ASH Draft Recommendations for Diagnosis of VTE

INTRODUCTION

American Society of Hematology (ASH) guidelines are based on a systematic review of available evidence. Through a structured process, a guideline panel makes judgements about the evidence and forms recommendations.

The public comment period occurs after recommendations are formed but before a manuscript report of the guidelines has been finalized and before ASH organizational approval of the guidelines. Comments collected during the open comment period are provided to the guideline panel for review prior to finalizing the guidelines.

These draft recommendations are not final and therefore are not intended for use or citation.

To submit comments on the draft recommendations, please visit http://vtediagnosis.questionpro.com. Only comments submitted via the online survey will be reviewed by the guideline panel.

The public comment period for these draft recommendations is December 5, 2017 – January 15, 2018.

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Low probability</th>
<th>Moderate probability</th>
<th>High probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE¹</td>
<td>5%</td>
<td>20%</td>
<td>50%</td>
</tr>
<tr>
<td>DVT²</td>
<td>10%</td>
<td>35%</td>
<td>50%</td>
</tr>
<tr>
<td>UE DVT³</td>
<td>10%</td>
<td>-</td>
<td>40%</td>
</tr>
</tbody>
</table>


RECOMMENDATIONS

**Question 1:** In a patient population with a low clinical probability of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose a first episode PE?

The ASH guideline panel recommends using a strategy starting with D-dimer for diagnosing PE in a population with low prevalence/pretest probability (5%), followed by i) VQ scan or ii) CTPA. If D-dimer is not readily available, alternate acceptable strategies include performing a VQ scan or CTPA alone, with additional testing with CUS of the lower extremities or CTPA is non-diagnostic. (Strong recommendation for D-dimer based on high certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy studies; Conditional recommendation for VQ scan over CTPA based on very low certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy).

The ASH guideline panel recommends against using a positive D-dimer alone to diagnose PE, and against additional testing following negative CTPA or diagnostic VQ scan in a population with low prevalence/pretest probability (5%).

**Question 2:** In a patient population with an intermediate clinical probability of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose a first episode PE?

The ASH guideline panel suggests using a strategy starting with D-dimer for diagnosing PE in a population with moderate prevalence/pretest probability (20%), followed by i) VQ scan or ii) CTPA. If D-dimer is not readily available, alternate acceptable strategies include performing a VQ scan or CTPA alone. Patients who are likely to have a non-diagnostic VQ scan should undergo CTPA. Additional testing with CTPA is recommended if the VQ scan is non-diagnostic. (Strong recommendation for D-dimer based on high certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy studies; Conditional recommendation for VQ scan or CTPA based on very low certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy).
The ASH guideline panel **recommends against** using a positive D-dimer alone to diagnose PE, and against additional testing following negative CTPA or diagnostic VQ scan in a population with intermediate prevalence/pretest probability (20%).

**Question 3:** In a patient population with a high clinical probability of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose a first episode PE?

The ASH guideline panel **suggests** using a strategy starting with CTPA for diagnosing PE in a population with high prevalence/pretest probability (50/75%), followed by additional testing with CUS or VQ scan if CTPA is negative. If CTPA is not readily available, VQ scan may be acceptable if non-diagnostic scans are followed by CTPA. (**Strong recommendation for CTPA based on very low certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy studies; Conditional recommendation for VQ scan based on very low certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy).**

The ASH guideline panel **recommends against** using a positive D-dimer alone to diagnose PE, and against using D-dimer as a subsequent test following a negative CT scan in a population with high prevalence/pretest probability (50/75%).

**Question 4:** In patients with a prior history of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose recurrent PE?

The ASH guideline panel **suggests** using a strategy starting with D-dimer for diagnosing recurrent PE in patients with a prior history of PE and a low prevalence/pretest probability. Patients with a negative D-dimer do not undergo further testing and all other patients (positive D-dimer, non-low Wells pretest probability) undergo CTPA alone with no additional testing. (**Conditional recommendation for D-dimer and CTPA based on low certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy studies).**

**Question 5:** In a patient population with a low clinical probability of lower extremity deep vein thrombosis (DVT) what is the optimal diagnostic strategy to diagnose a first episode DVT?

The ASH guideline panel **recommends** using a strategy starting with D-dimer followed by CUS or CUS/whole leg US alone for diagnosing DVT in a population with low prevalence/pretest probability (10%). (**Strong recommendation for D-dimer based on moderate certainty in the evidence about effects on clinical outcomes and moderate certainty in the evidence about diagnostic accuracy studies; Conditional recommendation for CUS/whole leg US based on very low certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy).**

The ASH guideline panel **recommends against** using a positive D-dimer alone to diagnose DVT, and against additional testing following negative CUS in a population with low prevalence/pretest probability (10%).

**Question 6:** In a patient population with an intermediate clinical probability of lower extremity deep vein thrombosis (DVT) what is the optimal diagnostic strategy to diagnose a first episode DVT?

The ASH guideline panel **suggests** using a strategy starting with CUS for diagnosing DVT in a population with intermediate prevalence/pretest probability (35%), followed by serial CUS if the initial CUS is negative. (**Conditional recommendation based on very low certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy).**

The ASH guideline panel **recommends against** using a positive D-dimer alone to diagnose DVT in a population with intermediate prevalence/pretest probability (35%).

**Question 7:** In a patient population with a high (50%, 75%) clinical probability of lower extremity deep vein thrombosis (DVT) what is the optimal diagnostic strategy to diagnose a first episode DVT?

The ASH guideline panel **suggests** using a strategy starting with CUS for diagnosing DVT in a population with high prevalence/pretest probability (>50%), followed by serial CUS if the initial CUS is negative. We recommend against a strategy based on a negative single proximal CUS or whole leg US alone when the prevalence is >75%. (**Conditional recommendation based on very low certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy).**

The ASH guideline panel **recommends against** using a positive D-dimer alone to diagnose DVT in a population with high prevalence/pretest probability (>50%).

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**Question 8:** In patients with a prior history of deep vein thrombosis (DVT), what is the optimal diagnostic strategy to diagnose recurrent DVT?

The ASH guideline panel **suggests** using a strategy starting with D-dimer for diagnosing recurrent DVT in patients with a low clinical probability. Patients with a negative D-dimer do not undergo further testing and all other patients (positive D-dimer, non-low pretest probability) undergo compression ultrasound. (*Conditional recommendation for D-dimer and CUS based on low certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy studies*).

**Question 9:** In a patient population with a low clinical probability (10%) of upper extremity deep vein thrombosis (UE DVT) what is the optimal diagnostic strategy to diagnose UE DVT?

The ASH guideline panel **suggests** a strategy starting with D-dimer for diagnosing UE DVT in a population with low prevalence/pretest probability (10%), followed by Duplex US if D-dimer is positive. If D-dimer is not readily available, performing a Duplex US is acceptable. (*Conditional recommendation for D-dimer based on low certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy studies*).

The ASH guideline panel **recommends against** using a positive D-dimer alone to diagnose UE DVT in a population with low prevalence/pretest probability (10%).

**Question 10:** In a patient population with a high clinical probability of upper extremity deep vein thrombosis (UE DVT) what is the optimal diagnostic strategy to diagnose UE DVT?

The ASH guideline panel **suggests** a strategy of either D-dimer followed by duplex US/serial duplex US, or duplex US/serial duplex US for diagnosing UE DVT in a population with high prevalence/pretest probability (40%). (*Conditional recommendation based on low certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy studies*).

The ASH guideline panel **recommends against** using a positive D-dimer alone to diagnose UE DVT in a population with high prevalence/pretest probability (40%).
Question 1. In a patient population with a low clinical probability of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose a first episode PE?

**Diagnosis of Pulmonary Embolism: Diagnostic Pathways Assessed**

a. CTPA

- Positive CTPA → anticoagulate
- Negative CTPA → no treatment

b. CTPA

- Positive CTPA → anticoagulate
- Negative CTPA → D-dimer
  - D-dimer positive → anticoagulate
  - D-dimer negative → no treatment
c. CTPA
- Positive CTPA $\rightarrow$ anticoagulate
- Negative CTPA $\rightarrow$ D-dimer
  - D-dimer positive $\rightarrow$ proximal CUS
    - Positive proximal CUS $\rightarrow$ anticoagulate
    - Negative proximal CUS $\rightarrow$ no treatment
  - D-dimer negative $\rightarrow$ no treatment

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d. CTPA
- Positive CTPA $\rightarrow$ anticoagulate
- Negative CTPA $\rightarrow$ D-dimer
  - D-dimer positive $\rightarrow$ proximal CUS
    - Positive proximal CUS $\rightarrow$ anticoagulate
    - Negative proximal CUS $\rightarrow$ serial US
      - Positive serial US $\rightarrow$ anticoagulate
      - Negative serial US $\rightarrow$ no treatment
  - D-dimer negative $\rightarrow$ no treatment
e. CTPA

- Positive CTPA $\rightarrow$ anticoagulate
- Negative CTPA $\rightarrow$ proximal CUS
  - Positive proximal CUS $\rightarrow$ anticoagulate
  - Negative proximal CUS $\rightarrow$ no treatment

f. CTPA

- Positive CTPA $\rightarrow$ anticoagulate
- Negative CTPA $\rightarrow$ proximal CUS
  - Positive proximal CUS $\rightarrow$ anticoagulate
  - Negative proximal CUS $\rightarrow$ serial US
    - Positive serial US $\rightarrow$ anticoagulate
    - Negative serial US $\rightarrow$ no treatment
g. CTPA
- Positive CTPA → anticoagulate
- Negative CTPA → VQ scan
  - High probability VQ scan → anticoagulate
  - Low/Intermediate VQ scan → proximal CUS
    - Positive proximal CUS → anticoagulate
    - Negative proximal CUS → no treatment
  - Normal VQ scan → no treatment

h. CTPA
- Positive CTPA → anticoagulate
- Negative CTPA → pulmonary angiography
  - Positive pulmonary angiography → anticoagulate
  - Negative pulmonary angiography → no treatment
i. VQ scan
- High probability VQ scan → anticoagulate
- Low/intermediate probability VQ scan → CTPA
  - Positive CTPA → anticoagulate
  - Negative CTPA → no treatment
- Normal VQ scan → no treatment

j. VQ scan
- High probability VQ scan → anticoagulate
- Low/intermediate probability VQ scan → proximal CUS
  - Positive Proximal CUS → anticoagulate
  - Negative proximal CUS → no treatment
- Normal VQ scan → no treatment
k. D-dimer

- Positive D-dimer → anticoagulate
- Negative D-dimer → no treatment

l. D-dimer

- Positive D-dimer → CTPA
  - Positive CTPA → anticoagulate
  - Negative CTPA → no treatment
- Negative D-dimer → no treatment
m. D-dimer

- Positive D-dimer → VQ scan
  - High probability VQ scan → anticoagulate
  - Low/Intermediate probability VQ scan → CTPA
    - Positive CTPA → anticoagulate
    - Negative CTPA → no treatment
  - Normal VQ scan → no treatment
- Negative D-dimer → no treatment

n. D-dimer

- Positive D-dimer → VQ scan
  - High probability VQ scan → anticoagulate
  - Low/Intermediate probability VQ scan → proximal CUS
    - Positive proximal CUS → anticoagulate
    - Negative proximal CUS → no treatment
  - Normal VQ scan → no treatment
- Negative D-dimer → no treatment
o. D-dimer
- Positive D-dimer → CTPA
- Negative D-dimer → VQ Scan
  - High probability VQ scan → anticoagulate
  - Low/intermediate probability VQ scan → CTPA
    - Positive CTPA → anticoagulate
    - Negative CTPA → no treatment
  - Normal VQ scan → no treatment

p. D-Dimer
- Positive D-Dimer → anticoagulate
- Negative D-Dimer → CTPA
  - Positive CTPA → anticoagulate
  - Negative CTPA → no treatment
q. D-Dimer

- Positive D-Dimer → anticoagulate
- Negative D-Dimer → VQ Scan
  - High probability VQ scan → anticoagulate
  - Low/intermediate probability VQ scan → CTPA
    - Positive CTPA → anticoagulate
    - Negative CTPA → no treatment
  - Normal VQ scan → no treatment

Note: in the algorithms, watchful waiting will follow negative tests and low/normal probability unless stated otherwise.

<table>
<thead>
<tr>
<th>Legend</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>anticoagulation</td>
</tr>
<tr>
<td>PE</td>
<td>pulmonary embolism</td>
</tr>
<tr>
<td>PTP</td>
<td>pretest probability</td>
</tr>
<tr>
<td>CTPA</td>
<td>computed tomography pulmonary angiography</td>
</tr>
<tr>
<td>VQ</td>
<td>ventilation perfusion</td>
</tr>
<tr>
<td>US</td>
<td>ultrasound</td>
</tr>
<tr>
<td>CUS</td>
<td>compression ultrasound</td>
</tr>
</tbody>
</table>
Question 1. In a patient population with a low clinical probability of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose a first episode PE?

| POPULATION: | Patients with a low clinical probability of suspected first episode pulmonary embolism (PE) |
| EVALUATED TESTS: | CT pulmonary angiography (CTPA), D-dimer, Proximal compression ultrasound (CUS), Ventilation Perfusion (VQ) scan |
| PURPOSE OF THE TEST: | Detection of pulmonary embolism |
| ROLE OF THE TEST: | Detection of pulmonary embolism |
| LINKED TREATMENTS: | Anticoagulation |
| ANTICIPATED OUTCOMES: | False Negative; False Positive; True Negative; True Positive; Mortality; Recurrent Pulmonary Embolism; Major Bleed; Hemorrhagic Stroke |
| SETTING: | Inpatient and outpatient |
| PERSPECTIVE: | Clinical recommendation - population perspective |
| SUBGROUPS: | 1. Population that is likely to have a diagnostic VQ scan result |
| | 2. Population that is unlikely to have a diagnostic VQ scan result |

**BACKGROUND:**

Pulmonary embolism (PE) is a potentially life-threatening condition that may be prevented and can be treated with anticoagulant therapy (Rodger 2006). The diagnostic accuracy of a test can vary with the strength of clinical suspicion (Irwig 2002). The clinical probability of a condition can assist with determining which tests to use to diagnose PE. Standardized clinical decision rules (CDRs) are used to determine clinical probability for PE (Van Es 2012). Prevalence of disease varies depending on the clinical probability of the population. In patients with low clinical probability, prevalence of disease was deemed to be 5% (Ceriani 2010).

Various diagnostic tests are currently used for the diagnosis of PE including D-Dimer assays, computed tomography pulmonary angiography (CTPA), ventilation perfusion (VQ) scanning, and compression ultrasonography (CUS) of the lower extremities (indirect). Imaging tests for PE such as CTPA and VQ lung scanning are expensive, time consuming and are associated with radiation exposure. In addition, the contrast used in CTPA can result in nephrotoxicity and allergic reactions. Therefore, inexpensive strategies with less risk to patients are needed to exclude PE efficiently (Bates 2016).
### Assessment

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
</table>
| Is the problem a priority?                    | ○ No  
○ Probably no  
○ Probably yes  
● Yes  
○ Varies  
○ Don't know | The overall annual incidence of pulmonary emboli (PE) is quoted at 60–70 cases per 100,000. Associated with significant morbidity and mortality, prompt diagnosis and expeditious therapeutic intervention is of paramount importance for optimal patient management (Warren 2012). The fear of missing a diagnosis of this life-threatening disease has led to an increase in the use of invasive diagnostic strategies, with a significant rise of imaging studies such as computed tomographic pulmonary angiography (CTPA) or ventilation perfusion (VQ) scanning over the last decade (Smith-Bindman 2012; Schissler 2013). Subsequently, it has also been reported that PE has become over diagnosed (Wiener 2013; Sheh 2012). Physicians often order CTPA, although PE is unlikely and a D-dimer test result is negative (Adams 2013). Given that CTPA is associated with radiation exposure, nephrotoxicity and allergic reactions, VQ lung scanning may offer an option with less risk. Several clinical decision rules can estimate pretest probability for PE and guide diagnostic testing. |                                                                                                                                                                                                                                          |
| How accurate is the test?                     | CTPA  
Patient or population: Patients with suspected pulmonary embolism  
New test: CTPA  
Setting: Inpatient and outpatient  
Pooled sensitivity: 0.93 (95% CI: 0.88 to 0.96)  
Pooled specificity: 0.98 (95% CI: 0.96 to 0.99) | The panel noted that for CTPA the inconclusive results reported are low, and likely not reflective of the real-world setting. The panel noted that for D-dimer, a negative result in patients with low clinical probability can rule out PE. However, a positive D-dimer result cannot be used as a standalone test to diagnose PE and initiate anticoagulant treatment. Therefore, the rating of very inaccurate applies to the diagnostic pathways where D-dimer is being used as an individual test. The panel noted that the quality of evidence of age-adjusted D-dimer may |                                                                                                                                                                                                                                          |
| D-dimer to rule in PE                         | ○ Very inaccurate  
○ Inaccurate  
○ Accurate  
○ Very accurate  
○ Don't know |                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                          |
| D-dimer to rule out PE                        | ○ Very inaccurate  
○ Inaccurate  
○ Accurate  
○ Very accurate  
○ Don't know |                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                          |
○ Very accurate
○ Don't know

incorrectly appear to be
higher than D-dimer due to
the limited number of
Proximal CUS
CI: Confidence interval
studies on age-adjusted D1
Ceriani
E
et
al.
J
Thromb
Haemost
2010;8(5):957.
Pooled
prevalence
of
PE
with
low
PTP
in
North
American
studies
dimer. The panel suggests
○ Very inaccurate
6.5%
(5%
used
in
table)
high certainty of evidence
○ Inaccurate
2
Disease
prevalence
applies
to
the
index
test
in
each
pathway.
Prevalence
applied
to
the
accuracy
of
each
for negative D-dimer, with or
○ Accurate
subsequent
test
depends
on
the
result
of
the
previous
test
in
the
pathway.
without age-adjustment, to
○ Very accurate
Explanations
rule out PE.
○ Don't know
a. Certainty of evidence not downgraded for risk of bias, although few studies had a combination of reference
VQ Scan (VQ 1 and standards that were judged to be acceptable by a panel of clinical experts.
The panel noted that the
VQ 2 evidence
b. Certainty of evidence was downgraded for serious unexplained inconsistency in sensitivity, with a range from
accuracy of VQ scanning was
profiles)
63% to 99.2%. Minor inconsistency for specificity noted but judged to be insufficient to downgrade the certainty of difficult to consider given
evidence.
that patients with non○ Very inaccurate
c. Certainty of evidence was downgraded for indirectness in instances where this test was not the index test in a
diagnostic scans would not
○ Inaccurate
diagnostic pathway. There was a lack of data on the accuracy of this test following a previous test in a pathway.
be anticoagulated or
○ Accurate
Thus, sensitivity and specificity used for modeling in these instances were based on the test accuracy of the
discharged based on this
○ Very accurate
individual test rather than using the test in a pathway.
result. The two sets of
○ Don't know
accuracy results provided
High Probability
D-dimer
each represent this
VQ Scan (VQ 3
Patient or population: Patients with suspected pulmonary embolism
low/intermediate probability
evidence profile)
New test: D-Dimer
VQ scan group either being
Setting: Inpatient and outpatient
anticoagulated (VQ1) or
○ Very inaccurate
Pooled sensitivity: 0.97 (95% CI: 0.96 to 0.98) | Pooled specificity: 0.39 (95% CI: 0.36 to 0.43)
discharged (VQ2).
○ Inaccurate
Complications arising from
the diagnostic test

Number of results per 1,000 patients
tested (95% CI)

Test result

D

○ Accurate
○ Very accurate
○ Don't know

ra
f

t

Not reported

True positives

Prevalence 5%1,2 in patients with
suspected PE

49 (48 to 49)

False negatives

1 (1 to 2)

True negatives

372 (340 to 406)

False positives

578 (544 to 610)

Inconclusive test results

0

Number of
participants
(studies)

30
(20568)
30
(20568)
20469
(30)

Certainty of the
Evidence (GRADE)

⨁⨁⨁◯

MODERATE a,b,c
⨁⨁⨁◯

MODERATE a,b,c
-

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The panel noted that for high
probability VQ scans, it was
difficult to consider it very
accurate due to it
representing a theoretical
population without any
inconclusive results.


Complications arising from the diagnostic test

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence 5%(^1,2) in patients with suspected PE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>True positives</td>
<td>50 (49 to 50)</td>
<td>2885 (1)</td>
<td>✭✭✭✭✭ HIGH (^a)</td>
</tr>
<tr>
<td>False negatives</td>
<td>0 (0 to 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True negatives</td>
<td>445 (426 to 465)</td>
<td>2885 (1)</td>
<td>✭✭✭✭✭ HIGH (^a)</td>
</tr>
<tr>
<td>False positives</td>
<td>505 (485 to 524)</td>
<td>2885 (1)</td>
<td>✭✭✭✭✭ HIGH (^a)</td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>0</td>
<td>2885 (1)</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^1\)Cerani E et al. J Thromb Haemost 2010;8(5):957. Pooled prevalence of PE with low PTP in North American studies 6.5% (5% used in table)

\(^2\)Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

Explanations

a. Certainty of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that were judged to be acceptable by a panel of clinical experts.

b. Minor inconsistency for sensitivity noted but judged to be insufficient to downgrade the certainty of evidence. Certainty of evidence was downgraded for serious unexplained inconsistency in specificity, with a range from 12.8% to 64%.

c. Certainty of evidence was downgraded for indirectness in instances where this test was not the index test in a diagnostic pathway. There was a lack of data on the accuracy of this test following a previous test in a pathway. Thus, sensitivity and specificity used for modeling in these instances were based on the test accuracy of the individual test rather than using the test in a pathway.

Age-adjusted D-dimer

Patient or population: Patients with suspected pulmonary embolism

New test: Age-Adjusted D-dimer

Setting: Inpatient and outpatient

Pooled sensitivity: 0.99 (95% CI: 0.98 to 1.00) | Pooled specificity: 0.47 (95% CI: 0.45 to 0.49)
### Complications arising from the diagnostic test

Not reported

<table>
<thead>
<tr>
<th>CI: Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>1Ceriani E et al. J Thromb Haemost 2010;8(5):957. Pooled prevalence of PE with low PTP in North American studies 6.5% (5% used in table)</td>
</tr>
<tr>
<td>2Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.</td>
</tr>
</tbody>
</table>

#### Explanations

a. Certainty of evidence not downgraded for imprecision given the large population size, though only one prospective age-adjusted D-dimer study was identified for analysis.

#### Proximal CUS

**Patient or population:** Patients with suspected pulmonary embolism  
**New test:** Proximal Compression Ultrasound  
**Setting:** Inpatient and outpatient  

**Pooled sensitivity:** 0.49 (95% CI: 0.31 to 0.66)  
**Pooled specificity:** 0.96 (95% CI: 0.95 to 0.98)

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positives</td>
<td>24 (16 to 33)</td>
<td>1715 (7)</td>
<td>☘◘◘◘ LOW a,b,c</td>
</tr>
<tr>
<td>False negatives</td>
<td>26 (17 to 34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True negatives</td>
<td>917 (901 to 927)</td>
<td>1715 (7)</td>
<td>☘◘◘◘ LOW a,b,c</td>
</tr>
<tr>
<td>False positives</td>
<td>33 (23 to 49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>0</td>
<td>1715 (7)</td>
<td>◘◘◘◘ Low a,b,c</td>
</tr>
</tbody>
</table>

**Complications arising from the diagnostic test**

Not reported

<table>
<thead>
<tr>
<th>CI: Confidence interval</th>
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<tr>
<td>1Ceriani E et al. J Thromb Haemost 2010;8(5):957. Pooled prevalence of PE with low PTP in North American studies 6.5% (5% used in table)</td>
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<tr>
<td>2Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.</td>
</tr>
</tbody>
</table>
**Explanations**

a. Certainty of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that were judged to be acceptable by a panel of clinical experts.

b. Certainty of evidence was downgraded for serious unexplained inconsistency in sensitivity, with a range from 18.4% to 96.7%. Minor inconsistency for specificity noted but judged to be insufficient to downgrade the certainty of evidence.

c. Certainty of evidence downgraded for indirectness because of lack of data on the accuracy of this test following a previous test in a pathway. Sensitivity and specificity used for modeling are based on the test accuracy of the individual test rather than using the test in a pathway.

**VQ 1: VQ scan with high probability scan interpreted as positive, normal/low/intermediate scan as negative**

**Patient or population:** Patients with suspected pulmonary embolism

**New test:** VQ scan with high probability interpreted as positive, normal/low/intermediate scan as negative

**Setting:** Inpatient and outpatient

**Pooled sensitivity:** 0.58 (95% CI: 0.50 to 0.66) | **Pooled specificity:** 0.98 (95% CI: 0.96 to 0.99)

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence 5%&lt;sup&gt;1,2&lt;/sup&gt; in patients with suspected PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True positives</td>
<td>29 (25 to 33)</td>
<td>3994 (13)</td>
<td>⬠⬠⬠◯ MODERATE&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>False negatives</td>
<td>21 (17 to 25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True negatives</td>
<td>935 (916 to 943)</td>
<td>3994 (13)</td>
<td>⬠⬠⬠◯ MODERATE&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>False positives</td>
<td>15 (7 to 34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>1849</td>
<td>3994 (13)</td>
<td></td>
</tr>
<tr>
<td>Complications arising from the diagnostic test</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: Confidence interval

<sup>1</sup>Ceriani E et al. J Thromb Haemost 2010;8(5):957. Pooled prevalence of PE with low PTP in North American studies 6.5% (5% used in table)

<sup>2</sup>Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

**Explanations**

a. Certainty of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that were judged to be acceptable by a panel of clinical experts.
b. Certainty of evidence was downgraded for serious unexplained inconsistency in sensitivity, with a range from 13.9% to 84.6%. Minor inconsistency for specificity noted but judged to be insufficient to downgrade the certainty of evidence.

c. Certainty of evidence was downgraded for indirectness in instances where this test was not the index test in a diagnostic pathway. There was a lack of data on the accuracy of this test following a previous test in a pathway. Thus, sensitivity and specificity used for modeling in these instances were based on the test accuracy of the individual test rather than using the test in a pathway.

**VQ 2: VQ scan with high/intermediate/low probability scan interpreted as positive, normal scan as negative**

**Patient or population:** Patients with suspected pulmonary embolism  
**New test:** VQ scan with high/intermediate/low probability interpreted as positive, normal scan as negative  
**Setting:** Inpatient and outpatient  
**Pooled sensitivity:** 0.98 (95% CI: 0.95 to 0.99) | **Pooled specificity:** 0.36 (95% CI: 0.27 to 0.45)

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence 5% in patients with suspected PE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>True positives</td>
<td>49 (48 to 50)</td>
<td>3994 (13)</td>
<td>🌝☉☉☉ MODERATE a,b,c</td>
</tr>
<tr>
<td>False negatives</td>
<td>1 (0 to 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True negatives</td>
<td>338 (255 to 431)</td>
<td>3994 (13)</td>
<td>🌝☉☉☉ MODERATE a,b,c</td>
</tr>
<tr>
<td>False positives</td>
<td>612 (519 to 695)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>1849</td>
<td>3994 (13)</td>
<td>-</td>
</tr>
</tbody>
</table>

**CI:** Confidence interval  
1 Ceriani E et al. J Thromb Haemost 2010;8(5):957. Pooled prevalence of PE with low PTP in North American studies 6.5% (5% used in table)  
2 Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

**Explanations**

a. Certainty of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that were judged to be acceptable by a panel of clinical experts.
b. Minor inconsistency for sensitivity noted but judged to be insufficient to downgrade the certainty of evidence. Certainty of evidence was downgraded for serious unexplained inconsistency in specificity, with a range from 10.9% to 81.8%.

c. Certainty of evidence was downgraded for indirectness in instances where this test was not the index test in a diagnostic pathway. There was a lack of data on the accuracy of this test following a previous test in a pathway. Thus, sensitivity and specificity used for modeling in these instances were based on the test accuracy of the individual test rather than using the test in a pathway.

**VQ 3: VQ scan with high probability scan as positive, normal scan as negative**

**Patient or population:** Patients with suspected pulmonary embolism

**New test:** VQ scan with High probability scan as positive, Normal scan as negative

**Setting:** Inpatient and outpatient

**Pooled sensitivity:** 0.96 (95% CI: 0.91 to 0.98) | **Pooled specificity:** 0.95 (95% CI: 0.89 to 0.98)

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positives</td>
<td>48 (46 to 49)</td>
<td>1799 (13)</td>
<td>⬤⬤⬤⬤ HIGH a,b,c</td>
</tr>
<tr>
<td>False negatives</td>
<td>2 (1 to 4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True negatives</td>
<td>904 (841 to 932)</td>
<td>1799 (13)</td>
<td>⬤⬤⬤⬤ HIGH a,b,c</td>
</tr>
<tr>
<td>False positives</td>
<td>46 (18 to 109)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>0</td>
<td>1799 (13)</td>
<td>-</td>
</tr>
</tbody>
</table>

**Complications arising from the diagnostic test**

- Not reported

CI: Confidence interval

1 Ceriani E et al. J Thromb Haemost 2010;8(5):957. Pooled prevalence of PE with low PTP in North American studies 6.5% (5% used in table)

2 Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

**Explanations**

a. Certainty of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that were judged to be acceptable by a panel of clinical experts.

b. Minor inconsistency for sensitivity noted but judged to be insufficient to downgrade the certainty of evidence. Minor inconsistency for specificity noted but judged to be insufficient to downgrade the certainty of evidence.
c. Certainty of evidence was downgraded for indirectness in instances where this test was not the index test in a diagnostic pathway. There was a lack of data on the accuracy of this test following a previous test in a pathway. Thus, sensitivity and specificity used for modeling in these instances were based on the test accuracy of the individual test rather than using the test in a pathway.

<table>
<thead>
<tr>
<th>Judgment</th>
<th>Research Evidence</th>
<th>Additional Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CERTAINTY OF THE EVIDENCE OF TEST ACCURACY</strong></td>
<td></td>
<td>The panel noted high certainty of evidence for negative D-dimer, with or without age-adjustment, to rule out PE.</td>
</tr>
<tr>
<td>What is the overall certainty of the evidence of test accuracy?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Very low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Low (Proximal CUS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Moderate (CTPA, VQ scan)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ High (Age-adjusted D-dimer or D-dimer to rule out PE, High probability/Normal VQ scan)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ No included studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS</td>
<td>What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the pathway?</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>○ Very low</td>
<td>○ Low</td>
<td></td>
</tr>
<tr>
<td>○ Moderate</td>
<td>○ High</td>
<td></td>
</tr>
<tr>
<td>○ Varies</td>
<td>○ No included studies</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT</th>
<th>How certain is the link between pathway results and management decisions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Very low</td>
<td>○ Low</td>
</tr>
<tr>
<td>○ Moderate</td>
<td>○ High</td>
</tr>
<tr>
<td>○ No included studies</td>
<td></td>
</tr>
</tbody>
</table>

The link between test results and management is unique in venous thromboembolism. With PE diagnosis, positive results will be treated with anticoagulation (regardless of the chances of false positives).

The panel noted there is no direct benefit for any of the diagnostic pathways. There is a burden with serial ultrasound for patients having to return to the hospital. The data varies on the adverse effects associated with radiation exposure, contrast-induced nephropathy, allergy to contrast, or contrast extravasation associated with CTPA or radiation and perfusion agent risks associated with VQ scan.

The panel noted high certainty in the link between test results and management decisions. However, the panel also noted that for patients with sub-segmental PE, the link may not be as certain.
Certainty of Effects

What is the overall certainty of the evidence of effects of the overall pathway?

- Very low
- Low
- Moderate
- High
- No included studies

What is the overall certainty of the evidence of effects of the pathway to rule out PE?

- Very low
- Low
- Moderate
- High
- No included studies

D-dimer to exclude PE

<table>
<thead>
<tr>
<th>Studies</th>
<th>Number of PE/Number of patients included</th>
<th>Number of PE in non-high PTP</th>
<th>Number of non-high PTP and negative D-dimer</th>
<th>Lost to follow up</th>
<th>Anticoagulated during follow up</th>
<th>3-month VTE risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perrier 1999</td>
<td>104/444</td>
<td>74</td>
<td>151</td>
<td>0</td>
<td>4</td>
<td>0/147</td>
</tr>
<tr>
<td>Perrier 2004</td>
<td>222/965</td>
<td>159</td>
<td>275</td>
<td>1</td>
<td>12</td>
<td>0/262</td>
</tr>
<tr>
<td>Steeghs 2005</td>
<td>46/331</td>
<td>29</td>
<td>170</td>
<td>0</td>
<td>3</td>
<td>0/167</td>
</tr>
<tr>
<td>Perrier 2005</td>
<td>194/756</td>
<td>115</td>
<td>232</td>
<td>2</td>
<td>10</td>
<td>0/220</td>
</tr>
<tr>
<td>Van Belle 2006</td>
<td>674/3306</td>
<td>122</td>
<td>409</td>
<td>0</td>
<td>18</td>
<td>1/391</td>
</tr>
<tr>
<td>Goekoop 2007</td>
<td>111/876</td>
<td>80</td>
<td>450</td>
<td>6</td>
<td>5</td>
<td>0/439</td>
</tr>
<tr>
<td>Righini 2008</td>
<td>357/1693</td>
<td>315</td>
<td>561</td>
<td>2</td>
<td>19</td>
<td>0/540</td>
</tr>
</tbody>
</table>


While there was high certainty of evidence on outcomes of patients with a false negative test result, certainty of evidence was downgraded for the overall pathway as the studies were longitudinal observational studies evaluating the effects of only D-dimer and there were few events reported.

Values

Is there important uncertainty or variability in how people value different outcomes?

- Important uncertainty or variability
- Possibly important uncertainty or variability
- Probably no important uncertainty or variability
- No important uncertainty or variability

The numbers shown below are utilities, representing the strength of an individual’s preferences for different outcomes. They are measured on a scale, with zero reflecting states of health equivalent to death/worst imaginable health and one reflecting perfect health/ best imaginable health.

Systematic reviews found that the relative importance of the outcomes is as follows:

- Pulmonary embolism: 0.63-0.93 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004)
- Deep vein thrombosis: 0.64-0.99 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016)
- Deep vein thrombosis patients’ own current health: 0.95 (Time trade off) (Locadia 2004)
- Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg 2013, Locadia 2004)
- Minor intracranial bleeding event: 0.75 (standard gamble) (Hogg 2013)
- Major intracranial bleeding event: 0.15 (standard gamble) (Hogg 2013) Central nervous system bleeding: 0.29-0.60 (standard gamble) (Lenert 1997, O’Meara 1994)

The panel placed a high value on decreasing the number of false negative test results over decreasing false positive test results.

The panel also placed a high value on decreasing radiation exposure and reducing the number of tests required in a
Studies additionally described the following regarding the relative importance of outcomes and patients’ preferences:

In a survey study (Geyer 2014) based on a shared decision-making model, the researchers provided patients with a standardized description of the diagnostic workup for PE, described the risks of CTPA in low pretest probability patients and the risks of deferring imaging assuming a D-dimer was less than twice the value normally considered positive. With the decision aid, of the 203 patients in the study, 63% of patients favored undergoing CTPA; while seventy-four patients (37%) elected to defer CTPA. The mostly frequent reasons for decline include risk of malignancy, contrast-induced nephropathy, or allergy. Other than those common reasons, 20 patients deferred CTPA testing because they believed it was unnecessary. Patients with a previous PE diagnosis were less likely to defer CTPA testing. Most patients (n=109 [85%]) who accepted CTPA testing, had concerns about missing a PE.

Results of Panel Utility Rating Survey:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean Utility Rating (SD) All Panels (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>False Negative Test Result</td>
<td>0.60 (0.23)</td>
</tr>
<tr>
<td>False Positive Test Result</td>
<td>0.62 (0.21)</td>
</tr>
<tr>
<td>True Negative Test Result</td>
<td>0.91 (0.15)</td>
</tr>
<tr>
<td>True Positive Test Result</td>
<td>0.76 (0.19)</td>
</tr>
<tr>
<td>Inconclusive Test Result</td>
<td>0.69 (0.18)</td>
</tr>
<tr>
<td>Radiation Exposure</td>
<td>0.84 (0.14)</td>
</tr>
<tr>
<td>Contrast Induced Nephropathy</td>
<td>0.56 (0.20)</td>
</tr>
<tr>
<td>Pulmonary Embolism – Moderate Marker State</td>
<td>0.42 (0.15)</td>
</tr>
<tr>
<td>Proximal DVT – Moderate Marker State</td>
<td>0.58 (0.14)</td>
</tr>
<tr>
<td>Distal DVT – Moderate Marker State</td>
<td>0.64 (0.16)</td>
</tr>
<tr>
<td>Upper Extremity DVT – Moderate Marker State</td>
<td>0.61 (0.16)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>0.33 (0.23)</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>0.12 (0.10)</td>
</tr>
<tr>
<td>Chronic Thrombotic Pulmonary Hypertension</td>
<td>0.34 (0.15)</td>
</tr>
</tbody>
</table>

* Utility rating by panel members from 0 (dead) to 1 (full health)

* BALANCE OF DESIRABLE AND UNDESIRABLE EFFECTS*

**Rank the top pathways in order of which provides the best balance of desirable and undesirable effects to diagnostic pathway.**

The panel considered that there would not be important variability in how people value the different outcomes.

**Modelling of Diagnostic Test Accuracy**

**Note:** See pathways on Page 1
Pathways A-H begin with CTPA
Pathways I-J begin with VQ

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The panel judged the ranking of the pathways based on a threshold of false negative patients and a threshold of misdiagnosed patients (combination of false negative and false positive results).

Pathways highlighted in green were judged as the top ranked pathways that provided the best balance of desirable and undesirable effects. These pathways remained below a threshold of 20 false negative results per 1000 patients tested (≤2%) and a threshold of 50 misdiagnosed results per 1000 patients tested (≤5%).

