Age-adjusted vs conventional D-dimer thresholds in the diagnosis of venous thromboembolism

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Age-Adjusted vs Conventional D-dimer Thresholds in the Diagnosis of Venous Thromboembolism
Nikki Caldwell and Kirsten Zimmerman
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Abstract

Context: D-dimer measurements are vital in the diagnosis and exclusion of venous thromboembolism (VTE). D-dimer levels increase with age, causing many older individuals to be subject to unnecessary imaging in the diagnostic process. The implementation of an age-adjusted D-dimer may help to improve specificity of the test, therefore, preventing further imaging.

Objective: To assess whether the application of age-adjusted cutoff values (age x 10 µg/L) compared to a conventional cutoff value (500 µg/L) improves diagnostic accuracy of the D-dimer test in older individuals (>50 years) with suspected venous thromboembolism (VTE) without compromising safety.

Methods: A PubMed search was conducted utilizing the term “age-adjusted D-dimer” with the addition of the MeSH terms “Sensitivity and Specificity” and limitation to English studies from the past five years. A review was performed on three studies that compared the efficacy of age-adjusted D-dimer to conventional cutoff values in patients > 50 years old.

Results: Scouten et al. found that the specificity of the conventional cutoff decreased with age, from 66.8% in patients less than 50 to 14.7% in those aged >80. Specificity was increased to 35.2% with the use of age-adjusted cutoffs. Sensitivities remained above 97% with the age-adjusted cutoff in all categories. Sharp et al. found that the age-adjusted D-dimer threshold was more specific (64%) versus the conventional cutoff off 500 µg/L (54%), but less sensitive (93% versus 98%). Righini et al. found that the sensitivity of the D-dimer test did not change with the application of an age-adjusted threshold, but the specificity increased from 30.8% to 43.5% versus the conventional cutoff.

Conclusion: The use of age-adjusted values for the D-dimer test improves specificity without compromising sensitivity, effectively improving clinical usefulness of the D-dimer test and reducing imaging among patients >50 years with suspected venous thromboembolism (VTE).

Abbreviations and Acronyms
Venous thromboembolism – VTE
Pulmonary embolism – PE
Deep vein thrombosis – DVT
Emergency department – ED
Computed tomography – CT
Contrast induced nephropathy – CIN
Computed tomography pulmonary angiography – CTPA
Confidence interval – CI
Introduction

Venous thromboembolism (VTE) is the leading cause of morbidity and mortality in hospitalized patients, prompting research on the most effective diagnostic technique. D-dimer concentrations are commonly measured in the workup for the patient with non-high clinical probability of VTE, whereas patients with high probability would be candidates for immediate diagnostic imaging. Non-high clinical probability is typically determined with the use of Wells score for deep vein thrombosis (DVT) and pulmonary emboli (PE) and with the use of the revised Geneva score for PE. These clinical probability rules use items such as age, past history of DVT and PE, and clinical signs and symptoms to assign a low, intermediate or high probability to patients with suspected VTE.

High levels of D-dimer, one of the byproducts of fibrinolysis, indicate acute clotting and fibrinolytic processes occurring in the body. The D-dimer test’s high sensitivity makes it one of the preferred first line tests for excluding VTE in patients with symptoms of a PE or DVT and a non-high clinical probability. However, specificity for the D-dimer test is low, subjecting many patients with D-dimer values above the cutoff value to unnecessary imaging. Many factors alter the specificity of the D-dimer test, such as duration of symptoms, extent of thrombosis, anticoagulant therapy, inflammatory diseases, cancer, pregnancy, and previous VTE. In addition, D-dimer naturally increases with age. As a result, many older patients (age >50 years) have a D-dimer concentration higher than the conventional cutoff value (500 µg/L) in the absence of thromboembolism. This further reduces the specificity of the test significantly and leads to unnecessary imaging in a large portion of the elderly population presenting with VTE symptoms and a non-high clinical probability. Patients are subjected to increased risks from radiation and contrast agents and the burden of increased cost of care. To increase the specificity, it has been suggested that the D-dimer cutoff be increased for patients over the age of 50. Therefore, the use of an age-adjusted D-dimer cutoff (age x 10) is gaining popularity. To date, no consensus has been made as to whether this method is safe and effective for the elderly population. This study researches the efficacy of using an age-adjusted D-dimer cutoff to exclude VTE in patients >50 years of age with a non-high clinical probability.

