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Editorial

D-dimer testing after anticoagulant discontinuation to predict recurrent venous thromboembolism

The duration of anticoagulant treatment after a first venous thromboembolism (VTE) depends on the risk of a VTE recurrence, which is mostly determined by the presence, type, persistence, and severity of VTE provoking factors [1,2]. In particular, if a major provoking factor persists over time, i.e. as it is often the case for cancer and cancer treatment, an indefinite anticoagulant treatment is usually considered in the absence of active bleeding or severe bleeding risk factors. Vice versa, if the VTE provoking risk factor is transient, for instance a major surgical intervention or trauma, anticoagulation can be discontinued after a standard short 3-month course of anticoagulation, as the risk of recurrence is deemed to be minimal.

In patients without identifiable provoking risk factors, the risk of recurrent VTE after anticoagulant discontinuation is considerable and, therefore, the duration of anticoagulation is often extended beyond the first three months [1,2]. A number of strategies have been developed to optimize the secondary prevention in these patients, namely to minimize the overall risk of either VTE recurrence or anticoagulant-associated bleeding. A first strategy consists in the identification of patients in whom anticoagulation can be safely discontinued. Most of the available validated risk assessment models developed to predict the risk of recurrent VTE include age, sex, and D-dimer values measured after anticoagulant discontinuation or during active anticoagulant treatment [3–6]. Risk models to predict anticoagulant-associated bleeding often also incorporate age and sex, as well as renal insufficiency, hypertension, cancer, anaemia and use of platelet inhibitors, but have not yet been adequately validated to be used to decide on anticoagulant discontinuation [7,8]. In most patients with a first-episode VTE without identifiable risk factors, however, a second strategy is usually preferred and an extended anticoagulation in a reduced dose is recommended based on the evidence from large phase III trials [9,10].

D-dimer is a fibrin degradation product reaching very high level during active fibrinolysis, which occurs in case of intravascular fibrin deposition (i.e. after acute VTE, bleeding, or disseminated intravascular coagulation), or extravascular fibrin deposition (i.e. during active infections, adult respiratory distress syndrome or other inflammatory states) [11]. D-dimer levels correlate with the magnitude of fibrin production and its turnover. In clinical practice, a normal D-dimer can exclude acute proximal deep vein thrombosis or pulmonary embolism in symptomatic patients who present with a low pre-test clinical probability of having VTE [11]. When measured at the time of VTE diagnosis, D-dimer levels might represent an indirect indicator of thrombus size and have a modest predictive value for short-term adverse outcomes, including recurrence [12–14]. When tested after discontinuation of a standard-course anticoagulant therapy, a persisting positive D-dimer may reflect the underlying coagulation activation and proinflammatory status of comorbidities, and support the decision to extend anticoagulation [11]. While evidence on the predictive value of D-dimer in this setting is accumulating, its use as a stand-alone test in clinical practice is not self-evident as outcome trials are missing. Hence, more studies are necessary before the role of D-dimer measurement in the decision on the optimal duration of treatment of VTE without identifiable risk factors can be definitively determined.

In the systematic review and meta-analysis authored by Di Minno and colleagues, the authors studied the association between a positive or elevated D-dimer measured after oral anticoagulant therapy with the risk of VTE recurrence, and provided absolute risks of recurrence in patients with persistent or normal D-dimer levels [15]. A total of 26 studies involving 10,725 patients were included. The data showed that subjects with persistently abnormal D-dimer levels after anticoagulation discontinuation were characterized by an absolute risk of recurrence of 16.1% vs 7.4% in those with normal levels, with a considerable overall absolute 10%-point difference between groups. This seems to be a strong argument pro incorporating D-dimer measurement in the clinical course of VTE in routine clinical practice but upon close reading, several concerns can be raised regarding the clinical consequences of these findings.

The first notable finding is the substantial *statistical* heterogeneity of the included studies (I^2 62% for the primary analysis), as also underlined by the authors of the study. This does not come as a surprise as, in fact, the studies identified by the systematic review of the literature differed considerably in study design and ranged from prospective management studies in patients with unprovoked VTE to retrospective cohorts focusing only on provoked VTE events. Moreover, they included patients who received a variable duration of anticoagulation. The definition of provoking factor itself [16] also largely varied across studies, for instance including or not cancer, and could not be prespecified for this study. Accounting for this huge heterogeneity, a sensitivity analyses was attempted, which confirmed the direction of the association across specific study subgroups. Even so, the heterogeneous different follow-up time after the index VTE and anticoagulant discontinuation across studies, ranging from 3 to 62 months, remains a major concern. It is known that the highest risk of VTE recurrence is observed within 3–6 months of anticoagulant discontinuation. The largest risk difference between patients with a positive vs. negative D-dimer, therefore, is expected during this period. Accounting for the period after the first 6 months may have led to a relevant underestimation of the strength of the association between D-dimer and VTE recurrence. Moreover, it remains subject of debate whether a single biomarker measurement can predict future events, which may occur years after the snapshot assessment.

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Second, focusing on annual (or annualized) recurrence risks at different stages of post-VTE follow-up not only better reflects reality, but allows to estimate the clinical utility of an intervention, in contrast to relative measures of risks (i.e. relative risks), of discrimination (c-statistic), and to absolute risks [17]. This would provide a more useful reference to compare with the expected rate of major bleeding. Therefore, generally stating that D-dimer had a good discrimination for future recurrence is important information for speculation, but may have little clinical impact. In the era of long-term anticoagulation with reduced- or standard-dose direct oral anticoagulants, estimating the hazard of a recurrent or bleeding event is crucial for yearly re-evaluations of the indication to anticoagulant treatment.

A third major point of debate, which has been occupying researchers for the past decades, concerns the actual D-dimer testing. Indeed, misclassification bias should not be underestimated as a number of factors may influence the results and, in addition, there is evidence that D-dimer assays cannot be interchangeably performed [11]. Different techniques and different assays for each technique are available. It has been shown that these are characterized by different sensitivity and predictive values for the future risk of VTE recurrence [18].

The ultimate question is whether a large meta-analysis of studies designed approximately with the same purpose, but characterized by substantial heterogeneity for the key elements, provides a higher level of evidence than individual management studies with a prespecified protocol, focusing on a well-defined population undergoing standard D-dimer assessment and follow-up visits. Is it better to increase precision by enlarging the number of patients in a pooled analysis (despite obvious differences) or rely on the results of individual, often preliminary, studies? One may argue either way but we are in favour of the latter, also recalling a quote that has been attributed to different historical figures, including a few methodologists and statisticians: “it is better to be roughly right than precisely wrong”.

The authors should be commended for the huge work performed, which even despite methodological limitations provides new pieces of the puzzle [15]. In the end, current evidence is insufficient and guidelines are still contradictory with regard to recommendations on the application of D-dimer testing in the therapeutic management of VTE. It seems clear that D-dimer values interpreted in the context of demographic and clinical factors (e.g. by applying a validated risk model) better reflect VTE recurrence than a stand-alone D-dimer test. There is an increasing number of risk assessment models in other fields of medicine that aim at accounting for as many predictors as possible. Unprecedented computational capacities allow for these artificial intelligence-based algorithms that undoubtedly will find their way into clinical practice. Since a decision to extend anticoagulation is not made in an acute or emergency setting, more complex risk assessment models may be more appropriate than oversimplified one-fits-all strategies not accounting for clinical information.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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