

## D-Dimer Confusion: *Not all D-dimers are the Same.*

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A “D-dimer” is not one, standardized test. There are at least 23 products on the market, utilizing several different processes and/or equipment, that are called “D-dimer”. They may vary significantly in sensitivity, specificity, and most importantly, negative predictive values. One study found “wide variation in assay performance” and ascribed this to differences in biochemical and technical characteristics of the assays, among other reasons.<sup>1</sup> And, for some D-dimer tests there are issues of subjective interpretation and observer dependency.<sup>2</sup> Negative predictive value cutoffs may vary depending on the type of equipment used to perform the assay.<sup>3</sup> And, there are two different units used to express quantitative D-dimer results, the actual numbers of D-dimer molecules in ng/mL, or the fibrinogen equivalent unit (FEU). An FEU is approximately equal to 2ng/mL, and this has created confusion regarding cut-off values reported in the literature.

Pulmonary embolism (PE) is an all too common cause of morbidity and mortality. Documenting the presence of thrombosis could significantly aid the clinician in the proper management of these patients. The D-dimer assay’s ability to detect the presence of a degradation product of crosslinked fibrin is becoming a routine part of the overall assessment for DVT and PE.

D-dimer levels above normal “cut-off” values are present in nearly all patients with recent venous thrombosis, but also occur in many other situations, including advancing age, pregnancy, trauma, the postoperative period, inflammatory states, and cancer, making a positive result of little use clinically. A negative D-dimer though, would imply no active clotting, and this information, if reliable, would significantly affect treatment decisions, and decrease the need for more expensive diagnostic procedures.

One of the original uses for D-dimer involved the diagnosis of disseminated intravascular coagulation (DIC). The D-dimer assays for DIC are not necessarily appropriate for use to rule out PE or DVT, but this distinction is not always obvious. In 2004, the College of American Pathologists Coagulation Resource Committee found “significant confusion” among laboratories regarding what units of measure are used in reporting results as well as “...evidence

that many laboratories are using the wrong cutoff for their particular assay.”<sup>4</sup> There are some reports that D-dimer assay results are related to the amount of clot present, and it may be much less sensitive to isolated calf vein thrombosis.<sup>5</sup>

It is important to know which type of assay is being used because there is such tremendous variation in available D-dimer tests. They can be grouped into many different categories. The “gold standard” for D-dimer assays is the Enzyme-Linked Immunosorbent Assay (ELISA), but it is cumbersome and various “rapid” ELISAs have been developed. The other basic types of assays are plasma agglutination, whole-blood agglutination, and immunoturbidimetric methods, and there are multiple versions of these on the market. New D-dimer tests are continuing to appear; the FDA approved another as recently as February, 2005. The negative predictive values vary for each type of exam, but in general, all the ELISA assays appear to have more favorable values with respect to ruling out PE or DVT. Reports on the sensitivity and specificity for the presence of thrombosis for these tests are influenced by the population being studied, and by the threshold (cut off) used to define a negative test.<sup>1</sup> The “standard” ELISA test, has limited clinical utility since it takes about 8 hours to perform and is “laboratory intensive.” The other exams however, including the “rapid” ELISAs, can be performed in 2 to 35 minutes.<sup>6</sup>

A clinical prediction rule (probability assessment) for the likelihood of venous thrombosis is frequently recommended to enhance negative predictive values.<sup>7</sup> The criteria proposed by Wells et al<sup>8</sup> appear to be widely accepted but there are others. There are many studies supporting the concept that a low pretest probability and a negative D-dimer assay can rule out PE and/or DVT, safely eliminating the need for an imaging study for certain classes of patients.<sup>1,3,5,6,7,9</sup> The advantages to the patient and cost effectiveness of this approach seem obvious. At times, it is difficult to distinguish chronic venous thrombosis from acute by ultrasound or other imaging procedures, and a negative D-dimer would be very useful in these situations in eliminating unnecessary treatment or repeated testing.