Pathways highlighted in yellow provided a less acceptable balance of desirable and undesirable effects. These pathways remained below a threshold of 50 false negative results per 1000 patients tested (≤5%) and 100 misdiagnosed results per 1000 patients (≤10%).

Pathways highlighted in red did not provide an acceptable balance of desirable and undesirable effects.

Table 1: In a patient population with a low clinical probability (5%) of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose a first episode PE?

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G1</th>
<th>G2</th>
<th>H</th>
<th>I1</th>
<th>I2</th>
<th>J1</th>
<th>J2</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP</td>
<td>47</td>
<td>50</td>
<td>48</td>
<td>49</td>
<td>48</td>
<td>49</td>
<td>50</td>
<td>49</td>
<td>50</td>
<td>48</td>
<td>47</td>
<td>43</td>
<td>34</td>
</tr>
<tr>
<td>FP</td>
<td>19</td>
<td>587</td>
<td>41</td>
<td>53</td>
<td>47</td>
<td>74</td>
<td>62</td>
<td>54</td>
<td>19</td>
<td>42</td>
<td>30</td>
<td>44</td>
<td>36</td>
</tr>
<tr>
<td>TN</td>
<td>931</td>
<td>363</td>
<td>909</td>
<td>887</td>
<td>903</td>
<td>876</td>
<td>888</td>
<td>896</td>
<td>931</td>
<td>908</td>
<td>920</td>
<td>906</td>
<td>914</td>
</tr>
<tr>
<td>FN</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>7</td>
<td>16</td>
</tr>
</tbody>
</table>

Table 1: Continued

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>K</th>
<th>L</th>
<th>M1</th>
<th>M2</th>
<th>N1</th>
<th>N2</th>
<th>O1</th>
<th>O2</th>
<th>P</th>
<th>Q1</th>
<th>Q2</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP</td>
<td>49</td>
<td>45</td>
<td>46</td>
<td>46</td>
<td>42</td>
<td>33</td>
<td>47</td>
<td>47</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>FP</td>
<td>580</td>
<td>12</td>
<td>25</td>
<td>19</td>
<td>27</td>
<td>22</td>
<td>28</td>
<td>23</td>
<td>587</td>
<td>596</td>
<td>591</td>
</tr>
<tr>
<td>TN</td>
<td>371</td>
<td>938</td>
<td>925</td>
<td>931</td>
<td>923</td>
<td>928</td>
<td>922</td>
<td>927</td>
<td>363</td>
<td>354</td>
<td>359</td>
</tr>
<tr>
<td>FN</td>
<td>2</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>8</td>
<td>17</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

TP-patient correctly identified as having PE and anticoagulated
FP-patient incorrectly identified as having PE and unnecessarily anticoagulated
TN- patient correctly identified as not having PE and not anticoagulated
FN - patient incorrectly identified as not having PE and will not receive needed anticoagulation

Assumptions associated with modelling:
1. Disease prevalence in a low clinical probability population was determined be 50 per 1000 patients (5%).
2. Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.
3. The panel judged the ranking of pathways with the best balance of desirable and undesirable effects based on thresholds of false negative patients and misdiagnosed patients (false negative and false positive). These rankings are depicted in the table as green being the most acceptable, yellow being less acceptable, and red being unacceptable.

The panel noted undesirable as increasing the number of patients with false positive and false negative test results (i.e. receive unnecessary anticoagulation or morbidity/mortality from missed diagnosis).

The panel noted radiation exposure as a concern with CTPA, but weighed it with acceptance of the risk to
acceptable balance of desirable and undesirable effects and were ranked lowest. These pathways were above the threshold of 50 false negative results per 1000 patients tested (>5%) and 100 misdiagnosed results per 1000 patients (>10%).

4. Due to the lack of data on accuracy of serial ultrasound, the sensitivity and specificity for proximal compression ultrasound was used to represent serial ultrasound. In addition, serial ultrasound was determined to be one follow-up test after initial ultrasound.

5. Test accuracy for CTPA, D-dimer and proximal CUS were derived from these tests being used as a standalone test. These sensitivity and specificity results were used when the test was the first test of the pathway. These accuracy results were also used if the test was a subsequent test in a pathway.

6. The panel recognized two distinct populations undergoing VQ scan: patients likely to have a diagnostic scan (high probability or normal result) versus patients likely to have a non-diagnostic scan (low/intermediate probability). In the first population, it was assumed 80% would have a diagnostic scan and 20% would be non-diagnostic. Sensitivity analyses was completed to reveal no change in accuracy results of an alternative distribution with 70% diagnostic and 30% non-diagnostic scans. In the second population, it was assumed 40% of patients would have a diagnostic scan and 60% would be non-diagnostic.

7. For patients undergoing VQ scan, we assumed patients with normal or very low probability results would not be anticoagulated. Low or intermediate probability (non-diagnostic) scans would always be followed up with subsequent testing. Patients with high probability scans would be anticoagulated.

Table 2: Data abstraction from studies with data on direct pathways

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Outcomes</th>
<th>L 5%</th>
<th>L 20%</th>
<th>L 50%</th>
<th>L 75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP</td>
<td>48</td>
<td>191</td>
<td>477</td>
<td>715</td>
<td></td>
</tr>
<tr>
<td>FP</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>TN</td>
<td>945</td>
<td>786</td>
<td>497</td>
<td>249</td>
<td></td>
</tr>
<tr>
<td>FN</td>
<td>2</td>
<td>9</td>
<td>23</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>


Contrast induced nephropathies, allergic reactions, and extravasation

<table>
<thead>
<tr>
<th>Index test</th>
<th>Reference test</th>
<th>Safety Outcome (as defined by study)</th>
<th>Incidence and details</th>
</tr>
</thead>
</table>

Balance of desirable and undesirable effects:

For this guideline question, in addition to the diagnostic test accuracy outcomes, the panel considered two key criteria in determining which pathways provided the best balance of desirable and undesirable effects, which were minimizing radiation exposure and minimizing the number of tests used.

These two criteria were considered in determining which of the pathways that met the acceptable thresholds for diagnostic test accuracy (i.e. the pathways highlighted in green), provided the best balance of effects.
<table>
<thead>
<tr>
<th>Year</th>
<th>Modality</th>
<th>Contrast Medium</th>
<th>Complication</th>
<th>Creatinine Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ost 2001</td>
<td>CT</td>
<td>PA</td>
<td>Contrast induced nephropathy/ARF</td>
<td>Creatinine was not serially measured throughout study. However, increase in creatinine 0.01 +/- 0.38 mg/dL noted in CT only group without conventional angiography and 0.2 +/- 0.9 mg/dL in the CT + conventional angiography group. 3/103 (3%) patients had an increase in creatinine greater than 1 mg/dL with max of 7.2 mg/dL. All returned to the normal reference range at 3-month follow up</td>
</tr>
<tr>
<td>Pesavento 2011</td>
<td>CT</td>
<td>None</td>
<td>Severe acute renal failure</td>
<td>CT: 1/367 (0.27%)</td>
</tr>
<tr>
<td>Stein 2006</td>
<td>CT</td>
<td>CC</td>
<td>Allergic reaction</td>
<td>CT: 4/1095 (&lt;1%); mild</td>
</tr>
<tr>
<td>Yazici 2016</td>
<td>CT</td>
<td>None</td>
<td>Contrast nephropathy</td>
<td>24/174 (13%)</td>
</tr>
<tr>
<td>Coche 2003</td>
<td>CT</td>
<td>CT, VQ</td>
<td>Contrast nephropathy (creatinine increase)</td>
<td>1/69 (1%)</td>
</tr>
<tr>
<td>Mitchell 2006</td>
<td>CT</td>
<td>None</td>
<td>Contrast nephropathy (creatinine increase)</td>
<td>All: 44/1224 (4%) or paired: 44/354 (12%)</td>
</tr>
<tr>
<td>Righini 2008</td>
<td>PW (DD-leg US-CT)</td>
<td>APW (DD-CT)</td>
<td>Allergic reaction</td>
<td>PW: 1/509 (0.2%) (rash) APW: 2/535 (0.4%) (rash)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Extravasation of contrast</td>
<td>PW: 1/509 (0.2%) APW: 2/535 (0.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe acute renal failure</td>
<td>PW: 0/509 (0%) APW: 0/535 (0%)</td>
</tr>
</tbody>
</table>

**References:**


**Radiation exposure associated with CTPA**

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Estimated ‘effective dose’ of radiation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT: Chest</td>
<td>4.5 mSv (range 3.8-5.2 mSv)</td>
<td>Phillips, 2015</td>
</tr>
<tr>
<td></td>
<td>5.2 mSv</td>
<td>Kanal, 2017</td>
</tr>
<tr>
<td></td>
<td>Range: 2.7 - 15 mSv</td>
<td>Jones, 2012 and Janbabanezhad, 2015</td>
</tr>
<tr>
<td>VQ</td>
<td>2.2 mSv</td>
<td>Jones, 2012</td>
</tr>
<tr>
<td></td>
<td>2.5 mSv</td>
<td>Phillips, 2015</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mettler, 2008</td>
</tr>
</tbody>
</table>


In Hurwitz et al, estimated relative risks for breast and lung cancer incidences were 1.002–1.011 and 1.005–1.022, respectively. In addition, Brenner and Elliot estimated the lifetime attributable cancer death risk in 45-year-old adults who underwent a full-body CT test to be around 0.08%. The relationship between radiation exposure to cancer induction was limited and incredibly variable in literature and, therefore, not modelled.


**How large are the resource requirements (costs) for CTPA?**

<table>
<thead>
<tr>
<th>Cost of Diagnostic Test</th>
<th>Diagnostic test</th>
<th>Peer-review articles and Other sources</th>
<th>CPT (Current Procedural Terminology)-4 Codes/cost</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The panel noted that the costs for CTPA are large, but vary based on setting and the cost to the patient.

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| How large are the resource requirements (costs) for D-Dimer? | D-dimer test | $256 ($271 in 2017)  

| | | ○ Large costs  
| | | ○ Moderate costs  
| | | ○ Negligible costs and savings  
| | | ○ Large savings  
| | | ○ Don’t know  

| | | ○ Large costs  
| | | ○ Moderate costs  
| | | ○ Negligible costs and savings  
| | | ○ Large savings  
| | | ○ Don’t know  

| How large are the resource requirements (costs) for Proximal CUS? | | |  

| | | ○ Large costs  
| | | ○ Moderate costs  
| | | ○ Negligible costs and savings  
| | | ○ Large savings  
| | | ○ Don’t know  

| How large are the resource requirements (costs) for serial CUS? | | |  

| | | ○ Large costs  
| | | ○ Moderate costs  
| | | ○ Negligible costs and savings  

| | | ○ Large costs  
| | | ○ Moderate costs  
| | | ○ Negligible costs and savings  

| References: |  

<table>
<thead>
<tr>
<th>CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES</th>
<th>What is the certainty of the evidence of resource requirements (costs) for CTPA?</th>
<th>The panel noted uncertainty in the actual costs of the tests.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>○ Very low</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ Low</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ Moderate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ High</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ No included studies</td>
<td></td>
</tr>
</tbody>
</table>

6. Based on CADTH report; The cost consists of diagnostic tests costs and physician interpretation cost, and it is in Canadian dollars in 2017.
7. [https://pricinghealthcare.com/prices/CenterForMedicalImaging](https://pricinghealthcare.com/prices/CenterForMedicalImaging)
<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
</table>
| What is the certainty of the evidence of resource requirements (costs) for D-Dimer? | - Very low
- Low
- Moderate
- High
- No included studies |
| What is the certainty of the evidence of resource requirements (costs) for proximal CUS? | - Very low
- Low
- Moderate
- High
- No included studies |
| What is the certainty of the evidence of resource requirements (costs) for serial CUS? | - Very low
- Low
- Moderate
- High
- No included studies |
| What is the certainty of the evidence of resource requirements (costs) for VQ scan? | - Very low
- Low |
| ○ Moderate  |
| ○ High      |
| ○ No included studies  |

**What is the certainty of the evidence of resource requirements (costs) for Pulmonary Angiography?**

| ○ Very low  |
| ○ **Low**   |
| ○ Moderate  |
| ○ High      |
| ○ No included studies  |
### Cost Effectiveness of Diagnostic Pathways Evaluated

The panel judged pathways starting with a D-dimer test as most cost-effective considering the lower cost of the test.

We identified the following in our systematic review of cost-effectiveness:

#### CTPA:

Evidence on the cost-effectiveness of CTPA is inconsistent. The included studies varied in regards to the compared strategy, the setting, the time frame, and the methods. In general, a CTPA strategy was considered effective, mostly associated with improved survival. Whether it is cost-effective or not is still uncertain in the literature.

In Batalles 2009, CTPA was cost-effective compared with pulmonary magnetic resonance angiography, and was the most effective strategy. A study by van Erkel et al (van Erkel 1996) found that CTPA reduces mortality and improves cost-effectiveness in the diagnostic workup of suspected PE when compared with VQ scanning, compression US, D-dimer assay, and conventional angiography strategies. In Oudkerk 1993, compared with the treatment for all strategy with lowest mortality but highest cost, pulmonary angiography strategies with or without prior VQ lung scanning and ultrasonography of the legs have comparable low mortality and morbidity rates, costs savings of approximately 40%, and inappropriate treatment in fewer than 5% of patients. Paterson et al (Paterson 2001) found higher costs for CTPA as the initial diagnostic test but with improved expected survival when compared with a gradual algorithm of VQ scanning ± compression US ± CTPA.

In Doyle 2004, researchers in the US conducted a decision analytic model on diagnostic tests of PE in women, to determine which strategy is the most cost-effective with the least number of deaths from PE. Of the strategies compared (compression US, VQ scanning, and spiral CT), spiral CT as the initial diagnostic regimen was found to be the most cost-effective at $17,208 per life saved. In contrast, Henschke et al (Henschke 1994) concluded CTPA was not cost-effective compared with ultrasound.


#### D-Dimer:

Several cost-effectiveness analyses compared the diagnostic strategies with D-dimer, and use CTPA according to the D-dimer with other strategies, including no test, or treatment for all, or universal CTPA or VQ scan. In general, the strategy of combining D-dimer with other diagnostic testing was suggested to be cost-effective, or cost-saving. (Duriseti 2010, Duriseti 2006, Elias 2004, Humphreys 2004, Lee 2011, Perrier 1997, Perrier 2003, Righini 2007, Van Beek 1996, Van Erkel 1996)

#### Proximal CUS:

No evidence identified on the cost-effectiveness of proximal compression ultrasound.

#### VQ Scan:

Cost-effectiveness analyses compared VQ scan versus other diagnosis strategies. None of the reports compared VQ scan with CTPA suggested VQ scan was cost-effective (Batalles 2009, Doyle 2004, Paterson 2001, and van Erkel...
While another report suggested VQ scan is cost-effective compared with CT alone (Larcos 2000), with 20.1 additional lives saved per 1,000 patients, at a cost of $940 per life year gained.


**Impact on health equity of diagnostic pathways evaluated**

The panel judged the pathways requiring the least number of tests as having the least impact, and not decreasing health equity.

We identified the following regarding the impact on health equity with the different tests:

**CTPA:**
No research evidence identified.

**D-Dimer:**
Canadian provinces with larger populations tended to have a large proportion of hospitals with the capability to measure D-dimer levels for VTE diagnosis, whereas less populated provinces were more likely to send samples to centralized analysis facilities for D-dimer testing. (Southern 2014)

**Proximal CUS:**
No research evidence identified.

**VQ Scan:**
No research evidence identified.

The panel noted that for pathways starting with CTPA, adding any further testing will have no impact, and additional tests would therefore disadvantage patients in low income categories.

**Acceptability of diagnostic pathways evaluated to key stakeholders**

The panel considered all pathways evaluated as acceptable.

Studies described the following regarding acceptability from key stakeholders:

**General (Radiology & Population):**
A survey assessing the knowledge/practice patterns of emergency department (ED) physicians related to radiation exposure showed that 9 out of 10 preferred VQ scanning for patients <30 years of age or those with a history of recent CT scans when diagnosing PE, which was confirmed by retrospective chart review. Physician knowledge of precise radiation exposure for each diagnostic test was low, but the majority were aware that VQ scans exposed patients to less radiation than CTPA. (Ahn 2014)

In a study among nursing home patients with suspected VTE, referral for additional diagnostic investigations was withheld in almost 40%. In providers’ decisions to forgo diagnostic investigations, they incorporated the estimated relative impact of the potential disease; the potential net-benefits of diagnostic investigations and whether performing investigations agreed with established management goals in advance care planning. (Schouten 2014)

The panel noted as an acceptability issue whether patients would prefer to wait for a VQ scan if not immediately available, or to obtain CTPA immediately but with increased radiation exposure.
A study among physicians who had previously referred patients for any VTE screening examination showed that physicians had a lack of basic knowledge regarding lower extremity venous anatomy, charges for the different diagnostic tests used to diagnose VTE, and current treatment standards for VTE. (Zierler 2002)

CTPA
A survey among 62 radiologists and 52 ED physicians showed that CT is the overwhelmingly preferred technique for the diagnosis of PE. (Jha 2010)

D-Dimer alone or in combination with other imaging test:
Thrombosis and hemostasis specialists reported that just over half uses D-dimer for diagnosing DVT and two-thirds for diagnosing PE. 30% relied on clinical judgment to assess pre-clinical probability for DVT and 41% for PE. (Squizzato 2010)
There are at least 28 different combinations of measurement units used to report D-dimer results for thrombotic disorders worldwide as reported by providers. The majority used fixed cut-off rather than age-adjusted threshold values for D-dimer. (Lippi 2015)

CTPA or VQ scan following a negative or positive D-Dimer:
Of ED patients with a suspected VTE and a negative D-dimer result 14% underwent at least 1 imaging study, and of patients with a positive D-dimer result 48% did not undergo imaging. (Teismann 2009)
A survey among 62 radiologists and 52 ED physicians showed that CT is the overwhelmingly preferred technique for the diagnosis of PE. The role of ventilation-perfusion scintigraphy increases when the use of iodinated contrast material is contraindicated and MRI does not seem to have an important role in practice. (Jha 2010)
More than half of CTPAs for PE were avoidable and 12% of CTPAs were done on patients with low risk and negative D-dimer assay. (Perelas 2014, Perelas 2015)

Proximal CUS:
Patient level of discomfort during point-of-care US of the heart, lungs and deep veins for respiratory symptoms is very low and the vast majority of patients would accept being assessed by this method if the patients once again had to be examined for possible disease. (Laursen 2015)

VQ Scan and CTPA
A survey among 62 radiologists and 52 ED physicians showed that CT is the overwhelmingly preferred technique for the diagnosis of PE. The role of VQ scanning increases when the use of iodinated contrast material is contraindicated and MRI does not seem to have an important role in practice. (Jha 2010)

Studies described the following regarding feasibility and barriers to use:

General (Radiology & Population):
Feasibility:
The panel considered all pathways as feasible,

Feasibility to implement diagnostic pathways evaluated

The panel noted that in terms of feasibility, many institutions do not offer VQ scanning on nights and
however noting specific considerations for feasibility of testing with VQ scan, D-dimer, and proximal CUS.

A retrospective chart review showed that there was substantial variation in utilization and diagnostic yield of advanced radiography for PE, which was largely explained by patient-, hospital- and provider-level characteristics. (Kindermann 2014)

A prospective cohort study among outpatients with suspected PE from ED’s showed that 43% received inappropriate diagnostic management. Risk factors associated with inappropriate diagnostic management were age >75 years, heart failure, chronic lung disease, current or recent pregnancy, currently receiving anticoagulation, and the lack of a written diagnostic algorithm and clinical probability scoring in the ED. Inappropriate management was associated with thromboembolism occurrence. (Roy 2006)

**Implementation:**
A study assessing the impact of a hospital-based educational and form-based intervention on clinician adherence to diagnostic imaging guidelines for suspected PE found improved adherence among clinicians who received the intervention. Failure to adhere with diagnostic imaging guidelines when requesting radiological testing was common. (Agarwal 2012)

**CTPA:**
**Feasibility:**
A retrospective study on CTPA examinations showed that there was considerable inter-physician variability in the utilization and PE positivity rates of CTPA within a single institution. (Chen 2015)

A chart review with 3-month phone follow-up among ED patients undergoing investigations for suspected PE showed that compliance with a clinical pathway was more likely if exclusively done by ED physicians and was associated with a lower use of CTPA. (Ng 2011)

A retrospective hospital radiology among CT angiography procedures showed that in 2009 CTPA was performed more often with relatively fewer PE cases identified compared with 2006. (David 2012)

A survey on ED visits (12% involved chest pain, pneumonia or hemoptysis) showed that CT use among patients with chest pain increased dramatically from 2001 to 2007. The PE diagnosis to CT ratio was low (2.7%). (Feng 2013)

**Implementation:**
A computerized decision support tool decreased CTPA orders and diagnostic yield increased following the intervention. Inter-physician variability in CTPA order adherence post intervention was significant. (Prevedello 2013)

Adherence to guidelines for use of CTPA for PE diagnosis improved among ED physicians who received a performance feedback intervention vs. those who did not. Diagnostic yields remained unchanged in control and intervention groups. (Raja 2015)

weekends. For VQ scanning to be utilized as the first test in a pathway, there may be situations where patients may be required to wait until it is available.

When VQ scanning is used, the panel noted the requirement for a chest x-ray to be obtained first.

The panel also noted that for some institutions, access to test results for ultrasound may not be quick, and that in some centres obtaining results of a D-dimer test requires sending out to another centre for analysis, which impacts access to quick test results and feasibility.
Mandatory adherence to diagnostic protocols was shown to increase the rate of positive CTPAs for PE and to decrease the rate of negative CTPAs. Predictors of diagnostic yield included: previous DVT and clinical signs of DVT, while COPD was found to be negatively associated with PE. (Walen 2016)

**D-Dimer alone or in combination with other imaging test:**

**Feasibility:**
Using a combination of the Wells’ simplified dichotomous clinical decision rule and D-dimer test, which could be completed in 90% of patients, PE could be ruled out in 51% of patients with suspected PE without further testing, which had a failure rate of only 0.4%. (Goekoop 2007)

Less than half of physicians reviewed the D-dimer result for PE after patient examination, and the knowledge of an abnormal D-dimer test result before seeing the patient led to a higher clinical decision rule score at patient examination. (Gibson 2009)

Following at least one D-dimer test for DVT or PE, the strategy for further diagnostic testing was inappropriate in 31% with 9 out of 10 being overutilization of diagnostic imaging. (Arnason 2007)

Widespread D-dimer testing did not reduce referrals for imaging and is likely to have resulted in increased referrals. Increased imaging led to over-diagnosis of clinically insignificant PE and alternative strategies are required to reduce PE death rates. (Segard 2013)

**Implementation:**
Increasing the D-dimer threshold from 0.4µg/mL to 1.0µg/mL increased CTPA diagnostic yield for PE from 4.7% to 11.7%, but still 9% of patients with a D-dimer below the threshold underwent CTPA. (Char 2014)

Computer systems prompting provision of clinical probability factors and D-dimer value to assess the risk of PE and associated need for CTPA lowered the use of CTPA and its yield. (Murthy 2016, Ong 2013)

**Proximal CUS:**
No research evidence identified.

**VQ Scan:**
No research evidence identified.
Conclusions

In a patient population with a low clinical probability of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose a first episode PE?

<table>
<thead>
<tr>
<th>TYPE OF RECOMMENDATION</th>
<th>Strong recommendation against the intervention</th>
<th>Conditional recommendation against the intervention</th>
<th>Conditional recommendation for either the intervention or the comparison</th>
<th>Conditional recommendation for the intervention</th>
<th>Strong recommendation for the intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECOMMENDATION</td>
<td>The ASH guideline panel <strong>recommends</strong> using a strategy starting with D-dimer for diagnosing PE in a population with low prevalence/pretest probability (5%), followed by i) VQ scan or ii) CTPA. If D-dimer is not readily available, alternate acceptable strategies include performing a VQ scan or CTPA alone, with additional testing with CUS of the lower extremities or CTPA is non-diagnostic. (Strong recommendation for D-dimer based on high certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy studies; Conditional recommendation for VQ scan over CTPA based on very low certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Remarks**: In the D-dimer strategy, a negative D-dimer rules out PE and no additional testing or anticoagulation is provided. VQ scan is preferred over CTPA as the subsequent test to limit radiation exposure. Additional testing is performed if the VQ scan is non-diagnostic.

The ASH guideline panel **recommends against** using a positive D-dimer alone to diagnose PE, and against additional testing following negative CTPA or diagnostic VQ scan in a population with low prevalence/pretest probability (5%).

**Remarks**: We considered a diagnostic VQ scan result as normal or high probability, non-diagnostic VQ scan as low or intermediate probability. Providers need to be aware of the variability in terminology at their individual institutions. The panel prioritized limiting the number of diagnostic tests and radiation exposure.

**JUSTIFICATION**
The panel considered a strategy with D-dimer testing first to reduce cost, ensure feasibility, and reduce radiation exposure. D-dimer alone was considered not sufficient as a rule-in test, and must be followed by another test. If CTPA is used as a first test, it should not be followed by other tests as no additional benefit is achieved and there is further cost, impacting health equity.

**SUBGROUP CONSIDERATIONS**
We considered the two subgroups of likely to have a diagnostic VQ scan and non-diagnostic VQ scan which are reflected in the recommendations above. A baseline chest X-ray prior to VQ scan can determine the likelihood of having a diagnostic VQ scan.

**IMPLEMENTATION CONSIDERATIONS**
Noted importance of promoting D-dimer first strategy.
<table>
<thead>
<tr>
<th>MONITORING AND EVALUATION</th>
<th></th>
</tr>
</thead>
</table>
Appendix 1: Modelling of Diagnostic Test Accuracy

Note: See diagnostic pathway diagrams on Page 1

Pathways A-H begin with CTPA
Pathways I-J begin with VQ
Pathways K-Q begin with D-dimer

Table 1: In a patient population with a *low* clinical probability (5%) of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose a first episode PE?

| Outcomes | A  | B  | C  | D  | E  | F  | G1 | G2 | H  | I1 | I2 | J1 | J2 | K  | L  | M1 | M2 | N1 | N2 | O1 | O2 | P  | Q1 | Q2 |
|----------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| TP-patient correctly identified as having PE and anticoagulated | 47 | 50 | 48 | 49 | 48 | 49 | 50 | 49 | 50 | 48 | 47 | 43 | 34 | 49 | 45 | 46 | 42 | 33 | 47 | 47 | 50 | 50 |
| FP-patient incorrectly identified as having PE and unnecessarily anticoagulated | 19 | 587 | 41 | 53 | 47 | 74 | 62 | 54 | 19 | 42 | 30 | 44 | 36 | 580 | 12 | 25 | 19 | 27 | 22 | 28 | 23 | 587 | 596 | 591 |
| TN-patient correctly identified as not having PE and not anticoagulated | 931 | 363 | 909 | 887 | 903 | 876 | 888 | 896 | 931 | 908 | 920 | 906 | 914 | 371 | 938 | 925 | 931 | 923 | 928 | 922 | 927 | 363 | 354 | 359 |
| FN-patient incorrectly identified as not having PE and will not receive needed anticoagulation | 4  | 0  | 2  | 1  | 2  | 1  | 0  | 1  | 0  | 2  | 3  | 7  | 16 | 2  | 5  | 4  | 4  | 8  | 17 | 3  | 3  | 0  | 0  | 0  |
Appendix 2: Natural Progression and Treatment Effects

When making a decision regarding which pathway to recommend for diagnosing PE, one must acknowledge that there will be patients who will have negative consequences because of an incorrect test result and thus an incorrect diagnosis. Patients who receive unnecessary anticoagulation (false positive) or do not receive necessary anticoagulation (false negative) are subject to the risks of bleeding, may suffer complications or may die. Tables 2 and 3 provide some insight into the frequency of these outcomes.

**True positive**: patients correctly identified as having PE and correctly anticoagulated
**True negative**: patients correctly identified as not having PE and correctly not anticoagulated
**False positive**: patients incorrectly identified as having PE and receive unnecessary anticoagulation
**False negative**: patients incorrectly identified as not having PE and will not receive necessary anticoagulation

Outcomes studied include:
- Hemorrhagic stroke
- Major bleeding
- Mortality
- Recurrent PE

**Table 2: Outcomes by Test Result**

<table>
<thead>
<tr>
<th>Test accuracy results</th>
<th>Consequences</th>
<th>Results from published SR</th>
<th>Results from treatment guideline (GL3-Q3, LMWH/VKA)*</th>
<th>Targeted search of primary studies</th>
<th>Panel survey results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TP</strong></td>
<td>Mortality: all cause</td>
<td>2.0% (6m)*</td>
<td></td>
<td>In-hospital: 10.5% 1 week: 5.3% 2 weeks: 8.5% 1 month: 10.4% 3 months: 9.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mortality from PE w 3 months</td>
<td>1.5% (3m)^</td>
<td>0.1% (6m)**</td>
<td>In-hospital: 4.7% 1 week: 2.0% 2 weeks: 2.3% 1 month: 6.3% 3 months: 2.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recurrence on AC w 3 months</td>
<td></td>
<td>1.0% (6m)*</td>
<td>In-hospital: 1.4%</td>
<td></td>
</tr>
</tbody>
</table>

In-hospital: 10.5% 1 week: 5.3% 2 weeks: 8.5% 1 month: 10.4% 3 months: 9.8%
Recurrence PE population: 2 weeks: 33.7% 3 months: 46.8%

Recurrent PE population:
In-hospital: 0.0% 1 week: 50.0% 3 months: 51.9%

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<table>
<thead>
<tr>
<th></th>
<th></th>
<th>1 week: 4.0%</th>
<th>3 months: 3.7%</th>
<th>4.2% (1y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic thromboembolic pulmonary HTN</td>
<td>2.1% (6m)*</td>
<td>1 month: 5.2%</td>
<td>3 months: 6.7%</td>
<td>3.3% (1y)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal major bleeding</td>
<td>0.2% (6m)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td></td>
<td>3 months: 0.6% (ICH)</td>
<td>1.7% (ICH; 1y)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.1% (6m)*</td>
<td>1 month: 5.2%</td>
<td>3 months: 6.7%</td>
<td>3.3% (1y)</td>
</tr>
<tr>
<td>Fatal major bleeding</td>
<td>0.2% (6m)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality from PE w 3 months</td>
<td></td>
<td>3 months: 0.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality from PE w 3 months</td>
<td></td>
<td>2 weeks: 26%</td>
<td>3 months: 40.0%</td>
<td>30.5% (1y)</td>
</tr>
<tr>
<td>Recurrence on AC w 3 months</td>
<td></td>
<td>2 weeks: 53%</td>
<td>3 months: 27.8%</td>
<td>23% (1y)</td>
</tr>
</tbody>
</table>

* Median event rates from included RCTs in Q3 from GL3
# Event rates from SR by Carrier 2010, which was also used in Q3 for GL3
^ Event rate from SR by Douketis 1998

Table 2. Outcomes by Diagnostic Pathway

<table>
<thead>
<tr>
<th>A</th>
<th>B-H</th>
<th>I</th>
<th>J</th>
<th>K</th>
<th>L</th>
<th>M-Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality - PE</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Engelke, 2006: 2/96</td>
<td>- Parent 2007: 0/84 deaths in TN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Jouveshomme, 2007: 3/156</td>
<td>- Dunn, 2002: 0/547 deaths in TN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ceylan, 2011: 13/122</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Gottstater, 2000: 3/215</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Subramaniam, 2007: 1/494</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recurrent PE</th>
<th>None reported</th>
<th>None reported</th>
<th>None reported</th>
<th>None reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Abcarian, 2004: 0/247 in TN</td>
<td>- Den Exter 2013: (n=832) 4.5% in patients with delay in presentation, 2.4% in patients without delay in presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Parent 2007: 0/84 in TN</td>
<td>- Perrier, 2001: 3/118 in TP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Parent 2007: 0/84</td>
<td>- Parent 2007: 0/84</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Hemorrhagic stroke

None reported

None reported

None reported

None reported

None reported

Perrier, 2001: 2/118 in TP, 1/181 in TN

Major Bleed

None reported

None reported

None reported

None reported

None reported

None reported

None reported

None reported

None reported

REFERENCES.

References of Background:


Irwig L, Bossuyt P, Glasziou P, Lijmer J. Designing studies to ensure that estimates of test accuracy are transferable. BMJ 2002; 324: 669–71


Wiener RS, Schwartz LM, Woloshin S. When a test is too good: how CT pulmonary angiograms find pulmonary emboli that do not need to be found. BMJ 2013;347:f3368–f3368.

References of included accuracy studies:


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References related to natural progression:

References – SR for Baseline Risk PE Mortality in TP

References – Studies for Baseline Risk Mortality & Recurrent PE – Q3 from GL3


References – Study for Baseline Risk PE mortality, Major Bleeding & Major bleeding mortality – Q3 from GL3


References related to clinical outcomes:


References related to prevalence:

References related to values and preferences:


References related to cost and cost effectiveness:


References related to Acceptability, Feasibility, Equity, Implementation:


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Question 2. In a patient population with an intermediate clinical probability of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose a first episode PE?

**Diagnosis of Pulmonary Embolism: Diagnostic Pathways Assessed**

a. CTPA
   - Positive CTPA → anticoagulate
   - Negative CTPA → no treatment

b. CTPA
   - Positive CTPA → anticoagulate
   - Negative CTPA → D-dimer
     - D-dimer positive → anticoagulate
     - D-dimer negative → no treatment
c. CTPA
- Positive CTPA → anticoagulate
- Negative CTPA → D-dimer
  - D-dimer positive → proximal CUS
    - Positive proximal CUS → anticoagulate
    - Negative proximal CUS → no treatment
  - D-dimer negative → no treatment


d. CTPA
- Positive CTPA → anticoagulate
- Negative CTPA → D-dimer
  - D-dimer positive → proximal CUS
    - Positive proximal CUS → anticoagulate
    - Negative proximal CUS → serial US
      - Positive serial US → anticoagulate
      - Negative serial US → no treatment
  - D-dimer negative → no treatment
e. CTPA

- Positive CTPA → anticoagulate
- Negative CTPA → proximal CUS
  - Positive proximal CUS → anticoagulate
  - Negative proximal CUS → no treatment

f. CTPA

- Positive CTPA → anticoagulate
- Negative CTPA → proximal CUS
  - Positive proximal CUS → anticoagulate
  - Negative proximal CUS → serial US
    - Positive serial US → anticoagulate
    - Negative serial US → no treatment
g. CTPA
- Positive CTPA → anticoagulate
- Negative CTPA → VQ scan
  - High probability VQ scan → anticoagulate
  - Low/Intermediate VQ scan → proximal CUS
    - Positive proximal CUS → anticoagulate
    - Negative proximal CUS → no treatment
  - Normal VQ scan → no treatment

h. CTPA
- Positive CTPA → anticoagulate
- Negative CTPA → pulmonary angiography
  - Positive pulmonary angiography → anticoagulate
  - Negative pulmonary angiography → no treatment
i. VQ scan
- High probability VQ scan → anticoagulate
- Low/intermediate probability VQ scan → CTPA
  - Positive CTPA → anticoagulate
  - Negative CTPA → no treatment
- Normal VQ scan → no treatment

j. VQ scan
- High probability VQ scan → anticoagulate
- Low/intermediate probability VQ scan → proximal CUS
  - Positive Proximal CUS → anticoagulate
  - Negative proximal CUS → no treatment
- Normal VQ scan → no treatment
k. D-dimer

- Positive D-dimer → anticoagulate
- Negative D-dimer → no treatment

l. D-dimer

- Positive D-dimer → CTPA
  - Positive CTPA → anticoagulate
  - Negative CTPA → no treatment
- Negative D-dimer → no treatment
m. D-dimer

- Positive D-dimer → VQ scan
  - High probability VQ scan → anticoagulate
  - Low/intermediate probability VQ scan → CTPA
    - Positive CTPA → anticoagulate
    - Negative CTPA → no treatment
  - Normal VQ scan → no treatment
- Negative D-dimer → no treatment

n. D-dimer

- Positive D-dimer → VQ scan
  - High probability VQ scan → anticoagulate
  - Low/intermediate probability VQ scan → proximal CUS
    - Positive proximal CUS → anticoagulate
    - Negative proximal CUS → no treatment
  - Normal VQ scan → no treatment
- Negative D-dimer → no treatment
o. D-dimer
- Positive D-dimer $\rightarrow$ CTPA
- Negative D-dimer $\rightarrow$ VQ Scan
  - High probability VQ scan $\rightarrow$ anticoagulate
  - Low/Intermediate probability VQ scan $\rightarrow$ CTPA
    - Positive CTPA $\rightarrow$ anticoagulate
    - Negative CTPA $\rightarrow$ no treatment
  - Normal VQ scan $\rightarrow$ no treatment

p. D-Dimer
- Positive D-Dimer $\rightarrow$ anticoagulate
- Negative D-Dimer $\rightarrow$ CTPA
  - Positive CTPA $\rightarrow$ anticoagulate
  - Negative CTPA $\rightarrow$ no treatment
q. D-Dimer

- Positive D-Dimer $\rightarrow$ anticoagulate
- Negative D-Dimer $\rightarrow$ VQ Scan
  - High probability VQ scan $\rightarrow$ anticoagulate
  - Low/intermediate probability VQ scan $\rightarrow$ CTPA
    - Positive CTPA $\rightarrow$ anticoagulate
    - Negative CTPA $\rightarrow$ no treatment
  - Normal VQ scan $\rightarrow$ no treatment

Note: in the algorithms, watchful waiting will follow negative tests and low/normal probability unless stated otherwise.

