DEM Journal Club

Article Appraisal

Article: Age-Adjusted D-Dimer Cuttoff LEvels to Rule Out Pulmonary Embolism: The Adjust PE Study. Righini M et al. JAMA, March 19, 2014, Vol 311, #11, pp 1117-1124.

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Background and Study Objective(s)	D-Dimer is often used as part of the work-up for PE in low risk patients. However, false positives are common for many reasons, particularly in the elderly, and it is well documented that d-dimer tends to increase with age. Previous researchers have suggest raising the d-dimer threshold in elderly patients. The ADJUST-PE group had already retrospectively derived and validated an "age x 10" D-dimer cutoff strategy, while in comparison other groups have advocated for an arbitrary cut-off of 750. A systematic review in the BMJ in 2013 of 13 cohorts (all retrospective) including 12,497 patients that concluded an age x 10 strategy increases specificity without significant effect on sensitivity. However, until this study, the effects of implementing an age-based cutoff in real patients had never been prospectively evaluated.
Study Design	This was a prospective, management outcome study. There was no comparison group. A European study including the Netherlands, Belgium, France, and Switzerland. Six different, but high sensitivity, d-dimer assays were used in the study. Dates of the trial: January 2010 to February 2013. Inclusion criteria: all consecutive outpatients > 18 years old presenting to ED with suspected PE (defined as acute onset/worsening of SOB or CP without an other obvious cause). Exclusion criteria: suspicion raised more than 24 hours after admission (inpatients), lack of consent, life expectancy < 3 months, inaccessible to follow-up, pregnant, anticoagulated for another reason, allergy to contrast medium, renal dysfunction (CrCl < 30). Patients initially were determined to be high or low risk based on the simplified, revised Geneva Score or Two-level Wells Score. The high risk group had CTPA. The low risk received a D-dimer. D-dimer above 'age x 10' mandated CTPA and below this cutoff patients were observed. All patients had follow-up at 3 months with a structured telephone interview. The primary outcome was the rate of adjudicated and symptomatic VTE events within 3 months. This was defined as a DVT seen on ultrasound, or high-probability V/Q scan, or at least segmental PE (sub-segmental were NOT significant).
Results	There were 4420 patients assessed for suspected PE. 1074 were excluded, mostly for published exclusions (only 21 where d-dimer was not obtained). In the end, 324 patients were included in the final analysis. The overall prevalence of PE was 19%. 426 patients (12.8%) were high probability and received CTPA first-line. 2898 patients (87.2%) were low risk. 817 patients had a D-dimer < 500. In this group there was 1 failure (0.1%) - 2 deaths, 8 suspected. 337 patients (11.6%) had a D-dimer between 500 and their age-adjusted cutoff. In this group there was 1 failure (0.3%) - 7 deaths, 7 suspected In the elderly patient sub-group analysis of 766 patients, 673 (87.9%) were scored low risk. Of them, the percentage that were excluded with D-dimer testing level increased from 6.4% (43) with a conventional threshold to 29.7% (200) with the age-adjusted cutoff. There were no failures in this group at 3 months follow-up.
Validity of Results	The trial was registered on clinicaltrials.gov and the published manuscript was consistent with the planned study and analysis. The rates of PE and proportion of patients with elevated D-dimer levels were consistent with previous trials investigating PE, which led to appropriate sample size calculations leading into the trial. However questions it was noted at Journal Club surrounding that with the low rate of pathway failure it seems unlikely that there would be any statistical difference between groups had this been investigated. Also of concern, was the fact it was which patients were evaluated using the Well's and Geneva clinical scores. Concerns were also raised over the multiple treatment failures suspected in each group, and the fact that the adjudication panel decided a minority of these constituted VTE. The background of this panel or their potential biases was unclear.
Generalizability of Results	It was felt that this trial addressed a common ED issue and included patients that we are likely to see. However concerns were raised regarding the generalizability of the results. The high prevalence of PE was noted, which is consistent with previous European trials but much higher than most North American studies. However, this was felt to be a "conservative bias" that likely makes the conclusion of safety of this protocol even more robust. Of perhaps greater concern was the fact that so few of the D-dimer results were "low" using a standard cutoff (overall rate for all assays 28%), even with assays known to be used locally with different performance characteristics. A lot of discussion ensued over the fact that this likely explained by us having a lower threshold to work-up patients for PE and therefore testing patients at lower risk. It was felt to be unclear that an age-adjusted cutoff would lead to the same results locally.
The Bottom Line	This study adds to the current literature base in support of using age-adjusted d-dimer cutoff levels. Despite lingering questions about differences in our lab and population, adjusted the cut-off for D-dimer to "Age x 10" for patients over age 50 could be reasonably applied in our setting.