Case

Mr. R.D. is a 67-year-old male with no significant past medical history that presents to the clinic complaining of right lower extremity swelling. His D-dimer is 640 µg/L. Does he need further testing for a DVT at this time?

PICO

| Population: Older patients (>50 years) with suspected venous thromboembolism (VTE) |
| Intervention: Age-adjusted D-dimer cutoff (age x 10 µg/L) |
| Control: Conventional D-dimer cutoff (500 µg/L) |
| Outcome: Increased accuracy in the exclusion of VTE using a D-dimer assay in older patients (>50 years) |

Clinical Question

In patients over 50 years of age, does an age-adjusted D-dimer cutoff as compared to the conventional cutoff value increase the accuracy in the exclusion of VTE?
Methods

An initial PubMed search was conducted in September 2016 using the search term “age adjusted D-dimer” to retrieve 47 articles. This search was narrowed further by limiting the search to “English,” limiting the publication date to the last five years, and implementing MeSH terms “Sensitivity and Specificity” to yield 10 articles. A meta-analysis and systematic review article was selected as the primary article. Two articles were excluded, as they were included in the previously selected meta-analysis. Five more articles were excluded on the basis of low statistical power and because many of them included extraneous outcomes that were unrelated to the clinical question. Thus, three articles remained, including the primary meta-analysis, a prospective study, and a retrospective cohort study with high statistical power. This selection process is summarized in Figure 1.

Statistical methods used in this review include sensitivity, specificity, positive predictive value, negative predictive value, and negative likelihood ratio of both the conventional and age-adjusted thresholds. Sensitivity and specificity were provided in study 1, but the data used to calculate these values were not supplied, therefore, positive and negative predictive values were unable to be calculated. All of the statistical calculations for study 2 used in the review were provided by the original study. Study 3 did not provide sensitivity and specificity; however, these values were calculated by the authors of this review using original data from the study. Sensitivity and specificity were then used to calculate negative likelihood ratios, which were applied to a nomogram to find post-test probabilities. Pre-test probability was calculated based on the case for this review using the Wells criteria for DVT.

Results

Study 1:
Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis. Schouten et al.²

Objective
The objective of this study was to determine the accuracy of age-adjusted D-dimer cutoff values compared to the conventional cutoff value in identifying VTE in patients > 50 years old.
Study Design
This is a systematic review and meta-analysis comparing 13 cohorts from five separate studies identified by searching Medline and Embase. Eligible studies consisted of primary research articles that compared consecutive patients with a clinical suspicion of VTE, performed D-dimer testing using both the age-adjusted and conventional cutoff values, and confirmed diagnosis with reference testing. Studies containing patients at a high risk for thrombosis, defined as perioperative patients or patients with previous thrombosis, cancer, or coagulation disorders were excluded. The revised tool for quality assessment of diagnostic accuracy studies (QUADAS-2) was used to evaluate the quality of the chosen studies.

The studies included patients in the emergency department (ED), one primary care office, outpatient clinics, and inpatients with symptoms and signs of VTE. Risk was determined using either a revised Geneva score or the Wells criteria in all but one study. Patients considered to have a non-high clinical probability had a revised Geneva score of <10 or a Wells score of <4 for PE, and a Wells score of ≤2 or ≤1 for DVT. One study used a clinical probability of <80% as determined by the treating physician as their risk stratification method. 12 of the 13 studies used three-month event-free follow-up to confirm results. One study used diagnostic imaging.

