The combination of four different clinical decision rules and an age-adjusted D-dimer cut-off increases the number of patients in whom acute pulmonary embolism can safely be excluded

Josien van Es1; Inge Mos2; Renée Douma3; Petra Erkens3,4; Marc Durian5; Tessa Nizet6; Anja van Houten7; Herman Hofstee8; Hugo ten Cate9; Eric Ullmann6; Harry Büller1; Menno Huisman2; P. W. Kamphuisen1

1Academic Medical Center – Vascular Medicine, Amsterdam, Netherlands; 2Leiden University Medical Center – General Internal Medicine – Endocrinology, Leiden, Netherlands; 3Maastricht University Medical Center – Lab Clinical Thrombosis and Haemostasis, Cardiovascular Research Institute Maastricht, Maastricht, Netherlands; 4Maastricht University Medical Center – Internal Medicine, Maastricht, Netherlands; 5Erasmus University Medical Center – Hematology, Rotterdam, Netherlands; 6Rijnstate Hospital – Pulmonary Medicine, Arnhem, Netherlands; 7Maasstad Hospital – Internal and Pulmonal Medicine, Rotterdam, Netherlands; 8VU University Medical Center – Internal Medicine, Amsterdam, Netherlands

Summary

Four clinical decision rules (CDRs) (Wells score, Revised Geneva Score (RGS), simplified Wells score and simplified RGS) safely exclude pulmonary embolism (PE), when combined with a normal D-dimer test. Recently, an age-adjusted cut-off of the D-dimer (patient’s age x 10 μg/l) safely increased the number of patients above 50 years in whom PE could safely be excluded. We validated the age-adjusted D-dimer test and assessed its performance in combination with the four CDRs in patients with suspected PE. A total of 414 consecutive patients with suspected PE were older than 50 years were included. The proportion of patients in whom PE could be excluded with an ‘unlikely’ clinical probability combined with a normal age-adjusted D-dimer test was calculated and compared with the proportion using the conventional D-dimer cut-off. We assessed venous thromboembolism (VTE) failure rates during three months follow-up. In patients above 50 years, a normal age-adjusted D-dimer level in combination with an ‘unlikely’ CDR substantially increased the number of patients in whom PE could be safely excluded: from 13–14% to 19–22% in all CDRs similarly. In patients over 70 years, the number of exclusions was nearly four-fold higher, and the original Wells score excluded most patients, with an increase from 6% to 21% combined with the conventional and age-adjusted D-dimer cut-off, respectively. The number of VTE failures was also comparable in all CDRs. In conclusion, irrespective of which CDR is used, the age-adjusted D-dimer substantially increases the number of patients above 50 years in whom PE can be safely excluded.

Keywords

Clinical studies, pulmonary embolism, epidemiological studies, aging

Introduction

The clinical presentation of patients with suspected acute pulmonary embolism (PE) is nonspecific and varies widely, from only limited symptoms, to severe dyspnea, pain on exertion, syncope, or even cardiogenic shock. Moreover, although the incidence of PE increases with age from one per 1,000 to nearly eight per 1,000 in older-aged patients (1–4), the prevalence of objectively proven PE in patients with suspected PE is relatively low, about 20–30% (5, 6).

For the determination of probability in the diagnostic work-up of PE standardised clinical decision rules (CDRs) combined with a D-dimer test are commonly used (7): an ‘unlikely’ CDR combined with a D-dimer test result safely excludes PE in 20–40% of the patients with suspected PE (6, 8). However, the specificity of the D-dimer test is 30–40% and even decreases with age, whereas aging, on the other hand, increases the risk of PE (9–12). This lower specificity makes the D-dimer less useful to exclude PE in older patients (6, 13–16). In addition, avoiding imaging tests such as computed tomography (CT) scans would have several advantages for (older) patients, in which the risk of contrast nephropathy and unnecessary radiation may be considerable. It has recently been shown that an age-adjusted cut-off of the D-dimer (patient’s age x 10 μg/l) in combination with an unlikely CDR greatly increased the number of patients above 50 years in whom PE could safely be excluded (17). This adjusted D-dimer cut-off has however not yet been validated in another prospective cohort of patients with suspected PE.