<table>
<thead>
<tr>
<th>Legend</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>anticoagulation</td>
</tr>
<tr>
<td>PE</td>
<td>pulmonary embolism</td>
</tr>
<tr>
<td>PTP</td>
<td>pretest probability</td>
</tr>
<tr>
<td>CTPA</td>
<td>computed tomography pulmonary angiography</td>
</tr>
<tr>
<td>VQ</td>
<td>ventilation perfusion</td>
</tr>
<tr>
<td>US</td>
<td>ultrasound</td>
</tr>
<tr>
<td>CUS</td>
<td>compression ultrasound</td>
</tr>
</tbody>
</table>
Question 2. In a patient population with an intermediate clinical probability of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose a first episode PE?

| POPULATION: | Patients with an intermediate clinical probability of suspected first episode pulmonary embolism (PE) |
| EVALUATED TESTS: | CT pulmonary angiography (CTPA), D-dimer, Proximal compression ultrasound (CUS), Ventilation Perfusion (VQ) scan |
| PURPOSE OF THE TEST: | Detection of pulmonary embolism |
| ROLE OF THE TEST: | Detection of pulmonary embolism |
| LINKED TREATMENTS: | Anticoagulation |
| ANTICIPATED OUTCOMES: | False Negative; False Positive; True Negative; True Positive; Mortality; Recurrent Pulmonary Embolism; Major Bleed; Hemorrhagic Stroke |
| SETTING: | Inpatient and outpatient |
| PERSPECTIVE: | Clinical recommendation - population perspective |
| SUBGROUPS: | 1. Population that is likely to have a diagnostic VQ scan result  
2. Population that is unlikely to have a diagnostic VQ scan result |

**BACKGROUND:**

Pulmonary embolism (PE) is a potentially life-threatening condition that may be prevented and can be treated with anticoagulant therapy (Rodger 2006). The diagnostic accuracy of a test can vary with the strength of clinical suspicion (Irwig 2002). The clinical probability of a condition can assist with determining which tests to use to diagnose PE. Standardized clinical decision rules (CDRs) are used to determine clinical probability for PE (Van Es 2012). Prevalence of disease varies depending on the clinical probability of the population. In patients with an intermediate clinical probability, prevalence of disease was deemed to be 20% (Ceriani 2010). Various diagnostic tests are currently used for the diagnosis of PE including D-dimer assays, computed tomography pulmonary angiography (CTPA), ventilation perfusion (VQ) scanning, and compression ultrasonography (CUS) of the lower extremities (indirect). Imaging tests for PE such as CTPA and VQ lung scanning are expensive, time consuming and are associated with radiation exposure. In addition, the contrast used in CTPA can result in nephrotoxicity and allergic reactions. Therefore, inexpensive strategies with less risk to patients are needed to exclude PE efficiently (Bates 2016).
**Assessment**

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Is the problem a priority?</strong></td>
<td>• Yes, probably yes, probably no, no, varies, don't know.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The overall annual incidence of pulmonary emboli (PE) is quoted at 60–70 cases per 100,000. Associated with significant morbidity and mortality, prompt diagnosis and expeditious therapeutic intervention is of paramount importance for optimal patient management (Warren 2012). The fear of missing a diagnosis of this life-threatening disease has led to an increase in the use of invasive diagnostic strategies, with a significant rise of imaging studies such as computed tomographic pulmonary angiography (CTPA) or ventilation perfusion (VQ) scanning over the last decade (Smith-Bindman 2012; Schissler 2013). Subsequently, it has also been reported that PE has become over-diagnosed (Wiener 2013; Sheh 2012). Physicians often order CTPA, although PE is unlikely and a D-dimer test result is negative (Adams 2013). Given that CTPA is associated with radiation exposure, nephrotoxicity and allergic reactions, VQ lung scanning may offer an option with less risk. Several clinical decision rules can estimate pretest probability for PE and guide diagnostic testing.</td>
<td></td>
</tr>
</tbody>
</table>

| **How accurate is the test?**  | CTPA                                                                                |                            |
|                                | Patient or population: Patients with suspected pulmonary embolism                  |                            |
|                                | New test: CTPA                                                                      |                            |
|                                | Setting: Inpatient and outpatient                                                   |                            |
|                                | Pooled sensitivity: 0.93 (95% CI: 0.88 to 0.96) |                            |
|                                | Pooled specificity: 0.98 (95% CI: 0.96 to 0.99)                                     |                            |
| Test result                    | Number of results per 1,000 patients tested (95% CI)                               |                            |
|                                | Prevalence 20% ≤ in patients with suspected PE                                      |                            |
| True positives                 | 185 (175 to 192)                                                                   | 3929 (15)                  |
| False negatives                | 15 (8 to 25)                                                                       |                            |
| True negatives                 | 786 (770 to 793)                                                                   |                            |
| False positives                | 14 (7 to 30)                                                                       |                            |
|                                | Number of participants (studies)                                                   |                            |
|                                | Certainty of the Evidence (GRADE)                                                   |                            |
|                                | MODERATE a,b,c                                                                      |                            |

The panel noted that for CTPA the inconclusive results reported are low, and likely not reflective of the real-world setting.

| D-dimer to rule in PE         |                                                                                   |                            |
|                                | Very inaccurate                                                                   |                            |
|                                | Inaccurate                                                                       |                            |
|                                | Accurate                                                                         |                            |
|                                | Very accurate                                                                    |                            |
|                                | Don't know                                                                       |                            |
| D-dimer to rule out PE         |                                                                                   |                            |
|                                | Very inaccurate                                                                   |                            |
|                                | Inaccurate                                                                       |                            |
|                                | Accurate                                                                         |                            |
|                                | Very accurate                                                                    |                            |
|                                | Don't know                                                                       |                            |

The panel noted that for D-dimer, a negative result in patients with low clinical probability can rule out PE. However, a positive D-dimer result cannot be used as a standalone test to diagnose PE and initiate anticoagulant treatment. Therefore, the rating of very inaccurate applies to the diagnostic pathways where D-dimer is being used as an individual test.

The panel noted that the quality of evidence of age-adjusted D-dimer may
### Proximal CUS
- Very inaccurate
- Inaccurate
- Accurate
- Very accurate
- Don't know

### VQ Scan (VQ 1 and VQ 2 evidence profiles)
- Very inaccurate
- Inaccurate
- Accurate
- Very accurate
- Don't know

### High Probability VQ Scan (VQ 3 evidence profile)
- Very inaccurate
- Inaccurate
- Accurate
- Very accurate
- Don't know

### VQ Scan (VQ 1 and VQ 2 evidence profiles)
- Very inaccurate
- Inaccurate
- Accurate
- Very accurate
- Don't know

### VQ Scan (VQ 3 evidence profile)
- Very inaccurate
- Inaccurate
- Accurate
- Very accurate
- Don't know

---

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positives</td>
<td>195 (192 to 197)</td>
<td>30 (20568)</td>
<td>MODERATE a,b,c</td>
</tr>
<tr>
<td>False negatives</td>
<td>5 (3 to 8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: Confidence interval
2 Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

**Explanations**
- a. Certainty of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that were judged to be acceptable by a panel of clinical experts.
- b. Certainty of evidence was downgraded for serious unexplained inconsistency in sensitivity, with a range from 63% to 99.2%. Minor inconsistency for specificity noted but judged to be insufficient to downgrade the certainty of evidence.
- c. Certainty of evidence was downgraded for indirectness in instances where this test was not the index test in a diagnostic pathway. There was a lack of data on the accuracy of this test following a previous test in a pathway. Thus, sensitivity and specificity used for modeling in these instances were based on the test accuracy of the individual test rather than using the test in a pathway.

**D-dimer**

**Patient or population:** Patients with suspected pulmonary embolism

**New test:** D-Dimer

**Setting:** Inpatient and outpatient

**Pooled sensitivity:** 0.97 (95% CI: 0.96 to 0.98) | **Pooled specificity:** 0.39 (95% CI: 0.36 to 0.43)

The panel noted that the accuracy of VQ scanning was difficult to consider given that patients with non-diagnostic scans would not be anticoagulated or discharged based on this result. The two sets of accuracy results provided each represent this low/intermediate probability VQ scan group either being anticoagulated (VQ1) or discharged (VQ2).

Incorrectly appear to be higher than D-dimer due to the limited number of studies on age-adjusted D-dimer. The panel suggests high certainty of evidence for negative D-dimer, with or without age-adjustment, to rule out PE.
<table>
<thead>
<tr>
<th>True negatives</th>
<th>314 (286 to 342)</th>
<th>30 (20568)</th>
<th>MODERATE a,b,c</th>
</tr>
</thead>
<tbody>
<tr>
<td>False positives</td>
<td>486 (458 to 514)</td>
<td>20469 (30)</td>
<td></td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>0</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Complications arising from the diagnostic test</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CI:** Confidence interval

2 Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

**Explanations**

a. Certainty of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that were judged to be acceptable by a panel of clinical experts.

b. Minor inconsistency for sensitivity noted but judged to be insufficient to downgrade the certainty of evidence. Certainty of evidence was downgraded for serious unexplained inconsistency in specificity, with a range from 12.8% to 64%.

c. Certainty of evidence was downgraded for indirectness in instances where this test was not the index test in a diagnostic pathway. There was a lack of data on the accuracy of this test following a previous test in a pathway. Thus, sensitivity and specificity used for modeling in these instances were based on the test accuracy of the individual test rather than using the test in a pathway.

**Age-adjusted D-dimer**

**Patient or population:** Patients with suspected pulmonary embolism

**New test:** Age-adjusted D-dimer

**Setting:** Inpatient and outpatient

**Pooled sensitivity:** 0.99 (95% CI: 0.98 to 1.00) | **Pooled specificity:** 0.47 (95% CI: 0.45 to 0.49)
<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence 20%(^1,2) in patients with suspected PE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>True positives</td>
<td>199 (197 to 200)</td>
<td>2885 (1)</td>
<td>⬤⬤⬤⬤ HIGH (^a)</td>
</tr>
<tr>
<td>False negatives</td>
<td>1 (0 to 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True negatives</td>
<td>374 (358 to 391)</td>
<td>2885 (1)</td>
<td>⬤⬤⬤⬤ HIGH (^a)</td>
</tr>
<tr>
<td>False positives</td>
<td>426 (409 to 442)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>0</td>
<td>2885 (1)</td>
<td>-</td>
</tr>
<tr>
<td>Complications arising from the diagnostic test</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: Confidence interval
\(^2\) Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

Explanations
\(^a\) Certainty of evidence not downgraded for imprecision given the large population size, although only one prospective age-adjusted D-dimer study was identified for analysis.

Proximal CUS
Patient or population: Patients with suspected pulmonary embolism
New test: Proximal compression ultrasound
Setting: Inpatient and outpatient
Pooled sensitivity : 0.49 (95% CI: 0.31 to 0.66) | Pooled specificity : 0.96 (95% CI: 0.95 to 0.98)
<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence 20%(^1,2) in patients with suspected PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True positives</td>
<td>97 (63 to 133)</td>
<td>1715 (7)</td>
<td>☀ ☀ ☀ ☀ LOW (^a,b,c)</td>
</tr>
<tr>
<td>False negatives</td>
<td>103 (67 to 137)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True negatives</td>
<td>772 (758 to 781)</td>
<td>1715 (7)</td>
<td>☀ ☀ ☀ ☀ LOW (^a,b,c)</td>
</tr>
<tr>
<td>False positives</td>
<td>28 (19 to 42)</td>
<td>1715 (7)</td>
<td>☀ ☀ ☀ ☀ LOW (^a,b,c)</td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>0</td>
<td>1715 (7)</td>
<td>-</td>
</tr>
<tr>
<td>Complications arising from the diagnostic test</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: Confidence interval
\(^2\) Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

Explanation
a. Certainty of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that were judged to be acceptable by a panel of clinical experts.
b. Certainty of evidence was downgraded for serious unexplained inconsistency in sensitivity, with a range from 18.4% to 96.7%. Minor inconsistency for specificity noted but judged to be insufficient to downgrade the certainty of evidence.
c. Certainty of evidence downgraded for indirectness because of lack of data on the accuracy of this test following a previous test in a pathway. Sensitivity and specificity used for modeling are based on the test accuracy of the individual test rather than using the test in an algorithm.

VQ 1: VQ scan with high probability scan interpreted as positive, normal/low/intermediate scan as negative
Patient or population: Patients with suspected pulmonary embolism
New test: VQ scan with high probability scan interpreted as positive, normal/low/intermediate scan as negative
**Setting:** Inpatient and outpatient

**Pooled sensitivity:** 0.58 (95% CI: 0.50 to 0.66) | **Pooled specificity:** 0.98 (95% CI: 0.96 to 0.99)

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence 20%(^1,2) in patients with suspected PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True positives</td>
<td>116 (99 to 131)</td>
<td>3994 (13)</td>
<td>⬤⬤⬤⬤ ◯ MODERATE (^{a,b,c})</td>
</tr>
<tr>
<td>False negatives</td>
<td>84 (69 to 101)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True negatives</td>
<td>787 (771 to 794)</td>
<td>3994 (13)</td>
<td>⬤⬤⬤⬤ ◯ MODERATE (^{a,b,c})</td>
</tr>
<tr>
<td>False positives</td>
<td>13 (6 to 29)</td>
<td>3994 (13)</td>
<td></td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>1849</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications arising from</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>the diagnostic test</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CI:** Confidence interval


\(^2\) Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

**Explanations**

- a. Certainty of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that were judged to be acceptable by a panel of clinical experts.
- b. Certainty of evidence was downgraded for serious unexplained inconsistency in sensitivity, with a range from 13.9% to 84.6%. Minor inconsistency for specificity noted but judged to be insufficient to downgrade the certainty of evidence.
- c. Certainty of evidence was downgraded for indirectness in instances where this test was not the index test in a diagnostic pathway. There was a lack of data on the accuracy of this test following a previous test in a pathway. Thus, sensitivity and specificity used for modeling in these instances were based on the test accuracy of the individual test rather than using the test in a pathway.
### VQ 2: VQ scan with high/intermediate/low probability scan interpreted as positive, normal scan as negative

**Patient or population:** Patients with suspected pulmonary embolism  
**New test:** VQ scan with high/intermediate/low probability scan interpreted as positive, normal scan as negative  
**Setting:** Inpatient and outpatient  
**Pooled sensitivity:** 0.98 (95% CI: 0.95 to 0.99)  
**Pooled specificity:** 0.36 (95% CI: 0.27 to 0.45)

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence 20%(^1,2) in patients with suspected PE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>True positives</td>
<td>196 (191 to 198)</td>
<td>3994 (13)</td>
<td>MODERATE (^a,b,c)</td>
</tr>
<tr>
<td>False negatives</td>
<td>4 (2 to 9)</td>
<td>3994 (13)</td>
<td></td>
</tr>
<tr>
<td>True negatives</td>
<td>285 (214 to 363)</td>
<td>3994 (13)</td>
<td>MODERATE (^a,b,c)</td>
</tr>
<tr>
<td>False positives</td>
<td>515 (437 to 586)</td>
<td>3994 (13)</td>
<td></td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>1849</td>
<td>3994 (13)</td>
<td></td>
</tr>
<tr>
<td>Complications arising from the diagnostic test</td>
<td></td>
<td></td>
<td>Not reported</td>
</tr>
</tbody>
</table>

CI: Confidence interval  
\(^2\) Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.  
**Explanations**  
a. Certainty of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that were judged to be acceptable by a panel of clinical experts.
b. Minor inconsistency for sensitivity noted but judged to be insufficient to downgrade the certainty of evidence. Certainty of evidence was downgraded for serious unexplained inconsistency in specificity, with a range from 10.9% to 81.8%.
c. Certainty of evidence was downgraded for indirectness in instances where this test was not the index test in a diagnostic pathway. There was a lack of data on the accuracy of this test following a previous test in a pathway. Thus, sensitivity and specificity used for modeling in these instances were based on the test accuracy of the individual test rather than using the test in a pathway.

VQ 3: VQ scan with high probability scan as positive, normal scan as negative
Patient or population: Patients with suspected pulmonary embolism
New test: VQ scan with high probability scan as positive, normal scan as negative
Setting: Inpatient and outpatient
Pooled sensitivity: 0.96 (95% CI: 0.91 to 0.98) | Pooled specificity: 0.95 (95% CI: 0.89 to 0.98)

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence 20%1,2 in patients with suspected PE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>True positives</td>
<td>192 (183 to 197)</td>
<td>1799 (13)</td>
<td>★★★★★ HIGH a,b,c</td>
</tr>
<tr>
<td>False negatives</td>
<td>8 (3 to 17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True negatives</td>
<td>762 (708 to 785)</td>
<td>1799 (13)</td>
<td>★★★★★ HIGH a,b,c</td>
</tr>
<tr>
<td>False positives</td>
<td>38 (15 to 92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>0</td>
<td>1799 (13)</td>
<td>-</td>
</tr>
<tr>
<td>Complications arising from the diagnostic test</td>
<td></td>
<td>Not reported</td>
<td></td>
</tr>
</tbody>
</table>

CI: Confidence interval
2 Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.
**Explanations**

a. Certainty of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that were judged to be acceptable by a panel of clinical experts.

b. Minor inconsistency for sensitivity noted but judged to be insufficient to downgrade the certainty of evidence. Minor inconsistency for specificity noted but judged to be insufficient to downgrade the certainty of evidence.

c. Certainty of evidence was downgraded for indirectness in instances where this test was not the index test in a diagnostic pathway. There was a lack of data on the accuracy of this test following a previous test in a pathway. Thus, sensitivity and specificity used for modeling in these instances were based on the test accuracy of the individual test rather than using the test in a pathway.

<table>
<thead>
<tr>
<th>Judgment</th>
<th>Research Evidence</th>
<th>Additional Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CERTAINTY OF THE EVIDENCE OF TEST ACCURACY</strong></td>
<td>What is the overall certainty of the evidence of test accuracy?</td>
<td>The panel noted high certainty of evidence for negative D-dimer, with or without age-adjustment, to rule out PE.</td>
</tr>
<tr>
<td>○ Very low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Low (Proximal CUS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Moderate (CTPA, VQ scan)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ High (Age-adjusted D-dimer or D-dimer to rule out PE, High probability/Normal VQ scan)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ No included studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS</td>
<td>What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the pathway?</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>□ Very low</td>
<td>□ Low</td>
<td></td>
</tr>
<tr>
<td>□ Moderate</td>
<td>□ High</td>
<td></td>
</tr>
<tr>
<td>□ <strong>Varies</strong></td>
<td>□ No included studies</td>
<td></td>
</tr>
</tbody>
</table>

The panel noted there is no direct benefit for any of the diagnostic pathways. There is a burden with serial ultrasound for patients having to return to the hospital. The data varies on the adverse effects associated with radiation exposure, contrast-induced nephropathy, allergy to contrast, or contrast extravasation associated with CTPA or radiation and perfusion agent risks associated with VQ scan.

<table>
<thead>
<tr>
<th>CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT DECISIONS</th>
<th>How certain is the link between pathway results and management decisions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Very low</td>
<td>□ Low</td>
</tr>
<tr>
<td>□ Moderate</td>
<td>□ <strong>High</strong></td>
</tr>
<tr>
<td>□ No included studies</td>
<td></td>
</tr>
</tbody>
</table>

The link between test results and management is unique in venous thromboembolism. With PE diagnosis, positive results will be treated with anticoagulation (regardless of the chances of false positives). The panel noted high certainty in the link between test results and management decisions. However, the panel also noted that for patients with sub-segmental PE, the link may not be as certain.
### CERTAINTY OF EFFECTS

**What is the overall certainty of the evidence of effects of the pathway?**
- Very low
- Low
- Moderate
- High
- No included studies

**What is the overall certainty of the evidence of effects of the pathway to rule out PE?**
- Very low
- Low
- Moderate
- High
- No included studies

### VALUES

**Is there important uncertainty or variability in how people value different outcomes?**
- Important uncertainty or variability
- Possibly important uncertainty or variability
- Probably no important uncertainty or variability
- No important uncertainty or variability

The numbers shown below are utilities, representing the strength of an individual's preferences for different outcomes. They are measured on a scale, with zero reflecting states of health equivalent to death/worst imaginable health and one reflecting perfect health/ best imaginable health.

**Systematic reviews found that the relative importance of the outcomes is as follows:**

- **Pulmonary embolism:** 0.63-0.93 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004)
- **Deep vein thrombosis:** 0.64-0.99 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016)
- **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off) (Locadia 2004)
- **Gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off) (Hogg 2013, Locadia 2004)
- **Minor intracranial bleeding event:** 0.75 (standard gamble) (Hogg 2013)
- **Major intracranial bleeding event:** 0.15 (standard gamble) (Hogg 2013)
- **Central nervous system bleeding:** 0.29-0.60 (standard gamble) (Lenert 1997, O'Meara 1994)

While there was high certainty of evidence on outcomes of patients with a false negative test result, certainty of evidence was downgraded for the overall pathway as the studies were longitudinal observational studies evaluating the effects of only D-dimer and there were few events reported.

<table>
<thead>
<tr>
<th>D-dimer to exclude PE</th>
<th>Studies</th>
<th>Number of PE/Number of patients included</th>
<th>Number of PE in non-high PTP</th>
<th>Number of non-high PTP and negative D-dimer</th>
<th>Lost to follow up</th>
<th>Anticoagulated during follow up</th>
<th>3-month VTE risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Perrier 1999</td>
<td>104/444</td>
<td>74</td>
<td>151</td>
<td>0</td>
<td>4</td>
<td>0/147</td>
</tr>
<tr>
<td></td>
<td>Perrier 2004</td>
<td>222/965</td>
<td>159</td>
<td>275</td>
<td>1</td>
<td>12</td>
<td>0/262</td>
</tr>
<tr>
<td></td>
<td>Steeghs 2005</td>
<td>46/331</td>
<td>29</td>
<td>170</td>
<td>0</td>
<td>3</td>
<td>0/167</td>
</tr>
<tr>
<td></td>
<td>Perrier 2005</td>
<td>194/756</td>
<td>115</td>
<td>232</td>
<td>2</td>
<td>10</td>
<td>0/220</td>
</tr>
<tr>
<td></td>
<td>Van Belle 2006</td>
<td>674/3306</td>
<td>122</td>
<td>409</td>
<td>0</td>
<td>18</td>
<td>0/139</td>
</tr>
<tr>
<td></td>
<td>Goekoop 2007</td>
<td>111/876</td>
<td>80</td>
<td>450</td>
<td>6</td>
<td>5</td>
<td>0/439</td>
</tr>
<tr>
<td></td>
<td>Righini 2008</td>
<td>357/1693</td>
<td>315</td>
<td>561</td>
<td>2</td>
<td>19</td>
<td>0/540</td>
</tr>
</tbody>
</table>


The panel placed a high value on decreasing the number of false negative test results over decreasing false positive test results.

The panel also placed a high value on decreasing radiation exposure and reducing the number of tests required in a diagnostic pathway.

The panel considered that there would not be important
Studies additionally described the following regarding the relative importance of outcomes and patients’ preferences:

In a survey study (Geyer 2014) based on a shared decision-making model, the researchers provided patients with a standardized description of the diagnostic workup for PE, described the risks of CTPA in low pretest probability patients and the risks of deferring imaging assuming a D-dimer was less than twice the value normally considered positive. With the decision aid, of the 203 patients in the study, 63% of patients favored undergoing CTPA; while seventy-four patients (37%) elected to defer CTPA. The mostly frequent reasons for decline include risk of malignancy, contrast-induced nephropathy, or allergy. Other than those common reasons, 20 patients deferred CTPA testing because they believed it was unnecessary. Patients with a previous PE diagnosis were less likely to defer CTPA testing. Most patients (n=109 [85%]) who accepted CTPA testing, had concerns about missing a PE.

Results of Panel Utility Rating Survey:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean Utility Rating (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>False Negative Test Result</td>
<td>0.60 (0.23)</td>
</tr>
<tr>
<td>False Positive Test Result</td>
<td>0.62 (0.21)</td>
</tr>
<tr>
<td>True Negative Test Result</td>
<td>0.91 (0.15)</td>
</tr>
<tr>
<td>True Positive Test Result</td>
<td>0.76 (0.19)</td>
</tr>
<tr>
<td>Inconclusive Test Result</td>
<td>0.69 (0.18)</td>
</tr>
<tr>
<td>Radiation Exposure</td>
<td>0.84 (0.14)</td>
</tr>
<tr>
<td>Contrast Induced Nephropathy</td>
<td>0.56 (0.20)</td>
</tr>
<tr>
<td>Pulmonary Embolism – Moderate Marker State</td>
<td>0.42 (0.15)</td>
</tr>
<tr>
<td>Proximal DVT – Moderate Marker State</td>
<td>0.58 (0.14)</td>
</tr>
<tr>
<td>Distal DVT – Moderate Marker State</td>
<td>0.64 (0.16)</td>
</tr>
<tr>
<td>Upper Extremity DVT – Moderate Marker State</td>
<td>0.61 (0.16)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>0.33 (0.23)</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>0.12 (0.10)</td>
</tr>
<tr>
<td>Chronic Thrombotic Pulmonary Hypertension</td>
<td>0.34 (0.15)</td>
</tr>
</tbody>
</table>

* Utility rating by panel members from 0 (dead) to 1 (full health)

BALANCE OF DESIRABLE AND UNDESIRABLE EFFECTS

Rank the top pathways in order of which provides the best balance of desirable and undesirable effects

Modelling of Diagnostic Test Accuracy

Note: See pathways on Page 1
Pathways A-H begin with CTPA
Pathways I-J begin with VQ

Desirable and undesirable effects:
The panel considered desirable effects as increasing the...
The panel judged the ranking of the pathways based on a threshold of false negative patients and a threshold of misdiagnosed patients (combination of false negative and false positive results). Pathways highlighted in green were judged as the top ranked pathways that provided the best balance of desirable and undesirable effects. These pathways remained below a threshold of 20 false negative results per 1000 patients tested (≤2%) and a threshold of 50 misdiagnosed results per 1000 patients tested (≤5%).

Pathways highlighted in yellow provided a less acceptable balance of desirable and undesirable effects. These pathways remained below a threshold of 50 false negative results per 1000 patients tested (≤5%) and 100 false positive results per 1000 patients tested (≤5%).

Table 1: In a patient population with an intermediate clinical probability (20%) of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose a first episode PE?

<table>
<thead>
<tr>
<th>Pathway</th>
<th>TP</th>
<th>FP</th>
<th>TN</th>
<th>FN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>TP</td>
<td>186</td>
<td>200</td>
<td>193</td>
<td>196</td>
</tr>
<tr>
<td>FP</td>
<td>16</td>
<td>494</td>
<td>30</td>
<td>44</td>
</tr>
<tr>
<td>TN</td>
<td>784</td>
<td>306</td>
<td>770</td>
<td>756</td>
</tr>
<tr>
<td>FN</td>
<td>14</td>
<td>0</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 1: Continued

<table>
<thead>
<tr>
<th>Pathway</th>
<th>K</th>
<th>L</th>
<th>M1</th>
<th>M2</th>
<th>N1</th>
<th>N2</th>
<th>O1</th>
<th>O2</th>
<th>P</th>
<th>Q1</th>
<th>Q2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>K</td>
<td>L</td>
<td>M1</td>
<td>M2</td>
<td>N1</td>
<td>N2</td>
<td>O1</td>
<td>O2</td>
<td>P</td>
<td>Q1</td>
<td>Q2</td>
</tr>
<tr>
<td>TP</td>
<td>194</td>
<td>180</td>
<td>185</td>
<td>183</td>
<td>168</td>
<td>132</td>
<td>186</td>
<td>186</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>FP</td>
<td>488</td>
<td>10</td>
<td>21</td>
<td>16</td>
<td>22</td>
<td>19</td>
<td>23</td>
<td>20</td>
<td>494</td>
<td>502</td>
<td>498</td>
</tr>
<tr>
<td>TN</td>
<td>312</td>
<td>790</td>
<td>779</td>
<td>784</td>
<td>778</td>
<td>781</td>
<td>777</td>
<td>780</td>
<td>306</td>
<td>298</td>
<td>302</td>
</tr>
<tr>
<td>FN</td>
<td>6</td>
<td>20</td>
<td>15</td>
<td>17</td>
<td>32</td>
<td>68</td>
<td>14</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

TP - patient correctly identified as having PE and anticoagulated
FP - patient incorrectly identified as having PE and unnecessarily anticoagulated
TN - patient correctly identified as not having PE and not anticoagulated
FN - patient incorrectly identified as not having PE and will not receive needed anticoagulation

Assumptions associated with modelling:
1. Disease prevalence in an intermediate clinical probability population was determined be 200 per 1000 patients (20%).
2. Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.
3. The panel judged the ranking of pathways with the best balance of desirable and undesirable effects based on thresholds of false negative patients and misdiagnosed patients (false negative and false positive). These rankings are depicted in the table as green being the most acceptable, yellow being less acceptable, and red being unacceptable.

Balance of desirable and undesirable effects:
misdiagnosed results per 1000 patients (≤10%).

Pathways highlighted in red did not provide an acceptable balance of desirable and undesirable effects and were ranked lowest. These pathways were above the threshold of 50 false negative results per 1000 patients tested (>5%) and 100 misdiagnosed results per 1000 patients (>10%).

4. Due to the lack of data on accuracy of serial ultrasound, the sensitivity and specificity for proximal compression ultrasound was used to represent serial ultrasound. In addition, serial ultrasound was determined to be one follow-up test after initial ultrasound.

5. Test accuracy for CTPA, D-dimer and proximal CUS were derived from these tests being used as a standalone test. These sensitivity and specificity results were used when the test was the first test of the pathway. These accuracy results were also used if the test was a subsequent test in a pathway.

6. The panel recognized two distinct populations undergoing VQ scan: patients likely to have a diagnostic scan (high probability or normal result) versus patients likely to have a non-diagnostic scan (low/intermediate probability). In the first population, it was assumed 80% would have a diagnostic scan and 20% would be non-diagnostic. Sensitivity analyses was completed to reveal no change in accuracy results of an alternative distribution with 70% diagnostic and 30% non-diagnostic scans. In the second population, it was assumed 40% of patients would have a diagnostic scan and 60% would be non-diagnostic.

7. For patients undergoing VQ scan, we assumed patients with normal or very low probability results would not be anticoagulated. Low or intermediate probability (non-diagnostic) scans would always be followed up with subsequent testing. Patients with high probability scans would be anticoagulated.

Table 2: Data abstraction from studies with data on direct pathways

<table>
<thead>
<tr>
<th>Pathway</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L 5%</td>
<td>L 20%</td>
<td>L 50%</td>
<td>L 75%</td>
</tr>
<tr>
<td>TP</td>
<td>48</td>
<td>191</td>
<td>477</td>
<td>715</td>
</tr>
<tr>
<td>FP</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>TN</td>
<td>945</td>
<td>786</td>
<td>497</td>
<td>249</td>
</tr>
<tr>
<td>FN</td>
<td>2</td>
<td>9</td>
<td>23</td>
<td>35</td>
</tr>
</tbody>
</table>


## Contrast induced nephropathies, allergic reactions, and extravasation

<table>
<thead>
<tr>
<th>Study</th>
<th>Index test</th>
<th>Reference test</th>
<th>Safety Outcome (as defined by study)</th>
<th>Incidence and details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ost 2001</td>
<td>CT</td>
<td>PA</td>
<td>Contrast induced nephropathy/ARF</td>
<td>Creatinine was not serially measured throughout study. However, increase in creatinine 0.01 +/- 0.38 mg/dL noted in CT only group without conventional angiography and 0.2 +/- 0.9 mg/dL in the CT + conventional angiography group. 3/103 (3%) patients had an increase in creatinine greater than 1 mg/dL with max of 7.2 mg/dL. All returned to the normal reference range at 3-month follow up.</td>
</tr>
<tr>
<td>Pesavento 2011</td>
<td>CT</td>
<td>None</td>
<td>Severe acute renal failure</td>
<td>CT: 1/367 (0.27%)</td>
</tr>
<tr>
<td>Stein 2006</td>
<td>CT</td>
<td>CC</td>
<td>Allergic reaction</td>
<td>CT: 4/1095 (&lt;1%); mild</td>
</tr>
<tr>
<td>Yazici 2016</td>
<td>CT</td>
<td>None</td>
<td>Contrast nephropathy</td>
<td>24/174 (13%)</td>
</tr>
<tr>
<td>Coche 2003</td>
<td>CT</td>
<td>CT, VQ</td>
<td>Contrast nephropathy (creatinine increase)</td>
<td>1/69 (1%)</td>
</tr>
<tr>
<td>Mitchell 2006</td>
<td>CT</td>
<td>None</td>
<td>Contrast nephropathy (creatinine increase)</td>
<td>All: 44/1224 (4%) or paired: 44/354 (12%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe acute renal failure</td>
<td>0/1224 (0%)</td>
</tr>
<tr>
<td>Righini 2008</td>
<td>PW (DD-leg US-CT)</td>
<td>APW (DD-CT)</td>
<td>Allergic reaction</td>
<td>PW: 1/509 (0.2%) (rash)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Extravasation of contrast</td>
<td>APW: 2/535 (0.4%) (rash)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe acute renal failure</td>
<td>PW: 0/509 (0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>APW: 0/535 (0%)</td>
</tr>
</tbody>
</table>

DD = D-dimer; PW = pathway; APW = alternative pathway; CT=Computed Tomography; PA=Pulmonary Angiography; VQ=Ventilation Perfusion Scan; ARF=Acute Renal Failure

References:

Radiation exposure associated with CTPA

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Estimated ‘effective dose’ of radiation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT: Chest</td>
<td>4.5 mSv (range 3.8-5.2 mSv)</td>
<td>Phillips, 2015</td>
</tr>
<tr>
<td></td>
<td>5.2 mSv</td>
<td>Kanal, 2017</td>
</tr>
<tr>
<td></td>
<td>Range: 2.7 - 15 mSv</td>
<td>Jones, 2012 and Janbabanezhad, 2015</td>
</tr>
<tr>
<td>VQ</td>
<td>2.2 mSv</td>
<td>Jones, 2012</td>
</tr>
<tr>
<td></td>
<td>2.5 mSv</td>
<td>Phillips, 2015</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mettler, 2008</td>
</tr>
</tbody>
</table>

In Hurwitz et al, estimated relative risks for breast and lung cancer incidences were 1.002–1.011 and 1.005–1.022, respectively. In addition, Brenner and Elliston estimated the lifetime attributable cancer death risk in 45-year-old adults who underwent a full-body CT test to be around 0.08%. The relationship between radiation exposure to cancer induction was limited and incredibly variable in literature and, therefore, not modelled.

**How large are the resource requirements (costs) for CTPA?**
- Large costs
- Moderate costs
- Negligible costs and savings
- Moderate savings
- Large savings
- Don't know

**How large are the resource requirements (costs) for D-Dimer?**
- Large costs
- Moderate costs
- Negligible costs and savings
- Moderate savings
- Large savings
- Don't know

**How large are the resource requirements (costs) for Proximal CUS?**
- Large costs
- Moderate costs
- Negligible costs and savings
- Moderate savings
- Large savings
- Don't know

---

### RESOURCES REQUIRED

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Peer-review articles and Other sources$[^1]$</th>
<th>CPT (Current Procedural Terminology)-4 Codes/cost $[^1,2]$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CTPA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Other sources: $300-$400 | 71275 - CT angiography chest  
Facility/Non-Facility price: $269.00-390.74  
Opps facility/non-facility payment amount: $315.31-463.95 |
| Ventilation/perfusion lung scan | $400 ($520 in 2017) $[^8]$  
Facility/Non-Facility price: $35.35 - $361.27  
Opps Facility/Non-Facility payment amount: $282.88 - $492.19 |
| Pulmonary angiography | Angiography: $1000 ($1300 in 2017) $[^6]$ |                                                         |
| Ultrasonography       | Compression ultrasonography: $200 ($260 in 2017) $[^6]$  
Facility/Non-Facility price: $26.18-115.39  
Opps Facility/Non-Facility payment amount: $95.77-183.25 |
| Lower Extremity       |                                             |                                                         |
| Ultrasonography       | Compression ultrasonography: $200 ($260 in 2017) $[^6]$  
Doppler ultrasound: $602.30 $[^7]$  
Other sources: USound:  
leg/foot: $133-$233  
abdomen/hip/pelvis: $77-$300 | 76856-US exam pelvic complete  
Facility/Non-Facility price: $33.56-144.34  
Opps Facility/Non-Facility payment amount: $95.61-192.55 |
| Compression ultrasound of extremity veins |                                             | 93970 - Extremity study  
Facility/Non-Facility price: $33.34-262.08  
Opps Facility/Non-Facility payment amount: $191.98-345.03 |
| Duplex scan of lower extremities |                                             | 93925-Lower extremity study  
Facility/Non-Facility price: $37.86 - $361.27  
Opps Facility/Non-Facility payment amount: $191.52 - $350.20 |
| Venography, extremity |                                             | 75820- Vein x-ray arm/leg  
Facility/Non-Facility price: $33.34-149.42  
Opps Facility/Non-Facility payment amount: $580.65-964.81 |

*[^1]* Costs and charges were obtained from a U.S. perspective, in dollars.
*[^2]* Costs differ between insurance carriers.

The panel noted that the costs for CTPA are large, but vary based on setting and the cost to the patient may vary depending on coverage.

The panel noted that the data showing costs based on CPT codes do not reflect what patients are charged in different settings, and are likely an under-representation of what patients and insurers pay.

Given this, the panel noted that the reported costs for D-dimer seem very high, however this may be reflective of the U.S. setting and may differ between settings.