2x2 tables were created using the true and false positive and negative rates derived by the reference tests. They were categorized into different age groups (≤50, 51-60, 61-70, 71-80, >80). The tables were used to determine prevalence, sensitivity, and specificity of VTE in each age category. A random effects bivariate regression model was used for the meta-analysis. This statistical model analyzes relationships between variables which have been derived from different populations. In this case, the true and false positive and negative rates from the 13 separate cohorts and five different age categories were included in the analysis.

The authors also constructed hypothetical cohorts with 1,000 patients per age category and D-dimer cutoff level. Hypothetical cases of VTE were determined by multiplying 1,000 by the average prevalence of VTE for each age category as found in the studies used for the meta-analysis. True positives and negatives were calculated for each age group, as well as the effects of prevalence on each one. True positives were calculated by multiplying the number of hypothetical cases by the estimated sensitivity of the D-dimer test for the particular age category. True negatives were calculated by multiplying the number of hypothetical non-cases by the estimated specificity. Results were also multiplied by the minimum and maximum prevalence of VTE in each age category.

Results
The meta-analysis showed that the use of an age-adjusted D-dimer cutoff significantly (P<0.005) increased specificity in age categories >50 years of age compared to the conventional cutoff. Specificity still decreased as age increased, but at a much less pronounced rate. Using the conventional method, specificity decreased remarkably as age increased, dropping from 66.8% in patients less than age 50 to 14.7% in patients over the age of 80. Using age-adjusted values, specificity decreased to 35.2% in patients aged greater than 80. Overall sensitivity and specificity were also calculated for the entire cohort aged greater than 50. Sensitivity was 99.3% (95% confidence interval 98.4% to 99.7%) for the conventional cutoff and 97.8% (95.9% to 98.9%) for the age-adjusted cutoff. Specificity was 36.1% (30.8% to 41.7%) for conventional cutoff and 48.8% (42.9% to 54.7%) for age-adjusted.

The hypothetical cohorts were used to determine how many patients would have avoided imaging, correctly or incorrectly, by the use of age-adjusted D-dimer. As shown in Table 1,
using age-adjusted cutoffs greatly increased the number of patients that avoided unnecessary testing, while only missing a minute number of cases. The number of missed cases would be comparable to the failure rate of the conventional cutoff value for patients <50 years, a rate of 3 per 1,000. The age-adjusted cutoff also increased the positive predictive value in patients over 80 to 21.2%, almost increasing it to that of patients younger than 50, 29.1%.

Table 1. Number of imaging studies avoided and VTE cases missed with age-adjusted cutoffs

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Unnecessary imaging studies avoided</th>
<th>VTE cases missed</th>
</tr>
</thead>
<tbody>
<tr>
<td>51-60</td>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>61-70</td>
<td>85</td>
<td>2</td>
</tr>
<tr>
<td>71-80</td>
<td>155</td>
<td>3</td>
</tr>
<tr>
<td>&gt;80</td>
<td>175</td>
<td>4</td>
</tr>
</tbody>
</table>

Study 2:
An Age-Adjusted D-dimer Threshold for Emergency Department Patients with Suspected Pulmonary Embolus: Accuracy and Clinical Implication. Sharp et al.5

Objective
To determine the accuracy of an age-adjusted D-dimer threshold to detect PE in ED patients over 50 years old.

Study Design
This was a retrospective cohort study of suspected pulmonary embolism ED visits within the 14 emergency departments operated by Kaiser Permanente Southern California. The study included all ED visits from 2008 to 2013 for members older than 50 years who received a D-dimer test. To ensure every PE diagnosis was captured, claims for care outside the system within the given time period were included as well. Only patients with membership continuing 30 days after the encounter were included in this study.

