Point-Of-Care D-Dimer Testing: A Review of Diagnostic Accuracy, Clinical Utility, and Safety
SUMMARY WITH CRITICAL APPRAISAL  Point-Of-Care D-Dimer Testing

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**Context and Policy Issues**

Pulmonary embolism (PE) is a common and potentially fatal diagnosis.\(^1\)\(^2\) Most PE results from development of a blood clot in the deep venous system that travels through the heart and into the pulmonary vasculature.\(^3\) Risk factors for PE can be inherited or acquired, such as prolonged immobility including long travel, recent surgery or trauma, active malignancy, use of estrogen containing contraception, and prior episodes of venous thromboembolism (VTE).\(^2\)\(^3\) Approximately half of first presentation PE is in the absence of identifiable risk factors.\(^3\) Clinical presentation of PE can be quite vague and ranges from subtle symptoms of tachycardia, dyspnea, cough, or chest pain, to a sudden onset of obstructive shock.\(^2\)\(^4\) Because of the wide variability in presentation of PE, diagnosis can be challenging and clinicians must be vigilant in considering PE as part of their differential diagnosis in the appropriate clinical context.\(^1\)\(^2\)

The initial diagnostic pathway for PE in ambulatory outpatients is to first consider the hemodynamic stability of the patient, and then the clinical probability of PE.\(^1\)\(^3\)\(^5\) In patients who are hemodynamically stable, pre-test probability of PE can be evaluated using a clinical prediction rule. One commonly used tool is the Wells Score for PE.\(^5\) This scoring system assigns points for the presence of signs and symptoms of deep venous thrombus (DVT), prior DVT or PE, immobilization (for more than 3 days) or surgery within 4 weeks, tachycardia (heart rate over 100), hemoptysis, malignancy, and the lack of alternative diagnosis more likely than PE.\(^2\)\(^3\) The Wells score stratifies patients into 3 categories; low risk (score <2), intermediate risk (score 2 to 6) or high risk (score >6).\(^6\) Alternatively, patients can be stratified into dichotomous categories of PE unlikely (score ≤4) or PE likely (score >4).\(^6\) The revised Geneva score is an alternative prediction rule validated in PE.\(^4\)\(^5\) This scoring system considers similar signs and symptoms to those used by the Wells score as well as age >65 years.\(^1\)\(^4\)

In patients with a low pre-test probability of PE, the Pulmonary Embolism Rule Out Criteria (PERC) should be applied.\(^3\)\(^4\) If the patient meets all the PERC criteria, no further investigations are recommended.\(^3\)\(^4\)

Otherwise, in patients with a low or intermediate pre-test probability of PE, the next step is D-dimer testing. If the D-dimer is negative, no further investigations are recommended.\(^1\)\(^2\)\(^5\)\(^6\) A meta-analysis from 2010 demonstrated a high negative predictive value (NPV) of PE and low mortality in patients, who had a Wells score ≤4 combined with a normal D-dimer test.\(^6\) D-dimers are fibrin degradation products that appear in the blood when the coagulation cascade is active, such as when a clot is present, and may be measured in a qualitative or quantitative manner.\(^5\)\(^7\)\(^8\) There is some evidence to suggest that age adjusted D-dimer testing may increase specificity for VTE.\(^1\)\(^3\) The most commonly used D-dimer assays are enzyme linked immunosorbent assays (ELISA) performed on whole blood in a laboratory.\(^7\) If the D-dimer is elevated (≥500ng/mL) then diagnostic imaging, such as a computed tomography pulmonary angiogram (CT-PA) or a ventilation perfusion (V/Q) scan should be undertaken.\(^1\)\(^2\)\(^5\) In patients with a high pre-test probability of PE, there is no role for D-dimer
testing. Rather, patients should proceed directly to imaging and undergo either a CT-PA, or in situations where a CT-PA is contraindicated or unavailable, a V/Q scan. In Canada, physicians may practice in areas outside urban centres. Rural and remote areas in Canada may not have access to advanced diagnostic imaging, such as CT scanners or nuclear medicine testing (i.e., V/Q scans). In some cases, patients requiring these investigations are transferred to centres with the needed technological capability. In patients with low pre-test probability of PE, D-dimer testing becomes an important clinical tool in risk stratifying patients, who require further diagnostic imaging to rule out a PE. Not all health care centres have the capability of timely processing of D-dimer tests in central laboratories. Recently, Point of Care (POC) D-dimer testing has become available.

This report focuses on evidence for the diagnostic accuracy, clinical utility, and safety of POC D-dimer testing in adult patients presenting with symptoms of PE outside of tertiary and quaternary care settings.

