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Review Article

Clinical Decision Rules and D-dimer in Venous Thromboembolism: Current controversies and future research priorities

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ABSTRACT

Venous thromboembolism (VTE) is a potentially lethal clinical condition that is suspected in patients with common clinical complaints, in many and varied, clinical care settings. Once VTE is diagnosed, optimal therapeutic management (thrombolysis, IVC filters, type and duration of anticoagulants) and ideal therapeutic management settings (outpatient, critical care) are also controversial. Clinical prediction tools, including clinical decision rules and D-Dimer, have been developed, and some validated, to assist clinical decision making along the diagnostic and therapeutic management paths for VTE. Despite these developments, practice variation is high and there remain many controversies in the use of the clinical prediction tools. In this narrative review, we highlight challenges and controversies in VTE diagnostic and therapeutic management with a focus on clinical decision rules and D-Dimer.

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Introduction

Venous thromboembolism (VTE), comprising both deep vein thrombosis (DVT) and pulmonary embolism (PE), are common, potentially lethal yet treatable clinical conditions [1]. Clinical Decision Rules (CDRs) are decision making tools, using combinations of simple available clinical predictors to define an outcome in the present, in other words a diagnosis (or a probability of disease), or an outcome in the future, in other words a prognosis (or probability of an outcome), either of which leads to a diagnostic course of action or a therapeutic course of action [2]. CDRs and/or D-dimer have a crucial place in the diagnostic and therapeutic management of VTE. These tools permit us to judiciously and safely use diagnostic imaging for VTE diagnosis, select the right treatment setting for initial therapeutic management of VTE (intensive care unit, ward or home) and select which patients will derive net benefit from anticoagulant therapies.

The focus of this narrative review will be to review current controversies in the use of clinical decision rules and/or D-dimer in the diagnostic and therapeutic management of VTE. We will highlight wide international practice variations, even among experts in thrombosis, and also highlight challenges in knowledge translation for most clinicians that impact putting research findings into routine clinical practice. These challenges are largely reflective of the absence of level IA evidence to guide practice in these areas and the need to develop and validate simple and widely available tools that are easy to adopt in routine clinical practice.

Methodologic Standards for Clinical Predictors

High quality evidence to support routine use of CDRs, and other clinical prediction tools, requires that they are developed and validated strictly following methodologic guidelines (see Table 1). Standards for their development and validation were first published more than 20 years ago [3], were updated and which have formed the basis for a quality assessment framework we should consider before adopting CDRs in our daily practice [2]. These standards require adherence to methodologic guidelines at the development, validation and impact analysis stage (see Table 1). If this is the case, in the long run, they usually perform up to expectations. However, on the other end of the spectrum, many CDRs are developed with minimal adherence to methodologic guidelines, are never validated and ultimately, generally, these rules fail to meet expectations. Similarly, single predictors (e.g. D-dimer), can be viewed as the simplest of CDRs and their use in routine clinical practice should be limited to those clinical applications where validation and impact analysis have also been conducted.

CDRs select and combine the best independent predictors (risk factors, symptoms, clinical signs and results of simple diagnostic tests) for a diagnosis or prognosis. The most useful CDRs are accurate, reproducible, simple and easy to apply. CDRs should be sensible i.e. have a clear purpose (e.g. exclude DVT), be relevant (e.g. exclude clinically important DVT), demonstrate content validity (e.g. be composed of well recognised independent predictors), be concise (e.g. simple rules containing limited items will be remembered), and be easy to use in the intended clinical application (e.g. don't require a computer to calculate at the bedside). The use of the rule should provide a probability of disease (e.g. >10% likelihood of DVT) or prognosis (e.g. 15% risk of recurrent VTE) and should imply a course of diagnostic (e.g. needs an ultrasound to rule out DVT) or therapeutic action (e.g. continue anticoagulants indefinitely).

Construction of valid, accurate and reproducible CDRs follows a strict methodology. Levels of evidence can be attributed to CDRs depending on whether or not they have gone through all the methodological steps (Levels 1 to 4). Level 4 corresponds to a rule that is derived but not prospectively validated: it needs to be further evaluated before clinical application. Validation of the CDR in an independent cohort of patients is a crucial next step. In fact, the rule is built as a "tailored suit" for the derivation cohort. In other words, it is important to ensure that the "suit" will fit all the populations in which it is intended to be applied. Level 3 rules have been prospectively validated but in only one narrow sample: physicians may consider their use with caution and only if patients in their clinical setting are similar to those included in validation study. Level 2 rules have demonstrated their accuracy in either a large prospective study including a broad spectrum of the disease, or in several different smaller settings. They can be used in various settings with confidence in their accuracy. Finally, the impact of use of the rule, its clinical utility and safety of managing patients on the basis of the rule "in the real world" should be demonstrated in a prospective management outcome study. In these studies, use of the rule in usual practice is measured along with the performance of the rule in usual practice. Level 1 rules have been prospectively validated in a different population and the impact of use of the rule has been measured and demonstrates a change in clinician behaviour with beneficial consequences. Level 1 rules can be used with the confidence that they can change clinician behaviour and improve patients' outcomes.

Table 1
Methodologic characteristics and criteria required to develop and validate clinical decision rules and why they are important to follow.

Stage	Methodologic Criteria	Why?
Development	Describe patient characteristics	To ensure generalizability and applicability of the results to reader's clinical practice
	Broad spectrum of disease	To ensure that CDR can segregate patients with subtle or not obvious disease
	Outcome clearly defined, important, assessed blindly and is the gold standard	To ensure that the CDR predicts the right outcome in an unbiased manner
	Complete set of potential predictors that are clearly defined and blindly and prospectively collected	To ensure all potential predictors can enter CDR. To ensure that predictors collected in a reproducible, accurate and unbiased manner.
	Reproducibility of potential predictors assessed	To maximise generalizability only reliable predictors (Kappa >0.6) should enter rule.
	Statistical techniques used to derive the rule are identified and valid	To ensure adequate power so important predictors have narrow estimates of effect. To ensure rule is not "overfit" and only works in the derivation cohort
	Final rule chosen based on simplicity and ability to provide a clear course of action.	To ensure the CDR is easy to use and remember so it is widely adoptable. To ensure thresholds for dividing outcomes are chosen for optimal repartition of patients across groups and optimal proportion of patients with outcomes in each group.
Validation	Apply the rule in an independent cohort of patients	To check the proportions of patients classified by the rule in each clinical probability group.
Impact assessment	Determine impact of use of the rule in the real world	To determine if the rule is used. To determine the rule's safety, accuracy and clinical utility in real world use.

Challenges and Controversies in VTE Diagnosis: Pretest Probability Assessment for Diagnostic Management of DVT or PE: Simplified Rules or The Original Rules?

The original Wells DVT CDR and the Wells PE CDR in addition to the Geneva CDR for PE, have been well evaluated in clinical research over the last 2 decades [4]. Nonetheless it is evident from published practice patterns that clinicians often do not use these rules [5]. The risk of this underuse is either over or under diagnosis of VTE [5]. Some of the