This study aimed to focus on those with a suspected pulmonary embolism, not deep vein thrombosis, therefore, only patients with a chief complaint related to possible pulmonary embolism, such as chest pain or dyspnea, were included. Those who underwent ultrasonographic imaging evaluation for deep vein thrombosis were also excluded. To ensure that only initial evaluations for pulmonary embolism were included, those with a pulmonary embolism diagnosis in the previous 30 days were also excluded. In the analysis of the data, patients with thrombophilia and cancer were identified due to their increased risk of pulmonary embolism.

The primary outcome of this study was an encounter diagnosis of acute PE. The individualized D-dimer was calculated by multiplying the patient’s age in year by ten. Additionally, the current D-dimer cutoff (500 ng/dL) and a higher fixed cutoff (1000 ng/dL) were used in calculations to compare sensitivity, specificity, positive and negative predictive values.

Patients receiving CT pulmonary angiography (CTPA), ventilation-perfusion scan, pulmonary angiography, or chest magnetic resonance angiography were identified and used to describe the proportion of ED patients receiving advanced imaging within 24 hours after their
arrival. The data was also stratified by patients receiving imaging who had a D-dimer below the standard cutoff and patients who did not receive imaging despite a D-dimer above the cutoff. Missed PEs were identified by reporting patients who neither received a diagnosis of PE nor received imaging to identify PE at the time of the ED encounter, but received a diagnosis of PE within 30 days of the initial encounter. These charts were then reviewed to determine whether the PE was present and missed at the initial ED visit or if it developed within 30 days after the visit.

To estimate the number of cases of contrast-induced nephropathy (CIN), episodes of severe renal failure, and deaths related to contrast-induced nephropathy, this study used previously published prospective findings to compare with their results. They identified patients with acute kidney injury and unspecified kidney failure within 30 days of the ED visit and further separated these results into those who received imaging and those who did not. These results were used to estimate the number of patients who would receive imaging according to different thresholds and determine their risk of imaging-related complications.

Results

This study found that the age-adjusted D-dimer was 92.9% sensitive and 63.9% specific with a positive predictive value of 4.1% and a negative predictive value of 99.8% for detecting PE. The standard cutoff was 98.0% sensitive and 54.4% specific with a positive predictive value of 3.4% and a negative predictive value of 99.9% for detecting PE. The higher fixed cutoff of 1000 ng/dL was 84.2% sensitive and 75.4% specific with a positive predictive value of 5.4% and a negative predictive value of 99.7% in the detection of PE.

In total, 12,486 patients (40.2%) received imaging in which 87% were CT pulmonary angiography, 10.5% were pulmonary perfusion scans, and 2.5% were chest CTs with contrast. Of those who received imaging, 1,323 (10.6%) had a D-dimer below the conventional threshold of 500 ng/dL, in which one third of these imaging procedures were documented as procedures to rule out other possible causes, such as aortic dissection. Five patients were identified with missed pulmonary embolisms (2.3%) that were detected within 30 days, all of whom had a D-dimer result above the age-adjusted cutoff.

During the 6-year study period, the expected number of missed PE diagnoses due to false negative D-dimer results would have been 36 with the age-adjusted threshold, 10 with the conventional threshold (500 ng/dL), and 80 with a threshold of 1,000 ng/dL. Although the application of an age-adjusted D-dimer would cause misdiagnosis of 26 more PEs than the conventional cut-off, it would also prevent 322 cases of CIN, 29 cases of severe renal failure, and 19 deaths related to CIN in this study. The results of each imaging-related outcome were used to estimate the number of each event per 10,000 suspected pulmonary embolism encounters, as seen in Table 2.

Table 2. Estimated clinical consequences of different D-dimer thresholds

<table>
<thead>
<tr>
<th>D-dimer threshold</th>
<th>Cases of Contrast-Induced Nephropathy</th>
<th>Severe Renal Failure</th>
<th>Deaths Related to CIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 ng/dL</td>
<td>511</td>
<td>44</td>
<td>29</td>
</tr>
<tr>
<td>1000 ng/dL</td>
<td>283</td>
<td>24</td>
<td>16</td>
</tr>
</tbody>
</table>
**Study 3:**

*Age Adjusted D-Dimer Cutoff Levels to Rule Out Pulmonary Embolism: The ADJUST-PE study.*

Righini et al.  