Research Questions

1. What is the diagnostic test accuracy of diagnostic pathways involving a clinical prediction rule in combination with point-of-care D-dimer testing in adult patients presenting with pulmonary embolism symptoms?

2. What is the clinical utility of diagnostic pathways involving a clinical prediction rule in combination with point-of-care D-dimer testing in adult patients presenting with pulmonary embolism symptoms?

3. What is the safety of diagnostic pathways involving a clinical prediction rule in combination with point-of-care D-dimer testing in adult patients presenting with pulmonary embolism symptoms?

Key Findings

In adult patients presenting from the community with symptoms of pulmonary embolism and a low pre-test probability based on the Wells score, a negative point of care D-dimer test demonstrated good diagnostic accuracy with high sensitivity and negative predictive value for pulmonary embolism compared to standard care. In elderly patients presenting from the community or a nursing home, the sensitivity and negative predictive value were slightly lower. A lower Wells score cut off improved the sensitivity and clinical utility of point of care D-dimer testing. There were no studies which addressed the safety of POC D-dimer testing in adult patients presenting with symptoms of pulmonary embolism that met the inclusion criteria.

Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between Jan 1, 2012 and Oct 17, 2017.
Literature Search Methods

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

### Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Adult patients ≥ 18 years undergoing testing for acute pulmonary embolism (excluding pediatric patients, patients with recurrent venous thromboembolism, and patients with suspected deep vein thrombosis, tertiary and quaternary care settings)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Pathways for diagnosing acute pulmonary embolism involving a clinical prediction rule (i.e., Wells or Geneva) in combination with</td>
</tr>
<tr>
<td></td>
<td>- point-of-care (POC) quantitative D-dimer testing or</td>
</tr>
<tr>
<td></td>
<td>- POC qualitative D-dimer testing</td>
</tr>
<tr>
<td>Comparator</td>
<td>Q1: Diagnostic reference standard (i.e., definitive diagnostic strategy for pulmonary embolism that includes risk stratification [e.g., clinical prediction rules, D-dimer testing] in combination with diagnostic imaging [e.g., computed tomography, ventilation perfusion scintigraphy], or diagnostic imaging alone)</td>
</tr>
<tr>
<td></td>
<td>- Q2 and 3:</td>
</tr>
<tr>
<td></td>
<td>• Pathways for diagnosing acute pulmonary embolism involving laboratory-based D-dimer testing in combination with a clinical prediction rule (i.e., Wells or Geneva);</td>
</tr>
<tr>
<td></td>
<td>• Pathways for diagnosing acute pulmonary embolism involving an alternative POC D-dimer test in combination with a clinical prediction rule (i.e., Wells or Geneva);</td>
</tr>
<tr>
<td></td>
<td>• Pathways for diagnosing acute pulmonary embolism involving a clinical prediction rule (i.e., Wells or Geneva) that do not include D-dimer testing</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Q1: Diagnostic test accuracy outcomes (e.g., sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], positive likelihood ratio [PLR], negative likelihood ratio [NLR])</td>
</tr>
<tr>
<td></td>
<td>- Q2: Primary:</td>
</tr>
<tr>
<td></td>
<td>• Clinical utility (failure rate [i.e., morbidity and mortality due to false negatives or false positives at 30 days’ follow-up])</td>
</tr>
<tr>
<td></td>
<td>- Secondary:</td>
</tr>
<tr>
<td></td>
<td>• Clinical utility (e.g., proportion of patients in the study cohort stratified to the group with low predicted probability of pulmonary embolism [sum of true- and false-negatives/total cohort], change in referring physician’s diagnostic thinking, change in patient management [including time to treatment provision], turnaround time, change in patient outcomes)</td>
</tr>
<tr>
<td></td>
<td>Q3: Harms (safety outcomes of imaging procedures [e.g., radiation exposure, computed tomography-attributed malignancy, contrast nephropathy, patient discomfort, allergic reactions])</td>
</tr>
<tr>
<td>Study Designs</td>
<td>HTA/Systematic Reviews/Meta-Analyses, Randomized Controlled Trials, Non-Randomized Studies</td>
</tr>
</tbody>
</table>
Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, were included as one of the studies in a systematic review (SR) or were published prior to 2012.

Critical Appraisal of Individual Studies

The included SR was critically appraised using the AMSTAR tool. Summary scores were not calculated for the included study; rather, a review of the strengths and limitations of the included study were described.

