Adjusting the Approach to Diagnosis of Deep Venous Thrombosis

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Guest Contributors

Marco E. Propersi, DO; Ryan P. Radecki, MD, MS

Editor's Note: *The Annals of Emergency Medicine Journal Club monthly provides a succinct review of high-impact articles from this and other premier medical journals relevant to emergency medicine. The reviews are followed by questions demonstrating principles by which readers—be they clinicians, academics, residents, or medical students—may critically appraise the literature. We are interested in receiving feedback about this feature. Please email journalclub@acep.org with your comments.*

ARTICLE IN REVIEW

Kearon C, de Wit K, Parpia S, et al. Diagnosis of deep vein thrombosis with D-dimer adjusted to clinical probability: prospective diagnostic management study. *BMJ.* 2022;376:e067378.

What Question Did This Investigation Aim to Answer?

In patients with possible deep venous thrombosis (DVT), can D-dimer thresholds adjusted for clinical probability, compared with a traditional DVT testing strategy, reduce imaging and safely exclude DVT?

What Study Design Did the Authors Choose?

Design: Prospective diagnostic management study.

Setting: Ten university-based emergency departments and outpatient clinics in Canada.

Population: One thousand five hundred-eight patients with signs and symptoms of DVT

Intervention: A novel "Designer D-Dimer DVT Diagnosis" (4D) pathway combined clinical pretest probability and initial D-dimer result to determine initial and subsequent ultrasonography.

Primary and Secondary Outcomes: The primary outcome was symptomatic, objectively verified venous thromboembolism (VTE), including proximal DVT or pulmonary embolism within 90 days. Secondary outcomes included subgroup analyses of the primary outcome and deaths from VTE and any cause.

Sponsors: The Canadian Institutes of Health Research. ClinicalTrials.gov: NCT02038530.

How Did the Authors Interpret the Results?

Of 1,508 enrolled patients, 1,275 were not diagnosed with a proximal DVT during initial evaluation or did not subsequently receive anticoagulation for another indication. During the 90-day follow-up on these 1,275 patients, 8 (0.6%; 95% confidence interval [CI] 0.3% to 1.2%) were diagnosed with a VTE. In the secondary subgroup analyses, subsequent VTE occurred in every clinical pretest category and no significant differences between groups were noted owing to wide CIs. There were 18 deaths in the study population during follow-up; no deaths were attributed to VTE.

With respect to ultrasound imaging, the 4D algorithm resulted in a mean of 0.72 ultrasounds per patient, whereas a conventional algorithm would have resulted in an expected 1.36 ultrasounds per patient. This represents a reduction in ultrasound usage by 47% (−0.64; 95% CI, −0.68 to −0.60).

The authors conclude that using the 4D diagnostic algorithm safely excludes DVT while reducing ultrasound imaging.

How Might This Study Impact Your Clinical Practice in the Emergency Department?

The 4D algorithm uses an adjusted D-dimer threshold according to the patients' Wells' pretest probability. This algorithm aligns with the current trend of adjusting D-dimer thresholds for VTE disease.[1,2] As with all novel algorithms, external validation remains critical prior to consideration of adoption. The complexity of the algorithm may be a barrier to implementation and uptake. However, if supported by subsequent evaluation, these data indicate important advantages in imaging resources utilization.

DISCUSSION POINTS

1. *Limiting the potential for bias is paramount for investigators conducting medical research. What biases affect the validity of this study?*

Multiple biases affect the measurement of outcomes in this study. The primary outcome was assessed via telephone, potentially introducing recall bias.[3] Recall bias affects internal validity when participants are inaccurate reporters of outcomes occurring during the conduct of a study. Classically, recall bias affects retrospective cohort studies. In these types of studies, patients enrolled with a particular outcome of interest (eg, autism spectrum disorder) may have an elevated recollection of vaccine-related adverse events. The effect on prospective studies is typically less profound but can affect results with longer follow-up timeframes or when multiple outcomes or events are asked to be recalled. In this study, the effect of recall bias should be small.

The presence of surveillance bias could also have confounded this study.[4] Patients undergoing an initial evaluation for DVT as part of a study may be more cognizant of the signs and symptoms of VTE and, therefore, more likely to seek evaluation for future symptoms. Greater awareness and potential intensity of follow-up may bias the observed frequency of VTE within 90 days.

Lastly, not all patients underwent a gold standard diagnostic on their initial evaluation. Patients for whom D-dimer thresholds excluded initial or repeat imaging did not receive an ultrasound during the initial evaluation. It is possible that DVT was present in some patients at that time, but their diagnosis was delayed until the 90-day follow-up period.

> 2. *How did the investigators handle patients lost to follow-up? How does loss to follow-up affect confidence in the data?*

In this study, there were 8 patients lost to follow-up. Investigators performed a "worst-case scenario" analysis on these patients, assigning them the incidence of subsequent VTE equal to the incidence observed in the "high clinical risk" population. Based on this specific scenario, the authors observed little appreciable difference affecting their final point estimate.

These types of estimates and "worst-case scenarios" are typically characterized as sensitivity analyses and explore the uncertainty of clinical outcomes in the data presented.[5] However, patients lost to follow-up may have a worse prognosis than those who completed the study.[6]

In a typical sensitivity analysis, patients lost to follow-up are assigned the primary outcome and would all be assumed to have sustained a DVT during the 90-day follow-up. Patients excluded from the analysis for protocol violations, as well as those initiated on anticoagulation, should likewise be considered for inclusion in such sensitivity analyses. These patients and how their outcomes are addressed may have substantial effects on the assumed safety of the 4D algorithm and serve as part of the justification for why additional confirmatory validation is necessary.

Author affiliations: From the Department of Emergency Medicine, Vassar Brothers Hospital in Nuvance Healthcare System, Poughkeepsie, NY (Propersi); and the Department of Emergency Medicine, Christchurch Hospital, Christchurch, New Zealand (Radecki).

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