**Objective**

This study examined the efficacy of using age-adjusted D-dimer levels in elderly patients with a suspected PE.

**Study Design**

This was a prospective cohort study including 3,324 patients presenting with symptoms of PE in emergency departments in Belgium, France, the Netherlands, and Switzerland between January 1, 2010 and February 28, 2013. Consecutive patients with PE symptoms and a non-high clinical probability based on the revised Geneva score or the Wells criteria underwent D-dimer testing. Patients whose D-dimer levels were below the conventional cutoff of 500 µg/L or between the conventional cutoff and their age-adjusted D-dimer were followed up for three months. Patients with a D-dimer higher than their age-adjusted cutoff, or those found to be at high risk of PE as determined by the aforementioned scoring systems, underwent CTPA and were considered for anticoagulant therapy depending on the results. Patients excluded from the study were patients in whom symptoms of a PE occurred more than 24 hours after being in the hospital, those on anticoagulation therapy, those with an allergy to contrast medium, impaired renal function, life expectancy of less than three months, ongoing pregnancy, or inaccessibility for follow-up.

Patients were divided into three groups depending on the outcome of their D-dimer results and statistical probability of PE. A fourth group was made focusing specifically on the efficacy of age-adjusted D-dimer in elderly patients, defined as those over the age of 75. 817 patients had a low probability and a D-dimer less than 500 µg/L. 337 patients had a low probability and a D-dimer above 500 µg/L but below their age-adjusted cutoff. The remaining 1,744 patients with a low probability had an elevated D-dimer according to both methods, and were grouped with the 426 patients who had a high clinical probability for further testing. There was a total of 766 elderly patients; 673 of those were considered to have a non-high clinical probability and were categorized to further examine the utility of the age-adjusted D-dimer in this age population. Each group underwent follow-up at three months. Several participants were lost to follow-up or placed on anticoagulants for other reasons and were therefore excluded from the study at that time.

Failure rate of the age-adjusted D-dimer cutoff was the primary outcome measured. It was determined by the number of thromboembolic events that occurred in the three-month follow-up period among patients with an initial negative D-dimer according to their age-adjusted cutoff. Events were assessed by three independent experts that were blinded to the D-dimer levels. Deaths were judged to be surely related, probably related, possibly related, or unrelated to PE. Sample sizes were determined by a previous retrospective study done by the authors and general characteristics of each patient were categorized. Means and standard deviations or medians and interquartile ranges were calculated for all continuous variables. Proportions were
used for categorical variable and the Wilson score method was used to determine a 95% confidence interval (CI).

Results

At three-month follow-up, those with a D-dimer less than 500 µg/L had a thromboembolic risk of 1 in 810 patients (0.1%). Risk for using the age-adjusted cutoff was found to be 1 in 331 patients (0.3%). Those with a high clinical probability or a high D-dimer underwent CTPA and other testing if necessary. 631 patients had a confirmed PE. The remaining 1,539 patients were followed for three months. Their risk was found to be 7 in 1,481 patients (0.5%). There was a total of 766 patients 75 years of age and older, with 673 of those having a non-high clinical probability. 43 of those patients had a D-dimer less than 500 µg/L and 157 had a D-dimer below their age-adjusted cutoff, totaling 200 patients. Five of those patients were lost to follow-up. In the remaining 195, there was no occurrence of VTE at three-month follow-up. Results are shown in Table 3.