Summary of Evidence

Quantity of Research Available

A total of 521 citations were identified in the literature search. Following screening of titles and abstracts, 488 citations were excluded and 33 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 35 publications were excluded for various reasons, while one publication met the inclusion criteria and was included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

One SR addressed the diagnostic test accuracy and clinical utility of POC D-dimer testing. There were no studies that met the inclusion criteria to address safety of POC D-dimer testing.

Summary of Study Characteristics

A summary of the characteristics of the included literature are briefly described below and detailed in Appendix 2.

Study Design

The SR included 4 publications which represented 2 unique studies. Three of the included publications were from the same parent study, the AMUSE-2 trial. One of the companion publications to the AMUSE-2 trial was a post-hoc analysis and the other was a sub-analysis that evaluated the frequency of alternative diagnosis to PE. The fourth publication enrolled patients via the AMUSE-2 trial. Both of the unique studies included in the SR were prospective cohort studies. The SR was published in 2017, and the included studies were published between 2012 and 2015.

Country of Origin

The SR was conducted by authors located in the Netherlands. The included studies were also conducted in centres in the Netherlands.

Patient Population

One study included in the SR was conducted in ambulatory adult patients presenting to primary care and the other study was conducted in elderly patients (≥60 years) presenting to primary care from the community or from a nursing home. Nursing home patients represented 44% of the study population. Patients in both studies were enrolled based on
the presence of symptoms suggestive of PE (sudden onset or deterioration of dyspnea, pleuritic chest pain, or unexplained cough). In both studies, participants were excluded if they were receiving anticoagulation. The mean age was 48 years in one study, and 76 years in the other study. The majority of participants were female in both studies, with women representing 71% and 66% of the included study populations. Patients with prior episodes of DVT or PE represented 14% and 13% of the study populations. In one study, 33% of the study participants were taking antiplatelet medications.

**Interventions and Comparators**

Both of the studies included in the SR compared a clinical prediction tool (Wells score) with subsequent qualitative POC D-dimer testing. One study referred all patients, regardless of their D-dimer result, to secondary care for reference testing according to local practices (most often D-Dimer testing followed by CT-PA, if indicated). The definition of secondary care was not reported. The other study referred patients with either a likely risk of PE (Wells score >4 points) or an abnormal D-dimer test to secondary care for further investigation. The POC D-dimer test used in both studies was the Clearview Simplify D-dimer assay from Inverness Medical. A D-dimer >80ng/mL was considered a positive test result.

**Outcomes**

The outcomes of interest in the SR were those of diagnostic accuracy including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), true negative results, and false negative results.

**Follow-up Period**

Both of the studies included in the SR followed patients up at 3 months.

**Summary of Critical Appraisal**

Strengths and limitations of the included study are provided in Appendix 3.

The overall quality of the SR was moderate. The SR reported an a priori study design. Titles and abstracts were screened in duplicate; however, full text articles were only screened by one reviewer and checked by a second reviewer. A comprehensive literature search was performed including checking reference lists and contacting authors. However, it was unclear whether the grey literature was searched. Data abstraction was performed by one reviewer and checked by all other authors. A list of included studies was provided; however, characteristics of the included studies were not fully reported. A list of excluded studies and the reason for exclusion was not reported. Quality of included studies was assessed using a standardized tool, the QUADAS-2. Quality assessment was performed by one reviewer and checked by a second. Meta-analysis was not undertaken due to heterogeneity, but the authors did not indicate if any statistical analyses were perform to measure it. Authors of the SR did not have any conflicts of interest but did not report potential conflicts of interest of the included studies. Publication bias was not assessed in the SR.

**Summary of Findings**

The overall findings are summarized below and details are available in Appendix 4.
1. What is the diagnostic test accuracy of diagnostic pathways involving a clinical prediction rule in combination with point-of-care D-dimer testing in adult patients presenting with pulmonary embolism symptoms?

**Sensitivity**

The sensitivity of a negative POC D-dimer test in participants with a Wells score of ≤4 was 95% in one study and 94% in the second study. The sensitivity improved to 97% when the Wells score cut-off was reduced to <2.

**Specificity**

The specificity of a negative POC D-dimer test in participants with a Wells score of ≤4 was 51% in one study and 38% in the second study. The specificity decreased to 32% when the Wells score cut-off was reduced to <2.

**Positive Predictive Value**

The PPV of a negative POC D-dimer test in participants with a Wells score of ≤4 was 21% in one study and 37% in the second study. The PPV remained relatively the same at 20% when the Wells score cut-off was reduced to <2.

**Negative Predictive Value**

The NPV of a negative POC D-dimer test in participants with a Wells score of ≤4 was 99% in one study and 94% in the second study. The NPV remained the same at 99% when the Wells score cut-off was reduced to <2.