The panel noted that for D-dimer costs from a health system perspective are moderate. Additionally, a diagnostic pathway starting with D-dimer would reduce cost compared to the other alternatives.
<table>
<thead>
<tr>
<th><strong>requirements (costs) for serial CUS?</strong></th>
<th><strong>How large are the resource requirements (costs) for VQ scan?</strong></th>
<th><strong>How large are the resource requirements (costs) for pulmonary angiography?</strong></th>
<th><strong>References:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Don’t know</td>
<td>○ Don’t know</td>
<td>○ Don’t know</td>
<td>13. Based on CADTH report; The cost consists of diagnostic tests costs and physician interpretation cost, and it is in Canadian dollars in 2017.</td>
</tr>
<tr>
<td><strong>How large are the resource requirements (costs) for VQ scan?</strong></td>
<td><strong>How large are the resource requirements (costs) for pulmonary angiography?</strong></td>
<td><strong>References:</strong></td>
<td></td>
</tr>
<tr>
<td>○ <strong>Large costs</strong></td>
<td>○ Large costs</td>
<td>○ Large costs</td>
<td>14. <a href="https://pricinghealthcare.com/prices/CenterForMedicalImaging">https://pricinghealthcare.com/prices/CenterForMedicalImaging</a></td>
</tr>
<tr>
<td>CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td></td>
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<tr>
<td><strong>What is the certainty of the evidence of resource requirements (costs) for CTPA?</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>⚫ Very low</td>
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<tr>
<td>⚫ Low</td>
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<tr>
<td>⚫ Moderate</td>
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<tr>
<td>⚫ High</td>
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<td></td>
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<tr>
<td>⚫ No included studies</td>
<td></td>
<td></td>
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<tr>
<td><strong>What is the certainty of the evidence of resource requirements (costs) for D-Dimer?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>⚫ Very low</td>
<td></td>
<td></td>
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<tr>
<td>⚫ Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>⚫ Moderate</td>
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<tr>
<td>⚫ High</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>⚫ No included studies</td>
<td></td>
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<tr>
<td><strong>What is the certainty of the evidence of resource requirements (costs) for proximal CUS?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>⚫ Very low</td>
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<td></td>
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<tr>
<td>⚫ Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>⚫ Moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>⚫ High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>⚫ No included studies</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

The panel noted uncertainty in the actual costs of the tests.
<table>
<thead>
<tr>
<th>Resource requirements (costs) for serial CUS?</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Very low</td>
</tr>
<tr>
<td>○ <strong>Low</strong></td>
</tr>
<tr>
<td>○ Moderate</td>
</tr>
<tr>
<td>○ High</td>
</tr>
<tr>
<td>○ No included studies</td>
</tr>
</tbody>
</table>

**What is the certainty of the evidence of resource requirements (costs) for VQ scan?**

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>○ Very low</td>
</tr>
<tr>
<td>○ <strong>Low</strong></td>
</tr>
<tr>
<td>○ Moderate</td>
</tr>
<tr>
<td>○ High</td>
</tr>
<tr>
<td>○ No included studies</td>
</tr>
</tbody>
</table>

**What is the certainty of the evidence of resource requirements (costs) for Pulmonary Angiography?**

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Very low</td>
</tr>
<tr>
<td>○ <strong>Low</strong></td>
</tr>
<tr>
<td>○ Moderate</td>
</tr>
<tr>
<td>○ High</td>
</tr>
<tr>
<td>○ No included studies</td>
</tr>
</tbody>
</table>
We identified the following in our systematic review of cost-effectiveness:

**COST EFFECTIVENESS**

**Cost effectiveness of diagnostic pathways evaluated**

The panel judged pathways starting with a D-dimer test as most cost-effective considering the lower cost of the test.

**CTPA:**
Evidence on the cost-effectiveness of CTPA is inconsistent. The included studies varied in regards to the compared strategy, the setting, the time frame, and the methods. In general, a CTPA strategy was considered effective, mostly associated with improved survival. Whether it is cost-effective or not is still uncertain in the literature.

In Batalles 2009, CTPA was cost-effective compared with pulmonary magnetic resonance angiography, and was the most effective strategy. A study by van Erkel et al (van Erkel 1996) found that CTPA reduces mortality and improves cost-effectiveness in the diagnostic workup of suspected PE when compared with VQ scanning, compression US, D-dimer assay, and conventional angiography strategies. In Oudkerk 1993, compared with the treatment for all strategy with lowest mortality but highest cost, pulmonary angiography strategies with or without prior VQ lung scanning and ultrasonography of the legs have comparable low mortality and morbidity rates, costs savings of approximately 40%, and inappropriate treatment in fewer than 5% of patients. Paterson et al (Paterson 2001) found higher costs for CTPA as the initial diagnostic test but with improved expected survival when compared with a gradual algorithm of VQ scanning ± compression US ± CTPA.

In Doyle 2004, researchers in the US conducted a decision analytic model on diagnostic tests of PE in women, to determine which strategy is the most cost-effective with the least number of deaths from PE. Of the strategies compared (compression US, VQ scanning, and spiral CT), spiral CT as the initial diagnostic regimen was found to be the most cost-effective at $17,208 per life saved. In contrast, Henschke et al (Henschke 1994) concluded CTPA was not cost-effective compared with ultrasound.


**D-Dimer:**
Several cost-effectiveness analyses compared the diagnostic strategies with D-dimer, and use CTPA according to the D-dimer with other strategies, including no test, or treatment for all, or universal CTPA or VQ scan. In general, the strategy of combining D-dimer with other diagnostic testing was suggested to be cost-effective, or cost-saving. (Duriseti 2010, Duriseti 2006, Elias 2004, Humphreys 2004, Lee 2011, Perrier 1997, Perrier 2003, Righini 2007, Van Beek 1996, Van Erkel 1996)

**Proximal CUS:**
No evidence identified on the cost-effectiveness of proximal compression ultrasound.

**VQ Scan:**
Cost-effectiveness analyses compared VQ scan versus other diagnosis strategies. None of the reports compared VQ scan with CTPA suggested VQ scan was cost-effective (Batalles 2009, Doyle 2004, Paterson 2001, and van Erkel 1996).
While another report suggested VQ scan is cost-effective compared with CT alone (Larcos 2000), with 20.1 additional lives saved per 1,000 patients, at a cost of $940 per life year gained.


<table>
<thead>
<tr>
<th>EQUITY</th>
<th>Impact on health equity of diagnostic pathways evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>We identified the following regarding the impact on health equity with the different tests:</td>
</tr>
<tr>
<td></td>
<td>CTPA: No research evidence identified.</td>
</tr>
<tr>
<td></td>
<td>D-Dimer: Canadian provinces with larger populations tended to have a large proportion of hospitals with the capability to measure D-dimer levels for VTE diagnosis, whereas less populated provinces were more likely to send samples to centralized analysis facilities for D-dimer testing. (Southern 2014)</td>
</tr>
<tr>
<td></td>
<td>Proximal CUS: No research evidence identified.</td>
</tr>
<tr>
<td></td>
<td>VQ Scan: No research evidence identified.</td>
</tr>
</tbody>
</table>

The panel noted that for pathways starting with CTPA, adding any further testing will have no impact, and additional tests would therefore disadvantage patients in low income categories.

<table>
<thead>
<tr>
<th>ACCEPTABILITY</th>
<th>Acceptability of diagnostic pathways evaluated to key stakeholders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Studies described the following regarding acceptability from key stakeholders:</td>
</tr>
<tr>
<td></td>
<td>General (Radiology &amp; Population):</td>
</tr>
<tr>
<td></td>
<td>A survey assessing the knowledge/practice patterns of emergency department (ED) physicians related to radiation exposure showed that 9 out of 10 preferred VQ scanning for patients &lt;30 years of age or those with a history of recent CT scans when diagnosing PE, which was confirmed by retrospective chart review. Physician knowledge of precise radiation exposure for each diagnostic test was low, but the majority were aware that VQ scans exposed patients to less radiation than CTPA. (Ahn 2014)</td>
</tr>
<tr>
<td></td>
<td>In a study among nursing home patients with suspected VTE, referral for additional diagnostic investigations was withheld in almost 40%. In providers’ decisions to forgo diagnostic investigations, they incorporated the estimated relative impact of the potential disease; the potential net-benefits of diagnostic investigations and whether performing investigations agreed with established management goals in advance care planning. (Schouten 2014)</td>
</tr>
<tr>
<td></td>
<td>A study among physicians who had previously referred patients for any VTE screening examination showed that physicians had a lack of basic knowledge regarding lower extremity venous anatomy, charges for the different diagnostic tests used to diagnose VTE, and current treatment standards for VTE. (Zierler 2002)</td>
</tr>
</tbody>
</table>

The panel noted as an acceptability issue whether patients would prefer to wait for a VQ scan if not immediately available, or to obtain CTPA immediately but with increased radiation exposure.
| CTPA | A survey among 62 radiologists and 52 ED physicians showed that CT is the overwhelmingly preferred technique for the diagnosis of PE. (Jha 2010) |
| D-Dimer alone or in combination with other imaging test: | Thrombosis and hemostasis specialists reported that just over half uses D-dimer for diagnosing DVT and two-thirds for diagnosing PE. 30% relied on clinical judgment to assess pre-clinical probability for DVT and 41% for PE. (Squizzato 2010) |
| There are at least 28 different combinations of measurement units used to report D-dimer results for thrombotic disorders worldwide as reported by providers. The majority used fixed cut-off rather than age-adjusted threshold values for D-dimer. (Lippi 2015) |
| CTPA or VQ scan following a negative or positive D-Dimer: | Of ED patients with a suspected VTE and a negative D-dimer result 14% underwent at least 1 imaging study, and of patients with a positive D-dimer result 48% did not undergo imaging. (Teismann 2009) |
| A survey among 62 radiologists and 52 ED physicians showed that CT is the overwhelmingly preferred technique for the diagnosis of PE. The role of ventilation–perfusion scintigraphy increases when the use of iodinated contrast material is contraindicated and MRI does not seem to have an important role in practice. (Jha 2010) |
| More than half of CTPAs for PE were avoidable and 12% of CTPAs were done on patients with low risk and negative D-dimer assay. (Perelas 2014, Perelas 2015) |
| Proximal CUS: | Patient level of discomfort during point-of-care US of the heart, lungs and deep veins for respiratory symptoms is very low and the vast majority of patients would accept being assessed by this method if the patients once again had to be examined for possible disease. (Laursen 2015) |
| VQ Scan and CTPA | A survey among 62 radiologists and 52 ED physicians showed that CT is the overwhelmingly preferred technique for the diagnosis of PE. The role of VQ scanning increases when the use of iodinated contrast material is contraindicated and MRI does not seem to have an important role in practice. (Jha 2010) |

<table>
<thead>
<tr>
<th>FEASIBILITY</th>
<th>Feasibility to implement diagnostic pathways evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>The panel considered all pathways as feasible, however noting specific considerations for</td>
<td>Studies described the following regarding feasibility and barriers to use:</td>
</tr>
<tr>
<td>General (Radiology &amp; Population):</td>
<td>Feasibility:</td>
</tr>
<tr>
<td>A retrospective chart review showed that there was substantial variation in utilization and diagnostic yield of advanced radiography for PE, which was largely explained by patient-, hospital- and provider-level characteristics. (Kindermann 2014)</td>
<td>The panel noted that in terms of feasibility, many institutions do not offer VQ scanning on nights and weekends. For VQ scanning to be utilized as the first test in a pathway, there may be situations where</td>
</tr>
</tbody>
</table>

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| feasibility of testing with VQ scan, D-dimer, and proximal CUS. | A prospective cohort study among outpatients with suspected PE from ED’s showed that 43% received inappropriate diagnostic management. Risk factors associated with inappropriate diagnostic management were age >75 years, heart failure, chronic lung disease, current or recent pregnancy, currently receiving anticoagulation, and the lack of a written diagnostic algorithm and clinical probability scoring in the ED. Inappropriate management was associated with thromboembolism occurrence. (Roy 2006)

**Implementation:**
A study assessing the impact of a hospital-based educational and form-based intervention on clinician adherence to diagnostic imaging guidelines for suspected PE found improved adherence among clinicians who received the intervention. Failure to adhere with diagnostic imaging guidelines when requesting radiological testing was common. (Agarwal 2012)

**CTPA:**
**Feasibility:**
A retrospective study on CTPA examinations showed that there was considerable inter-physician variability in the utilization and PE positivity rates of CTPA within a single institution. (Chen 2015)

A chart review with 3-month phone follow-up among ED patients undergoing investigations for suspected PE showed that compliance with a clinical pathway was more likely if exclusively done by ED physicians and was associated with a lower use of CTPA. (Ng 2011)

A retrospective hospital radiology among CT angiography procedures showed that in 2009 CTPA was performed more often with relatively fewer PE cases identified compared with 2006. (David 2012)

A survey on ED visits (12% involved chest pain, pneumonia or hemoptysis) showed that CT use among patients with chest pain increased dramatically from 2001 to 2007. The PE diagnosis to CT ratio was low (2.7%). (Feng 2013)

**Implementation:**
A computerized decision support tool decreased CTPA orders and diagnostic yield increased following the intervention. Inter-physician variability in CTPA order adherence post intervention was significant. (Prevedello 2013)

Adherence to guidelines for use of CTPA for PE diagnosis improved among ED physicians who received a performance feedback intervention vs. those who did not. Diagnostic yields remained unchanged in control and intervention groups. (Raja 2015)

Mandatory adherence to diagnostic protocols was shown to increase the rate of positive CTPAs for PE and to decrease the rate of negative CTPAs. Predictors of diagnostic yield included: previous DVT and clinical signs of DVT, while COPD was found to be negatively associated with PE. (Walen 2016) |
**D-Dimer alone or in combination with other imaging test:**

**Feasibility:**
Using a combination of the Wells’ simplified dichotomous clinical decision rule and D-dimer test, which could be completed in 90% of patients, PE could be ruled out in 51% of patients with suspected PE without further testing, which had a failure rate of only 0.4%. (Goekoop 2007)

Less than half of physicians reviewed the D-dimer result for PE after patient examination, and the knowledge of an abnormal D-dimer test result before seeing the patient led to a higher clinical decision rule score at patient examination. (Gibson 2009)

Following at least one D-dimer test for DVT or PE, the strategy for further diagnostic testing was inappropriate in 31% with 9 out of 10 being overutilization of diagnostic imaging. (Arnason 2007)

Widespread D-dimer testing did not reduce referrals for imaging and is likely to have resulted in increased referrals. Increased imaging led to over-diagnosis of clinically insignificant PE and alternative strategies are required to reduce PE death rates. (Segard 2013)

**Implementation:**
Increasing the D-dimer threshold from 0.4μg/mL to 1.0μg/mL increased CTPA diagnostic yield for PE from 4.7% to 11.7%, but still 9% of patients with a D-dimer below the threshold underwent CTPA. (Char 2014)

Computer systems prompting provision of clinical probability factors and D-dimer value to assess the risk of PE and associated need for CTPA lowered the use of CTPA an increase its yield. (Murthy 2016, Ong 2013)

**Proximal CUS:**
No research evidence identified.

**VQ Scan:**
No research evidence identified.
Conclusions

In a patient population with an intermediate clinical probability of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose a first episode PE?

<table>
<thead>
<tr>
<th>TYPE OF RECOMMENDATION</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Strong recommendation against the intervention</td>
<td>Conditional recommendation against the intervention</td>
<td>Conditional recommendation for either the intervention or the comparison</td>
<td>Conditional recommendation for the intervention</td>
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</table>

**RECOMMENDATION**

The ASH guideline panel suggests using a strategy starting with D-dimer for diagnosing PE in a population with moderate prevalence/pretest probability (20%), followed by i) VQ scan or ii) CTPA. If D-dimer is not readily available, alternate acceptable strategies include performing a VQ scan or CTPA alone. Patients who are likely to have a non-diagnostic VQ scan should undergo CTPA. Additional testing with CTPA is recommended if the VQ scan is non-diagnostic. (Strong recommendation for D-dimer based on high certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy studies; Conditional recommendation for VQ scan or CTPA based on very low certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy).

Remarks: If the D-dimer strategy is followed, a highly sensitive D-dimer assay is required. In the D-dimer strategy, a negative D-dimer rules out PE and no additional testing or anticoagulation is provided. VQ scan is preferred over CTPA as the subsequent test to limit radiation exposure. Additional testing with CTPA is performed if the VQ scan is non-diagnostic.

The ASH guideline panel recommends against using a positive D-dimer alone to diagnose PE, and against additional testing following negative CTPA or diagnostic VQ scan in a population with intermediate prevalence/pretest probability (20%).

Remarks: We considered a diagnostic VQ scan result as normal or high probability, non-diagnostic VQ scan as low or intermediate probability. Providers need to be aware of the variability in terminology at their individual institutions. The panel prioritized limiting the number of diagnostic tests and radiation exposure.

**JUSTIFICATION**

The panel considered a strategy with D-dimer testing first to reduce cost, ensure feasibility, and reduce radiation exposure. D-dimer alone was considered not sufficient as a rule-in test, and must be followed by another test. If CTPA is used as a first test, it should not be followed by other tests as no additional benefit is achieved and there is further cost, impacting health equity.

**SUBGROUP CONSIDERATIONS**

We considered the two subgroups of diagnostic VQ scan and non-diagnostic VQ scan which are reflected in the recommendations above. A baseline chest X-ray prior to VQ scan can determine the likelihood of having a diagnostic VQ scan.
<table>
<thead>
<tr>
<th>IMPLEMENTATION CONSIDERATIONS</th>
<th>A highly sensitive D-dimer assay is required for this strategy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MONITORING AND EVALUATION</td>
<td></td>
</tr>
</tbody>
</table>
**Appendix 1: Modelling of Diagnostic Test Accuracy**

**Note:** See diagnostic pathway diagrams on Page 1

Pathways A-H begin with CTPA  
Pathways I-J begin with VQ  
Pathways K-Q begin with D-dimer

**Table 1:** In a patient population with an *intermediate* clinical probability (20%) of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose a first episode PE?

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G1</th>
<th>G2</th>
<th>H</th>
<th>I1</th>
<th>I2</th>
<th>J1</th>
<th>J2</th>
<th>K</th>
<th>L</th>
<th>M1</th>
<th>M2</th>
<th>N1</th>
<th>N2</th>
<th>O1</th>
<th>O2</th>
<th>P</th>
<th>Q1</th>
<th>Q2</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP - patient correctly identified as having PE and anticoagulated</td>
<td>186</td>
<td>200</td>
<td>193</td>
<td>196</td>
<td>193</td>
<td>196</td>
<td>198</td>
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<td>200</td>
<td>191</td>
<td>188</td>
<td>173</td>
<td>136</td>
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<td>185</td>
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<td>168</td>
<td>132</td>
<td>186</td>
<td>186</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>FP - patient incorrectly identified as having PE and unnecessarily anticoagulated</td>
<td>16</td>
<td>494</td>
<td>30</td>
<td>44</td>
<td>40</td>
<td>62</td>
<td>52</td>
<td>46</td>
<td>16</td>
<td>35</td>
<td>26</td>
<td>37</td>
<td>30</td>
<td>488</td>
<td>10</td>
<td>21</td>
<td>16</td>
<td>22</td>
<td>19</td>
<td>23</td>
<td>20</td>
<td>494</td>
<td>502</td>
<td>498</td>
</tr>
<tr>
<td>TN - patient correctly identified as not having PE and not anticoagulated</td>
<td>784</td>
<td>306</td>
<td>770</td>
<td>756</td>
<td>760</td>
<td>738</td>
<td>748</td>
<td>754</td>
<td>784</td>
<td>765</td>
<td>774</td>
<td>763</td>
<td>770</td>
<td>312</td>
<td>790</td>
<td>779</td>
<td>784</td>
<td>778</td>
<td>781</td>
<td>777</td>
<td>780</td>
<td>306</td>
<td>298</td>
<td>302</td>
</tr>
<tr>
<td>FN - patient incorrectly identified as not having PE and will not receive needed anticoagulation</td>
<td>14</td>
<td>0</td>
<td>7</td>
<td>4</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>9</td>
<td>12</td>
<td>27</td>
<td>64</td>
<td>6</td>
<td>20</td>
<td>15</td>
<td>17</td>
<td>32</td>
<td>68</td>
<td>14</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Appendix 2: Natural Progression and Treatment Effects

When making a decision regarding which pathway to recommend for diagnosing PE, one must acknowledge that there will be patients who will have negative consequences because of an incorrect test result and thus an incorrect diagnosis. Patients who receive unnecessary anticoagulation (false positive) or do not receive necessary anticoagulation (false negative) are subject to the risks of bleeding, may suffer complications or may die. Tables 2 and 3 provide some insight into the frequency of these outcomes.

**True positive:** patients correctly identified as having PE and correctly anticoagulated  
**True negative:** patients correctly identified as not having PE and correctly not anticoagulated  
**False positive:** patients incorrectly identified as having PE and receive unnecessary anticoagulation  
**False negative:** patients incorrectly identified as not having PE and will not receive necessary anticoagulation

Outcomes studied include:  
Hemorrhagic Stroke  
Major Bleeding  
Mortality  
Recurrent PE

### Table 2: Outcomes by Test Result

<table>
<thead>
<tr>
<th>Test accuracy results</th>
<th>Consequences</th>
<th>Results from published SR</th>
<th>Results from treatment guideline (GL3-Q3, LMWH/VKA)*</th>
<th>Targeted search of primary studies</th>
<th>Panel survey results</th>
</tr>
</thead>
</table>
| **TP**                | Mortality: all cause | 2.0% (6m)*                | In-hospital: 10.5%  
1 week: 5.3%  
2 weeks: 8.5%  
1 month: 10.4%  
3 months: 9.8%  
**Recurrent PE population:**  
2 weeks: 33.7%  
3 months: 46.8% | 11.3% (1y) |
|                       | Mortality from PE w 3 months | 1.5% (3m)^                | In-hospital: 4.7%  
1 week: 2.0%  
2 weeks: 2.3%  
1 month: 6.3%  
3 months: 2.8%  
**Recurrent PE population:**  
In-hospital: 0.0%  
1 week: 50.0%  
3 months: 51.9% | |
|                       | Recurrence on AC w 3 months | 1.0% (6m)*                | In-hospital: 1.4% | 3.0% (1y) |

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### Table 2. Outcomes by Diagnostic Pathway

<table>
<thead>
<tr>
<th>Diagnostic Pathway</th>
<th>A</th>
<th>B, H</th>
<th>I</th>
<th>J</th>
<th>K</th>
<th>L</th>
<th>M-Q</th>
</tr>
</thead>
</table>

* Median event rates from included RCTs in Q3 from GL3

# Event rates from SR by Carrier 2010, which was also used in Q3 for GL3

^ Event rate from SR by Douketis 1998
<table>
<thead>
<tr>
<th></th>
<th>Mortality - PE</th>
<th>None reported</th>
<th>None reported</th>
<th>None reported</th>
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<tr>
<td>Anderson, 2007</td>
<td>2/133</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
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<tr>
<td>Van Belle 2006</td>
<td>PE+ 55/764</td>
<td>PE- 129/1500</td>
<td>None reported</td>
<td>None reported</td>
</tr>
<tr>
<td>Engelke, 2006</td>
<td>2/96</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
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<tr>
<td>Jouveshomme, 2007</td>
<td>3/156</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
</tr>
<tr>
<td>Musset, 2002</td>
<td>3/345</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
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<tr>
<td>Atasoy, 2015</td>
<td>8/67</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
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<tr>
<td>Ceylan, 2011</td>
<td>13/122</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
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<tr>
<td>Gottstater, 2000</td>
<td>3/215</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
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<tr>
<td>Subramaniam, 2007</td>
<td>1/494</td>
<td>None reported</td>
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<td>None reported</td>
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<tr>
<td>Douma, 2011</td>
<td>0/168</td>
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<td>Djurabi, 2008</td>
<td>0/1057</td>
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<tr>
<td>Taira, 2010</td>
<td>0/497</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
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<tr>
<td>Abcarian, 2004</td>
<td>0/247</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
</tr>
<tr>
<td>Parent 2007</td>
<td>0/84 deaths in TN</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
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<tr>
<td>Dunn, 2002</td>
<td>0/547 deaths in TN</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
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<tr>
<td>Ray, 2007</td>
<td>0/205 deaths in TN</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
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<tr>
<td>Le Gal 2006</td>
<td>0/308</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
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<tr>
<td>Perrier, 2005</td>
<td>2/523</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
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<tr>
<td>Van Belle, 2006</td>
<td>8/1436 in TN</td>
<td>None reported</td>
<td>None reported</td>
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<table>
<thead>
<tr>
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<td>None reported</td>
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<td>None reported</td>
</tr>
<tr>
<td>Abcarian, 2004</td>
<td>0/247 in TN</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
</tr>
<tr>
<td>Parent 2007</td>
<td>0/84 in TN</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
</tr>
<tr>
<td>Den Exter 2013</td>
<td>(n=832) 4.5%</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
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<tr>
<td>Perrier, 2001</td>
<td>3/118 in TP</td>
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<td>None reported</td>
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<tr>
<td>Van Belle, 2006</td>
<td>18/1436 in TN</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
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<tr>
<td>Van Belle, 2006</td>
<td>20/674 in TP</td>
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<td>None reported</td>
<td>None reported</td>
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<tr>
<td>Courtney, 2010</td>
<td>1/332</td>
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<tr>
<td>Hemorrhagic stroke</td>
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<td>None reported</td>
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<td>-------------------</td>
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### REFERENCES.

References of Background:


Irwig L, Bossuyt P, Glasziou P, Lijmer J. Designing studies to ensure that estimates of test accuracy are transferable. BMJ 2002; 324: 669-71


Wiener RS, Schwartz LM, Woloshin S. When a test is too good: how CT pulmonary angiograms find pulmonary emboli that do not need to be found. BMJ 2013;347:f3368-f3368.

References of included accuracy studies:


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doi:10.1007/s003300050345


doi:10.1007/s003300050345


References related to natural progression:

References – SR for Baseline Risk PE Mortality in TP


References – Studies for Baseline Risk Mortality & Recurrent PE – Q3 from GL3


References – Study for Baseline Risk PE mortality, Major Bleeding & Major bleeding mortality – Q3 from GL3

References related to clinical outcomes:


Choi, Won-Ho, Sung Uk Kwon, Yoon Jung Jwa, Jung A. Kim, Yun-Ho Choi, Je Ho Chang, Hoon Jung, Joon Hyung Doh, June Namgung, Sung Yun Lee, and Won Ro Lee. 2009. 'The Pulmonary Embolism Severity Index in Predicting the Prognosis of Patients With Pulmonary Embolism', The Korean Journal of Internal Medicine, 24: 123-27.


References related to prevalence:


References related to values and preferences:


References related to cost and cost effectiveness:


References related to Acceptability, Feasibility, Equity, Implementation:


Question 3. In a patient population with a high clinical probability of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose a first episode PE?

**Diagnosis of Pulmonary Embolism: Diagnostic Pathways Assessed**

a. CTPA
- Positive CTPA → anticoagulate
- Negative CTPA → no treatment

b. CTPA
- Positive CTPA → anticoagulate
- Negative CTPA → D-dimer
  - D-dimer positive → anticoagulate
  - D-dimer negative → no treatment
c. CTPA
- Positive CTPA → anticoagulate
- Negative CTPA → D-dimer
  - D-dimer positive → proximal CUS
    - Positive proximal CUS → anticoagulate
    - Negative proximal CUS → no treatment
  - D-dimer negative → no treatment


d. CTPA
- Positive CTPA → anticoagulate
- Negative CTPA → D-dimer
  - D-dimer positive → proximal CUS
    - Positive proximal CUS → anticoagulate
    - Negative proximal CUS → serial US
      - Positive serial US → anticoagulate
      - Negative serial US → no treatment
  - D-dimer negative → no treatment
e. CTPA

- Positive CTPA → anticoagulate
- Negative CTPA → proximal CUS
  - Positive proximal CUS → anticoagulate
  - Negative proximal CUS → no treatment

f. CTPA

- Positive CTPA → anticoagulate
- Negative CTPA → proximal CUS
  - Positive proximal CUS → anticoagulate
  - Negative proximal CUS → serial US
    - Positive serial US → anticoagulate
    - Negative serial US → no treatment
g. CTPA
- Positive CTPA → anticoagulate
- Negative CTPA → VQ scan
  - High probability VQ scan → anticoagulate
  - Low/intermediate VQ scan → proximal CUS
    - Positive proximal CUS → anticoagulate
    - Negative proximal CUS → no treatment
  - Normal VQ scan → no treatment

h. CTPA
- Positive CTPA → anticoagulate
- Negative CTPA → pulmonary angiography
  - Positive pulmonary angiography → anticoagulate
  - Negative pulmonary angiography → no treatment
i. VQ scan

- High probability VQ scan → anticoagulate
- Low/intermediate probability VQ scan → CTPA
  - Positive CTPA → anticoagulate
  - Negative CTPA → no treatment
- Normal VQ scan → no treatment

j. VQ scan

- High probability VQ scan → anticoagulate
- Low/intermediate probability VQ scan → proximal CUS
  - Positive Proximal CUS → anticoagulate
  - Negative proximal CUS → no treatment
- Normal VQ scan → no treatment
k. D-dimer

- Positive D-dimer → anticoagulate
- Negative D-dimer → no treatment

![Pathway K](image)

l. D-dimer

- Positive D-dimer → CTPA
  - Positive CTPA → anticoagulate
  - Negative CTPA → no treatment
- Negative D-dimer → no treatment

![Pathway L](image)
m. D-dimer

- Positive D-dimer → VQ scan
  - High probability VQ scan → anticoagulate
  - Low/Intermediate probability VQ scan → CTPA
    - Positive CTPA → anticoagulate
    - Negative CTPA → no treatment
  - Normal VQ scan → no treatment
- Negative D-dimer → no treatment

n. D-dimer

- Positive D-dimer → VQ scan
  - High probability VQ scan → anticoagulate
  - Low/Intermediate probability VQ scan → proximal CUS
    - Positive proximal CUS → anticoagulate
    - Negative proximal CUS → no treatment
  - Normal VQ scan → no treatment
- Negative D-dimer → no treatment
o. D-dimer
- Positive D-dimer → CTPA
- Negative D-dimer → VQ Scan
  - High probability VQ scan → anticoagulate
  - Low/intermediate probability VQ scan → CTPA
    - Positive CTPA → anticoagulate
    - Negative CTPA → no treatment
  - Normal VQ scan → no treatment

```plaintext
Pathway C
Patients with suspected PE

PTP Assessment

D-Dimer

Positive
- CTPA
  - Positive CTPA → anticoagulate
  - Negative CTPA → no treatment

Negative
- VQ Scan
  - Positive VQ Scan → anticoagulate
  - Normal VQ Scan → no treatment
```

p. D-Dimer
- Positive D-Dimer → anticoagulate
- Negative D-Dimer → CTPA
  - Positive CTPA → anticoagulate
  - Negative CTPA → no treatment

```plaintext
Pathway P
Patients with suspected PE

PTP Assessment

D-Dimer

Positive
- CTPA
  - Positive CTPA → anticoagulate
  - Negative CTPA → no treatment

Negative
- VQ Scan
  - Positive VQ Scan → anticoagulate
  - Normal VQ Scan → no treatment
```
q. D-Dimer

- Positive D-Dimer → anticoagulate
- Negative D-Dimer → VQ Scan
  - High probability VQ scan → anticoagulate
  - Low/intermediate probability VQ scan → CTPA
    - Positive CTPA → anticoagulate
    - Negative CTPA → no treatment
  - Normal VQ scan → no treatment

Note: in the algorithms, watchful waiting will follow negative tests and low/normal probability unless stated otherwise.

<table>
<thead>
<tr>
<th>Legend</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
</tr>
<tr>
<td>PE</td>
</tr>
<tr>
<td>PTP</td>
</tr>
<tr>
<td>CTPA</td>
</tr>
<tr>
<td>VQ</td>
</tr>
<tr>
<td>US</td>
</tr>
<tr>
<td>CUS</td>
</tr>
</tbody>
</table>
Question 3. In a patient population with a high clinical probability of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose a first episode PE?

<table>
<thead>
<tr>
<th>POPULATION:</th>
<th>Patients with a high clinical probability of suspected first episode pulmonary embolism (PE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVALUATED TESTS:</td>
<td>CT pulmonary angiography (CTPA), D-dimer, Proximal compression ultrasound (CUS), Ventilation Perfusion (VQ) scan</td>
</tr>
<tr>
<td>PURPOSE OF THE TEST:</td>
<td>Detection of pulmonary embolism</td>
</tr>
<tr>
<td>ROLE OF THE TEST:</td>
<td>Detection of pulmonary embolism</td>
</tr>
<tr>
<td>LINKED TREATMENTS:</td>
<td>Anticoagulation</td>
</tr>
<tr>
<td>ANTICIPATED OUTCOMES:</td>
<td>False Negative; False Positive; True Negative; True Positive; Mortality; Recurrent Pulmonary Embolism; Major Bleed; Hemorrhagic Stroke</td>
</tr>
<tr>
<td>SETTING:</td>
<td>Inpatient and outpatient</td>
</tr>
<tr>
<td>PERSPECTIVE:</td>
<td>Clinical recommendation - population perspective</td>
</tr>
</tbody>
</table>
| SUBGROUPS: | 1. Population that is likely to have a diagnostic VQ scan result  
2. Population that is unlikely to have a diagnostic VQ scan result |

**BACKGROUND:**

Pulmonary embolism (PE) is a potentially life-threatening condition that may be prevented and can be treated with anticoagulant therapy (Rodger 2006). The diagnostic accuracy of a test can vary with the strength of clinical suspicion (Irwig 2002). The clinical probability of a condition can assist with determining which tests to use to diagnose PE. Standardized clinical decision rules (CDRs) are used to determine clinical probability for PE (Van Es 2012). Prevalence of disease varies depending on the clinical probability of the population. In patients with high clinical probability, prevalence of disease was deemed to be at either 50% or 75% (Ceriani 2010).

Various diagnostic tests are currently used for the diagnosis of PE including D-dimer assays, computed tomography pulmonary angiography (CTPA), ventilation perfusion (VQ) scanning, and compression ultrasonography (CUS) of the lower extremities (indirect). Imaging tests for PE such as CTPA and VQ lung scanning are expensive, time consuming and are associated with radiation exposure. In addition, the contrast used in CTPA can result in nephrotoxicity and allergic reactions. Therefore, inexpensive strategies with less risk to patients are needed to exclude PE efficiently (Bates 2016).
Assessment

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
</table>
| **Is the problem a priority?**                 | ○ No  
○ Probably no  
○ Probably yes  
● Yes  
○ Varies  
○ Don't know                                                                                                                                         |                           |
| The overall annual incidence of pulmonary emboli (PE) is quoted at 60–70 cases per 100,000. Associated with significant morbidity and mortality, prompt diagnosis and expeditious therapeutic intervention is of paramount importance for optimal patient management (Warren 2012). The fear of missing a diagnosis of this life-threatening disease has led to an increase in the use of invasive diagnostic strategies, with a significant rise of imaging studies such as computed tomographic pulmonary angiography (CTPA) or ventilation perfusion (VQ) scanning over the last decade (Smith-Bindman 2012; Schissler 2013). Subsequently, it has also been reported that PE has become over diagnosed (Wiener 2013; Sheh 2012). Physicians often order CTPA, although PE is unlikely and a D-dimer test result is negative (Adams 2013). Given that CTPA is associated with radiation exposure, nephrotoxicity and allergic reactions, VQ lung scanning may offer an option with less risk. Several clinical decision rules can estimate pretest probability for PE and guide diagnostic testing. |                           |
| **How accurate is the test?**                  | **CTPA**  
Patient or population: Patients with suspected pulmonary embolism  
New test: CTPA  
Setting: Inpatient and outpatient  
Pooled sensitivity: 0.93 (95% CI: 0.88 to 0.96) | MODERATE a,b,c             |
| ○ Very inaccurate  
○ Inaccurate  
○ Accurate  
○ Very accurate  
○ Don't know                                                                                                                                         |                           |
| ○ Very inaccurate  
○ Inaccurate  
○ Accurate  
○ Very accurate  
○ Don't know                                                                                                                                         |                           |
| **D-dimer to rule in PE**                      |                                                                                                                                             |                           |
| ○ Very inaccurate  
○ Inaccurate  
○ Accurate  
○ Very accurate  
○ Don't know                                                                                                                                         |                           |
| **D-dimer to rule out PE**                     |                                                                                                                                             |                           |
| ○ Very inaccurate  
○ Inaccurate  
○ Accurate                                                                                                                                             |                           |
| **Test result**                                | **Number of results per 1,000 patients tested (95% CI)**                                                                                      |                           |
| True positives                                 | 464 (438 to 480)  
Prevalence 50%\(^1,2\) in patients with suspected PE                                                                                 | 3929 (15)                |
| False negatives                                | 36 (20 to 62)  
Prevalence 75%\(^1,2\) in patients with suspected PE                                                                                     |                           |
| True negatives                                 | 491 (482 to 496)  
Prevalence 75%\(^1,2\) in patients with suspected PE                                                                                     |                           |
| Number of participants (studies)              | 695 (656 to 719)  
Prevalence 75%\(^1,2\) in patients with suspected PE                                                                                     |                           |
| Certainty of the Evidence (GRADE)             | 246 (241 to 248)  
Prevalence 75%\(^1,2\) in patients with suspected PE                                                                                     |                           |
| The panel noted that for CTPA the inconclusive results reported are low, and likely not reflective of the real-world setting. The panel noted that for D-dimer, a positive D-dimer result cannot be used as a standalone test to diagnose PE and initiate anticoagulant treatment. Therefore, the rating of very inaccurate applies to the diagnostic pathways where D-dimer is being used as an individual test. D-dimer is more accurate to rule out PE in low than high clinical probability patients. The panel noted that the accuracy of VQ scanning |                           |
### False positives

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positives</td>
<td>487 (480 to 492)</td>
<td>730 (719 to 737)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Count</td>
<td>95% CI</td>
<td>Certainty of Evidence</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------</td>
<td>-----------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td><strong>False negatives</strong></td>
<td>13 (8 to 20)</td>
<td>20 (13 to 31)</td>
<td>MODERATE a,b,c</td>
</tr>
<tr>
<td><strong>True negatives</strong></td>
<td>196 (179 to 214)</td>
<td>98 (90 to 107)</td>
<td>MODERATE a,b,c</td>
</tr>
<tr>
<td><strong>False positives</strong></td>
<td>304 (286 to 321)</td>
<td>152 (143 to 160)</td>
<td>MODERATE a,b,c</td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>0</td>
<td>20469 (30)</td>
<td>-</td>
</tr>
</tbody>
</table>

CI: Confidence interval
2 Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

**Explanations**

a. Certainty of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that were judged to be acceptable by a panel of clinical experts.
b. Minor inconsistency for sensitivity noted but judged to be insufficient to downgrade the certainty of evidence. Certainty of evidence was downgraded for serious unexplained inconsistency in specificity, with a range from 12.8% to 64%.
c. Certainty of evidence was downgraded for indirectness in instances where this test was not the index test in a diagnostic pathway. There was a lack of data on the accuracy of this test following a previous test in a pathway. Thus, sensitivity and specificity used for modeling in these instances were based on the test accuracy of the individual test rather than using the test in a pathway.