Table 3. PE events during three-month follow-up categorized by clinical probability and D-dimer concentration

<table>
<thead>
<tr>
<th></th>
<th>D dimer &lt;500 µg/L</th>
<th>D dimer &gt;500 but &lt; age adjusted cutoff</th>
<th>D dimer &gt; age adjusted cutoff or patient with high probability</th>
<th>Elderly patients (&gt;75 years old) with non-high probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>817</td>
<td>337</td>
<td>1,539</td>
<td>673</td>
</tr>
<tr>
<td>Patients lost to follow-up</td>
<td>7</td>
<td>6</td>
<td>58</td>
<td>5</td>
</tr>
<tr>
<td>Patients with PE during follow-up</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

2x2 tables were created by the authors of this study to further analyze the results, as seen in tables 4 and 5. Sensitivity was the same, at 99.9%, for both the conventional and age-adjusted cutoff. Specificity was 30.8% for the conventional cutoff, but rose to 43.5% using age-adjusted values. For both cutoffs, negative predictive value was found to be 99.9%. The conventional cutoff resulted in a positive predictive value of 25.9%, while the age-adjusted cutoff resulted in a positive predictive value of 29.9%.

Table 4. 2x2 for the age-adjusted cutoff

<table>
<thead>
<tr>
<th></th>
<th>VTE</th>
<th>No VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>+D-dimer</td>
<td>631</td>
<td>1481</td>
</tr>
<tr>
<td>-D-dimer</td>
<td>2</td>
<td>1139</td>
</tr>
</tbody>
</table>

Table 5. 2x2 for the conventional cutoff

<table>
<thead>
<tr>
<th></th>
<th>VTE</th>
<th>No VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>+D-dimer</td>
<td>632</td>
<td>1811</td>
</tr>
<tr>
<td>-D-dimer</td>
<td>1</td>
<td>809</td>
</tr>
</tbody>
</table>
Discussion

The data from this review concludes that an age-adjusted cutoff value for D-dimer increases the specificity of the D-dimer test without compromising sensitivity, therefore, improving the clinical utility of the test and reducing unnecessary imaging in patients >50 years. These results were consistent throughout the studies, as seen in Table 6. However, limitations exist in the analysis of this data, and further research is warranted before the implementation of these recommendations in ED management of patients with suspected VTE.

Table 6. Overview of Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conventional Cutoff (%)</td>
<td>Age-Adjusted Cutoff (%)</td>
<td>Conventional Cutoff (%)</td>
<td>Age-Adjusted Cutoff (%)</td>
</tr>
<tr>
<td>Study 1</td>
<td>99.3%</td>
<td>97.8%</td>
<td>36.1%</td>
<td>48.8%</td>
</tr>
<tr>
<td>Study 2</td>
<td>98.0%</td>
<td>92.9%</td>
<td>54.4%</td>
<td>63.9%</td>
</tr>
<tr>
<td>Study 3</td>
<td>99.9%</td>
<td>99.9%</td>
<td>30.8%</td>
<td>43.5%</td>
</tr>
</tbody>
</table>

Study 1 was a meta-analysis including five cohort studies with a total of 12,497 patients, a large enough study size to adequately represent the population. All of the studies chosen in this review had a significant degree of similarity in selecting patients, focusing only on patients with a non-high clinical probability. Other strengths of this study include the stratification of data into predefined age groups and D-dimer cutoff values and the use of reference testing to further support the D-dimer outcome.

A potential limitation of this study is that the included publications came from only three research groups. While this introduces the potential for publication bias from the sources, the authors of this meta-analysis state that funnel plots estimating effect size against study size gave no indication for bias, and that adding more studies would not have significantly altered the results. Study selection was also decreased due to the use of other methods to adjust the D-dimer cutoff values. It has also been suggested that a fixed cut-off of 750 µg/L be used in patients >60 or >70 years. Due to differences in the sensitivity and specificity of D-dimer assays, different methods, and lack of categorization of age groups, any studies with a fixed cutoff had to be excluded. The authors do note a degree of heterogeneity in the sensitivity and specificity of the D-dimer tests among the studies due to the use of different assays. Previous studies have shown that enzyme linked fluorescent assays have a higher sensitivity and lower specificity than second generation latex assays. The authors were not able to control for this variation in the research; therefore, they could not determine the differences between the two assays.