2. What is the clinical utility of diagnostic pathways involving a clinical prediction rule in combination with point-of-care D-dimer testing in adult patients presenting with pulmonary embolism symptoms?

**Failure Rate**

Failures were defined as subsequent diagnosis of PE within 3 months follow-up in participants who had a negative POC D-dimer test result. Failure rates (i.e., false negative) in participants with a Wells score of ≤4 was 1.5% in one study and 5.9% in the second study. Failure rates decreased to 1.2% when the Wells score cut-off was reduced to <2.

**Efficacy**

Efficacy was defined as participants who were considered low-risk for PE based on both a low pre-test probability combined with a negative POC D-dimer test. In one study, 45% of participants with a Wells score of ≤4 were considered low risk for PE compared to 29% of participants in the other study. When the Wells score cut-off was reduced to <2, only 28% of participants were considered to be low risk for PE.

3. What is the safety of diagnostic pathways involving a clinical prediction rule in combination with point-of-care D-dimer testing in adult patients presenting with pulmonary embolism symptoms?

No clinical studies fulfilling the selection criteria were identified.

**Limitations**

The main limitation of the evidence included in this report is the low quality of the evidence included in the SR. Both of the studies included in the SR had a high risk of bias. It is unclear whether the investigators adhered to the currently accepted standard of practice in
the diagnosis of PE. In one of the included studies, patients with a likely risk of PE (according to the Wells score) or positive POC D-dimer test were referred to secondary care to receive leg ultrasounds rather than a CT-PA or V/Q scan. The other study included in the SR referred all patients to secondary care for reference testing which was left to the discretion of the treating physician. Even when POC D-dimer tests were elevated, approximately one third of patients did not receive reference testing in the form of diagnostic imaging. Verification bias, therefore, may have been introduced in the study results. Study recruitment occurred over a 3-year period for one of the studies during which time 598 patients were enrolled. The low enrollment may suggest the presence of selection bias or a lack of generalizability.

The patient population in one of the studies included patients from the community or nursing homes. The risk of PE in individuals who reside in a nursing home may be different from those residing in the community. For example, patients who reside in a nursing home, may be less mobile and at higher risk for PE. Patients who present to primary care compared to those who present to the emergency department, maybe managed differently depending on the setting and how clinicians interpret their symptoms. Both studies included in the SR were conducted in the Netherlands where risk factors for PE such as genetics may differ compared to the Canadian population. Finally, not all centres in Canada may have access to the reference standard which was used in the included SR. These factors may limit the generalizability of the study findings to the Canadian population.

Conclusions and Implications for Decision or Policy Making

One SR with two included prospective cohort studies evaluated the diagnostic accuracy and clinical utility of POC D-dimer testing in patients who were presented to primary care from either the community or nursing homes with symptoms suggestive of PE. Diagnostic accuracy differed between the two cohort studies and was dependent on the patient population enrolled in the trial. The study which enrolled elderly patients (≥60 years) and included patients from nursing homes had lower NPV and higher false negative rate compared to the other study which enrolled only community dwelling adults who were, on average, almost 30 years younger. This implies that POC D-dimer testing may not be appropriate in an older patient population, especially those who reside in a nursing home. The POC D-dimer test used provided a qualitative result based on a single break point value. Since D-dimer cut off values may change with age, older individuals may require the use of either a quantitative POC D-dimer assay or a qualitative POC test with age dependent results.

The study populations in the included SR were patients who were presented to primary care. No evidence that met the inclusion criteria for this report was found that addressed the diagnostic accuracy or clinical utility of POC D-dimer testing in patients who were presented to emergency departments outside of tertiary and quaternary care settings.

There were no studies which addressed the safety of POC D-dimer testing in adult patients presenting with symptoms of PE that met the inclusion criteria. There is evidence that primary care physicians have expressed a desire to have access to POC testing, specifically D-dimer testing to help expedite investigations. In centres where a central laboratory or diagnostic imaging services are unavailable, POC D-dimer testing has the potential to prevent unnecessary patient transfers between centres and unnecessary exposure to radiation.
Based on the available evidence, in community dwelling patients who present to primary care with symptoms suggestive of PE and who have a low pre-test probability (based on the Wells score), POC D-dimer testing has a high sensitivity and a high NPV with low false negative rate. These findings suggest that POC D-dimer testing maybe a reasonable approach to assist clinicians in determining which patients do not require further diagnostic testing in the form of imaging as part of the workup for diagnosing PE.
References