**Age-adjusted D-dimer**

**Patient or population:** Patients with suspected pulmonary embolism

**New test:** Age-adjusted D-dimer

**Setting:** Inpatient and outpatient

**Pooled sensitivity:** 0.99 (95% CI: 0.98 to 1.00) | **Pooled specificity:** 0.47 (95% CI: 0.45 to 0.49)
<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence 50%(^1,2) in patients with suspected PE</td>
<td>Prevalence 75%(^1,2) in patients with suspected PE</td>
<td></td>
</tr>
<tr>
<td>True positives</td>
<td>498 (492 to 500)</td>
<td>746 (738 to 749)</td>
<td>2885 (1)</td>
</tr>
<tr>
<td>False negatives</td>
<td>2 (0 to 8)</td>
<td>4 (1 to 12)</td>
<td></td>
</tr>
<tr>
<td>True negatives</td>
<td>234 (224 to 245)</td>
<td>117 (112 to 122)</td>
<td>2885 (1)</td>
</tr>
<tr>
<td>False positives</td>
<td>266 (255 to 276)</td>
<td>133 (128 to 138)</td>
<td></td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>0</td>
<td></td>
<td>2885 (1)</td>
</tr>
<tr>
<td>Complications arising from the diagnostic test</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: Confidence interval


\(^2\)Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

Explanations

\(^a\) Certainty of evidence not downgraded for imprecision given the large population size, though only one prospective age-adjusted D-dimer study was identified for analysis.

Proximal CUS

**Patient or population:** Patients with suspected pulmonary embolism

**New test:** Proximal compression ultrasound

**Setting:** Inpatient and outpatient

**Pooled sensitivity:** 0.49 (95% CI: 0.31 to 0.66) | **Pooled specificity:** 0.96 (95% CI: 0.95 to 0.98)
<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence 50%(^1,2) in patients with suspected PE</td>
<td>Prevalence 75%(^1,2) in patients with suspected PE</td>
<td></td>
</tr>
<tr>
<td>True positives</td>
<td>244 (157 to 332)</td>
<td>365 (235 to 498)</td>
<td>1715 (7)</td>
</tr>
<tr>
<td>False negatives</td>
<td>256 (168 to 343)</td>
<td>385 (252 to 515)</td>
<td>LOW (^a,b,c)</td>
</tr>
<tr>
<td>True negatives</td>
<td>483 (474 to 488)</td>
<td>241 (237 to 244)</td>
<td>LOW (^a,b,c)</td>
</tr>
<tr>
<td>False positives</td>
<td>17 (12 to 26)</td>
<td>9 (6 to 13)</td>
<td></td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>0</td>
<td>1715 (7)</td>
<td>-</td>
</tr>
<tr>
<td>Complications arising from the diagnostic test</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: Confidence interval
\(^2\)Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

Explanations
- a. Certainty of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that were judged to be acceptable by a panel of clinical experts.
- b. Certainty of evidence was downgraded for serious unexplained inconsistency in sensitivity, with range from 18.4% to 96.7%. Minor inconsistency for specificity noted but judged to be insufficient to downgrade the certainty of evidence.
- c. Certainty of evidence downgraded for indirectness because of lack of data on the accuracy of this test following a previous test in a pathway. Sensitivity and specificity used for modeling are based on the test accuracy of the individual test rather than using the test in an algorithm.

VQ 1: VQ scan with high probability scan interpreted as positive, normal/low/intermediate scan as negative
Patient or population: Patients with suspected pulmonary embolism
New test: VQ scan with high probability scan interpreted as positive, normal/low/intermediate scan as negative
### Setting:
Inpatient and outpatient

**Pooled sensitivity:** 0.58 (95% CI: 0.50 to 0.66)  |  **Pooled specificity:** 0.98 (95% CI: 0.96 to 0.99)

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence 50%(^1,2) in patients with suspected PE</td>
<td>Prevalence 75%(^1,2) in patients with suspected PE</td>
<td></td>
</tr>
<tr>
<td>True positives</td>
<td>289 (248 to 329)</td>
<td>434 (372 to 493)</td>
<td>3994 (13)</td>
</tr>
<tr>
<td>False negatives</td>
<td>211 (171 to 252)</td>
<td>316 (257 to 378)</td>
<td>MODERATE (^{a,b,c})</td>
</tr>
<tr>
<td>True negatives</td>
<td>492 (482 to 497)</td>
<td>246 (241 to 248)</td>
<td>3994 (13)</td>
</tr>
<tr>
<td>False positives</td>
<td>8 (3 to 18)</td>
<td>4 (2 to 9)</td>
<td>MODERATE (^{a,b,c})</td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>1849</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications arising from the diagnostic test</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CI:** Confidence interval


\(^2\) Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

**Explanations**

a. Certainty of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that were judged to be acceptable by a panel of clinical experts.

b. Certainty of evidence was downgraded for serious unexplained inconsistency in sensitivity, with a range from 13.9% to 84.6%. Minor inconsistency for specificity noted but judged to be insufficient to downgrade the certainty of evidence.

c. Certainty of evidence was downgraded for indirectness in instances where this test was not the index test in a diagnostic pathway. There was a lack of data on the accuracy of this test following a previous test in a pathway. Thus, sensitivity and specificity used for modeling in these instances were based on the test accuracy of the individual test rather than using the test in a pathway.
**VQ 2: VQ scan with high/intermediate/low probability scan interpreted as positive, normal scan as negative**

**Patient or population:** Patients with suspected pulmonary embolism  
**New test:** VQ scan with high/intermediate/low probability scan interpreted as positive, normal scan as negative  
**Setting:** Inpatient and outpatient  
**Pooled sensitivity:** 0.98 (95% CI: 0.95 to 0.99) | **Pooled specificity:** 0.36 (95% CI: 0.27 to 0.45)  

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence 50%&lt;sup&gt;1,2&lt;/sup&gt; in patients with suspected PE</td>
<td>Prevalence 75%&lt;sup&gt;1,2&lt;/sup&gt; in patients with suspected PE</td>
<td></td>
</tr>
<tr>
<td>True positives</td>
<td>490 (477 to 496)</td>
<td>734 (716 to 743)</td>
<td>3994 (13)</td>
</tr>
<tr>
<td>False negatives</td>
<td>10 (4 to 23)</td>
<td>16 (7 to 34)</td>
<td>3994 (13)</td>
</tr>
<tr>
<td>True negatives</td>
<td>178 (134 to 227)</td>
<td>89 (67 to 114)</td>
<td>3994 (13)</td>
</tr>
<tr>
<td>False positives</td>
<td>322 (273 to 366)</td>
<td>161 (136 to 183)</td>
<td>3994 (13)</td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>1849</td>
<td>3994 (13)</td>
<td>-</td>
</tr>
</tbody>
</table>

**Complications arising from the diagnostic test**  
Not reported

---

**CI:** Confidence interval  
<sup>2</sup>Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.  

**Explanations**  
a. Certainty of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that were judged to be acceptable by a panel of clinical experts.  
b. Minor inconsistency for sensitivity noted but judged to be insufficient to downgrade the certainty of evidence. Certainty of evidence was downgraded for serious unexplained inconsistency in specificity, with a range from 10.9% to 81.8%.
c. Certainty of evidence was downgraded for indirectness in instances where this test was not the index test in a diagnostic pathway. There was a lack of data on the accuracy of this test following a previous test in a pathway. Thus, sensitivity and specificity used for modeling in these instances were based on the test accuracy of the individual test rather than using the test in a pathway.

VQ 3: VQ scan with high probability scan as positive, normal scan as negative
Patient or population: Patients with suspected pulmonary embolism
New test: VQ scan with high probability scan as positive, normal scan as negative
Setting: Inpatient and outpatient
Pooled sensitivity: 0.96 (95% CI: 0.91 to 0.98) | Pooled specificity: 0.95 (95% CI: 0.89 to 0.98)

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence 50%(^1,2) in patients with suspected PE</td>
<td>Prevalence 75%(^1,2) in patients with suspected PE</td>
<td></td>
</tr>
<tr>
<td>True positives</td>
<td>481 (457 to 492)</td>
<td>722 (686 to 738)</td>
<td>1799 (13)</td>
</tr>
<tr>
<td>False negatives</td>
<td>19 (8 to 43)</td>
<td>28 (12 to 64)</td>
<td></td>
</tr>
<tr>
<td>True negatives</td>
<td>476 (443 to 491)</td>
<td>238 (221 to 245)</td>
<td>1799 (13)</td>
</tr>
<tr>
<td>False positives</td>
<td>24 (9 to 57)</td>
<td>12 (5 to 29)</td>
<td></td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>0</td>
<td></td>
<td>1799 (13)</td>
</tr>
<tr>
<td>Complications arising from the diagnostic test</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: Confidence interval
\(^1\)Ceriani E et al. J Thromb Haemost 2010;8(5):957
\(^2\) Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.
Explanations

a. Certainty of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that were judged to be acceptable by a panel of clinical experts.

b. Minor inconsistency for sensitivity noted but judged to be insufficient to downgrade the certainty of evidence. Minor inconsistency for specificity noted but judged to be insufficient to downgrade the certainty of evidence.

c. Certainty of evidence was downgraded for indirectness in instances where this test was not the index test in a diagnostic pathway. There was a lack of data on the accuracy of this test following a previous test in a pathway. Thus, sensitivity and specificity used for modeling in these instances were based on the test accuracy of the individual test rather than using the test in a pathway.
<table>
<thead>
<tr>
<th>Judgment</th>
<th>Research Evidence</th>
<th>Additional Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CERTAINTY OF THE EVIDENCE OF TEST ACCURACY</strong></td>
<td></td>
<td>The panel noted that the certainty of evidence of age-adjusted D-dimer may incorrectly appear to be higher than D-dimer due to the limited number of studies on age-adjusted D-dimer.</td>
</tr>
<tr>
<td>What is the overall certainty of the evidence of test accuracy?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Very low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Low (Proximal CUS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Moderate (CTPA, D-dimer, VQ scan)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ High (Age-adjusted D-dimer, High probability/Normal VQ scan)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ No included studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CERTAINTY OF THE EVIDENCE OF MANAGEMENT’S EFFECTS</strong></td>
<td></td>
<td>The panel noted there is no direct benefit for any of the diagnostic pathways. There is a burden with serial ultrasound for patients having to return to the hospital. The data varies on the adverse effects associated with radiation exposure, contrast-induced nephropathy, allergy to contrast, or contrast extravasation associated with CTPA or radiation and perfusion agent risks associated with VQ scan.</td>
</tr>
<tr>
<td>What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the pathway?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Very low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Varies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ No included studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT</td>
<td>How certain is the link between pathway results and management decisions?</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>○ Very low</td>
<td>The link between test results and management is unique in venous thromboembolism. With PE diagnosis, positive results will be treated with anticoagulation (regardless of the chances of false positives).</td>
<td></td>
</tr>
<tr>
<td>○ Low</td>
<td>The panel noted high certainty in the link between test results and management decisions. However, the panel also noted that for patients with sub-segmental PE, the link may not be as certain.</td>
<td></td>
</tr>
<tr>
<td>○ Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ No included studies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CERTAINTY OF EFFECTS</th>
<th>What is the overall certainty of the evidence of effects of the pathway?</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Very low</td>
<td></td>
</tr>
<tr>
<td>○ Low</td>
<td></td>
</tr>
<tr>
<td>○ Moderate</td>
<td></td>
</tr>
<tr>
<td>○ High</td>
<td></td>
</tr>
<tr>
<td>○ No included studies</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VALUES</th>
<th>Is there important uncertainty or variability in how people value different outcomes?</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Important uncertainty or variability</td>
<td>The numbers shown below are utilities, representing the strength of an individual’s preferences for different outcomes. They are measured on a scale, with zero reflecting states of health equivalent to death/worst imaginable health and one reflecting perfect health/ best imaginable health.</td>
</tr>
<tr>
<td>○ Possibly important uncertainty or variability</td>
<td>Systematic reviews found that the relative importance of the outcomes is as follows:</td>
</tr>
<tr>
<td>○ Probably no important uncertainty or variability</td>
<td>Pulmonary embolism: 0.63-0.93 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004)</td>
</tr>
<tr>
<td>○ No important uncertainty or variability</td>
<td>Deep vein thrombosis: 0.64-0.99 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016)</td>
</tr>
<tr>
<td></td>
<td>Deep vein thrombosis patients' own current health: 0.95 (Time trade off) (Locadia 2004)</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg 2013, Locadia 2004)</td>
</tr>
<tr>
<td></td>
<td>Minor intracranial bleeding event: 0.75 (standard gamble) (Hogg 2013)</td>
</tr>
<tr>
<td></td>
<td>The panel placed a high value on decreasing the number of false negative test results over decreasing false positive test results.</td>
</tr>
<tr>
<td></td>
<td>The panel also placed a high value on decreasing radiation exposure and reducing the number of tests required in a diagnostic pathway.</td>
</tr>
<tr>
<td></td>
<td>The panel considered that there would not</td>
</tr>
</tbody>
</table>
Major intracranial bleeding event: 0.15 (standard gamble) (Hogg 2013) Central nervous system bleeding: 0.29-0.60 (standard gamble) (Lenert 1997, O’Meara 1994)

Studies additionally described the following regarding the relative importance of outcomes and patients’ preferences:

In a survey study (Geyer 2014) based on a shared decision-making model, the researchers provided patients with a standardized description of the diagnostic workup for PE, described the risks of CTPA in low pretest probability patients and the risks of deferring imaging assuming a D-dimer was less than twice the value normally considered positive. With the decision aid, of the 203 patients in the study, 63% of patients favored undergoing CTPA; while seventy-four patients (37%) elected to defer CTPA. The mostly frequent reasons for decline include risk of malignancy, contrast-induced nephropathy, or allergy. Other than those common reasons, 20 patients deferred CTPA testing because they believed it was unnecessary. Patients with a previous PE diagnosis were less likely to defer CTPA testing. Most patients (n=109 [85%]) who accepted CTPA testing, had concerns about missing a PE.

Results of Panel Utility Rating Survey:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean Utility Rating (SD) All Panels (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>False Negative Test Result</td>
<td>0.60 (0.23)</td>
</tr>
<tr>
<td>False Positive Test Result</td>
<td>0.62 (0.21)</td>
</tr>
<tr>
<td>True Negative Test Result</td>
<td>0.91 (0.15)</td>
</tr>
<tr>
<td>True Positive Test Result</td>
<td>0.76 (0.19)</td>
</tr>
<tr>
<td>Inconclusive Test Result</td>
<td>0.69 (0.18)</td>
</tr>
<tr>
<td>Radiation Exposure</td>
<td>0.84 (0.14)</td>
</tr>
<tr>
<td>Contrast Induced Nephropathy</td>
<td>0.56 (0.20)</td>
</tr>
<tr>
<td>Pulmonary Embolism – Moderate Marker State</td>
<td>0.42 (0.15)</td>
</tr>
<tr>
<td>Proximal DVT – Moderate Marker State</td>
<td>0.58 (0.14)</td>
</tr>
<tr>
<td>Distal DVT – Moderate Marker State</td>
<td>0.64 (0.16)</td>
</tr>
<tr>
<td>Upper Extremity DVT – Moderate Marker State</td>
<td>0.61 (0.16)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>0.33 (0.23)</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>0.12 (0.10)</td>
</tr>
<tr>
<td>Chronic Thrombotic Pulmonary Hypertension</td>
<td>0.34 (0.15)</td>
</tr>
</tbody>
</table>

* Utility rating by panel members from 0 (dead) to 1 (full health)

Desirable and undesirable effects:
desirable and undesirable effects to which provides the least balance.

The panel judged the ranking of the pathways based on a threshold of false negative patients and a threshold of misdiagnosed patients (combination of false negative and false positive results).

Pathways highlighted in green were judged as the top ranked pathways that provided the best balance of desirable and undesirable effects. These pathways remained below a threshold of 20 false negative results per 1000 patients tested (≤2%) and a threshold of 50 misdiagnosed results per 1000 patients tested (≤5%).

Pathways highlighted in yellow provided a less acceptable balance of desirable and undesirable effects. These pathways remained below a threshold of 50 false negative results per 1000 pathways A-H begin with CTPA
Pathways I-J begin with VQ
Pathways K-Q begin with D-dimer

Table 1: In a patient population with a high clinical probability (50%) of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose a first episode PE?

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>TP</td>
<td>465</td>
</tr>
<tr>
<td>FP</td>
<td>10</td>
</tr>
<tr>
<td>TN</td>
<td>490</td>
</tr>
<tr>
<td>FN</td>
<td>35</td>
</tr>
</tbody>
</table>

Table 1: Continued

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>K</td>
</tr>
<tr>
<td>TP</td>
<td>485</td>
</tr>
<tr>
<td>FP</td>
<td>305</td>
</tr>
<tr>
<td>TN</td>
<td>195</td>
</tr>
<tr>
<td>FN</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 2: In a patient population with a high clinical probability (75%) of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose a first episode PE?

The panel considered desirable effects as increasing the number of patients with true positive and true negative test results (i.e. patients accurately diagnosed and treated).

The panel considered undesirable as increasing the number of patients with false positive and false negative test results (i.e. receive unnecessary anticoagulation or morbidity/mortality from missed diagnosis).

The panel noted that for CTPA, alternate diagnoses may be revealed which would be a desirable effect. This is an effect that does not extend to VQ scanning, which is intended for PE diagnosis only.

The panel noted radiation exposure as a concern with CTPA, but weighed it with acceptance of the risk to obtain a definitive and quick diagnosis.
patients tested (≤5%) and 100 misdiagnosed results per 1000 patients (≤10%).

Pathways highlighted in red did not provide an acceptable balance of desirable and undesirable effects and were ranked lowest. These pathways were above the threshold of 50 false negative results per 1000 patients (>5%) and 100 misdiagnosed results per 1000 patients (>10%).

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G1</th>
<th>G2</th>
<th>H</th>
<th>I1</th>
<th>I2</th>
<th>J1</th>
<th>J2</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP</td>
<td>698</td>
<td>748</td>
<td>722</td>
<td>735</td>
<td>723</td>
<td>736</td>
<td>743</td>
<td>733</td>
<td>750</td>
<td>716</td>
<td>707</td>
<td>650</td>
<td>509</td>
</tr>
<tr>
<td>FP</td>
<td>5</td>
<td>154</td>
<td>9</td>
<td>14</td>
<td>12</td>
<td>19</td>
<td>16</td>
<td>14</td>
<td>5</td>
<td>11</td>
<td>8</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>TN</td>
<td>245</td>
<td>96</td>
<td>241</td>
<td>236</td>
<td>238</td>
<td>231</td>
<td>234</td>
<td>236</td>
<td>245</td>
<td>239</td>
<td>242</td>
<td>239</td>
<td>241</td>
</tr>
<tr>
<td>FN</td>
<td>53</td>
<td>2</td>
<td>28</td>
<td>15</td>
<td>27</td>
<td>14</td>
<td>7</td>
<td>17</td>
<td>0</td>
<td>35</td>
<td>44</td>
<td>101</td>
<td>242</td>
</tr>
</tbody>
</table>

Table 2: Continued

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>K</th>
<th>L</th>
<th>M1</th>
<th>M2</th>
<th>N1</th>
<th>N2</th>
<th>O1</th>
<th>O2</th>
<th>P</th>
<th>Q1</th>
<th>Q2</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP</td>
<td>728</td>
<td>677</td>
<td>694</td>
<td>685</td>
<td>630</td>
<td>493</td>
<td>698</td>
<td>698</td>
<td>748</td>
<td>749</td>
<td>749</td>
</tr>
<tr>
<td>FP</td>
<td>153</td>
<td>3</td>
<td>7</td>
<td>5</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td>154</td>
<td>157</td>
<td>156</td>
<td></td>
</tr>
<tr>
<td>TN</td>
<td>98</td>
<td>247</td>
<td>243</td>
<td>245</td>
<td>243</td>
<td>244</td>
<td>243</td>
<td>244</td>
<td>96</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>FN</td>
<td>23</td>
<td>73</td>
<td>56</td>
<td>65</td>
<td>120</td>
<td>257</td>
<td>52</td>
<td>52</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

TP - patient correctly identified as having PE and anticoagulated
FP - patient incorrectly identified as having PE and unnecessarily anticoagulated
TN - patient correctly identified as not having PE and not anticoagulated
FN - patient incorrectly identified as not having PE and will not receive needed anticoagulation

Assumptions associated with modelling:
1. Disease prevalence in a high clinical probability population was determined be 500 per 1000 patients (50%) or 750 per 1000 patients (75%).
2. Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.
3. The panel judged the ranking of pathways with the best balance of desirable and undesirable effects based on thresholds of false negative patients and misdiagnosed patients (false negative and false positive). These rankings are depicted in the table as green being the most acceptable, yellow being less acceptable, and red being unacceptable.

Balance of desirable and undesirable effects:
For this guideline question, in addition to the diagnostic test accuracy outcomes, the panel considered two key criteria in determining which pathways provided the best balance of desirable and undesirable effects, which were minimizing radiation exposure and minimizing the number of tests used.

These two criteria were considered in determining which of the pathways that met the acceptable thresholds for diagnostic test accuracy (i.e. the pathways highlighted in green), provided the best balance of effects.
4. Due to the lack of data on accuracy of serial ultrasound, the sensitivity and specificity for proximal compression ultrasound was used to represent serial ultrasound. In addition, serial ultrasound was determined to be one follow-up test after initial ultrasound.

5. Test accuracy for CTPA, D-dimer and proximal CUS were derived from these tests being used as a standalone test. These sensitivity and specificity results were used when the test was the first test of the pathway. These accuracy results were also used if the test was a subsequent test in a pathway.

6. The panel recognized two distinct populations undergoing VQ scan: patients likely to have a diagnostic scan (high probability or normal result) versus patients likely to have a non-diagnostic scan (low/intermediate probability). In the first population, it was assumed 80% would have a diagnostic scan and 20% would be non-diagnostic. Sensitivity analyses was completed to reveal no change in accuracy results of an alternative distribution with 70% diagnostic and 30% non-diagnostic scans. In the second population, it was assumed 40% of patients would have a diagnostic scan and 60% would be non-diagnostic.

7. For patients undergoing VQ scan, we assumed patients with normal or very low probability results would not be anticoagulated. Low or intermediate probability (non-diagnostic) scans would always be followed up with subsequent testing. Patients with high probability scans would be anticoagulated.

Table 3: Data abstraction from studies with data on direct pathways

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Outcomes</th>
<th>L 5%</th>
<th>L 20%</th>
<th>L 50%</th>
<th>L 75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP</td>
<td></td>
<td>48</td>
<td>191</td>
<td>477</td>
<td>715</td>
</tr>
<tr>
<td>FP</td>
<td></td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>TN</td>
<td></td>
<td>945</td>
<td>786</td>
<td>497</td>
<td>249</td>
</tr>
<tr>
<td>FN</td>
<td></td>
<td>2</td>
<td>9</td>
<td>23</td>
<td>35</td>
</tr>
</tbody>
</table>


## Contrast induced nephropathies, allergic reactions, and extravasation

<table>
<thead>
<tr>
<th>Index test</th>
<th>Reference test</th>
<th>Safety Outcome (as defined by study)</th>
<th>Incidence and details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ost 2001</td>
<td>CT</td>
<td>Contrast induced nephropathy/ARF</td>
<td>Creatinine was not serially measured throughout study. However, increase in creatinine 0.01 +/- 0.38 mg/dL noted in CT only group without conventional angiography and 0.2 +/- 0.9 mg/dL in the CT + conventional angiography group. 3/103 (3%) patients had an increase in creatinine greater than 1 mg/dL with max of 7.2 mg/dL. All returned to the normal reference range at 3-month follow up.</td>
</tr>
<tr>
<td>Pesavento 2011</td>
<td>CT</td>
<td>None</td>
<td>Severe acute renal failure</td>
</tr>
<tr>
<td>Stein 2006</td>
<td>CT</td>
<td>CC</td>
<td>Allergic reaction</td>
</tr>
<tr>
<td>Yazici 2016</td>
<td>CT</td>
<td>None</td>
<td>Contrast nephropathy</td>
</tr>
<tr>
<td>Coche 2003</td>
<td>CT</td>
<td>CT, VQ</td>
<td>Contrast nephropathy</td>
</tr>
<tr>
<td>Mitchell 2006</td>
<td>CT</td>
<td>None</td>
<td>Contrast nephropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe acute renal failure</td>
</tr>
<tr>
<td>Righini 2008</td>
<td>PW (DD-leg US-CT)</td>
<td>APW (DD-CT)</td>
<td>Allergic reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Extravasation of contrast</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe acute renal failure</td>
</tr>
</tbody>
</table>

DD = D-dimer; PW = pathway; APW = alternative pathway; CT=Computed Tomography; PA=Pulmonary Angiography; VQ=Ventilation Perfusion Scan; ARF=Acute Renal Failure

References:


**Radiation exposure associated with CTPA**

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Estimated ‘effective dose’ of radiation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT: Chest</td>
<td>4.5 mSv (range 3.8-5.2 mSv) 5.2 mSv Range: 2.7 - 15 mSv</td>
<td>Phillips, 2015 Kanal, 2017 Jones, 2012 and Janbabanezhad, 2015</td>
</tr>
<tr>
<td>VQ</td>
<td>2.2 mSv 2.5 mSv</td>
<td>Jones, 2012 Phillips, 2015 Mettler, 2008</td>
</tr>
</tbody>
</table>


In Hurwitz et al, estimated relative risks for breast and lung cancer incidences were 1.002–1.011 and 1.005–1.022, respectively. In addition, Brenner and Elliston estimated the lifetime attributable cancer death risk in 45-year-old adults who underwent a full-body CT test to be around 0.08%. The relationship between radiation exposure to cancer induction was limited and incredibly variable in literature and, therefore, not modelled.

### RESOURCES REQUIRED

#### How large are the resource requirements (costs) for CTPA?
- **Large costs**
- **Moderate costs**
- **Negligible costs and savings**
- **Moderate savings**
- **Large savings**
- **Don't know**

#### How large are the resource requirements (costs) for D-Dimer?
- **Large costs**
- **Moderate costs**
- **Negligible costs and savings**
- **Moderate savings**
- **Large savings**
- **Don't know**

#### How large are the resource requirements (costs) for Proximal CUS?
- **Large costs**
- **Moderate costs**
- **Negligible costs and savings**
- **Moderate savings**
- **Large savings**
- **Don't know**

---

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Peer-review articles and Other sources</th>
<th>CPT (Current Procedural Terminology)-4 Codes/cost 1,2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CTPA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-dimer test</td>
<td>$256 ($271 in 2017) 4,5</td>
<td></td>
</tr>
<tr>
<td><strong>Chest</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Computed tomographic angiography, chest</td>
<td>Computed tomography: $500 ($650 in 2017) 6 655.85 7</td>
<td>71275 - CT angiography chest</td>
</tr>
<tr>
<td>Other sources:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$300-$400</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ventilation/perfusion lung scan</strong></td>
<td>$400 ($520 in 2017) 6</td>
<td>78580 - Lung perfusion imaging</td>
</tr>
<tr>
<td>Other sources:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$300-$400</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary angiography</strong></td>
<td>Angiography: $1000 ($1300 in 2017) 6</td>
<td>76604 - US exam chest</td>
</tr>
<tr>
<td><strong>Ultrasoundography</strong></td>
<td>Compression ultrasonography: $200 ($260 in 2017) 6 602.30 7</td>
<td>76856-US exam pelvic complete</td>
</tr>
<tr>
<td>Other sources:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>leg/foot: $133-$233</td>
<td></td>
<td></td>
</tr>
<tr>
<td>abdomen/hip/pelvis: $77-$300</td>
<td>93970 - Extremity study</td>
<td></td>
</tr>
<tr>
<td>Compression ultrasound of extremity veins</td>
<td>93970 - Extremity study</td>
<td>Facility/Non-Facility price: $33.34-262.08</td>
</tr>
<tr>
<td>Opps Facility/Non-Facility payment amount:</td>
<td>$191.98-345.03</td>
<td></td>
</tr>
<tr>
<td>Duplex scan of lower extremities</td>
<td>93970 - Lower extremity study</td>
<td>Facility/Non-Facility price: $37.86 - $361.27</td>
</tr>
<tr>
<td>Opps Facility/Non-Facility payment amount:</td>
<td>$191.52 - $350.20</td>
<td></td>
</tr>
<tr>
<td><strong>Venography, extremity</strong></td>
<td>75820 - Vein x-ray arm/leg</td>
<td></td>
</tr>
<tr>
<td>Facility/Non-Facility price: $33.34-149.42</td>
<td>93970 - Lower extremity study</td>
<td>Facility/Non-Facility price: $33.34-262.08</td>
</tr>
<tr>
<td>Opps Facility/Non-Facility payment amount:</td>
<td>$191.98-345.03</td>
<td></td>
</tr>
<tr>
<td><strong>requirements (costs) for serial CUS?</strong></td>
<td>Opps Facility/Non-Facility payment amount: $580.65-964.81</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>○ Large costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ <strong>Moderate costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Negligible costs and savings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Moderate savings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Large savings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Don't know</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>How large are the resource requirements (costs) for VQ scan?</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Large costs</td>
<td></td>
</tr>
<tr>
<td>○ Moderate costs</td>
<td></td>
</tr>
<tr>
<td>○ Negligible costs and savings</td>
<td></td>
</tr>
<tr>
<td>○ Moderate savings</td>
<td></td>
</tr>
<tr>
<td>○ Large savings</td>
<td></td>
</tr>
<tr>
<td>○ Don't know</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>How large are the resource requirements (costs) for pulmonary angiography?</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Large costs</td>
<td></td>
</tr>
<tr>
<td>○ Moderate costs</td>
<td></td>
</tr>
<tr>
<td>○ Negligible costs and savings</td>
<td></td>
</tr>
<tr>
<td>○ Moderate savings</td>
<td></td>
</tr>
<tr>
<td>○ Large savings</td>
<td></td>
</tr>
<tr>
<td>○ Don't know</td>
<td></td>
</tr>
</tbody>
</table>

References:


18. 1 US dollar in 2012 equals to about $1.0662 in 2017 (http://www.in2013dollars.com/)


20. Based on CADTH report; The cost consists of diagnostic tests costs and physician interpretation cost, and it is in Canadian dollars in 2017.

21. https://pricinghealthcare.com/prices/CenterForMedicalImaging
<table>
<thead>
<tr>
<th>CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES</th>
<th>What is the certainty of the evidence of resource requirements (costs) for CTPA?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>○ Very low</td>
</tr>
<tr>
<td></td>
<td>○ Low</td>
</tr>
<tr>
<td></td>
<td>○ Moderate</td>
</tr>
<tr>
<td></td>
<td>○ High</td>
</tr>
<tr>
<td></td>
<td>○ No included studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What is the certainty of the evidence of resource requirements (costs) for D-Dimer?</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Very low</td>
</tr>
<tr>
<td>○ Low</td>
</tr>
<tr>
<td>○ Moderate</td>
</tr>
<tr>
<td>○ High</td>
</tr>
<tr>
<td>○ No included studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What is the certainty of the evidence of resource requirements (costs) for proximal CUS?</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Very low</td>
</tr>
<tr>
<td>○ Low</td>
</tr>
<tr>
<td>○ Moderate</td>
</tr>
<tr>
<td>○ High</td>
</tr>
<tr>
<td>○ No included studies</td>
</tr>
</tbody>
</table>

The panel noted uncertainty in the actual costs of the tests.
<table>
<thead>
<tr>
<th>resource requirements (costs) for serial CUS?</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Very low</td>
</tr>
<tr>
<td>○ <strong>Low</strong></td>
</tr>
<tr>
<td>○ Moderate</td>
</tr>
<tr>
<td>○ High</td>
</tr>
<tr>
<td>○ No included studies</td>
</tr>
</tbody>
</table>

**What is the certainty of the evidence of resource requirements (costs) for VQ scan?**

| ○ Very low |
| ○ **Low**  |
| ○ Moderate |
| ○ High     |
| ○ No included studies                      |

**What is the certainty of the evidence of resource requirements (costs) for Pulmonary Angiography?**

| ○ Very low |
| ○ **Low**  |
| ○ Moderate |
| ○ High     |
| ○ No included studies                      |
Cost effectiveness of diagnostic pathways evaluated

The panel judged pathways starting with a D-dimer test as most cost-effective considering the lower cost of the test.

We identified the following in our systematic review of cost-effectiveness:

CTPA:
Evidence on the cost-effectiveness of CTPA is inconsistent. The included studies varied in regards to the compared strategy, the setting, the time frame, and the methods. In general, a CTPA strategy was considered effective, mostly associated with improved survival. Whether it is cost-effective or not is still uncertain in the literature.

In Batalles 2009, CTPA was cost-effective compared with pulmonary magnetic resonance angiography, and was the most effective strategy. A study by van Erkel et al (van Erkel 1996) found that CTPA reduces mortality and improves cost-effectiveness in the diagnostic workup of suspected PE when compared with VQ scanning, compression US, D-dimer assay, and conventional angiography strategies. In Oudkerk 1993, compared with the treatment for all strategy with lowest mortality but highest cost, pulmonary angiography strategies with or without prior VQ lung scanning and ultrasonography of the legs have comparable low mortality and morbidity rates, costs savings of approximately 40%, and inappropriate treatment in fewer than 5% of patients. Paterson et al (Paterson 2001) found higher costs for CTPA as the initial diagnostic test but with improved expected survival when compared with a gradual algorithm of VQ scanning ± compression US ± CTPA.

In Doyle 2004, researchers in the US conducted a decision analytic model on diagnostic tests of PE in women, to determine which strategy is the most cost-effective with the least number of deaths from PE. Of the strategies compared (compression US, VQ scanning, and spiral CT), spiral CT as the initial diagnostic regimen was found to be the most cost-effective at $17,208 per life saved. In contrast, Henschke et al (Henschke 1994) concluded CTPA was not cost-effective compared with ultrasound.


D-Dimer:
Several cost-effectiveness analyses compared the diagnostic strategies with D-dimer, and use CTPA according to the D-dimer with other strategies, including no test, or treatment for all, or universal CTPA or VQ scan. In general, the strategy of combining D-dimer with other diagnostic testing was suggested to be cost-effective, or cost-saving. (Duriseti 2010, Duriseti 2006, Elias 2004, Humphreys 2004, Lee 2011, Perrier 1997, Perrier 2003, Righini 2007, Van Beek 1996, Van Erkel 1996)

Proximal CUS:
No evidence identified on the cost-effectiveness of proximal compression ultrasound.
VQ Scan:
Cost-effectiveness analyses compared VQ scan versus other diagnosis strategies. None of the reports compared VQ scan with CTPA suggested VQ scan was cost-effective (Batalles 2009, Doyle 2004, Paterson 2001, and van Erkel 1996). While another report suggested VQ scan is cost-effective compared with CT alone (Larcos 2000), with 20.1 additional lives saved per 1,000 patients, at a cost of $940 per life year gained.


