes of providing some clarification, Verhovsek et al.[33] recently published a systematic review examining the use of D-dimer to predict recurrence after discontinuation of anticoagulant therapy for unprovoked VTE. The authors searched multiple databases up to early March 2008 and included all randomized controlled or prospective studies that measured D-dimer levels three weeks to 2 months after stopping anticoagulation in patients with VTE who received at least 3 months of treatment for an unprovoked episode. Some patients with weak VTE risk factors (such as hormone replacement therapy) may have been included as unprovoked events if the original studies labelled them as such. The review's major outcome was the annualized risk (risk per patient-year follow up) of recurrent VTE in patients with positive or negative D-dimer results after stopping anticoagulation. The pooled effect of D-dimer was evaluated using a mixed-effect Poisson model and adjusted for heterogeneity with a random-effects model, if needed. Ultimately, 7 studies (5 prospective cohorts and 2 randomized trials) were included in the review.[34-40] Of the 3225 patients, 1888 had a first unprovoked VTE and were included in the analysis. Follow up was greater than 12 months for all studies. 907 (48.0%) patients had a positive D-dimer (defined for each kit as the threshold value used in the exclusion of acute VTE) and, of those, 165 (18.2%) had recurrent VTE during 2426 person-years of follow up. Of the 981 patients with a negative D-dimer, 74 (7.5%) had recurrent VTE during 2040 person-years of follow up. The annualized risk of recurrence was 8.9% (95% CI, 5.8% to 11.9%) in those with a positive result vs. 3.5% (95% CI, 2.7% to 4.3%) if the D-dimer was negative with a pooled incidence rate ratio of 2.20 (95% CI, 1.65 to 2.94). No statistical heterogeneity or publication bias was found across studies for the negative D-dimer group, but statistically significant heterogeneity and possible publication bias were noted for the outcome of a positive D-dimer result.

This systematic review provides the first pooled analysis of D-dimer usage for predicting recurrent VTE after stopping anticoagulation for a first unprovoked episode. Methodology was rigorously adhered to and only high quality studies were included in the analysis. The authors provide several possible explanations for the observed heterogeneity in the positive D-dimer group, including variation in D-dimer cut-off points and differences in the events defined as VTE; some studies included calf and arm DVT, which may be less likely to recur. Perhaps the most significant limitations of this analysis were the variety of D-dimer tests used and the range of timing for D-dimer testing.

Despite the current limitations in the available data, we find it encouraging that investigators are developing an interest in determining how to risk stratify patients into categories that will help to decide who will need long-term anticoagulation and who will not. Advantages of a test like the D-dimer include its simplicity, relatively non-invasive means of sample procurement, quick turn around time, generally wide-spread availability, and the potential for repeat testing to perhaps monitor for changes in the risk of recurrence over time. Disadvantages of this technique include the wide variety of available tests, some of which use quantitative cut off levels. This may cause confusion in the interpretation of results and may necessitate separate validation studies for each D-dimer assay (much as was required for use of these tests in the evaluation of suspected VTE). Furthermore, the optimal time period for D-dimer testing has yet to be determined. To date, testing has been performed after

discontinuation of anticoagulation. Not only is this inconvenient for the patient, high risk individuals could potentially recur during their time off anticoagulants prior to D-dimer testing. Finally, it is important to note that the rate of recurrence in patients with a negative D-dimer result reported in the Verhovsek meta-analysis (point estimate of 3.5% and potentially as high as 4.3%) may not be low enough for all patients or clinicians to feel comfortable stopping treatment (for example, in those with poor tolerance for recurrent PE or DVT). Therefore, although the available results are promising, more research is required before we can optimally incorporate D-dimer testing into our decision making process about optimal anticoagulant duration for unprovoked VTE.

CONCLUSIONS VTE is both a treatable and preventable health issue. Recurrent VTE carries a significant risk of morbidity and mortality. However, long-term anticoagulation is inconvenient and has its own risks. With growing information on factors influencing the risk of recurrence, over time it should become easier to make sound clinical decisions regarding duration of anticoagulant therapy. With the potential for D-dimer, a quick and readily available blood test, to be incorporated into a decision making model, the ability to determine which patients can forgo the need for indefinite anticoagulation appears to be possible. Although it is becoming increasingly well recognized that the risk of recurrent VTE does not dissipate over time after an unprovoked VTE, there may be subcategories of risk in those with these unprovoked events. The question may no longer be "how long?" but rather "who can stop?".

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ARTYKUŁ POGLĄDOWY

Czy po zaprzestaniu leczenia przeciwkrzepliwego pierwszego samoistnego epizodu żylnej choroby zakrzepowo-zatorowej powinniśmy oznaczać dimer D w celu oceny ryzyka nawrotu?

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SŁOWA KLUCZOWE

czas trwania leczenia przeciwkrzepliwego, dimer D, nawrotowość, żylna choroba zatorowo-zakrzepowa

STRESZCZENIE

Nawracająca żylna choroba zakrzepowo-zatorowa niesie poważne ryzyko chorobowości i śmiertelności. Mimo że nawrotom można zapobiec dzięki stałemu leczeniu przeciwzakrzepowemu, jest ono niewygodne i wiąże się z ryzykiem poważnego krwawienia. W konsekwencji decyzja, czy kontynuować stosowanie leków przeciwkrzepliwych po upływie pierwszych 3 miesięcy leczenia czy nie, musi uwzględniać zarówno potencjalne zyski, jak i potencjalne ryzyko. U pacjentów, u których rozwinęła się samoistna żylna choroba zakrzepowo-zatorowa, decyzje te pozostają ściśle zbilansowane, a optymalny czas trwania terapii przeciwkrzepliwej pozostaje sporny. Ostatnie publikacje sugerują, że badanie stężenia dimerów D może być pomocne w stratyfikowaniu tych osób do grup większego i mniejszego ryzyka nawrotu po przerwaniu leczenia przeciwkrzepliwego. Nasza praca stanowi przegląd ostatnich danych związanych z użyciem stężenia dimerów D dla przewidywania ryzyka nawrotu żylnej choroby zakrzepowo-zatorowej oraz podaje, w jaki sposób test ten może ułatwić podejmowanie decyzji odnośnie do czasu trwania leczenia.

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