Appendix 1: Selection of Included Studies

521 citations identified from electronic literature search and screened

488 citations excluded

33 potentially relevant articles retrieved for scrutiny (full text, if available)

3 potentially relevant reports retrieved from other sources (grey literature, hand search)

36 potentially relevant reports

35 reports excluded:
- irrelevant population (15)
- irrelevant intervention (2)
- irrelevant comparator (1)
- already included in at least one of the selected systematic reviews (3)
- other (review articles, editorials) (14)

1 report included in review
Appendix 2: Characteristics of Included Publications

Table 1: Characteristics of Included Systematic Reviews

<table>
<thead>
<tr>
<th>First Author, Publication Year, County</th>
<th>Types and numbers of primary studies included</th>
<th>Population Characteristics</th>
<th>Intervention(s)</th>
<th>Comparator(s)</th>
<th>Clinical Outcomes, Length of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schols, 2017, The Netherlands</td>
<td>2 included studies (n= 892 participants)</td>
<td>Adult patients (≥18 years) with clinically suspected PE who present to primary care</td>
<td>Qualitative D-dimer POCT in combination with Wells Score</td>
<td>Wells Score without D-dimer POCT</td>
<td>Diagnostic accuracy (sensitivity, specificity, PPV, NPV) Follow-up: 3 months</td>
</tr>
<tr>
<td></td>
<td>1 included study had 3 publications</td>
<td>Elderly patients (≥60 years) with suspected PE</td>
<td></td>
<td>Standard clinical care</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Both prospective cohort studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Published between 2012 and 2015</td>
<td></td>
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</tbody>
</table>

PE = pulmonary embolism; POCT = point-of-care test; PPV = positive predictive value; NPV = negative predictive value
Appendix 3: Critical Appraisal of Included Publications

Table 1: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR\textsuperscript{15}

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Authors reported an \textit{a priori} study design</td>
<td>• Full text articles were screened by one reviewer and checked by a second reviewer</td>
</tr>
<tr>
<td>• Study titles and abstracts were screened by two reviewers independently and in duplicate</td>
<td>• Data abstraction was completed by one reviewer</td>
</tr>
<tr>
<td>• A comprehensive literature search was performed (four databases were searched without any search limits). Reference lists were checked and authors were contacted for full text publications of conference abstracts</td>
<td>• It is unclear whether the grey literature was searched</td>
</tr>
<tr>
<td>• A list of included studies was provided</td>
<td>• A list of excluded studies was not reported</td>
</tr>
<tr>
<td>• Scientific quality of included studies was assessed and documented</td>
<td>• Characteristics of included studies were not fully reported</td>
</tr>
<tr>
<td>• Quality of the included studies was considered when formulation conclusions</td>
<td>• All the included studies had a high risk of bias</td>
</tr>
<tr>
<td>• A meta-analysis was not undertaken secondary to heterogeneity across the included studies. A narrative synthesis was provided</td>
<td>• Included studies had a short (3-month) duration of follow-up</td>
</tr>
<tr>
<td>• Authors of the systematic review reported that they had no conflicts of interest</td>
<td>• Publication bias was not assessed</td>
</tr>
</tbody>
</table>

Schols\textsuperscript{19}
### Table 1: Summary of Findings of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Wells Cut-off</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
<th>Neg D-dimer test result n/N (%)</th>
<th>False Neg result n/N (%)</th>
<th>Author’s Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geersing</td>
<td>≤4 n=422</td>
<td>95</td>
<td>51</td>
<td>21</td>
<td>99</td>
<td>272/598 (45)</td>
<td>4/272 (1.5)</td>
<td>Authors conclude that evidence for GP use of POCT for acute cardiopulmonary symptoms is limited and not conclusive. They further state that studies using POCT D-dimer testing with a clinical decision rule (such as the Wells score) are promising. Finally, authors suggest that further research is needed to understand the role of POCT in primary care of patients with acute cardiopulmonary symptoms.</td>
</tr>
<tr>
<td></td>
<td>&lt;2 n=237</td>
<td>97</td>
<td>32</td>
<td>20</td>
<td>99</td>
<td>168/598 (28)</td>
<td>2/168 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Schouten</td>
<td>≤4 n=294</td>
<td>94</td>
<td>36</td>
<td>37</td>
<td>94</td>
<td>85/294 (29)</td>
<td>5/85 (5.9)</td>
<td></td>
</tr>
</tbody>
</table>

GP = General practitioners; PE = pulmonary embolism; N/A = not applicable; NPV = negative predictive value; POCT = point-of-care test; PPV = positive predictive value; Sens = sensitivity; Spec = specificity