Several CDRs in patients with suspected PE have been derived and validated (18–21). The most commonly used CDR is the Wells score, consisting of items obtained from history, such as risk factors for PE, physical examination, including heart rate and signs of DVT, and a subjective item where the physician can judge whether
an alternative diagnosis is more likely than PE (22) (Table 1). More recently, the Revised Geneva Score (RGS) was introduced. The RGS is comparable with the Wells score, but consists of more variables, such as age > 65 years (20, 23) (Table 1). In order to simplify the calculation of the scores, both Wells and RGS scores have been simplified: all items are assigned with one point (Table 1). In four different CDRs (Wells score, RGS, simplified Wells score and simplified RGS) have recently been validated prospectively and all showed a similar safety and clinical utility in patients with suspected PE (24). Because the (simplified) RGS includes the item age > 65 years, this CDR may be less specific in older patients. Since the Wells rule has no age-specific item, it may rule out PE in a higher percentage of patients above 50 years of age, especially in combination with the age-adjusted cut-off of the D-dimer. We performed a study to evaluate the four different CDRs’ performance and safety in combination with the age-adjusted D-dimer cut-off value in patients above 50 years of age.

**Methods**

We analysed the data from a recently published prospective cohort study, which included 807 consecutive in- and outpatients with clinically suspected acute PE (22). Patients were included in seven participating academic and non-academic medical centers in the Netherlands between July 2008 and November 2009. For the present analysis, only patients older than 50 years were included.

Patients were excluded if they were under the age of 18 years, had a life expectancy of less than three months, were treated with therapeutic-dose low-molecular-weight heparin or unfractionated heparin that was initiated 24 hours or more prior to eligibility assessment, received treatment with vitamin K antagonists, had a contraindication to helical CT scan because of allergy to intravenous iodinated contrast or renal insufficiency (creatinine clearance of < 30 ml/minute, using the Cockcroft-Gault formula), were pregnant or unable to return for follow-up. Patients were followed up for three months.

The ethical review boards of all participating hospitals approved the study protocol and informed consent was obtained from all included patients.

**Data analysis**

In the original study cohort, the Wells, simplified Wells, RGS and simplified RGS were calculated in all patients. PE was considered ‘unlikely’ in case of a Wells score of ≤ 4 points, a simplified Wells score of ≤ 1 point, an RGS score of ≤ 5 points and a simplified RGS score of ≤ 2 points. A score above the respective cut-offs of all CDRs, was indicated as PE ‘likely’.

Demographic data and additional relevant information (e.g. recent trauma or surgery, cancer, use of anticoagulants, duration of time since symptom onset and D-dimer test result) were collected on a Case Report Form (CRF), available in paper and digital format. A high-sensitivity quantitative D-dimer test was performed, depending on the local practice, either VIDAS D-dimer assay (BioMerieux, Marcy L’Etoile, France), Tinaquant assay (Roche Diagnostica, Indianapolis, IN, USA), STA-liatest D-di (Diagnostica Stago, Asnieres, France) or Innovance D-dimer (Siemens, Erlangen, Germany). The computerised design forced the physician to start the diagnostic process with clinical evaluation of the patient and to enter all variables necessary to calculate the four CDRs and the D-dimer test result into the computer. The computer program calculated the four individual CDR scores. If at least one of the four CDRs was classified as ‘likely’ or in case of an elevated
D-dimer result a CT scan was ordered. The physician initiated the next recommended step in the diagnostic process according to a predefined study flow: either exclusion of PE based on an unlikely CDR and a negative D-dimer level or performing a CT scan.

We investigated the efficiency, defined as the percentage of patients above 50 years in whom PE could be excluded by an 'unlikely' CDR in combination with a normal D-dimer, according the conventional cut-off value (500 μg/l) as well as the new age-adjusted cut-off value (age x 10 μg/l) for all CDRs. Besides, in order to investigate whether the efficiency increases with age, we also looked at patients above 70 years. Furthermore, the failure rate was calculated for each CDR in combination with the D-dimer, defined as the number of patients in whom venous thromboembolism (VTE) was diagnosed during the diagnostic evaluation or during follow-up, despite an unlikely CDR and normal age-adjusted D-Dimer. Student's t-test was applied for continuous variables and categorical data were analysed using the chi-square test. Exact 95% confidence intervals (CI) around the observed incidences were calculated. All analyses were performed using SPSS version 16.0 (SPSS, Chicago, IL, USA).

Table 2: Baseline characteristics of the patients with clinically suspected pulmonary embolism older than 50 years.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>65 (10%)</td>
</tr>
<tr>
<td>Female, n</td>
<td>225 (54%)</td>
</tr>
<tr>
<td>History of VTE</td>
<td>26 (6.3%)</td>
</tr>
<tr>
<td>Active malignancy</td>
<td>73 (18%)</td>
</tr>
<tr>
<td>Recent surgery or immobilisation</td>
<td>96 (23%)</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>20 (4.8%)</td>
</tr>
<tr>
<td>Heart rate &gt; 100 beats per minute</td>
<td>107 (26%)</td>
</tr>
<tr>
<td>Clinical signs of DVT</td>
<td>44 (11%)</td>
</tr>
<tr>
<td>Inpatient</td>
<td>163 (20%)</td>
</tr>
<tr>
<td>Negative D-dimer:</td>
<td></td>
</tr>
<tr>
<td>- Conventional cut-off (&lt; 500 μg/l)</td>
<td>68 (16.4%)</td>
</tr>
<tr>
<td>- Age-adjusted cut-off (&lt; age x 10 μg/l)</td>
<td>105 (25.4%)</td>
</tr>
</tbody>
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DVT, deep venous thrombosis; SD, standard deviation; VTE, venous thromboembolism.