Performance characteristics change depending on the makeup of the patient population. The utility of D-dimer testing is seriously decreased in some subsets of patients; those hospitalized for more than 3 days, over 60 years of age, or with high levels of C-reactive protein.<sup>10</sup> Higher levels of D-dimer also appear to be related to smoking, functional impairment, a history of stroke, and even racial differences with African-Americans having significantly higher levels than the general population.<sup>11</sup> None of these increases in measured D-dimer levels would lower the negative predictive value of the assays, but they would decrease the usefulness of the test in these populations.

The College of American Pathologists Coagulation Resource Committee sent a survey questioner regarding D-dimer issues. Of the 2,018 laboratories responding, 1,506 (75 percent) reported using the D-dimer to exclude venous thromboembolism (VTE). And among these, 11 different methods were being used. The majority (96.8 percent) used a quantitative method. Eight different combinations of type and magnitude of units were reported. All methods showed variability in the type and magnitude of the units. But perhaps the most alarming statistic; 39 percent were using a D-dimer cutoff value above that recommended by the manufacturer which "...may lead to many patients being erroneously excluded from VTE"<sup>12</sup> The committee makes some very specific recommendations to address these problems.

There are excellent D-dimer assays available to assess DVT and PE, but care must be taken to assure the one selected is suitable for the patient population, and that there is no confusion regarding cut-off levels or reporting values. In short, know what D-dimer is being used, and that it is appropriate for the patient being tested. A positive D-dimer result is clinically unhelpful in most cases.

<sup>1</sup> D-Dimer Testing for Deep Venous Thrombosis: A Metaanalysis; Heim S, Schectman J, Siadaty M, Philbrick J; Clinical Chemistry. 2004;50:1136-1147

<sup>2</sup> Observer dependency of the SimpliRed D-dimer assay in 81 consecutive patients with suspected pulmonary embolism. de Monye W, Huisman M, Pattynama P; Thromb Res. 1999 Nov 15;96(4):293-8.

<sup>3</sup> Evaluation of an automated, latex-enhanced turbidimetric D-dimer test (advanced D-dimer) and usefulness in the exclusion of acute thromboembolic disease. Wilson DB, Gard KM; Am J Clin Pathol. 2003 Dec;120(6):930-7

<sup>4</sup> D-dimer dance card fills up with new tests, uses. Parham, S; April 2005 Feature Story "CAP Today" College of American Pathologists. Available at [http://www.cap.org/apps/docs/cap\\_today/feature\\_stories/0405Ddimer.html](http://www.cap.org/apps/docs/cap_today/feature_stories/0405Ddimer.html)

<sup>5</sup> Laboratory Markers in the Diagnosis of Venous Thromboembolism. Caprini JA, Glase CJ, Anderson CB, Karen Hathaway D; Circulation. 2004;109:1-4 - 1-8

<sup>6</sup> D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. Stein PD, Hull RD, Patel KC, et al; ([Ann Intern Med.](#) 2004;140:589-602).

<sup>7</sup> Clinical practice. The evaluation of suspected pulmonary embolism. Fedullo PF, Tapson VF. N Engl J Med. 2003; 349: 1247-1256

<sup>8</sup> Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet. 1997; 350: 1795-1798

<sup>9</sup> Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Wells PS, Anderson DR, Rodger M, et al; Thromb Haemost. 2000 Mar;83(3):416-20

<sup>10</sup> Limitations of D-dimer testing in unselected inpatients with suspected venous thromboembolism. Brotman DJ, Segal JB, Jani JT, et al; Am J Med. 2003 Mar;114(4):276-82

<sup>11</sup> Age, Functional Status, and Racial Differences in Plasma D-Dimer Levels in Community-Dwelling Elderly Persons. Pieper CF, Murali K, Rao K, et al; The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 55:M649-M657 (2000)<sup>12</sup> D-dimer testing and reporting for the diagnosis of VTE: Proficiency testing finds too-high cutoffs and more. Cunningham MT, Olson JD; May 2005 Feature Story "CAP Today" College of American Pathologists. Available at [http://www.cap.org/apps/docs/cap\\_today/feature\\_stories/0505ddimer.html](http://www.cap.org/apps/docs/cap_today/feature_stories/0505ddimer.html)

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