<table>
<thead>
<tr>
<th>EQUITY</th>
<th>Impact on health equity of diagnostic pathways evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The panel judged the pathways requiring the least number of tests as having the least impact, and not decreasing health equity.</td>
</tr>
<tr>
<td></td>
<td>We identified the following regarding the impact on health equity with the different tests:</td>
</tr>
<tr>
<td></td>
<td><strong>CTPA:</strong> No research evidence identified.</td>
</tr>
<tr>
<td></td>
<td><strong>D-Dimer:</strong> Canadian provinces with larger populations tended to have a large proportion of hospitals with the capability to measure D-dimer levels for VTE diagnosis, whereas less populated provinces were more likely to send samples to centralized analysis facilities for D-dimer testing. (Southern 2014)</td>
</tr>
<tr>
<td></td>
<td><strong>Proximal CUS:</strong> No research evidence identified.</td>
</tr>
<tr>
<td></td>
<td><strong>VQ Scan:</strong> No research evidence identified.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACCEPTABILITY</th>
<th>Acceptability of diagnostic pathways evaluated to key stakeholders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The panel considered all pathways evaluated as acceptable.</td>
</tr>
<tr>
<td></td>
<td>Studies described the following regarding acceptability from key stakeholders:</td>
</tr>
<tr>
<td></td>
<td><strong>General (Radiology &amp; Population):</strong></td>
</tr>
<tr>
<td></td>
<td>A survey assessing the knowledge/practice patterns of emergency department (ED) physicians related to radiation exposure showed that 9 out of 10 preferred VQ scanning for patients &lt;30 years of age or those with a history of recent CT scans when diagnosing PE, which was confirmed by retrospective chart review. Physican knowledge of precise radiation exposure for each diagnostic test was low, but the majority were aware that VQ scans exposed patients to less radiation than CTPA. (Ahn 2014)</td>
</tr>
<tr>
<td></td>
<td>In a study among nursing home patients with suspected VTE, referral for additional diagnostic investigations was withheld in almost 40%. In providers’ decisions to forgo diagnostic investigations, they incorporated the estimated relative impact of the potential disease; the potential net-benefits of diagnostic investigations and</td>
</tr>
</tbody>
</table>

The panel noted that for pathways starting with CTPA, adding any further testing will have no impact, and additional tests would therefore disadvantage patients in low income categories.
whether performing investigations agreed with established management goals in advance care planning. (Schouten 2014)

A study among physicians who had previously referred patients for any VTE screening examination showed that physicians had a lack of basic knowledge regarding lower extremity venous anatomy, charges for the different diagnostic tests used to diagnose VTE, and current treatment standards for VTE. (Zierler 2002)

CTPA
A survey among 62 radiologists and 52 ED physicians showed that CT is the overwhelmingly preferred technique for the diagnosis of PE. (Jha 2010)

D-Dimer alone or in combination with other imaging test:
Thrombosis and hemostasis specialists reported that just over half uses D-dimer for diagnosing DVT and two-thirds for diagnosing PE. 30% relied on clinical judgment to assess pre-clinical probability for DVT and 41% for PE. (Squizzato 2010)
There are at least 28 different combinations of measurement units used to report D-dimer results for thrombotic disorders worldwide as reported by providers. The majority used fixed cut-off rather than age-adjusted threshold values for D-dimer. (Lippi 2015)

CTPA or VQ scan following a negative or positive D-Dimer:
Of ED patients with a suspected VTE and a negative D-dimer result 14% underwent at least 1 imaging study, and of patients with a positive D-dimer result 48% did not undergo imaging. (Teismann 2009)
A survey among 62 radiologists and 52 ED physicians showed that CT is the overwhelmingly preferred technique for the diagnosis of PE. The role of ventilation–perfusion scintigraphy increases when the use of iodinated contrast material is contraindicated and MRI does not seem to have an important role in practice. (Jha 2010)
More than half of CTPAs for PE were avoidable and 12% of CTPAs were done on patients with low risk and negative D-dimer assay. (Perelas 2014, Perelas 2015)

Proximal CUS:
Patient level of discomfort during point-of-care US of the heart, lungs and deep veins for respiratory symptoms is very low and the vast majority of patients would accept being assessed by this method if the patients once again had to be examined for possible disease. (Laursen 2015)

VQ Scan and CTPA
A survey among 62 radiologists and 52 ED physicians showed that CT is the overwhelmingly preferred technique for the diagnosis of PE. The role of VQ scanning increases when the use of iodinated contrast material is contraindicated and MRI does not seem to have an important role in practice. (Jha 2010)
### Feasibility to implement diagnostic pathways evaluated

The panel considered all pathways as feasible, however noting specific considerations for feasibility of testing with VQ scan, D-dimer, and proximal CUS.

### General (Radiology & Population):

**Feasibility:**
A retrospective chart review showed that there was substantial variation in utilization and diagnostic yield of advanced radiography for PE, which was largely explained by patient-, hospital- and provider-level characteristics. (Kindermann 2014)

A prospective cohort study among outpatients with suspected PE from ED’s showed that 43% received inappropriate diagnostic management. Risk factors associated with inappropriate diagnostic management were age >75 years, heart failure, chronic lung disease, current or recent pregnancy, currently receiving anticoagulation, and the lack of a written diagnostic algorithm and clinical probability scoring in the ED. Inappropriate management was associated with thromboembolism occurrence. (Roy 2006)

**Implementation:**
A study assessing the impact of a hospital-based educational and form-based intervention on clinician adherence to diagnostic imaging guidelines for suspected PE found improved adherence among clinicians who received the intervention. Failure to adhere with diagnostic imaging guidelines when requesting radiological testing was common. (Agarwal 2012)

### CTPA:

**Feasibility:**
A retrospective study on CTPA examinations showed that there was considerable inter-physician variability in the utilization and PE positivity rates of CTPA within a single institution. (Chen 2015)

A chart review with 3-month phone follow-up among ED patients undergoing investigations for suspected PE showed that compliance with a clinical pathway was more likely if exclusively done by ED physicians and was associated with a lower use of CTPA. (Ng 2011)

A retrospective hospital radiology among CT angiography procedures showed that in 2009 CTPA was performed more often with relatively fewer PE cases identified compared with 2006. (David 2012)

A survey on ED visits (12% involved chest pain, pneumonia or hemoptysis) showed that CT use among patients with chest pain increased dramatically from 2001 to 2007. The PE diagnosis to CT ratio was low (2.7%). (Feng 2013)

**Implementation:**

The panel noted that in terms of feasibility, many institutions do not offer VQ scanning on nights and weekends. For VQ scanning to be utilized as the first test in a pathway, there may be situations where patients may be required to wait until it is available.

When VQ scanning is used, the panel noted the requirement for a chest x-ray to be obtained first.

The panel also noted that for some institutions, access to test results for ultrasound may not be quick, and that in some centres obtaining results of a D-dimer test requires sending out to another centre for analysis, which impacts access to quick test results and feasibility.
A computerized decision support tool decreased CTPA orders and diagnostic yield increased following the intervention. Inter-physician variability in CTPA order adherence post intervention was significant. (Prevedello 2013)

Adherence to guidelines for use of CTPA for PE diagnosis improved among ED physicians who received a performance feedback intervention vs. those who did not. Diagnostic yields remained unchanged in control and intervention groups. (Raja 2015)

Mandatory adherence to diagnostic protocols was shown to increase the rate of positive CTPAs for PE and to decrease the rate of negative CTPAs. Predictors of diagnostic yield included: previous DVT and clinical signs of DVT, while COPD was found to be negatively associated with PE. (Walen 2016)

**D-Dimer alone or in combination with other imaging test:**

**Feasibility:**
Using a combination of the Wells’ simplified dichotomous clinical decision rule and D-dimer test, which could be completed in 90% of patients, PE could be ruled out in 51% of patients with suspected PE without further testing, which had a failure rate of only 0.4%. (Goekoop 2007)

Less than half of physicians reviewed the D-dimer result for PE after patient examination, and the knowledge of an abnormal D-dimer test result before seeing the patient led to a higher clinical decision rule score at patient examination. (Gibson 2009)

Following at least one D-dimer test for DVT or PE, the strategy for further diagnostic testing was inappropriate in 31% with 9 out of 10 being overutilization of diagnostic imaging. (Arnason 2007)

Widespread D-dimer testing did not reduce referrals for imaging and is likely to have resulted in increased referrals. Increased imaging led to over-diagnosis of clinically insignificant PE and alternative strategies are required to reduce PE death rates. (Segard 2013)

**Implementation:**
Increasing the D-dimer threshold from 0.4μg/mL to 1.0μg/mL increased CTPA diagnostic yield for PE from 4.7% to 11.7%, but still 9% of patients with a D-dimer below the threshold underwent CTPA. (Char 2014)

Computer systems prompting provision of clinical probability factors and D-dimer value to assess the risk of PE and associated need for CTPA lowered the use of CTPA an increase its yield. (Murthy 2016, Ong 2013)

**Proximal CUS:**
No research evidence identified.

**VQ Scan:**
No research evidence identified.
Conclusions

In a patient population with a high clinical probability of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose a first episode PE?

<table>
<thead>
<tr>
<th>TYPE OF RECOMMENDATION</th>
<th>Strong recommendation against the intervention</th>
<th>Conditional recommendation against the intervention</th>
<th>Conditional recommendation for either the intervention or the comparison</th>
<th>Conditional recommendation for the intervention</th>
<th>Strong recommendation for the intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECOMMENDATION</td>
<td>The ASH guideline panel <strong>suggests</strong> using a strategy starting with CTPA for diagnosing PE in a population with high prevalence/pretest probability (50/75%), followed by additional testing with CUS or VQ scan if CTPA is negative. If CTPA is not readily available, VQ scan may be acceptable if non-diagnostic scans are followed by CTPA. <strong>(Strong recommendation for CTPA based on very low certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy studies; Conditional recommendation for VQ scan based on very low certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy).</strong> The ASH guideline panel <strong>recommends against</strong> using a positive D-dimer alone to diagnose PE, and against using D-dimer as a subsequent test following a negative CT scan in a population with high prevalence/pretest probability (50/75%). <strong>Remarks:</strong> We considered a diagnostic VQ scan result as normal or high probability, non-diagnostic VQ scan as low or intermediate probability. Providers need to be aware of the variability in terminology at their individual institutions. The panel prioritized limiting the number of diagnostic tests and radiation exposure.</td>
<td></td>
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</tbody>
</table>

**JUSTIFICATION**

**SUBGROUP CONSIDERATIONS**

We considered the two subgroups of diagnostic VQ scan and non-diagnostic VQ scan which are reflected in the recommendations above. A baseline chest X-ray prior to VQ scan can determine the likelihood of having a diagnostic VQ scan.

**IMPLEMENTATION CONSIDERATIONS**

**MONITORING AND EVALUATION**

**RESEARCH PRIORITIES**

Appendix 1: Modelling of Diagnostic Test Accuracy

Note: See diagnostic pathway diagrams on Page 1

Pathways A-H begin with CTPA
Pathways I-J begin with VQ
Pathways K-Q begin with D-dimer

Table 1: In a patient population with a high clinical probability (50%) of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose a first episode PE?

| Outcomes                      | A  | B  | C  | D  | E  | F  | G1 | G2 | H  | I1 | I2 | J1 | J2 | K  | L  | M1 | M2 | N1 | N2 | O1 | O2 | P  | Q1 | Q2 |
|-------------------------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| TP-patient correctly identified as having PE and anticoagulated | 465 | 499 | 482 | 490 | 482 | 491 | 495 | 489 | 500 | 477 | 471 | 433 | 339 | 485 | 451 | 463 | 457 | 420 | 329 | 465 | 465 | 499 | 499 | 499 |
| FP-patient incorrectly identified as having PE and unnecessarily anticoagulated | 10  | 309 | 19  | 28  | 25  | 39  | 33  | 29  | 10  | 22  | 16  | 23  | 19  | 305 | 6  | 13  | 10  | 14  | 12  | 15  | 12  | 309 | 314 | 311 |
| TN-patient correctly identified as not having PE and not anticoagulated | 490 | 191 | 481 | 472 | 475 | 461 | 467 | 471 | 490 | 478 | 484 | 477 | 481 | 195 | 494 | 487 | 490 | 486 | 488 | 485 | 488 | 191 | 186 | 189 |
| FN-patient incorrectly identified as not having PE and will not receive needed anticoagulation | 35  | 1  | 18  | 10  | 18  | 9  | 5  | 11  | 0  | 23  | 29  | 67  | 161 | 15  | 49  | 37  | 43  | 80  | 171 | 35  | 35  | 1  | 1  | 1  |
Table 2: In a patient population with a high clinical probability (75%) of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose a first episode PE?

| Outcomes                              | A  | B  | C  | D  | E  | F  | G1 | G2 | H  | I1 | I2 | J1 | J2 | K  | L  | M1 | M2 | N1 | N2 | O1 | O2 | P  | Q1 | Q2 |
|---------------------------------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| TP-patient correctly identified as having PE and anticoagulated | 698| 748| 722| 735| 723| 736| 743| 733| 750| 716| 707| 650| 509| 728| 677| 694| 685| 630| 493| 698| 698| 748| 749| 749|
| FP-patient incorrectly identified as having PE and unnecessarily anticoagulated | 5  | 154| 9  | 14 | 12 | 19 | 16 | 14 | 5  | 11 | 8  | 12 | 10 | 153| 3  | 7  | 5  | 7  | 6  | 7  | 6  | 154| 157| 156|   |
| TN-patient correctly identified as not having PE and not anticoagulated   | 245| 96 | 241| 236| 238| 231| 234| 236| 245| 239| 242| 239| 241| 98 | 247| 243| 245| 243| 244| 243| 244| 96 | 93 | 94 |   |
| FN-patient incorrectly identified as not having PE and will not receive needed anticoagulation | 53 | 2  | 28 | 15 | 27 | 14 | 7  | 17 | 0  | 35 | 44 | 101| 242| 23 | 73 | 56 | 65 | 120| 257| 52 | 52 | 2  | 1  | 1  |   |
Appendix 2: Natural Progression and Treatment Effects

When making a decision regarding which pathway to recommend for diagnosing PE, one must acknowledge that there will be patients who will have negative consequences because of an incorrect test result and thus an incorrect diagnosis. Patients who receive unnecessary anticoagulation (false positive) or do not receive necessary anticoagulation (false negative) are subject to the risks of bleeding, may suffer complications or may die. Tables 2 and 3 provide some insight into the frequency of these outcomes.

**True positive**: patients correctly identified as having PE and correctly anticoagulated

**True negative**: patients correctly identified as not having PE and correctly not anticoagulated

**False positive**: patients incorrectly identified as having PE and receive unnecessary anticoagulation

**False negative**: patients incorrectly identified as not having PE and will not receive necessary anticoagulation

Outcomes studied include:
- Hemorrhagic Stroke
- Major Bleeding
- Mortality
- Recurrent PE

### Table 2: Outcomes by Test Result

<table>
<thead>
<tr>
<th>Test accuracy results</th>
<th>Consequences</th>
<th>Results from published SR</th>
<th>Results from treatment guideline (GL3-Q3, LMWH/VKA)*</th>
<th>Targeted search of primary studies</th>
<th>Panel survey results</th>
</tr>
</thead>
</table>
| **TP**                | Mortality: all cause | 2.0% (6m)* | In-hospital: 10.5%
1 week: 5.3%
2 weeks: 8.5%
1 month: 10.4%
3 months: 9.8%

**Recurrent PE population:**
2 weeks: 33.7%
3 months: 46.8%

<table>
<thead>
<tr>
<th></th>
<th>11.3% (1y)</th>
</tr>
</thead>
</table>
| Mortality from PE w 3 months | 1.5% (3m)^ | 0.1% (6m)" | In-hospital: 4.7%
1 week: 2.0%
2 weeks: 2.3%
1 month: 6.3%
3 months: 2.8%

**Recurrent PE population:**
In-hospital: 0.0%
1 week: 50.0%
3 months: 51.9%
| 3.0% (1y) | |
| Recurrence on AC w 3 months | 1.0% (6m)* | In-hospital: 1.4% | |

*Draft*
### Table 2. Outcomes by Diagnostic Pathway

<table>
<thead>
<tr>
<th>A</th>
<th>B-H</th>
<th>I</th>
<th>J</th>
<th>K</th>
<th>L</th>
<th>M-Q</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality – All Cause</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Anderson, 2007: 5/133 deaths in TP, 17/561 deaths in TN</td>
<td>None reported</td>
<td>None reported</td>
<td>- Righini, 2014: 2/810 TN, 7/331 for &gt;500 but &lt;age adjusted, 17/1744 &gt;age adjusted</td>
<td>Den Exter 2013 - (n=832) 7.6% in patients with delay in presentation, 6.6% in patients without delay</td>
<td>None reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Abcarian, 2004: 0/247 deaths in TN</td>
<td>Van Belle 2006 - 11/674 (TP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Legnani, 2010: 0/476</td>
<td>Douma 2011 - 18/1023</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Median event rates from included RCTs in Q3 from GL3
# Event rates from SR by Carrier 2010, which was also used in Q3 for GL3
^ Event rate from SR by Douketis 1998
| Mortality - PE | None reported | None reported | None reported | - Douma, 2011: 0/168
- Djurabi, 2008: 0/1057 deaths in TN
- Taira, 2010: 0/497
- Abcarian, 2004: 0/247 deaths in TN
- Parent 2007: 0/84 deaths in TN
- Dunn, 2002: 0/547 deaths in TN
- Ray, 2007: 0/205 deaths in TN
- Le Gal 2006: 0/308 |
| - Anderson, 2007: 2/133
- Van Belle 2006: PE+ 55/764, PE- 129/1500
- Engelke, 2006: 2/96
- Jouveshomme, 2007: 3/156
- Musset, 2002: 3/345
- Atasoy, 2015: 8/67
- Ceylan, 2011: 13/122
- Gottstater, 2000: 3/215
- Subramaniam, 2007: 1/494 | None reported | None reported | None reported |
| Recurrent PE | None reported | None reported | None reported | - Abcarian, 2004: 0/247 in TN
- Parent 2007: 0/84 in TN |
| - Perrier, 2005: 2/523
- Van Belle, 2006: 8/1436 in TN |
| - Den Exter 2013: (n=832) 4.5% in patients with delay in presentation, 2.4% in patients without delay in presentation
- Perrier, 2001: 3/118 in TP
- Van Belle, 2006: 18/1436 in TN
- Van Belle, 2006: 20/674 in TP
- Courtney, 2010: 1/332 | None reported | None reported | None reported |

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| Hemorrhagic stroke | None reported | None reported | None reported | None reported | None reported | - Perrier, 2001: 2/118 in TP, 1/181 in TN | None reported |

**REFERENCES.**

References of Background:


Irwig L, Bossuyt P, Glasziou P, Lijmer J. Designing studies to ensure that estimates of test accuracy are transferable. BMJ 2002; 324: 669–71


Wiener RS, Schwartz LM, Woloshin S. When a test is too good: how CT pulmonary angiograms find pulmonary emboli that do not need to be found. BMJ 2013;347:f3368–f3368.

References of included accuracy studies:


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References related to natural progression:

References – SR for Baseline Risk PE Mortality in TP

References – Studies for Baseline Risk Mortality & Recurrent PE – Q3 from GL3


References – Study for Baseline Risk PE mortality, Major Bleeding & Major bleeding mortality – Q3 from GL3

References related to clinical outcomes:


Choi, Won-Ho, Sung Uk Kwon, Yoon Jung Jwa, Jung A. Kim, Yun-Ho Choi, Je Ho Chang, Hoon Jung, Joon Hyung Doh, June Namgung, Sung Yun Lee, and Won Ro Lee. 2009. 'The Pulmonary Embolism Severity Index in Predicting the Prognosis of Patients With Pulmonary Embolism', The Korean Journal of Internal Medicine, 24: 123-27.


Ray, Patrick, Bensalem Bellick, Sophie Birolette, Jean-Sébastien Marx, Michel Arrock, and Bruno Riou. 2006. 'Referent d-dimer enzyme-linked immunosorbent assay testing is of limited value in the exclusion of thromboembolic disease: result of a practical study in an ED', The American Journal of Emergency Medicine, 24: 313-18.


References related to prevalence:

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References related to values and preferences:


References related to cost and cost effectiveness:


**References related to Acceptability, Feasibility, Equity, Implementation:**


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Question 4. In patients with a prior history of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose recurrent PE?

**Diagnosis of Pulmonary Embolism: Diagnostic Pathways Assessed**

- Clinical probability
  - Low clinical probability → D-dimer
    - Positive D-dimer → CTPA
      - Positive CTPA → anticoagulate
      - Negative CTPA → no treatment
    - Negative D-dimer → no treatment
  - High clinical probability → CTPA
    - Positive CTPA → anticoagulate
    - Negative CTPA → no treatment
**POPULATION:** Patients with suspected recurrent pulmonary embolism (PE)

**EVALUATED TESTS:** CT pulmonary angiography (CTPA), D-dimer, Proximal compression ultrasound (CUS), Ventilation perfusion (VQ) scan

**PURPOSE OF THE TEST:** Detection of recurrent pulmonary embolism (PE)

**ROLE OF THE TEST:** Detection of recurrent pulmonary embolism (PE)

**LINKED TREATMENTS:** Anticoagulation

**ANTICIPATED OUTCOMES:** False Negative; False Positive; True Negative; True Positive; Mortality; Recurrent Pulmonary Embolism; Major Bleeding; Hemorrhagic Stroke

**SETTING:** Inpatient and outpatient

**PERSPECTIVE:** Clinical recommendation - population perspective

**SUBGROUPS:**

**BACKGROUND:**
Pulmonary embolism (PE) is a potentially life-threatening condition that may be prevented and can be treated with anticoagulant therapy (Rodger 2006). The diagnostic accuracy of a test can vary with the strength of clinical suspicion (Irwig 2002). The clinical probability of a condition can assist with determining which tests to use to diagnose PE. While standardized clinical decision rules (CDRs) are used to determine clinical probability for PE, recurrent PE does not have a standardized CDR at this time (Van Es 2012).

Various diagnostic tests are currently used for the diagnosis of recurrent PE including D-Dimer assays, compression ultrasonography (CUS), computed tomography pulmonary angiography (CTPA) and ventilation perfusion (V/Q) scanning. Imaging tests for PE such as CTPA and V/Q lung scanning are expensive, time consuming and are associated with radiation exposure. Recurrent PE poses a particular challenge due to the difficulty in differentiating chronic from acute disease on radiologic imaging. In addition, the contrast used in CTPA can result in nephrotoxicity and allergic reactions. Therefore, inexpensive strategies with less risk to patients are needed to exclude PE efficiently (Bates 2016).
### Is the problem a priority?
- **No**
- **Probably no**
- **Probably yes**
- **Yes**
- **Varies**
- **Don't know**

The overall annual incidence of pulmonary emboli (PE) is quoted at 60–70 cases per 100,000. Associated with significant morbidity and mortality, prompt diagnosis and expeditious therapeutic intervention is of paramount importance for optimal patient management (Warren 2012). The fear of missing a diagnosis of this life-threatening disease has led to an increase in the use of invasive diagnostic strategies, with a significant rise of imaging studies such as computed tomographic pulmonary angiography (CTPA) or ventilation perfusion (V/Q) scanning over the last decade (Smith-Bindman 2012; Schissler 2013). Subsequently, it has also been reported that PE has become over diagnosed (Wiener 2013; Sheh 2012). Physicians often order CTPA, although pulmonary embolism is unlikely and a D-dimer test result is negative (Adams 2013). Given that CTPA is associated with radiation exposure, nephrotoxicity and allergic reactions, V/Q lung scanning may offer an option with less risk.

### How accurate is the pathway?

**D-dimer for low PTP, CTPA for low PTP with positive D-dimer and high PTP**
- **Very inaccurate**
- **Inaccurate**
- **Accurate**
- **Very accurate**
- **Don't know**

D-dimer
- **Very inaccurate**
- **Inaccurate**
- **Accurate**
- **Very accurate**
- **Don't know**

VQ Scan

<table>
<thead>
<tr>
<th><strong>Patient or population:</strong> Patients with suspected recurrent pulmonary embolism</th>
<th><strong>New test:</strong> D-dimer for patients with low clinical probability, CTPA for patients with low clinical probability patients and positive D-dimer or high clinical probability</th>
<th><strong>Setting:</strong> Inpatient and outpatient</th>
<th><strong>Pooled sensitivity:</strong> 0.97 (95% CI: 0.94 to 0.98)</th>
<th><strong>Pooled specificity:</strong> 1.00 (95% CI: 0.99 to 1.00)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positives</td>
<td>291 (284 to 295)</td>
<td>992 (3)</td>
<td></td>
</tr>
<tr>
<td>False negatives</td>
<td>9 (5 to 16)</td>
<td>12 (7 to 22)</td>
<td></td>
</tr>
<tr>
<td>True negatives</td>
<td>700 (694 to 700)</td>
<td>992 (3)</td>
<td></td>
</tr>
<tr>
<td>False positives</td>
<td>0 (0 to 6)</td>
<td>0 (0 to 5)</td>
<td></td>
</tr>
</tbody>
</table>

The panel noted that the inconclusive results reported are low, and likely not reflective of the real-world setting. The panel noted that for D-dimer, a negative result in patients with low clinical probability can rule out PE. However, a positive D-dimer result cannot be used as a standalone test to diagnose PE and initiate anticoagulant treatment. Therefore, the rating of very inaccurate applies to the context of the diagnostic pathways being assessed with D-dimer as an individual test.

While the panel was interested in evaluating D-dimer, CTPA, VQ Scan, and
Proximal CUS, there was a lack of evidence on accuracy of these tests in patients with recurrent PE. The panel felt that modelling with a lack of direct evidence on DTA for recurrent PE would be too indirect for decision-making. For decision-making the panel decided to use test pathways that are studied directly in the literature.

Explanations
a. Certainty of evidence was downgraded for imprecision given the small population size from the three recurrent PE study identified for analysis.

Patient or population: Patients with suspected recurrent pulmonary embolism
New test: D-dimer
Setting: Inpatient and outpatient

Pooled sensitivity: 1.00 (95% CI: 0.97 to 1.00) | Pooled specificity: 0.27 (95% CI: 0.21 to 0.34)

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positives</td>
<td>Prevalence 30%(^1,2,3,4) in patients suspected of having PE without risk factors.</td>
<td>300 (291 to 300)</td>
<td>304 (1)</td>
</tr>
<tr>
<td>False negatives</td>
<td>Prevalence 40%(^2,3,4) in patients suspected of having PE without risk factors.</td>
<td>0 (0 to 9)</td>
<td>0 (0 to 12)</td>
</tr>
<tr>
<td>True negatives</td>
<td>175 (135 to 223)</td>
<td>150 (115 to 191)</td>
<td>304 (1)</td>
</tr>
<tr>
<td>False positives</td>
<td>525 (477 to 565)</td>
<td>450 (409 to 485)</td>
<td></td>
</tr>
<tr>
<td>Judgment</td>
<td>Research Evidence</td>
<td>Additional Considerations</td>
<td></td>
</tr>
<tr>
<td>----------</td>
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<tr>
<td><strong>CERTAINTY OF THE EVIDENCE OF TEST ACCURACY</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>What is the overall certainty of the evidence of test accuracy?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Very low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- <strong>Low (D-dimer)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Moderate (D-dimer with CTPA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No included studies</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Inconclusive test results**

| 0 | 304 (1) |

**Complications arising from the diagnostic test**

Not reported

CI: Confidence interval

4 Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of the subsequent tests depends on the result of the previous test in the pathway.

**Explanations**

a. Certainty of evidence was downgraded for imprecision given the small population size from the one recurrent PE study identified for analysis.
b. Certainty of evidence was downgraded for risk of bias due to a secondary analysis of two prospective multicenter studies with a mixed population of recurrent and first-time pulmonary embolism patients.
<table>
<thead>
<tr>
<th>CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS</th>
<th>What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the pathway?</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Very low</td>
<td>The panel noted there is no direct benefit or burdens of the pathway. The data varies on the adverse effects associated with radiation exposure, contrast-induced nephropathy, allergy to contrast, or contrast extravasation associated with CTPA. In addition, the panel noted a high risk of radiation exposure from repeated CTPA in patients with history of pulmonary embolism and suspicion for recurrence.</td>
</tr>
<tr>
<td>○ Low</td>
<td></td>
</tr>
<tr>
<td>○ Moderate</td>
<td></td>
</tr>
<tr>
<td>○ High</td>
<td></td>
</tr>
<tr>
<td>○ Varies</td>
<td></td>
</tr>
<tr>
<td>○ No included studies</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT</th>
<th>How certain is the link between pathway results and management decisions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Very low</td>
<td>The link between test results and management is unique in venous thromboembolism. With PE diagnosis, positive results will be treated with anticoagulation (regardless of the chances of false positives).</td>
</tr>
<tr>
<td>○ Low</td>
<td>The panel noted high certainty in the link between test results and management decisions. However, the panel also noted that for patients with sub-segmental PE, the link may not be as certain.</td>
</tr>
<tr>
<td>○ Moderate</td>
<td></td>
</tr>
<tr>
<td>○ High</td>
<td></td>
</tr>
<tr>
<td>○ No included studies</td>
<td></td>
</tr>
</tbody>
</table>
### OUTCOMES BY TEST RESULTS

<table>
<thead>
<tr>
<th>Outcomes at 3 months</th>
<th>Le Gal et al.</th>
<th>Mos et al.</th>
<th>Sohne et al.</th>
<th>Douma et al.</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-fatal Venous Thromboembolism – after negative D-dimer in low clinical probability patients</strong></td>
<td>0/49</td>
<td>0/87</td>
<td>1/95</td>
<td>0/1</td>
<td>1/232 (0.43%)</td>
</tr>
<tr>
<td><strong>Fatal Venous Thromboembolism – after negative D-dimer in low clinical probability patients</strong></td>
<td>0/49</td>
<td>0/87</td>
<td>0/95</td>
<td>0/1</td>
<td>0/232 (0%)</td>
</tr>
<tr>
<td><strong>Non-fatal Venous Thromboembolism – after negative CTPA in low or high clinical probability patients</strong></td>
<td>Not reported</td>
<td>6/249 - PE</td>
<td>2/249</td>
<td>0/19</td>
<td>8/517 (1.5%)</td>
</tr>
<tr>
<td><strong>Fatal Venous Thromboembolism – after negative CTPA in low or high clinical probability patients</strong></td>
<td>Not reported</td>
<td>1/249 – PE</td>
<td>0/249</td>
<td>0/19</td>
<td>1/517 (0.19%)</td>
</tr>
</tbody>
</table>

While there was evidence on outcomes of patients with a false negative test result, certainty of evidence was downgraded as the studies were longitudinal observational studies evaluating the effects of implementing the pathway and there were few events reported.

### VALUES

The numbers shown below are utilities, representing the strength of an individual’s preferences for different outcomes. They are measured on a scale, with zero reflecting states of health equivalent to death/worst imaginable health and one reflecting perfect health/best imaginable health.

**Systematic reviews found that the relative importance of the outcomes is as follows:**

- Pulmonary embolism: 0.63-0.93 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004)
- Deep vein thrombosis: 0.64-0.99 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016)
- Deep vein thrombosis patients’ own current health: 0.95 (Time trade off) (Locadia 2004)
- Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg 2013, Locadia 2004)
- Minor intracranial bleeding event: 0.75 (standard gamble) (Hogg 2013)
- Major intracranial bleeding event: 0.15 (standard gamble) (Hogg 2013) Central nervous system bleeding: 0.29-0.60 (standard gamble) (Lenert 1997, O’Meara 1994)

**Studies additionally described the following regarding the relative importance of outcomes and patients’ preferences:**

In a survey study (Geyer 2014) based on a shared decision-making model, the researchers provided patients with a standardized description of the diagnostic workup for PE, described the risks of CTPA in low pretest probability patients and the risks of deferring imaging.

The panel noted that there was a lack of information on value of outcomes specifically for recurrent PE patients. The judgment is based on data from patients with first episode PE.

The panel placed a high value on decreasing the number of false negative test results over decreasing false positive test results.

The panel also placed a high value on decreasing radiation exposure and reducing the number of tests required in a diagnostic pathway.

The panel considered that there would not be important variability in...
assuming a D-dimer was less than twice the value normally considered positive. With the decision aid, of the 203 patients in the study, 63% of patients favored undergoing CTPA; while seventy-four patients (37%) elected to defer CTPA. The most frequent reasons for decline include risk of malignancy, contrast-induced nephropathy, or allergy. Other than those common reasons, 20 patients deferred CTPA testing because they believed it was unnecessary. Patients with a previous PE diagnosis were less likely to defer CTPA testing. Most patients (n=109 [85%]) who accepted CTPA testing had concerns about missing a PE.

Results of Panel Utility Rating Survey:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean Utility Rating (SD)* All Panels (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>False Negative Test Result</td>
<td>0.60 (0.23)</td>
</tr>
<tr>
<td>False Positive Test Result</td>
<td>0.62 (0.21)</td>
</tr>
<tr>
<td>True Negative Test Result</td>
<td>0.91 (0.15)</td>
</tr>
<tr>
<td>True Positive Test Result</td>
<td>0.76 (0.19)</td>
</tr>
<tr>
<td>Inconclusive Test Result</td>
<td>0.69 (0.18)</td>
</tr>
<tr>
<td>Radiation Exposure</td>
<td>0.84 (0.14)</td>
</tr>
<tr>
<td>Contrast Induced Nephropathy</td>
<td>0.56 (0.20)</td>
</tr>
<tr>
<td>Pulmonary Embolism – Moderate Marker State</td>
<td>0.42 (0.15)</td>
</tr>
<tr>
<td>Proximal DVT – Moderate Marker State</td>
<td>0.58 (0.14)</td>
</tr>
<tr>
<td>Distal DVT – Moderate Marker State</td>
<td>0.64 (0.16)</td>
</tr>
<tr>
<td>Upper Extremity DVT – Moderate Marker State</td>
<td>0.61 (0.16)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>0.33 (0.23)</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>0.12 (0.10)</td>
</tr>
<tr>
<td>Chronic Thrombotic Pulmonary Hypertension</td>
<td>0.34 (0.15)</td>
</tr>
</tbody>
</table>

* Utility rating by panel members from 0 (dead) to 1 (full health)
### Does the balance between desirable and undesirable effects favor the diagnostic pathway?

- **Favors pathway**
- **Probably favors pathway**
- **Does not favor pathway or no pathway**
- **Probably favors no pathway**
- **Favors no pathway**

### Contrast induced nephropathies, allergic reactions, and extravasation

<table>
<thead>
<tr>
<th>Year</th>
<th>Index test</th>
<th>Reference test</th>
<th>Safety Outcome (as defined by study)</th>
<th>Incidence and details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ost 2001</td>
<td>CT</td>
<td>PA</td>
<td>Contrast induced nephropathy/ARF</td>
<td>Creatinine was not serially measured throughout study. However, increase in creatinine 0.01 +/- 0.38 (mg/dL) noted in CT only group without conventional angiography and 0.2 +/- 0.9 (mg/dL) in the CT + conventional angiography group. 3/103 (3%) patients had an increase in creatinine greater than 1 (need units) with max of 7.2 (units). All returned to the normal reference range at 3-month follow up.</td>
</tr>
<tr>
<td>Pesavento 2011</td>
<td>CT</td>
<td>None</td>
<td>Severe acute renal failure</td>
<td>CT: 1/367 (0.27%)</td>
</tr>
<tr>
<td>Stein 2006</td>
<td>CT</td>
<td>CC</td>
<td>Allergic reaction</td>
<td>CT: 4/1095 (&lt;1%) Mild.</td>
</tr>
<tr>
<td>Yazici 2016</td>
<td>CT</td>
<td>None</td>
<td>Contrast nephropathy</td>
<td>24/174 (13%)</td>
</tr>
<tr>
<td>Coche 2003</td>
<td>CT</td>
<td>CT, VQ</td>
<td>Contrast nephropathy (creatinine increase)</td>
<td>1/69 (1%)</td>
</tr>
<tr>
<td>Mitchell 2006</td>
<td>CT</td>
<td>None</td>
<td>Contrast nephropathy (creatinine increase)</td>
<td>All: 44/1224 (4%) or paired: 44/354 (12%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe acute renal failure</td>
<td>0/1224 (0%)</td>
</tr>
<tr>
<td>Righini 2008</td>
<td>PW (DD-leg US-CT)</td>
<td>APW (DD-CT)</td>
<td>Allergic reaction</td>
<td>PW: 1/509 (0.2%) (rash) APW: 2/535 (0.4%) (rash)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Extravasation of contrast</td>
<td>PW: 1/509 (0.2%) APW: 2/535 (0.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe acute renal failure</td>
<td>PW: 0/509 (0%) APW: 0/535 (0%)</td>
</tr>
</tbody>
</table>

DD = D-dimer; PW = pathway; APW = alternative pathway; CT=Computed Tomography; PA=Pulmonary Angiography; VQ=Ventilation Perfusion Scan; ARF=Acute Renal Failure

References:

The panel considered desirable effects as increasing the number of patients with true positive and true negative test results (i.e. patients accurately diagnosed and treated).

The panel considered undesirable as increasing the number of patients with false positive and false negative test results (i.e. receive unnecessary anticoagulation or morbidity/mortality from missed diagnosis).

The panel noted radiation exposure as a concern with CTPA, but weighed it with acceptance of the risk to obtain a definitive and quick diagnosis.

The panel noted the pathway involving D-dimer with CTPA is recommended over CTPA alone due to the reduction of radiation exposure in a population that is at risk for repeated radiation from frequent imaging.

The panel noted that VQ may provide an alternative pathway for diagnosing recurrent PE that has not been studied.


**Radiation exposure associated with CTPA**

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Estimated ‘effective dose’ of radiation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT: Chest</td>
<td>4.5 mSv (range 3.8-5.2 mSv) 5.2 mSv Range: 2.7 - 15 mSv</td>
<td>Phillips, 2015 Kanal, 2017 Jones, 2012 and Janbabanezhad, 2015</td>
</tr>
</tbody>
</table>


In Hurwitz et al, estimated relative risks for breast and lung cancer incidences were 1.002–1.011 and 1.005–1.022, respectively. In addition, Brenner and Elliston estimated the lifetime attributable cancer death risk in 45-year-old adults who underwent a full-body CT test to be around 0.08%. The relationship between radiation exposure to cancer induction was limited and incredibly variable in literature and, therefore, not modelled.


**Balance of desirable and undesirable effects:**

For this guideline question, in addition to the diagnostic test accuracy outcomes, the panel considered two key criteria in determining which pathways provided the best balance of desirable and undesirable effects, which were minimizing radiation exposure and minimizing the number of tests used.
RESOURCES REQUIRED

How large are the resource requirements (costs) for CTPA?
- Large costs
- Moderate costs
- Negligible costs and savings
- Moderate savings
- Large savings
- Don't know

How large are the resource requirements (costs) for D-Dimer?
- Large costs
- Moderate costs
- Negligible costs and savings
- Moderate savings
- Large savings
- Don't know

Costs of diagnostic tests:

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Peer-review articles and Other sources&lt;sup&gt;3&lt;/sup&gt;</th>
<th>CPT (Current Procedural Terminology)-4 Codes/cost&lt;sup&gt;1,2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer test</td>
<td>$256 ($271 in 2017)&lt;sup&gt;4,5&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Computed tomographic angiography, chest</td>
<td>Computed tomography: $500 ($650 in 2017)&lt;sup&gt;6&lt;/sup&gt; $655.85&lt;sup&gt;7&lt;/sup&gt;</td>
<td>71275 -CT angiography chest Facility/Non-Facility price: $269.00-390.74 Opps facility/non-facility payment amount: $315.31-463.95</td>
</tr>
<tr>
<td>Other sources: $300-$400</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

References:

25. 1 US dollar in 2012 equals to about $1.0662 in 2017 (http://www.in2013dollars.com/)
27. Based on CADTH report; The cost consists of diagnostic tests costs and physician interpretation cost, and it is in Canadian dollars in 2017.
28. https://pricinghealthcare.com/prices/CenterForMedicalimaging

The panel noted that the costs for CTPA are large, but vary based on setting and the cost to the patient may vary depending on coverage.