Lastly, reference standards used to confirm or exclude VTE differed among publications. 12 of the 13 studies used a three-month event-free follow-up instead of imaging to confirm the absence of VTE. This could lead to a degree of bias due to differences in verification. It could
have also overestimated the diagnostic accuracy of the age-adjusted D-dimer, considering a small thrombus may be missed in these patients.

Study 2 was a retrospective cohort study with positive aspects, including a sample size of 31,094 patients taken from a diverse population. All tests and evaluations were performed by fully trained physicians, and data were extracted by trained research staff experienced in analysis of Kaiser Permanente’s data.

The lack of prospective data is an obvious limitation of this study. Other limitations of this study include evaluation and spectrum biases, causing differing results due to the application of any threshold to different samples, as well as inconsistency in interpretation of imaging. In addition, the review of missed PEs was conducted by the research team, who were not blinded to the eventual PE diagnosis, which may be a source of bias. This study also does not evaluate using a common decision-making tool such as Wells or PE rule-out criteria. However, the authors of this study found that a significant number of patients receive diagnostic testing, despite the use of current decision-making tools and recommendations.

Strengths of study 3 include its large, international sample size and the use of a blinded, independent committee to determine the cause of all suspected thromboembolic events or deaths in the follow-up period and their relation to the study. Limitations include the use of multiple D-dimer assays, which have been shown in prior studies to have differing sensitivities and specificities. Unlike the first study, however, results between the assays were homogenous. Another limitation is the study type. Had this study been a randomized control trial, researchers would have had a control group that used the conventional cutoff for diagnosis to compare to. Lastly, only one of the seven deaths in the patients with a D-dimer below the age-adjusted cutoff had an autopsy, the most definitive method to exclude PE. While the deaths were reviewed and ruled upon by a blinded committee, PE cannot technically be formally excluded.

When viewing these studies as a whole, limitations arise in the selection of patients, as two studies used the Wells criteria and revised Geneva score to determine a patient’s clinical probability of having a VTE, while the second article used clinical symptoms to determine likelihood. This may have altered the categorization of the patients and overall application of the results to a patient population.

Another shortcoming of this review is the varying prevalence of VTE within the study population. Study 2 had an overall prevalence of PE of 19% in the study population, while study 3 had an overall prevalence of 1.69%. Study 1 had a prevalence of VTE ranging from 12.3% in patients aged less than 50 years to 21.5% in patients aged 71-80. Considering that the main outcome of this review is the ability of D-dimer cutoffs to correctly identify VTE, the variation in prevalence among the studies may contribute to differing rates of detection. Finally, variations in follow-up contribute to the limitations of this review. Study 3 and many of the studies included in the meta-analysis (study 1) used a three-month follow-up, while the remaining studies used a 30-day follow-up. Those who were followed only after 30 days could have developed a VTE in the next two months, and these occurrences would not have been recorded.

In addition to these limitations, it must be considered that the studies included in this review took place in various settings and locations, including hospital outpatients, inpatients, and primary care facilities from Southern California, Belgium, France, and Switzerland among other locations. While this could be viewed as a source of variation among studies and considered a limitation, it could also be viewed as a positive aspect of this review, as it allows the results to be generalized to a large population of patients. Results were relatively consistent throughout the
studies, further confirming that an age-adjusted D-dimer threshold could be implemented in various settings across medicine.

Other strengths of this review include the large patient population, as seen in Table 7, with similar patient demographics and selection criteria. In addition, study design of each of the studies varied slightly, but focused on the same overall outcomes and resulted in the same general conclusions. This review also included three different types of studies, adding to the significance of the results and further suggesting that an age-adjusted D-dimer threshold can improve clinical utility of the D-dimer test.