Results

A total of 807 consecutive patients with suspected PE were included, of whom 456 were older than 50 years (57%). In 42 of these 456 patients, no D-dimer test was performed, all patients with a high clinical probability. In 110 of the remaining 414 patients older than 50 years (27%), PE was confirmed by CT. Table 2 shows the clinical characteristics of the cohort.

The conventional D-dimer test was normal in 68/414 patients (16.4%, 95% CI 13–20), of whom one patient had PE during follow-up (failure rate: 1.9%, 95% CI 0.2–6.7) (Table 2). The absolute increase in patients with an unlikely CDR and a normal D-dimer test according to the age-adjusted cut-off ranged from 6% (13.3 to 19.3% using the simplified Wells rule) to 7.7% (14.5 to 22.2 in the original Wells score). The increase was 5.3% for the D-dimer in combination with both the simplified and the original RGS (Table 3). Although not significant, the diagnostic yield for excluding PE with the conventional cut-off appeared to be highest in combination with the original Wells score (14.5%), compared to 13.5% with the simplified Wells and 13.8% with both original and simplified RGS. Similarly, the age-adjusted D-dimer cut-off in

Table 3: Proportion of patients with an unlikely CDR (Wells, simplified Wells, Revised Geneva Score, and simplified Revised Geneva Score) in whom pulmonary embolism can be excluded based on a negative D-dimer test using the age dependent cut-off.

<table>
<thead>
<tr>
<th>CDR unlikely and conventional D-dimer negative % (95% CI)</th>
<th>Wells</th>
<th>Simplified Wells</th>
<th>RGS</th>
<th>Simplified RGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=414</td>
<td>n=132</td>
<td>n=414</td>
<td>n=132</td>
<td>n=414</td>
</tr>
<tr>
<td>%</td>
<td>&gt;50 years</td>
<td>&gt;70 years</td>
<td>&gt;50 years</td>
<td>&gt;70 years</td>
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<td>---</td>
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</tr>
<tr>
<td>Failure rate % (95% CI)</td>
<td>1</td>
<td>14.5% (11.4-18.2)</td>
<td>6.1% (3.1-11.5)</td>
<td>13.3% (10.3-16.9)</td>
</tr>
<tr>
<td>CDR unlikely and age adjusted D-dimer negative % (95% CI)</td>
<td>18-26</td>
<td>22.2%</td>
<td>21%</td>
<td>19.3%</td>
</tr>
<tr>
<td>Failure rate % (95% CI)</td>
<td>2</td>
<td>2.2% (0.7-6.0)</td>
<td>3.6% (0-18)</td>
<td>2.5% (0-8.7)</td>
</tr>
</tbody>
</table>

CDR, clinical decision rule; CI, confidence interval; n, number; RGS, Revised Geneva Score.
combination with the Wells score resulted in the largest number of patients in whom PE could be excluded (22.2%) compared with the simplified Wells (19.3%, p=0.12) and with the RGS and simplified RGS (19.1%, p=0.09). The failure rates were similar for all CDRs. For the conventional cut-off this was one patient (Wells: 1.7%, 95% CI 0.3–8.9), simplified Wells: 1.8%, 95% CI 0–9.7, (simplified) RGS: 1.81%, 95% CI 0–9.3) compared with two patients for the age-adjusted cut-off (Wells: 2.2%, 95% CI 0–7.6, simplified Wells: 2.5%, 95% CI 0–8.7%, (simplified) RGS: 2.5%, 95% CI 0–8.9) (Table 3).

In patients aged >70 years, the number of patients in whom PE could be ruled out increased three- to four-fold with all four CDRs (Table 3). However, when comparing the diagnostic yield of the four CDRs in patients above 70 years, PE could be excluded in less patients using the original Wells rule: 21% compared to 17.4% with the simplified Wells score (p = 0.44) and to 12% with both simplified and original RGS (p < 0.05) (Table 3).