The panel noted that the data showing costs based on CPT codes do not reflect what patients are charged in different settings, and are likely an under-representation of what patients and insurers pay.

Given this, the panel noted that the reported costs for D-dimer seem very high, however this may be reflective of the U.S. setting and may differ between settings.

The panel noted that for D-dimer costs from a health system perspective are moderate. Additionally, a diagnostic pathway starting with D-dimer would reduce cost compared to the other alternatives.

The panel noted uncertainty in the actual costs of the tests.
<table>
<thead>
<tr>
<th>What is the certainty of the evidence of resource requirements (costs) for D-Dimer?</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Very low</td>
</tr>
<tr>
<td>○ <strong>Low</strong></td>
</tr>
<tr>
<td>○ Moderate</td>
</tr>
<tr>
<td>○ High</td>
</tr>
<tr>
<td>○ No included studies</td>
</tr>
</tbody>
</table>
### Cost Effectiveness of Diagnostic Pathways Evaluated

The panel judged pathways starting with a d-dimer test as most cost-effective considering the lower cost of the test.

We identified the following in our systematic review of cost-effectiveness:

**CTPA:**
Evidence on the cost-effectiveness of CTPA is inconsistent. The included studies varied in regards to the compared strategy, the setting, the time frame, and the methods. In general, a CTPA strategy was considered effective, mostly associated with improved survival. But whether it is cost-effective or not is still uncertain in the literature.

In Batalles 2009, CTPA was cost-effective compared with pulmonary magnetic resonance angiography, and was the most effective strategy. A study by van Erkel et al (van Erkel 1996) found that CTPA reduces mortality and improves cost-effectiveness in the diagnostic workup of suspected PE when compared with V/Q scanning, compression US, D-dimer assay, and conventional angiography strategies. In Oudkerk 1993, compared with the treatment for all strategy with lowest mortality but highest cost, pulmonary angiography strategies with or without prior V/Q lung scanning and ultrasonography of the legs have comparable low mortality and morbidity rates, costs savings of approximately 40%, and inappropriate treatment in fewer than 5% of patients. Paterson et al (Paterson 2001) found higher costs for CTPA as the initial diagnostic test but with improved expected survival when compared with a gradual algorithm of V/Q scanning ± compression US ± CTPA.

In Doyle 2004, researchers in the US conducted a decision analytic model on diagnostic tests of PE in women, to determine which strategy is the most cost-effective with the least number of deaths from PE. Of the strategies compared (compression US, V/Q scanning, and spiral CT), spiral CT as the initial diagnostic regimen was found to be the most cost-effective at $17,208 per life saved. In contrast, Henschke et al (Henschke 1994) concluded CTPA was not cost-effective compared with ultrasound.


**D-Dimer:**
Several cost-effectiveness analyses compared the diagnostic strategies with D-dimer, and use CTPA according to the D-dimer with other strategies, including no test, or treatment for all, or universal CTPA or VQ scan. In general, the strategy of combining D-dimer with other diagnostic testing was suggested to be cost-effective, or cost-saving. (Duriseti 2010, Duriseti 2006, Elias 2004, Humphreys 2004, Lee 2011, Perrier 1997, Perrier 2003, Righini 2007, Van Beek 1996, Van Erkel 1996)

The panel noted that the data reviewed was indirectly considered as it was based on information from patients with first episode PE.
### EQUITY

**Impact on health equity of diagnostic pathways evaluated**

We identified the following regarding the impact on health equity with the different tests:

**CTPA:**
No research evidence identified.

**D-Dimer:**
Canadian provinces with larger populations tended to have a large proportion of hospitals with the capability to measure D-dimer levels for VTE diagnosis, whereas less populated provinces were more likely to send samples to centralized analysis facilities for D-dimer testing. (Southern 2014)

The panel noted that the data reviewed was indirectly considered as it was based on information from patients with first episode PE.

### ACCEPTABILITY

**Acceptability of diagnostic pathways evaluated to key stakeholders**

The panel considered the pathway evaluated as acceptable.

Studies described the following regarding acceptability from key stakeholders:

**General (Radiology & Population):**
A survey assessing the knowledge/practice patterns of ED physicians related to radiation exposure showed that 9 out of 10 preferred V/Q scanning for patients <30 years of age or those with a history of recent CT scans when diagnosing PE, which was confirmed by retrospective chart review. Physician knowledge of precise radiation exposure for each diagnostic test was low, but the majority were aware that V/Q scans exposed patients to less radiation than CTPA. (Ahn 2014)

In a study among nursing home patients with suspected VTE, referral for additional diagnostic investigations was withheld in almost 40%. In providers’ decisions to forgo diagnostic investigations, they incorporated the estimated relative impact of the potential disease; the potential net-benefits of diagnostic investigations and whether performing investigations agreed with established management goals in advance care planning. (Schouten 2014)

A study among physicians who had previously referred patients for any VTE screening examination showed that physicians had a lack of basic knowledge regarding lower extremity venous anatomy, charges for the different diagnostic tests used to diagnose VTE, and current treatment standards for VTE. (Zierler 2002)

**CTPA**
A survey among 62 radiologists and 52 ED physicians showed that CT is the overwhelmingly preferred technique for the diagnosis of PE. (Jha 2010)

**D-Dimer alone or in combination with other imaging test:**
Thrombosis and hemostasis specialists reported that just over half always use D-dimer for diagnosing DVT and two-thirds for diagnosing PE. 30% relied on clinical judgment to assess pre-clinical probability for DVT and 41% for PE. (Squizzato 2010)

The panel noted that the data reviewed was indirectly considered as it was based on information from patients with first episode PE.
There are at least 28 different combinations of measurement units used to report D-dimer results for thrombotic disorders worldwide as reported by providers. The majority used fixed cut-off rather than age-adjusted threshold values for D-dimer. (Lippi 2015)

<table>
<thead>
<tr>
<th>Feasibility to implement diagnostic pathways evaluated</th>
<th>Studies described the following regarding feasibility and barriers to use:</th>
</tr>
</thead>
<tbody>
<tr>
<td>General (Radiology &amp; Population):</td>
<td>A retrospective chart review showed that there was substantial variation in utilization and diagnostic yield of advanced radiography for PE, which was largely explained by patient-, hospital- and provider-level characteristics. (Kindermann 2014)</td>
</tr>
<tr>
<td></td>
<td>A prospective cohort study among outpatients with suspected PE from ED’s showed that 43% received inappropriate diagnostic management. Risk factors associated with inappropriate diagnostic management were age &gt;75 years, heart failure, chronic lung disease, current or recent pregnancy, currently receiving anticoagulation, and the lack of a written diagnostic algorithm and clinical probability scoring in the ED. Inappropriate management was associated with thromboembolism occurrence. (Roy 2006)</td>
</tr>
<tr>
<td>Implementation:</td>
<td>A study assessing the impact of a hospital-based educational and form-based intervention on clinician adherence to diagnostic imaging guidelines for suspected PE found improved adherence among clinicians who received the intervention. Failure to adhere with diagnostic imaging guidelines when requesting radiological testing was common. (Agarwal 2012)</td>
</tr>
<tr>
<td>CTPA:</td>
<td>A retrospective study on CTPA examinations showed that there was considerable inter-physician variability in the utilization and PE positivity rates of CTPA within a single institution. (Chen 2015)</td>
</tr>
<tr>
<td></td>
<td>A chart review with 3-month phone follow-up among ED patients undergoing investigations for suspected PE showed that compliance with a clinical pathway was more likely if exclusively done by ED physicians and was associated with a lower use of CTPA. (Ng 2011)</td>
</tr>
<tr>
<td></td>
<td>A retrospective hospital radiology among CT angiography procedures showed that in 2009 CTPA was performed more often with relatively fewer PE cases identified compared with 2006. (David 2012)</td>
</tr>
<tr>
<td></td>
<td>A survey on ED visits (12% involved chest pain, pneumonia or hemoptysis) showed that CT use among patients with chest pain increased dramatically from 2001 to 2007. The PE diagnosis to CT ratio was low (2.7%). (Feng 2013)</td>
</tr>
<tr>
<td>Implementation:</td>
<td>The panel noted that for some institutions obtaining results of a d-dimer test requires sending out to another centre for analysis, which impacts access to quick test results and feasibility.</td>
</tr>
<tr>
<td></td>
<td>The panel noted that the data reviewed was indirectly considered as it was based on information from patients with first episode PE.</td>
</tr>
</tbody>
</table>
A computerized decision support tool decreased CTPA orders and diagnostic yield increased following the intervention. Inter-physician variability in CTPA order adherence post intervention was significant. (Prevedello 2013)

Adherence to guidelines for use of CTPA for PE diagnosis improved among ED physicians who received a performance feedback intervention vs. those who did not. Diagnostic yields remained unchanged in control and intervention groups. (Raja 2015)

Mandatory adherence to diagnostic protocols was shown to increase the rate of positive CTPA for PE and to decrease the rate of negative CTPA. Predictors of diagnostic yield included: previous DVT and clinical signs of DVT, while COPD was found to be negatively associated with PE. (Walen 2016)

**D-Dimer alone or in combination with other imaging test:**

**Feasibility:**
Using a combination of the Wells’ simplified dichotomous clinical decision rule and D-dimer test, which could be completed in 90% of patients, PE could be ruled out in 51% of patients with suspected PE without further testing, which had a failure rate of only 0.4%. (Goekoop 2007)

Less than half of physicians reviewed the D-dimer result for PE after patient examination, and the knowledge of an abnormal D-dimer test result before seeing the patient led to a higher clinical decision rule score at patient examination. (Gibson 2009)

Following at least one D-dimer test for DVT or PE, the strategy for further diagnostic testing was inappropriate in 31% with 9 out of 10 being overutilization of diagnostic imaging. (Arnason 2007)

Widespread D-dimer testing did not reduce referrals for imaging and is likely to have resulted in increased referrals. Increased imaging led to over-diagnosis of clinically insignificant PE and alternative strategies are required to reduce PE death rates. (Ségard 2013)

**Implementation:**
Increasing the D-dimer threshold from 0.4μg/mL to 1.0μg/mL increased CTPA diagnostic yield for PE from 4.7% to 11.7%, but still 9% of patients with a D-dimer below the threshold underwent CTPA. (Char 2014)

Computer systems prompting provision of clinical probability factors and D-dimer value to assess the risk of PE and associated need for CTPA lowered the use of CTPA an increase its yield. (Murthy 2016, Ong 2013).
Conclusions

In patients with a prior history of pulmonary embolism (PE), what is the optimal diagnostic strategy to diagnose recurrent PE?

<table>
<thead>
<tr>
<th>TYPE OF RECOMMENDATION</th>
<th>Strong recommendation against the intervention</th>
<th>Conditional recommendation against the intervention</th>
<th>Conditional recommendation for either the intervention or the comparison</th>
<th>Conditional recommendation for the intervention</th>
<th>Strong recommendation for the intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

**RECOMMENDATION**
The ASH guideline panel suggests using a strategy starting with D-dimer for diagnosing recurrent PE in patients with a prior history of PE and low prevalence/pretest probability. Patients with a negative D-dimer do not undergo further testing and all other patients (positive D-dimer, non-low Wells pretest probability) undergo CTPA alone with no additional testing. (*Conditional recommendation for D-dimer and CTPA based on low certainty in the evidence about clinical outcomes and low certainty in the evidence about diagnostic accuracy studies*).

*Remarks:* A clinical decision rule (Wells, Geneva) should be used to assess clinical probability of recurrent PE.

**JUSTIFICATION**
The panel considered a pathway starting with D-dimer testing to reduce cost, ensure feasibility, and reduce radiation exposure. A positive D-dimer test was considered insufficient to rule in a diagnosis of PE, and must be followed by another diagnostic test. Additional testing following a positive or negative CTPA is does not provide additional benefit and is associated with additional cost, impacting health equity.

**SUBGROUP CONSIDERATIONS**
The panel noted importance of promoting D-dimer first strategy for patients with low clinical probability.

**IMPLEMENTATION CONSIDERATIONS**
The panel noted importance of promoting D-dimer first strategy for patients with low clinical probability.

**MONITORING AND EVALUATION**

**RESEARCH PRIORITIES**
Existing CDR have not been validated in patients with suspected recurrence. Need to validate the Wells CDR for patients with recurrent PE. Need to evaluate VQ scan as a possible diagnostic modality given less radiation exposure for patients with recurrent PE. Need to assess relationship between radiation exposure and risk (e.g. cancer risk).
### Appendix 1: Natural Progression and Treatment Effects

When making a decision regarding which pathway to recommend for diagnosing PE, one must acknowledge that there will be patients who will have negative consequences because of an incorrect test result and thus an incorrect diagnosis. Patients who receive unnecessary anticoagulation (false positive) or do not receive necessary anticoagulation (false negative) are subject to the risks of bleeding, may suffer complications or may die. Tables 1 provides some insight into the frequency of these outcomes.

**True positive:** patients correctly identified as having PE and correctly anticoagulated  
**True negative:** patients correctly identified as not having PE and correctly not anticoagulated  
**False positive:** patients incorrectly identified as having PE and receive unnecessary anticoagulation  
**False negative:** patients incorrectly identified as not having PE and will not receive necessary anticoagulation

**Outcomes studied include:**  
Hemorrhagic Stroke  
Major Bleeding  
Mortality  
Recurrent PE

**Table 1: Outcomes by Test Result**

<table>
<thead>
<tr>
<th>Outcomes at 3 months</th>
<th>Le Gal et al.</th>
<th>Mos et al.</th>
<th>Sohne et al.</th>
<th>Douma et al.</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-fatal Venous Thromboembolism – after negative D-dimer in low clinical probability patients</strong></td>
<td>0/49</td>
<td>0/87</td>
<td>1/95</td>
<td>0/1</td>
<td>1/232 (0.43%)</td>
</tr>
<tr>
<td><strong>Fatal Venous Thromboembolism - after negative D-dimer in low clinical probability patients</strong></td>
<td>0/49</td>
<td>0/87</td>
<td>0/95</td>
<td>0/1</td>
<td>0/232 (0%)</td>
</tr>
<tr>
<td><strong>Non-fatal Venous Thromboembolism – after negative CTPA in low or high clinical probability patients</strong></td>
<td>Not reported</td>
<td>6/249 - PE</td>
<td>2/249</td>
<td>0/19</td>
<td>8/517 (1.5%)</td>
</tr>
<tr>
<td><strong>Fatal Venous Thromboembolism – after negative CTPA in low or high clinical probability patients</strong></td>
<td>Not reported</td>
<td>1/249 – PE</td>
<td>0/249</td>
<td>0/19</td>
<td>1/517 (0.19%)</td>
</tr>
</tbody>
</table>
REFERENCES.

References of Background:


Irwig L, Bossuyt P, Glasziou P, Gatsonis C, Lijmer J. Designing studies to ensure that estimates of test accuracy are transferable. BMJ 2002; 324: 669–71


References of included accuracy and outcome studies:


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References for treatment effect and natural progression:

References related to prevalence:


References related to values and preferences:


References related to cost and cost effectiveness:


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References related to Acceptability, Feasibility, Equity, Implementation:


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Question 5. In a patient population with a low clinical probability of lower extremity deep vein thrombosis (LE DVT) what is the optimal diagnostic strategy to diagnose a first episode LE DVT?

**Diagnosis of Lower Extremity Deep Vein Thrombosis: Diagnostic Pathways Assessed**

a. Whole leg US
   - Positive whole leg US → anticoagulate
   - Negative whole leg US → no treatment

b. Proximal CUS
   - Positive proximal CUS → anticoagulate
   - Negative proximal CUS → no treatment
c. Proximal CUS

- Positive proximal CUS → anticoagulate
- Negative proximal CUS → D-Dimer
  - Positive D-Dimer → anticoagulate
  - Negative D-Dimer → no treatment

Pathway C
Patients with suspected LE DVT

FTP Assessment

Proximal CUS

Positive

Negative

D-Dimer

Positive

Anticoagulate

Outcomes

Negative

Anticoagulate

Outcomes

Anticoagulate

Outcomes

Pathway D
Patients with suspected LE DVT

FTP Assessment

Proximal CUS

Positive

Negative

D-Dimer

Positive

Serial US

Anticoagulate

Outcomes

Negative

Serial US

Anticoagulate

Outcomes

No treatment

Outcomes

No treatment

Outcomes

Positive

Anticoagulate

Outcomes

Negative

Anticoagulate

Outcomes

No treatment

Outcomes

No treatment

Outcomes

Positive

Anticoagulate

Outcomes

Negative

Anticoagulate

Outcomes

No treatment

Outcomes

No treatment

Outcomes

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e. Proximal CUS

- Positive proximal CUS → anticoagulate
- Negative proximal CUS → Serial US
  - Positive Serial US → anticoagulate
  - Negative Serial US → no treatment

f. Proximal CUS

- Positive proximal CUS → anticoagulate
- Negative proximal CUS → D-Dimer
  - Positive D-Dimer → venography
    - Positive venography → anticoagulate
    - Negative venography → No treatment
  - Negative D-Dimer → No treatment

*Venography was deemed not suitable as a follow-up test due to the use of ultrasound as the accepted reference standard for DVT diagnosis.
g. D-dimer
- Positive D-dimer → anticoagulate
- Negative D-dimer → no treatment

h. D-dimer
- Positive D-dimer → proximal CUS
  - Positive proximal CUS → anticoagulate
  - Negative proximal CUS → no treatment
- Negative D-dimer → no treatment
i. D-dimer

- Positive D-dimer → whole leg/serial US
  - Positive whole leg/serial US → anticoagulate
  - Negative whole leg/serial US → no treatment
- Negative D-dimer → no treatment

** Whole Leg US sensitivity and specificity estimates were used to model Pathway J.

Note: in the algorithms, watchful waiting will follow negative tests and low/normal probability unless stated otherwise.

<table>
<thead>
<tr>
<th>Legend</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>deep vein thrombosis</td>
</tr>
<tr>
<td>US</td>
<td>ultrasound</td>
</tr>
<tr>
<td>CUS</td>
<td>compression ultrasound</td>
</tr>
</tbody>
</table>
Question 5. In a patient population with a low clinical probability of lower extremity deep vein thrombosis (LE DVT) what is the optimal diagnostic strategy to diagnose a first episode LE DVT?

| POPULATION: | Patients with a low clinical probability of suspected first episode lower extremity deep vein thrombosis (LE DVT) |
| EVALUATED TESTS: | Whole leg ultrasound (US), proximal compression ultrasound (CUS), Serial ultrasound (US), D-dimer |
| PURPOSE OF THE TEST: | Detection of lower extremity deep vein thrombosis |
| ROLE OF THE TEST: | Detection of lower extremity deep vein thrombosis |
| LINKED TREATMENTS: | Anticoagulation |
| ANTICIPATED OUTCOMES: | False Negative; False Positive; True Negative; True Positive; Mortality; Lower extremity deep vein thrombosis, Major Bleeding, Recurrent LE DVT |
| SETTING: | Inpatient and outpatient |
| PERSPECTIVE: | Clinical recommendation - population perspective |

**BACKGROUND:**
Lower extremity DVT (LE DVT) is suspected in patients with pain, swelling and/or warmth of the lower extremity. These clinical manifestations are nonspecific, and objective tests are required to confirm the diagnosis. LE DVT is associated with significant morbidity and can lead to post-thrombotic syndrome in up to 50% of cases (Kesieme, 2011). LE DVT is also clinically important as it can result in pulmonary embolism (PE). Diagnostic modalities to identify LE DVT include D-dimer assays, compression ultrasonography, duplex ultrasonography, and contrast enhanced venography. D-dimer, a fibrin degradation product, is typically elevated in the presence of DVT. While sensitive, D-dimer is frequently elevated with systemic illness and is a nonspecific test necessitating additional methods for diagnosis. Compression ultrasonography evaluates the compressibility, or lack thereof, of a venous segment to diagnose thrombosis. With acute DVT, compressibility is lost secondary to passive distension of the vein by thrombus (Robert-Ebadi, 2017). Duplex imaging can aid in examining venous flow as well. Venography is now infrequently performed as a diagnostic test for DVT, supplanted by duplex ultrasound as the reference standard for DVT diagnosis.
The exact incidence of deep venous thrombosis (DVT) of the lower extremities is unknown. One study reports an incidence of deep vein thrombosis in 48 per 100,000 patients (Anderson, 1991). However, LE DVT is about 10 times more common than upper extremity DVT. (Goldhaber, 2014). Associated with significant morbidity and mortality, accurate and efficient diagnosis and treatment is important. Not only can LE DVT lead to significant pain and post-thrombotic syndrome, LE DVT can embolize to the lungs causing morbidity and mortality from PE. D-dimer, while sensitive, is not a specific test that can definitively diagnose DVT. With improvements in technology and experience, ultrasonography, has become a more reliable tool to diagnose DVT (Robert-Ebadi, 2017).

The panel noted that for proximal CUS, whole leg US, and serial US, the inconclusive results reported are low, and likely not reflective of real-world settings. The panel noted that for D-dimer, the test is not used on a standalone basis to rule in a diagnosis and patients are not treated based on a positive test result. Therefore, the rating of very inaccurate applies to the context of the diagnostic pathways being assessed. The panel noted that for US tests, accuracy may differ based on the ultrasound operator (e.g. emergency department).
Whole leg US

**Patient or population:** Patients with suspected lower extremity deep vein thrombosis

**New test:** Whole Leg US

**Setting:** Inpatient and outpatient

**Pooled sensitivity:** 0.93 (95% CI: 0.89 to 0.96) | **Pooled specificity:** 0.98 (95% CI: 0.93 to 0.99)

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positives</td>
<td>93 (89 to 86)</td>
<td>1035 (7)</td>
<td>⬤⬤⬤⬤ HIGH a,b</td>
</tr>
<tr>
<td>False negatives</td>
<td>7 (4 to 11)</td>
<td>1205 (12)</td>
<td></td>
</tr>
<tr>
<td>True negatives</td>
<td>878 (840 to 893)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**D-dimer**

- **Very accurate**
- **Don't know**
- **Very inaccurate**
- **Inaccurate**
- **Accurate**
- **Very accurate**
- **Don't know**

<table>
<thead>
<tr>
<th>Inconclusive test results</th>
<th>19</th>
<th>2908 (12)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications arising from the diagnostic test</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: Confidence interval

1. Fancher T et al. BMJ 2004; 329(7470):821. Clinical PTP and rapid D-dimer testing; mean prevalence of DVT in accuracy studies 11%; mean prevalence of DVT in management studies 25%

2. Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

**Explanations**

a. Quality of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that were judged to be acceptable by the panel.

b. Although there was minor inconsistency for sensitivity, we did not downgrade for the quality of evidence.

c. Although there was minor inconsistency for specificity, we did not downgrade for the quality of evidence.

The panel noted that whole leg US detects proximal as well as calf DVT, and overtreatment can be an issue as not all calf (distal) DVT require treatment.
<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positives</td>
<td>98 (96 to 99)</td>
<td>2415 (6)</td>
<td>☑☑☑☑ HIGH a,b</td>
</tr>
<tr>
<td>False negatives</td>
<td>2 (1 to 4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**False positives**

| 22 (7 to 60) |

**Inconclusive test results**

| 8 |

**Complications arising from the diagnostic test**

| Not reported |

CI: Confidence interval

1 Fancher T et al. BMJ 2004; 329(7470):821. Clinical PTP and rapid D-dimer testing; mean prevalence of DVT in accuracy studies 11%; mean prevalence of DVT in management studies 25%

2 Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

**Explanations**

d. Quality of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that was judged to be acceptable by the panel.

e. Although there was minor inconsistency for sensitivity, we did not downgrade for the quality of evidence.

f. Although there was minor inconsistency for specificity, we did not downgrade for the quality of evidence.

**Serial US**

**Patient or population:** Patients with suspected lower extremity deep vein thrombosis

**New test:** Serial US

**Setting:** Inpatient and outpatient

**Pooled sensitivity:** 0.98 (95% CI: 0.96 to 0.99) | **Pooled specificity:** 0.998 (95% CI: 0.993 to 0.999)

---

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### Test Result Table

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positives</td>
<td>96 (92 to 98)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Explanations

- a. Quality of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that were judged to be acceptable by the panel.
- b. Although there was minor inconsistency for sensitivity, we did not downgrade for the quality of evidence.
- c. Although there was minor inconsistency for specificity, we did not downgrade for the quality of evidence.

### D-dimer

**Patient or population:** Patients with suspected lower extremity deep vein thrombosis

**New test:** D-dimer

**Setting:** Inpatient and outpatient

**Pooled sensitivity:** 0.96 (95% CI: 0.92 to 0.98) | **Pooled specificity:** 0.35 (95% CI: 0.28 to 0.43)

### Notes

1. Fancher T et al. BMJ 2004; 329(7470):821. Clinical PTP and rapid D-dimer testing; mean prevalence of DVT in accuracy studies 11%; mean prevalence of DVT in management studies 25%

2. Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.
<table>
<thead>
<tr>
<th>False negatives</th>
<th>4 (2 to 8)</th>
<th>4409 (14)</th>
<th>⬤⬤⬤◯ MODERATE \textsuperscript{a,b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>True negatives</td>
<td>318 (254 to 387)</td>
<td>4409 (14)</td>
<td>⬤⬤⬤◯ MODERATE \textsuperscript{a,c}</td>
</tr>
<tr>
<td>False positives</td>
<td>582 (513 to 646)</td>
<td>4409 (14)</td>
<td></td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>Not applicable</td>
<td>4409 (14)</td>
<td></td>
</tr>
<tr>
<td>Complications arising from the diagnostic test</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textbf{C}: Confidence interval

\textsuperscript{1}Fancher T et al. BMJ 2004; 329(7470):821. Clinical PTP and rapid D-dimer testing; mean prevalence of DVT in accuracy studies 11%; mean prevalence of DVT in management studies 25%

\textsuperscript{2}Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

\textbf{Explanations}

a. Quality of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that were judged to be acceptable by the panel.

b. Although there was minor inconsistency for sensitivity, we did not downgrade for the quality of evidence.

c. Quality of evidence was downgraded for serious unexplained inconsistency in specificity, with range from 16.3% to 92.2%. Multiple sensitivity analyses could not provide an explanation.
<table>
<thead>
<tr>
<th>CERTAINTY OF THE EVIDENCE OF TEST ACCURACY</th>
<th>Judgment</th>
<th>Research Evidence</th>
<th>Additional Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the overall certainty of the evidence of test accuracy?</td>
<td>Very low</td>
<td>Moderate (D-dimer)</td>
<td>No included studies</td>
</tr>
<tr>
<td>Low</td>
<td>High (Proximal CUS, Whole Leg US, Serial US)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS</td>
<td>What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?</td>
<td>Very low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Low</td>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No included studies</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT

<table>
<thead>
<tr>
<th>CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT</th>
<th>How certain is the link between test results and management decisions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Very low</td>
<td>The link between test results and management is unique in venous thromboembolism. With LE DVT diagnosis, all positive results are generally treated with anticoagulation (regardless of the chances of false positives).</td>
</tr>
<tr>
<td>o Low</td>
<td>The panel noted high certainty in the link between test results and management decisions. However, the panel also noted that for patients with calf DVT, the link may not be as certain.</td>
</tr>
<tr>
<td>o Moderate</td>
<td></td>
</tr>
<tr>
<td>o High</td>
<td></td>
</tr>
<tr>
<td>o No included studies</td>
<td></td>
</tr>
</tbody>
</table>

### CERTAINTY OF EFFECTS

<table>
<thead>
<tr>
<th>CERTAINTY OF EFFECTS</th>
<th>What is the overall certainty of the evidence of effects of the test?</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Very low</td>
<td>The panel noted the lack of direct data on patient outcomes, and a high level of uncertainty in the consequences for patients who receive a false negative test result.</td>
</tr>
<tr>
<td>o Low</td>
<td></td>
</tr>
<tr>
<td>o Moderate</td>
<td></td>
</tr>
<tr>
<td>o High</td>
<td></td>
</tr>
<tr>
<td>o No included studies</td>
<td></td>
</tr>
</tbody>
</table>

### VALUES

<table>
<thead>
<tr>
<th>VALUES</th>
<th>Is there important uncertainty or variability in how people value different outcomes?</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Important uncertainty or variability</td>
<td>The numbers shown below are utilities, representing the strength of an individual’s preferences for different outcomes. They are measured on a scale, with zero reflecting states of health equivalent to death/worst imaginable health and one reflecting perfect health/best imaginable health.</td>
</tr>
<tr>
<td>o Possibly important uncertainty or variability</td>
<td>Systematic reviews found that the relative importance of the outcomes is as follows:</td>
</tr>
<tr>
<td>o Probably no important uncertainty or variability</td>
<td>Pulmonary embolism: 0.63-0.93 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004)</td>
</tr>
<tr>
<td>o No important</td>
<td>Deep vein thrombosis: 0.64-0.99 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016)</td>
</tr>
</tbody>
</table>

The panel placed a high value on decreasing the number of false negative test results over decreasing false positive test results. The panel also placed a high value on reducing the number of false negative test results.
uncertainty or variability

- Deep vein thrombosis patients' own current health: 0.95 (Time trade off) (Locadia 2004)
- Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg 2013, Locadia 2004)
- Minor intracranial bleeding event: 0.75 (standard gamble) (Hogg 2013)
- Major intracranial bleeding event: 0.15 (standard gamble) (Hogg 2013)
- Central nervous system bleeding: 0.29-0.60 (standard gamble) (Lenert 1997, O'Meara 1994)

Results of Panel Utility Rating Survey:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean Utility Rating (SD)</th>
<th>All Panels (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>False Negative Test Result</td>
<td>0.60 (0.23)</td>
<td></td>
</tr>
<tr>
<td>False Positive Test Result</td>
<td>0.62 (0.21)</td>
<td></td>
</tr>
<tr>
<td>True Negative Test Result</td>
<td>0.91 (0.15)</td>
<td></td>
</tr>
<tr>
<td>True Positive Test Result</td>
<td>0.76 (0.19)</td>
<td></td>
</tr>
<tr>
<td>Inconclusive Test Result</td>
<td>0.69 (0.18)</td>
<td></td>
</tr>
<tr>
<td>Radiation Exposure</td>
<td>0.84 (0.14)</td>
<td></td>
</tr>
<tr>
<td>Contrast Induced Nephropathy</td>
<td>0.56 (0.20)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Embolism – Moderate Marker State</td>
<td>0.42 (0.15)</td>
<td></td>
</tr>
<tr>
<td>Proximal DVT – Moderate Marker State</td>
<td>0.58 (0.14)</td>
<td></td>
</tr>
<tr>
<td>Distal DVT – Moderate Marker State</td>
<td>0.64 (0.16)</td>
<td></td>
</tr>
<tr>
<td>Upper Extremity DVT – Moderate Marker State</td>
<td>0.61 (0.16)</td>
<td></td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>0.33 (0.23)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>0.12 (0.10)</td>
<td></td>
</tr>
<tr>
<td>Chronic Thrombotic Pulmonary Hypertension</td>
<td>0.34 (0.15)</td>
<td></td>
</tr>
</tbody>
</table>

* Utility rating by panel members from 0 (dead) to 1 (full health)

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**Rank the top pathways in order of which provides the best balance of desirable and undesirable effects to which provides the least balance.**

The panel judged the ranking of the pathways based on a threshold of false negative patients and a threshold of misdiagnosed patients (combination of false negative and false positive results).

Pathways highlighted in green were judged as the top ranked pathways that provided the best balance of desirable and undesirable effects. These pathways remained below a threshold of 20 false negative results per 1000 patients tested (≤2%) and a threshold of 50 misdiagnosed results per 1000 patients tested (≤5%).

Pathways highlighted in yellow provided a less acceptable balance of desirable and undesirable effects. These pathways remained below a threshold of 50 false negative results per 1000 patients tested (≤5%) and 100 misdiagnosed results per 1000 patients (≤10%).

Pathways highlighted in red did not provide an acceptable balance of desirable and undesirable effects. These pathways remained below a threshold of 50 false negative results per 1000 patients tested (≤5%) and 100 misdiagnosed results per 1000 patients (≤10%).

---

### Modelling of Diagnostic Test Accuracy

**Note:** See pathways on Page 1

Pathway A begins with Whole Leg US
Pathways B-F begin with Proximal CUS
Pathways G-I begin with D-dimer

**Table 1:** In a patient population with a low clinical probability of lower extremity deep vein thrombosis (LE DVT), what is the optimal diagnostic strategy to diagnose a first episode LE DVT?

<table>
<thead>
<tr>
<th>10%</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F*</th>
<th>G</th>
<th>H</th>
<th>I*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TP</strong></td>
<td>93</td>
<td>90</td>
<td>100</td>
<td>99</td>
<td>100</td>
<td>100</td>
<td>96</td>
<td>86</td>
<td>89</td>
</tr>
<tr>
<td><strong>FP</strong></td>
<td>22</td>
<td>14</td>
<td>587</td>
<td>15</td>
<td>10</td>
<td>15</td>
<td>14</td>
<td>582</td>
<td>9</td>
</tr>
<tr>
<td><strong>TN</strong></td>
<td>878</td>
<td>887</td>
<td>313</td>
<td>15</td>
<td>31</td>
<td>885</td>
<td>887</td>
<td>318</td>
<td>891</td>
</tr>
<tr>
<td><strong>FN</strong></td>
<td>7</td>
<td>10</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>14</td>
<td>11</td>
</tr>
</tbody>
</table>

*Venography was deemed not suitable as a follow-up test due to the use of ultrasound as the accepted reference standard for DVT diagnosis.

*Whole Leg US sensitivity and specificity estimates were used to model Pathway J.

TP-patient correctly identified as having LEDVT and anticoagulated
FP-patient incorrectly identified as having LEDVT and unnecessarily anticoagulated
TN- patient correctly identified as not having LEDVT and not anticoagulated
FN - patient incorrectly identified as not having LEDVT and will not receive needed anticoagulation

Assumptions associated with modelling:
1. Disease prevalence in a low clinical probability population was determined be 100 per 1000 patients (10%).
2. Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

---

### Desirable and undesirable effects:

The panel considered desirable effects as increasing the number of patients with true positive and true negative test result (i.e. patients accurately diagnosed and accurately treated).

The panel considered undesirable as increasing the number of patients with false positive and false negative test results (i.e. receive unnecessary anticoagulation or morbidity/ mortality from missed diagnosis).

**Balance of desirable and undesirable effects:**

For this guideline question, in addition to the diagnostic test accuracy outcomes, the panel prioritized minimizing the number of tests used to establish the diagnosis.

This was considered in determining which of
acceptable balance of desirable and undesirable effects and were ranked lowest. These pathways were above the threshold of 50 false negative results per 1000 patients tested (>5%) and 100 misdiagnosed results per 1000 patients (>10%).

3. The panel judged the ranking of pathways with the best balance of desirable and undesirable effects based on thresholds of false negative patients and misdiagnosed patients (false negative and false positive). These rankings are depicted in the table as green being the most acceptable, yellow being less acceptable, and red being unacceptable.

5. Test accuracy for D-dimer, proximal CUS, and whole leg US were derived from these tests being used as a standalone test. These sensitivity and specificity results were used when the test was the first test of the pathway. These accuracy results were also used if the test was a subsequent test in a pathway.

6. Pooled estimates from studies of high sensitivity D-dimer assays that are currently used in practice were used to model pathways.

The pathways that met the acceptable thresholds for diagnostic test accuracy (i.e. the pathways highlighted in green), provided the best balance of effects.

<table>
<thead>
<tr>
<th>RESOURCES REQUIRED</th>
<th>How large are the resource requirements (costs) for proximal CUS?</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Large costs</td>
<td>Moderate costs</td>
</tr>
<tr>
<td>○ Negligible costs and savings</td>
<td>Moderate savings</td>
</tr>
<tr>
<td>○ Large savings</td>
<td></td>
</tr>
</tbody>
</table>

| Costs of diagnostic tests: | | |
|---------------------------|--|--|--|
| Diagnostic test           | Peer-review articles and Other sources³ | CPT (Current Procedural Terminology)-4 Codes/cost¹² |
| D-dimer test              | $256 ($271 in 2017)⁴,⁵ | |
| Lower Extremity           | Compression ultrasonography: $200 ($260 in 2017)⁶ | 76856-US exam pelvic complete Facility/Non-Facility price: $33.56-144.34 |

The panel noted that the data showing costs based on CPT codes do not reflect what patients are charged in different settings, and are likely an under-representation of what patients and insurers pay.
<table>
<thead>
<tr>
<th>How large are the resource requirements (costs) for whole leg US?</th>
<th>Doppler ultrasound: $602.30</th>
<th>Opps Facility/Non-Facility payment amount: $95.61-192.55</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Don't know</td>
<td>○ Moderate costs</td>
<td>○ Negligible costs and savings</td>
</tr>
<tr>
<td>○ Large costs</td>
<td>○ Moderate savings</td>
<td>○ Large savings</td>
</tr>
<tr>
<td>○ Moderate costs</td>
<td>○ Don't know</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How large are the resource requirements (costs) for serial US?</th>
<th>Compression ultrasound of extremity veins</th>
<th>93970 - Extremity study Facility/Non-Facility price: $33.34-262.08 Opps Facility/Non-Facility payment amount: $191.98-345.03</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Don't know</td>
<td>○ Moderate costs</td>
<td>○ Negligible costs and savings</td>
</tr>
<tr>
<td>○ Large costs</td>
<td>○ Moderate savings</td>
<td>○ Large savings</td>
</tr>
<tr>
<td>○ Moderate costs</td>
<td>○ Don't know</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How large are the resource requirements (costs) for D-dimer?</th>
<th>Duplex scan of lower extremities</th>
<th>93925-Lower extremity study Facility/Non-Facility price: $37.86 - $361.27 Opps Facility/Non-Facility payment amount: $191.52 - $350.20</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Don't know</td>
<td>○ Moderate costs</td>
<td>○ Negligible costs and savings</td>
</tr>
<tr>
<td>○ Large costs</td>
<td>○ Moderate savings</td>
<td>○ Large savings</td>
</tr>
<tr>
<td>○ Moderate costs</td>
<td>○ Don't know</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>References:</th>
<th>Venography, extremity</th>
<th>75820- Vein x-ray arm/leg Facility/Non-Facility price: $33.34-149.42 Opps Facility/Non-Facility payment amount: $580.65-964.81</th>
</tr>
</thead>
<tbody>
<tr>
<td>31. <a href="https://pricinghealthcare.com/prices/CenterForMedicalImaging">https://pricinghealthcare.com/prices/CenterForMedicalImaging</a></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Given this, the panel noted that the reported costs for D-dimer seem high, however this may be reflective of the U.S. setting and may differ between settings.