Table 7. Overview of Studies

<table>
<thead>
<tr>
<th></th>
<th>Schouten et al.²</th>
<th>Sharp et al.⁵</th>
<th>Righini et al.⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, N</td>
<td>12,497</td>
<td>31,094</td>
<td>3,346</td>
</tr>
<tr>
<td>Patient population</td>
<td>Patients &gt;50 years with suspected VTE</td>
<td>Patients &gt;50 years with suspected PE</td>
<td>Patients &gt;50 years with clinically suspected acute PE</td>
</tr>
<tr>
<td>Study Type</td>
<td>Meta-analysis</td>
<td>Retrospective study</td>
<td>Prospective diagnostic management outcome study</td>
</tr>
<tr>
<td>Clinical tool used to determine possible VTE</td>
<td>PE: Revised Geneva score of &lt;10 or a Wells score of &lt;4 DVT: Wells score of either &lt;2 or &lt;1</td>
<td>Patients presenting with a chief complaint related to PE such as chest pain or dyspnea</td>
<td>Simplified, revised Geneva score or 2-level Wells score for PE</td>
</tr>
<tr>
<td>Follow-up period</td>
<td>12 studies: 3 months One study: 45 days</td>
<td>30 days</td>
<td>3 months</td>
</tr>
<tr>
<td>Patient Characteristics</td>
<td>Mean age: 60 yo Women: N/A Men: N/A</td>
<td>Mean age: 65 yo Women: 61% Men: 39%</td>
<td>Median age: 63 yo Women: 56.8% Men: 43.2%</td>
</tr>
<tr>
<td>Conclusion</td>
<td>Age-adjusted cutoff values for D-dimer tests increases specificity, without reducing sensitivity, thereby improving clinical utility.</td>
<td>An age-adjusted D-dimer limit is more accurate than a standard threshold to reduce imaging among older ED patients.</td>
<td>Compared with a fixed D-dimer cutoff, age-adjusted D-dimer cutoff was associated with a larger number of patients in which VTE can be ruled out.</td>
</tr>
</tbody>
</table>
Clinical Application

Mr. RD is a 67-year-old male with no significant medical history who presents to the clinic complaining of right lower extremity swelling. His D-dimer value is 640 µg/L. This is a positive D-dimer result according to the conventional cutoff (500 µg/L), meaning he would undergo further testing and potentially be placed on anticoagulants. However, his age-adjusted D-dimer cutoff is 670 µg/dL (age x 10), therefore, he would not qualify for further evaluation. According to the Wells criteria for DVT, he is at moderate risk for DVT, with a pre-test probability of 17%. This pre-test probability was applied to two nomograms, Figures 2 and 3, along with positive and negative likelihood ratios to determine the post-test probability of Mr. RD having a DVT. Figure 2 illustrates the negative post-test probability, meaning that if Mr. RD had a negative age-adjusted D-dimer, he would have less than a 2% chance of having a DVT based on these three studies. Figure 3 illustrates the positive post-test probability, meaning that if Mr. RD had a positive test, he would have a 15-30% chance of having a DVT based on these three studies and would most likely undergo further testing.

Figures 2 and 3. Nomograms with negative and positive likelihood ratios

Conclusion

D-dimer is a commonly used test for excluding VTE in patients with a non-high clinical probability. However, its use is limited in older patients (>50 years old) due to its decreasing specificity with increasing age, resulting in unnecessary testing and increased burden on these patients. Use of an age-adjusted D-dimer increases the number of patients in which VTE can be excluded without imaging. In addition to increasing specificity, sensitivity remained high among all studies. This study further supports the use of an age-adjusted D-dimer cutoff in patients >50
years old. Future studies that would be beneficial include a randomized control trial comparing the two cutoffs and examination of cost effectiveness and implementation into practice. The use of different D-dimer assays should also be addressed. Currently, studies are inconclusive as to whether different D-dimer assays affect the utility of the age-adjusted cutoff.

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