The failure rate in the patients older than 70 years was similar (one patient) for both cut-off values and all CDRs. Because the proportion of older patients in whom PE was excluded was larger using the age-adjusted cut-off, the failure rate in the age-adjusted D-dimer cut-off group was relatively lower compared with the conventional cut-off (p=0.04 for all CDRs; conventional D-dimer vs. age-adjusted D-dimer: Wells 12.5% vs. 3.6%, (95% CI 2.8–48 vs. 0.7–7.6), simplified Wells 14.3% vs. 4.3% (95% CI 3.2–52.7 vs. 0.1–22.0), (simplified) RGS: 25% vs. 6.3% (95% CI 0.6–72 vs. 0.5–28.6) (Table 3).

Discussion

This study confirms that four different CDRs combined with the new cut-off performed equally. The original Wells rule, however, excluded PE in significantly more patients than when combined with the (simplified) RGS in patients above 70 years, which may be due to the fact that the RGS includes the factor age already. For the simplified Wells and the (simplified) RGS, this difference was not significant. Previously, Douma et al. investigated the age-adjusted D-dimer in three prospective cohorts with a total of 5,132 consecutive patients with suspected PE (24). In one cohort, using the original Wells score in patients above 50 years of age, the proportion of patients in whom PE could be ruled out with the age-adjusted D-dimer cut-off value increased by 10% (95% CI 7–12), compared to the conventional D-dimer cut-off. In patients older than 70 years this increase was 14% (95% CI 11–25). These findings are in agreement with the present results, as we found an absolute increase in the proportion of patients in whom the diagnosis could be excluded using the Wells score of up to 15% in older patients when the age-adjusted D-dimer cut-off was used.

Furthermore, the age-adjusted D-dimer cut-off level, combined with an unlikely clinical probability score, increases the proportion of patients older than 50 years in whom PE can safely be excluded, in comparison to the conventional cut-off value of 500 μg/l. These results extend those found in the previous studies, since we now also show that not only the Wells and revised Geneva scores, but also the simplified Wells and simplified RGS have the same ability, with a slight advantage for the original Wells score in older patients (17, 24). The number of excluded PE of this new cut-off point increased significantly with age, with a nearly four-fold increase in the number of patients older than 70 years. However, it should be noted that the number of patients > 70 years were rather small. In addition, the age-adjusted cut-off value did not come at the expense of decreased safety, since no differences in the false negative rates between the conventional and the age-adjusted cut-off value was observed. Although there were very few patients with recurrent VTE during three months follow-up, the diagnostic failure rate even showed a relative decrease in the older-aged patients above 70 years.

Clinical relevance of the age-adjusted D-dimer

The age-adjusted cut-off reduced the number of patients in whom CT scan or other radiological imaging test is necessary to exclude PE. Theoretically, this will reduce the risk of contrast nephropathy, radiation exposure and the length of hospital stay, hence potentially reducing total costs. Furthermore, the number of patients in whom PE could be excluded using the age-adjusted D-dimer cut-off differed per CDR. The simplified rules are easier to compute compared to the original scores, since all items count for just one point. However, combined with either the conventional or the new D-dimer cut-off value, the original Wells score excluded more patients compared to the other CDRs in patients older than 70 years. This difference might be due to the item ‘age above 65 years’ in the (simplified) RGS, so older patients with suspected PE will get a higher CDR result when using both simplified and original RGS, thus increasing the rate of additional imaging tests.
Limitations

Although our study involved a cohort of consecutive patients with suspected PE, and the D-dimer levels and all items of the different CDRs were collected prospectively, the performance of the four different clinical CDRs combined with the age-adjusted D-dimer was analysed retrospectively. In addition, the number of patients was rather small and therefore the 95% CIs of the false negative rate are wide. There was, however, no significant difference between the failure rates of the four clinical CDRs or with the failure rates, obtained with the conventional and the age-adjusted D-dimer cut-off.

In this analysis we dichotomised the CDRs, since this stratification is easier to apply in clinical practice. Furthermore, the Wells rule has extensively been studied with these two categories. Nevertheless, the original scheme of low-, intermediate- and high category may lead to a higher number of excluded PE. Moreover, the failure rate in these older patients seemed to be lower with the age-adjusted D-dimer because of the increased number of exclusions of PE with the age-adjusted D-dimer cut-off. However, there is still a need for confirmation of our results in larger cohorts of patients.

Finally, different D-dimer assays were used in the participating centres. Although there was no significant difference between these assays and the new D-dimer cut-off, the study was not sufficiently powered to detect small differences.

Conclusions

Irrespective of which CDR is used in patients above 50 years of age, the age-adjusted cut-off D-dimer greatly increases the number of older patients in whom PE can be excluded, without the expense of safety. The original Wells score combined with the age-adjusted D-dimer cut-off might exclude PE in more patients above 70 years of age compared with the simplified Wells score and significantly more compared with both the original and the simplified RGS. However, prospective validation with more patients is needed to validate this.

Conflict of interest

None declared

References