

Journal Club Synopsis

Block 5 / Oct 29, 2013

Discussion Leader: Jon Juhasz, MD

Host: Roy Johnson, MD

Topic: Is there an age appropriate negative cutoff for the d-dimer test?

Clinical Scenario: You are working a typical ER shift and pick up a 72 y/o F with SOB and she has a history of CKD. Your attending asks you how you want to rule out a PE because "...you know you cannot PERC her because she is over 50." The patient has no history of DVTs or PEs, no hemoptysis, no unilateral leg swelling, doesn't have cancer, and no recent surgery. She looks well and in no distress. Her heart rate is 85 and pulse ox is 96%. The patient also states that she doesn't have any shortness of breath at rest. Your attending suggests that you order a D-dimer to make sure it isn't a PE. The D-dimer comes back at 260. Your attending curses mildly and tells you that "We now have to order the CT PE protocol." You reply, "Are you sure?... the D-dimer is barely above the negative cutoff and her creatinine is 1.4." Your attending tells you to just make sure she gets a liter of fluids before she goes to CT. Her CT PE protocol is negative. She gets admitted to cards. You check her chart the next day and her creatinine bumped to 1.8. Stress testing is unremarkable except for EF was estimated at 40%. She stays 2 more days in the hospital waiting for her creatinine to come down. She is discharged in good condition with diagnoses of dehydration, shortness of breath, CHF and CKD with AKI.

Was this D-Dimer in a 72 y/o F truly positive? Did we really "...have to order the CT PE protocol?" Can we injure our patients by "making them glow" in the "donut of truth?" Could there be a more appropriate way to interpret the D-Dimer results?

Introduction: Contrast induced nephropathy from a CT PE protocol does occur and can injure our patients. A recent study showed that as high as 1 in every 55 patients can have severe enough contrast induced nephropathy from a CT PE protocol that it results in dialysis or death. We reviewed ACEP's clinical policy (which antedates all literature that we evaluated during this journal club). ACEP-- "What is the role of quantitative D-dimer testing in the exclusion of PE? Level A Rx: In patients with a low pretest probability for PE, a negative quantitative D-dimer assay result can be used to exclude PE. Level B Rx: none specified, Level C Rx: In patients with an intermediate pretest probability for PE, a negative quantitative D-dimer assay result may be used to exclude PE."

The main problem with the current cutoffs for the D-dimer test is their exceptionally poor specificity. There has been a significant amount of literature recently published that supports utilizing the patient's age multiplied by 10 for the negative cutoff. This new negative cutoff (10 x age) greatly improves the specificity (nearly doubling it in patients over 70 years, improving specificity from 14-24% to 35-44%). Additionally, the new cutoff does not significantly change the sensitivity. The goal of this journal club was to scrutinize the literature on whether there is good evidence to support the new negative cutoff. We analyzed the package inserts on two different available d-dimer tests that we have at our local hospitals. The BCS XP Innovance test is reported in fibrinogen equivalent units, FEUs, with a negative cutoff commonly reported to be less than 500

microgram/Liter. The ACL TOP 500 D-Dimer Assay is reported in d dimer units, DDUs, and the negative cutoff is commonly less than 250 microgram/Liter.

Article 1:

Gimber LH, Ing TR, Takahashi JM, Goodman TL, Yoon HC. Computed Tomography Angiography in Patients Evaluated for Acute Pulmonary Embolism with Low Serum D-dimer Levels: A Prospective Study. *The Permanente Journal*, Fall 2009, Vol 13, No4, p 4-10.

Summary: This article is a prospective study that analyzes CT PE results with low D-dimers. This study used a D-dimer test that is reported in fibrinogen equivalent units (FEUs) with a typical negative cutoff of less than 400 micrograms/Liter. For their study, they included all patients that had a D-dimer less than 1000 micrograms/Liter and who underwent CT PE. The main take home finding from this study was that 1 patient out of 347 patients had an acute PE with a D-dimer <1000 micrograms/Liter. Additionally, this 1 patient was 50 years old and his D-dimer was 630. Although this article did not look at applying the new cutoff rule (10 x age), if we applied it, the 630 would have been positive. Their reported prevalence of PE in their study was around 5%. All the remaining 347 patients did not have a PE (including 6 indeterminates with questionable subsegmental emboli) according to the study radiologists and additional ancillary studies.

Article 2:

Penaloza and Kline et al. Performance of Age-Adjusted D-Dimer Cut-off to Rule Out Pulmonary Embolism. *Journal of Thrombosis and Haemostasis*, Vol 10, Issue y, Jul 2012, 1291-1296.

Summary: This article analyzed a “merged database of three prospectively collected databases” both in Europe and in the U.S. They analyzed the negative cutoff rule of 10 x patient’s age when the D-dimer test is in FEUs (common negative cutoff <500 micrograms/Liter) from 3 different tests, the Vidas, Liatest and MDA assays. They included 4537 patients in their study and their PE prevalence was 10%. They noticed this new rule to be most helpful in patients older than age 75. They found that this new rule had low negative likelihood ratios and the number needed to test to effectively rule out PE was significantly improved in this age group. Their conclusions were that the age-adjusted cut-off made the D-dimer more clinically useful in older patients but large prospective studies are required to confirm these results before implementation into daily Emergency Medicine practice.

Article 3:

Schouten HJ et al. Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis. *British Medical Journal*. May 2013, 326:2492.

Summary: The article pooled data from 13 cohort studies. All of the studies they analyzed were from 2010-2012 (the time when the idea of studying the age-adjusted cut-off rule began). That is why data prior to 2010 addressing the negative cutoff of D-dimer seems to be obsolete. This study utilized meta-analysis to determine the performance of the new negative cutoff. The

prevalence of DVT or PE reported in the studies they analyzed ranged from 5.1%-39%. Seven of the studies focused on PE, while 6 of the studies regarded DVT. Eight of the studies were published by Douma et al, 3 by Penalosa et al, 1 by Van Es, and 1 also by Schouten. Utilizing the age adjusted cutoff, the sensitivity decreased from 97.6%-100.0% to 97.0%-99.4%. The authors concluded that this decrease was not significant. As expected, the specificity increased, especially in those over age 70, from 14.7-24% to 35-44%. Their conclusions are similar to other studies. The data so far is reassuring, but a large prospective study is needed before it becomes standard.

Overall Discussion and Bottom Line

It is important to know the sensitivities and specificities of all the tests we use. The D-dimer historically has not been very clinically useful because of its poor specificity, particularly in older patients. To answer our clinical question, "Is there an age appropriate negative cutoff (10 x age) for the D-dimer test?" ... I would say "likely yes." However, as other authors have concluded, a large prospective study is needed to make this rule part of everyday clinical practice. Additionally, this new age adjusted cutoff is based upon D-dimer testing in FEUs where the cutoff is <500, not in DDUs with a negative cutoff of <250. It is likely that when the data is reported in DDUs, the age adjusted cutoff may be 5 x age. This also would need to be validated in prospective studies.