Review: several factors are associated with the performance of D-dimer assays for detecting deep venous thrombosis

Heim SW, Schectman JM, Siadat MS, *et al.* D-dimer testing for deep venous thrombosis: a metaanalysis. *Clin Chem* 2004;**50**:1136–47.

Clinical impact ratings GP/FP/Primary care ★★★★★☆ Internal medicine ★★★★★☆ Emergency medicine ★★★★★☆ Haematology ★★★★★☆

Q In symptomatic patients, what factors are associated with the performance of D-dimer assays for detecting lower extremity deep venous thrombosis (DVT)?

METHODS

Data sources: Medline (February 1995 to October 2003) and bibliographies of relevant articles.

Study selection and assessment: diagnostic studies that calculated sensitivities and specificities or provided paired data for comparing D-dimer assay results with lower extremity ultrasonography or venography for detecting acute DVT in symptomatic patients.

Outcome: diagnostic odds ratio (DOR) as a function of D-dimer assay while controlling for the reference standard, sample size, overall prevalence of disease, and patient mix of each study.

Factors associated with the performance (diagnostic odds ratio [DOR]) of D-dimer assays for detecting deep venous thrombosis in symptomatic patients*

Variable	Comparisons	Relative DOR (95% CI)
Assay	Dimertest v VIDAS	0.08 (0.03 to 0.20)
	NycoCard v VIDAS	0.28 (0.09 to 0.90)
	Turbiquant v VIDAS	0.20 (0.08 to 0.52)
Reference standard	Ultrasonography or ultrasonography and venography v venography	0.37 (0.19 to 0.74)

*CIs provided by author.

MAIN RESULTS

23 studies (3985 patients) met the selection criteria. Groups of D-dimer assays evaluated included first generation latex agglutination assays (D-dimer test, Dimertest, Dimertest II, and Nephelotex), second generation latex agglutination assays (Auto Dimertest, BC D-Dimer, IL Test, Liatest, LPIA, Tinaquant, and Turbiquant), membrane ELISAs (Instant IA and NycoCard), erythrocyte agglutination assays (SimpliRED), automated rapid ELFA (VIDAS), and microplate ELISAs (Asserachrom, Dimertest EIA, Dimertest GOLD EIA, Enzygnost, and Fibrinostika). Sensitivity varied from 51–100% and specificity from 19–94%. Multivariate analysis showed that only the Dimertest, NycoCard, and Tinaquant assays differed (all with lower discriminant ability) from the VIDAS assay (table). Reference standards included ultrasonography (8 studies), venography (7 studies), and a combination of ultrasonography and venography (8 studies). Multivariate analysis showed that choice of venography as the reference standard was associated with better assay performance (table). 14 of 23 studies were done exclusively in outpatient populations with a prevalence of DVT that ranged from 20–68%. The patient population of the other 9 studies was classified as mixed (for data analysis purposes), with 4 studies done exclusively in inpatient populations with a prevalence of 28–69%. Multivariate analysis showed that a 10% increase in prevalence of DVT in the study population was associated with poorer assay performance (relative DOR 0.78, {95% CI 0.67 to 0.95}*).

CONCLUSION

In symptomatic patients, biochemical and technical characteristics of the assays, disease prevalence, and choice of reference standard are associated with the wide variation in performance of D-dimer assays for diagnosing lower extremity deep venous thrombosis.

*Information provided by author.

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Commentary

Plasma D-dimer is emerging as a simple biological test that may rule out proximal DVT in selected patients. But an important question remains: In which patients and with what assay should we measure D-dimer?

The meta-analysis by Heim *et al* highlights some important points on D-dimer research: (1) Study samples are small and include different patient populations; (2) D-dimer assays rely on no less than 6 different laboratory methods; and (3) D-dimer diagnostic characteristics exhibit considerable heterogeneity.

While using DORs allows us to account for those differences in a multivariate model,¹ the approach has limitations. The DOR is the ratio of the positive and negative likelihood ratios. Therefore, it is a global index of diagnostic test performance and may be identical for a less sensitive but more specific D-dimer assay and a more sensitive but less specific test. Even the most specific assays are not specific enough to rule in DVT and D-dimer is only used to rule out DVT in combination with clinical probability. Hence, use of DORs may dampen true sensitivity difference between assays, and this is compounded by the small sample sizes. Be that as it may, as concluded by the authors, each D-dimer assay should be evaluated separately.

The most important evidence on the safety and clinical usefulness of a particular D-dimer assay would stem from well designed, large scale, management studies that allow a precise estimate of the 3 month thromboembolic risk in patients left untreated based on a D-dimer result below the cutpoint.^{2,3}

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