The panel noted that for D-dimer costs from a health system perspective are moderate.

Additionally, a diagnostic pathway starting with D-dimer would reduce costs by refining the population that requires an US. However, the panel noted that when the costs of D-dimer tests are high, it is more effective to go directly to US.

The panel noted that for the cost of serial US, the cost reported is usually for one more US, but that patients have to return to receive the test, creating indirect costs.
<table>
<thead>
<tr>
<th>CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>What is the certainty of the evidence of resource requirements (costs) for proximal CUS?</strong></td>
<td></td>
</tr>
<tr>
<td>○ Very low</td>
<td></td>
</tr>
<tr>
<td>○ Low</td>
<td></td>
</tr>
<tr>
<td>○ Moderate</td>
<td></td>
</tr>
<tr>
<td>○ High</td>
<td></td>
</tr>
<tr>
<td>○ No included studies</td>
<td></td>
</tr>
<tr>
<td><strong>What is the certainty of the evidence of resource requirements (costs) for whole leg US?</strong></td>
<td></td>
</tr>
<tr>
<td>○ Very low</td>
<td></td>
</tr>
<tr>
<td>○ Low</td>
<td></td>
</tr>
<tr>
<td>○ Moderate</td>
<td></td>
</tr>
<tr>
<td>○ High</td>
<td></td>
</tr>
<tr>
<td>○ No included studies</td>
<td></td>
</tr>
<tr>
<td><strong>What is the certainty of the evidence of resource requirements (costs) for serial US?</strong></td>
<td></td>
</tr>
<tr>
<td>○ Very low</td>
<td></td>
</tr>
<tr>
<td>○ Low</td>
<td></td>
</tr>
<tr>
<td>○ Moderate</td>
<td></td>
</tr>
<tr>
<td>○ High</td>
<td></td>
</tr>
<tr>
<td>○ No included studies</td>
<td></td>
</tr>
</tbody>
</table>

The panel noted uncertainty in the actual costs of the tests.

33. 1 US dollar in 2012 equals to about $1.0662 in 2017 (http://www.in2013dollars.com/)
35. Based on CADTH report; The cost consists of diagnostic tests costs and physician interpretation cost, and it is in Canadian dollars in 2017.
<table>
<thead>
<tr>
<th><strong>COST EFFECTIVENESS</strong></th>
<th>Cost effectiveness of diagnostic pathways evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The panel judged pathways starting with a d-dimer test as most cost-effective considering the lower cost of the test.</td>
</tr>
<tr>
<td></td>
<td>D-dimer: No evidence identified on the cost-effectiveness of proximal compression US.</td>
</tr>
<tr>
<td></td>
<td>Proximal CUS: No evidence identified on the cost-effectiveness of proximal compression US.</td>
</tr>
<tr>
<td></td>
<td>Whole Leg US: No evidence identified on the cost-effectiveness of whole leg US.</td>
</tr>
</tbody>
</table>
**EQUITY**

<table>
<thead>
<tr>
<th>Impact on health equity of diagnostic pathways evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>The panel judged the pathways requiring the least number of tests as having the least impact, and not decreasing health equity.</td>
</tr>
</tbody>
</table>

We identified the following regarding impact on health equity with the different tests:

- **D-dimer:** Canadian provinces with larger populations tended to have a large proportion of hospitals with capability to measure D-dimer levels for VTE, whereas less populated provinces were more likely to send samples to centralized analysis facilities for D-dimer testing. (Southern 2014)

- **Proximal CUS:** No research evidence identified.

- **Whole Leg US:** No research evidence identified.

---

**ACCEPTABILITY**

<table>
<thead>
<tr>
<th>Acceptability of diagnostic pathways evaluated to key stakeholders</th>
</tr>
</thead>
<tbody>
<tr>
<td>The panel considered all pathways evaluated as acceptable.</td>
</tr>
</tbody>
</table>

Studies described the following regarding acceptability from key stakeholders:

- **General (Radiology & Population):**
  
  In a study among nursing home patients with suspected VTE, referral for additional diagnostic investigations was withheld in almost 40%. In providers’ decisions to forgo diagnostic investigations, they incorporated the estimated relative impact of the potential disease; the potential net-benefits of diagnostic investigations and whether performing investigations agreed with established management goals in advance care planning. (Schouten 2014)

  A study among physicians who had previously referred patients for any VTE screening examination showed that physicians had a lack of basic knowledge regarding lower extremity venous anatomy, charges for the different diagnostic tests used to diagnose VTE, and current treatment standards for VTE. (Zierler 2002)

- **Proximal CUS:**
  
  Patient level of discomfort during point-of-care ultrasonography of the heart, lungs and deep veins for respiratory symptoms is very low and the vast majority of patients would accept being assessed by this method if the patients once again had to be examined for possible disease. (Laursen 2015)
## Feasibility to implement diagnostic pathways evaluated

The panel considered all pathways as feasible, however noting specific considerations for feasibility of testing with D-dimer, and proximal CUS.

<table>
<thead>
<tr>
<th>Feasibility</th>
<th>Studies described the following regarding feasibility and barriers to use:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Feasibility:</strong></td>
<td>Intensivist-performed compression ultrasonography for proximal lower extremity DVT showed high diagnostic accuracy (95%) compared with usual ultrasonography as performed by technicians and interpreted by radiologists. Time delay between ordering of ultrasonography and radiologist result was 14 hours. (Kory 2011)</td>
</tr>
<tr>
<td><strong>Implementation:</strong></td>
<td>Postponing after-hours venous duplex ultrasound testing for DVT to the next morning in patients who could receive LMWH, unless otherwise indicated by the vascular surgeon, was safe. After-hours ultrasound requests decreased and the rate of positive studies in off-hours increased. (Chaer 2010)</td>
</tr>
<tr>
<td></td>
<td>New practice guideline implementation increasing the number of duplex screening exams in trauma patients also increased the rate of DVT identification. (Haut 2007)</td>
</tr>
<tr>
<td><strong>D-Dimer:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Feasibility:</strong></td>
<td>Following at least one D-dimer test for DVT or PE, the strategy for further diagnostic testing was inappropriate in 31% with 9 out of 10 being overutilization of diagnostic imaging. (Arnason 2007)</td>
</tr>
<tr>
<td></td>
<td>The diagnostic work-up for DVT did not adhere to current guidelines with venous ultrasonography performed in 96%, D-dimer assay in 36% and venography in 6%. The rate of VTE at 90 days was 0.34% in patients in whom the diagnosis of DVT had been ruled out, and 2.50% in patients with inconclusive diagnostic workup. (Schellong 2009)</td>
</tr>
<tr>
<td><strong>Implementation:</strong></td>
<td>A policy to provide Point of Care Technology (POCT) laboratory results in the ED, including D-dimer for DVT, found no significant reduction in time to decision for patients with suspected DVT who received POCT testing. (Mogensen 2011)</td>
</tr>
</tbody>
</table>

The panel also noted that for some institutions, access to test results for US may not be quick, and that in some centers obtaining results of a D-dimer test requires sending out to another center for analysis, which impacts access to quick test results and feasibility.
| | Implementation of an evidence-based DVT probability scoring system as part of a clinical pathway from primary to secondary care showed that the ED waiting time decreased and initial D-dimer use increased, the latter indicating increased suspicion of DVT in primary care. Following D-dimer, ultrasound test use remained the same. (Campbell 2008) |

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Conclusions

In a patient population with a low clinical probability of lower extremity deep vein thrombosis (LE DVT), what is the optimal diagnostic strategy to diagnose a first episode LE DVT?

<table>
<thead>
<tr>
<th>TYPE OF RECOMMENDATION</th>
<th>Strong recommendation against the intervention</th>
<th>Conditional recommendation against the intervention</th>
<th>Conditional recommendation for the intervention or the comparison</th>
<th>Conditional recommendation for the intervention</th>
<th>Strong recommendation for the intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECOMMENDATION</td>
<td>The ASH guideline panel <strong>recommends</strong> using a strategy starting with D-dimer followed by CUS or CUS/whole leg US alone for diagnosing DVT in a population with low prevalence/pretest probability (10%). (Strong recommendation for D-dimer based on moderate certainty in the evidence about effects on clinical outcomes and moderate certainty in the evidence about diagnostic accuracy studies; Conditional recommendation for CUS/whole leg US based on very low certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy)**&lt;br&gt;&lt;br&gt;Remarks: In the D-dimer strategy, a negative D-dimer rules out DVT and no additional testing or anticoagulation is provided. A decision to start with D-dimer assumes the results will be obtained in a timely manner and that the cost of D-dimer screening is offset by avoiding unnecessary CUS in patients at low PTP for DVT.&lt;br&gt;&lt;br&gt;The ASH guideline panel <strong>recommends against</strong> using a positive D-dimer alone to diagnose DVT, and against additional testing following negative CUS in a population with low prevalence/pretest probability (10%).&lt;br&gt;&lt;br&gt;JUSTIFICATION</td>
<td>The panel considered a strategy with D-dimer testing first to reduce cost in a population with low prevalence of DVT. D-dimer alone was considered not sufficient as a rule-in test, and must be followed by another test. If CUS is used as a first test, it should not be followed by other tests as no additional benefit is achieved and there is further cost, impacting health equity.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUBGROUP CONSIDERATIONS</td>
<td>Noted importance of promoting D-dimer first strategy.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMPLEMENTATION CONSIDERATIONS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MONITORING AND EVALUATION</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RESEARCH PRIORITIES</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 1: Modelling of Diagnostic Test Accuracy

Note: See diagnostic pathway diagrams on Page 1

Pathways A begins with Whole Leg US
Pathways B-F begin with Proximal CUS
Pathways G-I begin with D-dimer

Table 1: In a patient population with a low clinical probability of lower extremity deep vein thrombosis (LEDVT), what is the optimal diagnostic strategy to diagnose a first episode LEDVT?

<table>
<thead>
<tr>
<th></th>
<th>Pathways</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>TP - patients correctly identified as having DVT and correctly anticoagulated</td>
<td>93</td>
</tr>
<tr>
<td>FP - patients incorrectly identified as having DVT and receive unnecessary anticoagulation</td>
<td>22</td>
</tr>
<tr>
<td>TN - patients correctly identified as not having DVT and correctly not treated</td>
<td>878</td>
</tr>
<tr>
<td>FN - patients incorrectly identified as not having DVT and will not receive necessary anticoagulation</td>
<td>7</td>
</tr>
</tbody>
</table>

*Venography was deemed not suitable as a follow-up test due to the use of ultrasound as the accepted reference standard for DVT diagnosis.

*Whole Leg US sensitivity and specificity estimates were used to model Pathway J.
Appendix 2: Natural Progression and Treatment Effects

When making a decision regarding which pathway to recommend for diagnosing LE DVT, one must acknowledge that there will be patients who will have negative consequences because of an incorrect test result and thus incorrect diagnosis. Patients who receive unnecessary anticoagulation (false positive) or do not receive necessary anticoagulation (false negative) are subject to the risks of bleeding, may suffer complications or may die. Tables 2 and 3 provide some insight into the frequency of these outcomes.

True positive: patients correctly identified as having LE DVT and correctly anticoagulated
True negative: patients correctly identified as not having LE DVT and correctly not anticoagulated
False positive: patients incorrectly identified as having LE DVT and receive unnecessary anticoagulation
False negative: patients incorrectly identified as not having LE DVT and will not receive necessary anticoagulation

Outcomes studied include:
- Lower extremity deep vein thrombosis
- Pulmonary embolism
- Hemorrhagic Stroke
- Major Bleeding
- Mortality
- Recurrent LE DVT

<table>
<thead>
<tr>
<th>Table 1. Clinical outcomes for LEDVT by pathway</th>
<th>B</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism</td>
<td>TOTAL: 18/407 (4%)</td>
<td></td>
</tr>
<tr>
<td>(Prandoni P 2002): (36 months; unttrt) 14/313 (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Anderson et al. 1999): (with treatment w/in 48 hrs) 4/24 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Birdwell 1998): (VTE in abnormal US) 4/70 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>TOTAL: 4/94 (4%)</td>
<td></td>
</tr>
<tr>
<td>(Anderson et al. 1999): 0/24 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Birdwell 1998): (mortality due to PE) 4/70 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td>TOTAL: 3/681 (0.4%)</td>
</tr>
<tr>
<td>(Bernardi 1998): (venous thromboembolic complications) 1/598 (0.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Bernardi 1998): thromboembolic complications (untreated and abnormal DD but had normal repeat US) 2/83 (2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Outcomes by Test Result

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<table>
<thead>
<tr>
<th>Test accuracy results</th>
<th>Consequences</th>
<th>Results from published SR</th>
<th>Results from treatment guideline*</th>
<th>Targeted search of primary studies</th>
<th>Panel survey results</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP</td>
<td>Mortality: all cause</td>
<td>2.0% (6m)*</td>
<td>6%</td>
<td>8.8% (1y)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mortality from DVT w 3 months</td>
<td>0.4% (PE mortality)^</td>
<td>0%</td>
<td>4.3% (1y)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recurrence on AC w 3 months</td>
<td>3.8% (3m)^</td>
<td>1.3% (6m; proximal DVT)</td>
<td>4.6%</td>
<td>5.6% (1y)</td>
</tr>
<tr>
<td></td>
<td>Development of PE</td>
<td>1.0% (6m)</td>
<td>1.0%</td>
<td>5.8% (1y)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Major bleeding</td>
<td>2.1% (6m)</td>
<td>3.1%</td>
<td>4.2% (1y)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fatal major bleeding</td>
<td>0.2% (6m)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemorrhagic stroke</td>
<td></td>
<td>2.0 (ICH; 1y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FP</td>
<td>Mortality: all cause</td>
<td>2.1% (6m)</td>
<td>3.1%</td>
<td>4.2% (1y)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fatal major bleeding</td>
<td>0.2% (6m)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TN</td>
<td>Mortality from DVT w 3 months</td>
<td>0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FN</td>
<td>Mortality: all cause</td>
<td></td>
<td>18.4% (1y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mortality from DVT w 3 months</td>
<td></td>
<td>10.5% (1y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recurrence on AC w 3 months</td>
<td></td>
<td>11.0% (1y)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Mortality, DVT and PE: median event rates from included RCTs, Major bleeding rate from Carrier 2010
# Carrier 2010 reported case fatality rate of 4.9% (6m) but VTE Treatment panel did not use this
$ Carrier 2010 reported recurrent PE rate of 3.6%, but VTE Treatment panel did not use this
^ Douketis 1998
REFERENCES

References of Background:


References of Included DTA studies:


References of Clinical Outcomes Studies:

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References related to prevalence:


References related to Patients Values and Preferences:


References related to Acceptability, Feasibility, Equity, Implementation:


Question 6. In a patient population with an intermediate clinical probability of lower extremity deep vein thrombosis (LE DVT) what is the optimal diagnostic strategy to diagnose a first episode LE DVT?

**Diagnosis of Lower Extremity Deep Vein Thrombosis: Diagnostic Pathways Assessed**

a. Whole leg US
   - Positive whole leg US → anticoagulate
   - Negative whole leg US → no treatment

b. Proximal CUS
   - Positive proximal CUS → anticoagulate
   - Negative proximal CUS → no treatment
c. Proximal CUS

- Positive proximal CUS → anticoagulate
- Negative proximal CUS → D-dimer
  - Positive D-dimer → anticoagulate
  - Negative D-dimer → no treatment

---

Pathway C

Patients with suspected LE DVT

PTP Assessment

Proximal CUS

- Positive
- Negative

- Positive D-Dimer
- Negative D-Dimer

Anticoagulate

Outcomes

---

d. Proximal CUS

- Positive proximal CUS → anticoagulate
- Negative proximal CUS → D-dimer
  - Positive D-dimer → serial US
    - Positive serial US → anticoagulate
    - Negative serial US → no treatment
  - Negative D-dimer → no treatment

---

Pathway D

Patients with suspected LE DVT

PTP Assessment

Proximal CUS

- Positive
- Negative

- Positive D-Dimer
- Negative D-Dimer

Serial US

- Positive
- Negative

Anticoagulate

No treatment

Outcomes

---
e. Proximal CUS

- Positive proximal CUS → anticoagulate
- Negative proximal CUS → Serial US
  - Positive Serial US → anticoagulate
  - Negative Serial US → no treatment

f. Proximal CUS

- Positive proximal CUS → anticoagulate
- Negative proximal CUS → D-Dimer
  - Positive D-Dimer → venography
    - Positive venography → anticoagulate
    - Negative venography → No treatment
  - Negative D-Dimer → No treatment

*Venography was deemed not suitable as a follow-up test due to the use of ultrasound as the accepted reference standard for DVT diagnosis.
g. D-dimer

- Positive D-dimer → anticoagulate
- Negative D-dimer → no treatment

h. D-dimer

- Positive D-dimer → proximal CUS
  - Positive proximal CUS → anticoagulate
  - Negative proximal CUS → no treatment
- Negative D-dimer → no treatment
i. D-dimer

- Positive D-dimer → whole leg/serial US
  - Positive whole leg/serial US → anticoagulate
  - Negative whole leg/serial US → no treatment
- Negative D-dimer → no treatment

** Whole Leg US sensitivity and specificity estimates were used to model Pathway J.

Note: in the algorithms, watchful waiting will follow negative tests and low/normal probability unless stated otherwise.

<table>
<thead>
<tr>
<th>Legend</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>deep vein thrombosis</td>
</tr>
<tr>
<td>US</td>
<td>ultrasound</td>
</tr>
<tr>
<td>CUS</td>
<td>compression ultrasound</td>
</tr>
</tbody>
</table>

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Question 6. In a patient population with an intermediate clinical probability of lower extremity deep vein thrombosis (LE DVT), what is the optimal diagnostic strategy to diagnose a first episode LE DVT?

| POPULATION: | Patients with an intermediate clinical probability of suspected first episode lower extremity deep vein thrombosis (LE DVT) |
| EVALUATED TESTS: | Whole leg ultrasound (US), proximal compression ultrasound (CUS), Serial ultrasound (US), D-dimer |
| PURPOSE OF THE TEST: | Detection of lower extremity deep vein thrombosis |
| ROLE OF THE TEST: | Detection of lower extremity deep vein thrombosis |
| LINKED TREATMENTS: | Anticoagulation |
| ANTICIPATED OUTCOMES: | False Negative; False Positive; True Negative; True Positive; Mortality; Lower extremity deep vein thrombosis, Major Bleeding, Recurrent LE DVT |
| SETTING: | Inpatient and outpatient |
| PERSPECTIVE: | Clinical recommendation - population perspective |

**BACKGROUND:**

Lower extremity DVT (LE DVT) is suspected in patients with pain, swelling and/or warmth of the lower extremity. These clinical manifestations are nonspecific, and objective tests are required to confirm the diagnosis. LE DVT is associated with significant morbidity and can lead to post-thrombotic syndrome in up to 50% of cases (Kesieme, 2011). LE DVT is also clinically important as it can result in pulmonary embolism (PE). Diagnostic modalities to identify LE DVT include D-dimer assays, compression ultrasonography, duplex ultrasonography, and contrast enhanced venography. D-dimer, a fibrin degradation product, is typically elevated in the presence of DVT. While sensitive, D-dimer is frequently elevated with systemic illness and is a nonspecific test necessitating additional methods for diagnosis. Compression ultrasonography evaluates the compressibility, or lack thereof, of a venous segment to diagnose thrombosis. With acute DVT, compressibility is lost secondary to passive distension of the vein by thrombus (Robert-Ebadi, 2017). Duplex imaging can aid in examining venous flow as well. Venography is now infrequently performed as a diagnostic test for DVT, supplanted by duplex ultrasound as the reference standard for DVT diagnosis.
### Assessment

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Is the problem a priority?</strong></td>
<td>The exact incidence of deep venous thrombosis (DVT) of the lower extremities is unknown. One study reports an incidence of deep vein thrombosis in 48 per 100,000 patients (Anderson, 1991). However LE DVT is about 10 times more common than upper extremity DVT. (Goldhaber, 2014). Associated with significant morbidity and mortality, accurate and efficient diagnosis and treatment is important. Not only can LE DVT lead to significant pain and post-thrombotic syndrome, LE DVT can embolize to the lungs causing morbidity and mortality from PE. D-dimer, while sensitive, is not a specific test that can definitively diagnose DVT. With improvements in technology and experience, ultrasonography, has become a more reliable tool to diagnose DVT (Robert-Ebadi, 2017).</td>
<td></td>
</tr>
<tr>
<td><strong>How accurate is the test?</strong></td>
<td></td>
<td>The panel noted that for proximal CUS, whole leg US, and serial US, the inconclusive results reported are low, and likely not reflective of real-world settings.</td>
</tr>
<tr>
<td><strong>Proximal CUS</strong></td>
<td>Proximal CUS</td>
<td>The panel noted that for D-dimer, the test is not used on a standalone basis to rule in a diagnosis and patients are not treated based on a positive test result. Therefore, the rating of very inaccurate applies to the context of the diagnostic pathways being assessed.</td>
</tr>
<tr>
<td><strong>Patient or population:</strong> Patients with suspected lower extremity deep vein thrombosis</td>
<td><strong>New test:</strong> Proximal CUS</td>
<td></td>
</tr>
<tr>
<td><strong>Setting:</strong> Inpatient and outpatient</td>
<td><strong>Pooled sensitivity:</strong> 0.90 (95% CI: 0.87 to 0.93)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Pooled specificity:</strong> 0.99 (95% CI: 0.98 to 0.99)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Number of results per 1,000 patients tested (95% CI)</strong></td>
<td><strong>Number of participants (studies)</strong></td>
</tr>
<tr>
<td><strong>Test result</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>True positives</td>
<td>315 (303 to 325)</td>
<td>2889 (12)</td>
</tr>
<tr>
<td>False negatives</td>
<td>35 (25 to 47)</td>
<td>2889 (12)</td>
</tr>
<tr>
<td>True negatives</td>
<td>640 (634 to 644)</td>
<td>2889 (12)</td>
</tr>
<tr>
<td>False positives</td>
<td>10 (6 to 16)</td>
<td>2889 (12)</td>
</tr>
<tr>
<td><strong>Whole Leg US</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Proximal CUS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patient or population:</strong> Patients with suspected lower extremity deep vein thrombosis</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Number of results per 1,000 patients tested (95% CI)</strong></td>
<td><strong>Number of participants (studies)</strong></td>
<td><strong>Quality of the Evidence (GRADE)</strong></td>
</tr>
<tr>
<td>True positives</td>
<td>315 (303 to 325)</td>
<td>2889 (12)</td>
</tr>
<tr>
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<td>2889 (12)</td>
</tr>
<tr>
<td>False positives</td>
<td>10 (6 to 16)</td>
<td>2889 (12)</td>
</tr>
<tr>
<td><strong>Serial US</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Proximal CUS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patient or population:</strong> Patients with suspected lower extremity deep vein thrombosis</td>
<td><strong>New test:</strong> Proximal CUS</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Setting:</strong> Inpatient and outpatient</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Pooled sensitivity:</strong> 0.90 (95% CI: 0.87 to 0.93)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Pooled specificity:</strong> 0.99 (95% CI: 0.98 to 0.99)</td>
<td></td>
</tr>
<tr>
<td><strong>Number of results per 1,000 patients tested (95% CI)</strong></td>
<td><strong>Number of participants (studies)</strong></td>
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<td>True positives</td>
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</tr>
<tr>
<td>False positives</td>
<td>10 (6 to 16)</td>
<td>2889 (12)</td>
</tr>
</tbody>
</table>

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Whole leg US

**Patient or population:** Patients with suspected lower extremity deep vein thrombosis

**New test:** Whole Leg US

**Setting:** Inpatient and outpatient

**Pooled sensitivity:** 0.93 (95% CI: 0.89 to 0.96) | **Pooled specificity:** 0.98 (95% CI: 0.93 to 0.99)

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positives</td>
<td>325 (311 to 335)</td>
<td>1035 (7)</td>
<td>HIGH \textsuperscript{a,b}</td>
</tr>
<tr>
<td>False negatives</td>
<td>25 (15 to 39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True negatives</td>
<td>634 (606 to 645)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Fancher T et al. BMJ 2004; 329(7470):821. Clinical PTP and rapid D-dimer testing; mean prevalence of DVT in accuracy studies 11%; mean prevalence of DVT in management studies 25%

\textsuperscript{b}Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

**Explanations**

- Quality of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that were judged to be acceptable by the panel.
- Although there was minor inconsistency for sensitivity, we did not downgrade for the quality of evidence.
- Although there was minor inconsistency for specificity, we did not downgrade for the quality of evidence.

The panel noted that whole leg US detects proximal as well as calf DVT, and overtreatment can be an issue as not all calf (distal) DVT require treatment.
### False positives

<table>
<thead>
<tr>
<th></th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positives</td>
<td>343 (336 to 346)</td>
<td>2415 (6)</td>
<td>⬤⬤⬤⬤ HIGH a,b</td>
</tr>
<tr>
<td>False negatives</td>
<td>7 (4 to 14)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: Confidence interval
2Fancher T et al. BMJ 2004; 329(7470):821. Clinical PTP and rapid D-dimer testing; mean prevalence of DVT in accuracy studies 11%; mean prevalence of DVT in management studies 25%
2Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

### Explanations

- j. Quality of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that was judged to be acceptable by the panel.
- k. Although there was minor inconsistency for sensitivity, we did not downgrade for the quality of evidence.
- l. Although there was minor inconsistency for specificity, we did not downgrade for the quality of evidence.

### Serial US

**Patient or population:** Patients with suspected lower extremity deep vein thrombosis

**New test:** Serial US

**Setting:** Inpatient and outpatient

**Pooled sensitivity:** 0.98 (95% CI: 0.96 to 0.99) | **Pooled specificity:** 0.998 (95% CI: 0.993 to 0.999)

<table>
<thead>
<tr>
<th>Test result</th>
<th>Prevalence 35%1,2 in intermediate-risk patients with suspected LE DVT</th>
<th>Number of participants (studies)</th>
<th>Quality of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positives</td>
<td>343 (336 to 346)</td>
<td>2415 (6)</td>
<td>⬤⬤⬤⬤ HIGH a,b</td>
</tr>
<tr>
<td>False negatives</td>
<td>7 (4 to 14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test result</td>
<td>Number of results per 1,000 patients tested (95% CI)</td>
<td>Number of participants (studies)</td>
<td>Quality of the Evidence (GRADE)</td>
</tr>
<tr>
<td>-------------</td>
<td>---------------------------------------------------</td>
<td>---------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>True positives</td>
<td>335 (321 to 343)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**True negatives**: 649 (645 to 649)

**False positives**: 1 (1 to 5)

**Inconclusive test results**: 0

**Complications arising from the diagnostic test**: Not reported

**CI**: Confidence interval

1. Fancher T et al. BMJ 2004; 329(7470):821. Clinical PTP and rapid D-dimer testing; mean prevalence of DVT in accuracy studies 11%; mean prevalence of DVT in management studies 25%

2. Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

**Explanations**

- Quality of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that was judged to be acceptable by the panel.
- Although there was minor inconsistency for sensitivity, we did not downgrade for the quality of evidence.
- Although there was minor inconsistency for specificity, we did not downgrade for the quality of evidence.

**D-dimer**

**Patient or population**: Patients with suspected lower extremity deep vein thrombosis

**New test**: D-dimer

**Setting**: Inpatient and outpatient

**Pooled sensitivity**: 0.96 (95% CI: 0.92 to 0.98) | **Pooled specificity**: 0.35 (95% CI: 0.28 to 0.43)
<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>False negatives</td>
<td>15 (7 to 29)</td>
<td>4409 (14)</td>
<td>⬤⬤⬤◯</td>
<td>MODERATE</td>
</tr>
<tr>
<td>True negatives</td>
<td>229 (183 to 280)</td>
<td>4409 (14)</td>
<td>⬤⬤⬤◯</td>
<td>MODERATE</td>
</tr>
<tr>
<td>False positives</td>
<td>421 (370 to 467)</td>
<td>4409 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>Not applicable</td>
<td>4409 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications arising from the diagnostic test</td>
<td>Not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: Confidence interval

1 Fancher T et al. BMJ 2004; 329(7470):821. Clinical PTP and rapid D-dimer testing; mean prevalence of DVT in accuracy studies 11%; mean prevalence of DVT in management studies 25%

2 Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

Explanations

d. Quality of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that were judged to be acceptable by the panel.

e. Although there was minor inconsistency for sensitivity, we did not downgrade for the quality of evidence.

f. Quality of evidence was downgraded for serious unexplained inconsistency in specificity, with range from 16.3% to 92.2%. Multiple sensitivity analyses could not provide an explanation.
## CERTAINTY OF THE EVIDENCE OF TEST ACCURACY

What is the overall certainty of the evidence of test accuracy?
- Very low
- Low
- Moderate (D-dimer)
- High (Proximal CUS, Whole Leg US, Serial US)
- No included studies

## CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS

What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?
- Very low
- Low
- Moderate
- High
- No included studies
## How certain is the link between test results and management decisions?
- **Very low**
- **Low**
- **Moderate**
- **High**
- **No included studies**

The link between test results and management is unique in venous thromboembolism. With LE DVT diagnosis, all positive results are generally treated with anticoagulation (regardless of the chances of false positives). The panel noted high certainty in the link between test results and management decisions. However, the panel also noted that for patients with calf DVT, the link may not be as certain.

## What is the overall certainty of the evidence of effects of the test?
- **Very low**
- **Low**
- **Moderate**
- **High**
- **No included studies**

The panel noted the lack of direct data on patient outcomes, and a high level of uncertainty in the consequences for patients who receive a false negative test result.
### Values

<table>
<thead>
<tr>
<th>Outcome</th>
<th>False Negative Test Result</th>
<th>False Positive Test Result</th>
<th>True Negative Test Result</th>
<th>True Positive Test Result</th>
<th>Inconclusive Test Result</th>
<th>False Positive Test Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>False Negative Test Result</td>
<td>0.58 (0.14)</td>
<td>0.60 (0.23)</td>
<td>0.62 (0.21)</td>
<td>0.76 (0.19)</td>
<td>0.69 (0.18)</td>
<td>0.84 (0.14)</td>
</tr>
<tr>
<td>False Positive Test Result</td>
<td>0.62 (0.21)</td>
<td>0.58 (0.14)</td>
<td>0.60 (0.23)</td>
<td>0.76 (0.19)</td>
<td>0.69 (0.18)</td>
<td>0.84 (0.14)</td>
</tr>
<tr>
<td>True Negative Test Result</td>
<td>0.91 (0.15)</td>
<td>0.91 (0.15)</td>
<td>0.91 (0.15)</td>
<td>0.91 (0.15)</td>
<td>0.91 (0.15)</td>
<td>0.91 (0.15)</td>
</tr>
<tr>
<td>True Positive Test Result</td>
<td>0.62 (0.21)</td>
<td>0.62 (0.21)</td>
<td>0.62 (0.21)</td>
<td>0.62 (0.21)</td>
<td>0.62 (0.21)</td>
<td>0.62 (0.21)</td>
</tr>
<tr>
<td>Inconclusive Test Result</td>
<td>0.69 (0.18)</td>
<td>0.69 (0.18)</td>
<td>0.69 (0.18)</td>
<td>0.69 (0.18)</td>
<td>0.69 (0.18)</td>
<td>0.69 (0.18)</td>
</tr>
</tbody>
</table>

**Systematic reviews found that the relative importance of the outcomes is as follows:**

- **Pulmonary embolism**: 0.63 - 0.93 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004)
- **Deep vein thrombosis**: 0.64 - 0.99 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Une 2016)
- **Gastrointestinal tract bleeding event**: 0.75 (standard gamble) (Hogg 2013, Locadia 2004)
- **Deep vein thrombosis patients' own current health**: 0.95 (time trade off) (Locadia 2004)
- **Minor intracranial bleeding event**: 0.15 (standard gamble) (Hogg 2013)
- **Major intracranial bleeding event**: 0.29 - 0.60 (standard gamble) (Lenert 1997, O'Meara 1994)
### Distal DVT – Moderate Marker State
0.64 (0.16)

### Upper Extremity DVT – Moderate Marker State
0.61 (0.16)

### Major Bleeding
0.33 (0.23)

### Hemorrhagic Stroke
0.12 (0.10)

### Chronic Thrombotic Pulmonary Hypertension
0.34 (0.15)

* Utility rating by panel members from 0 (dead) to 1 (full health)

---

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F*</th>
<th>G</th>
<th>H</th>
<th>I*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP</td>
<td>325</td>
<td>315</td>
<td>349</td>
<td>348</td>
<td>346</td>
<td>349</td>
<td>335</td>
<td>302</td>
<td>311</td>
</tr>
<tr>
<td>FP</td>
<td>16</td>
<td>10</td>
<td>424</td>
<td>11</td>
<td>20</td>
<td>10</td>
<td>421</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>TN</td>
<td>634</td>
<td>640</td>
<td>226</td>
<td>639</td>
<td>630</td>
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<td>229</td>
<td>644</td>
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</tr>
<tr>
<td>FN</td>
<td>25</td>
<td>35</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>15</td>
<td>48</td>
<td>39</td>
</tr>
</tbody>
</table>

*Venography was deemed not suitable as a follow-up test due to the use of ultrasound as the accepted reference standard for DVT diagnosis.

*Whole leg US sensitivity and specificity estimates were used to model Pathway J.

TP: patient correctly identified as having LEDVT and anticoagulated
FP: patient incorrectly identified as having LEDVT and unnecessarily anticoagulated
TN: patient correctly identified as not having LEDVT and not anticoagulated

---

### Modelling of Diagnostic Test Accuracy

**Note:** See pathways on Page 1

Pathway A begins with Whole Leg US
Pathways B-F begin with Proximal CUS
Pathways G-I begin with D-dimer

**Table 1:** In a patient population with an intermediate clinical probability of lower extremity deep vein thrombosis (LE DVT), what is the optimal diagnostic strategy to diagnose a first episode LE DVT?

**35%**

**Desirable and undesirable effects:**

The panel considered desirable effects as increasing the number of patients with true positive and true negative test results (i.e. patients accurately diagnosed and accurately treated).

The panel considered undesirable as increasing the number of patients with false positive and false negative test results (i.e. receive unnecessary anticoagulation or morbidity/mortality from missed diagnosis).

**Balance of desirable and undesirable effects:**

For this guideline question, in addition to the diagnostic test accuracy outcomes, the panel...
<table>
<thead>
<tr>
<th>Pathway Characteristics</th>
<th>Assumptions associated with modelling:</th>
<th>Prioritized minimizing the number of tests used.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathways highlighted in green provided a less acceptable balance of desirable and undesirable effects. These pathways remained below a threshold of 20 false negative results per 1000 patients tested (≤2%) and a threshold of 50 misdiagnosed results per 1000 patients tested (≤5%).</td>
<td>1. Disease prevalence in an intermediate clinical probability population was determined to be 350 per 1000 patients (35%).</td>
<td>This was considered in determining which of the pathways that met the acceptable thresholds for diagnostic test accuracy (i.e. the pathways highlighted in green), provided the best balance of effects.</td>
</tr>
<tr>
<td>Pathways highlighted in yellow provided a less acceptable balance of desirable and undesirable effects. These pathways remained below a threshold of 50 false negative results per 1000 patients tested (≤5%) and 100 misdiagnosed results per 1000 patients (≤10%).</td>
<td>2. Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.</td>
<td></td>
</tr>
<tr>
<td>Pathways highlighted in red did not provide an acceptable balance of desirable and undesirable effects</td>
<td>3. The panel judged the ranking of pathways with the best balance of desirable and undesirable effects based on thresholds of false negative patients and misdiagnosed patients (false negative and false positive). These rankings are depicted in the table as green being the most acceptable, yellow being less acceptable, and red being unacceptable.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Test accuracy for D-dimer, proximal CUS, whole leg US were derived from these tests being used as a standalone test. These sensitivity and specificity results were used when the test was the first test of the pathway. These accuracy results were also used if the test was a subsequent test in a pathway.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Pooled estimates from studies of high sensitivity D-dimer assays that are currently used in practice were used to model pathways.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
and were ranked lowest. These pathways were above the threshold of 50 false negative results per 1000 patients tested (>5%) and 100 misdiagnosed results per 1000 patients (>10%).

### RESOURCES REQUIRED

<table>
<thead>
<tr>
<th>How large are the resource requirements (costs) for Proximal CUS?</th>
<th>Costs of diagnostic tests:</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Large costs</td>
<td>Diagnostic test</td>
</tr>
<tr>
<td>○ Moderate costs</td>
<td>D-dimer test</td>
</tr>
<tr>
<td>○ Negligible costs and savings</td>
<td>Lower Extremity</td>
</tr>
<tr>
<td>○ Moderate savings</td>
<td>Ultrasonography</td>
</tr>
<tr>
<td>○ Large savings</td>
<td>Other sources: Ultrasonod: leg/foot: $133-$233 abdomen/hip/pelvis: $77-$300</td>
</tr>
<tr>
<td>○ Don't know</td>
<td>76856-US exam pelvic complete Facility/Non-Facility price: $33.56-$144.34 Opps Facility/Non-Facility payment amount: $95.61-$192.55</td>
</tr>
</tbody>
</table>

The panel noted that the data showing costs based on CPT codes do not reflect what patients are charged in different settings, and are likely an under-representation of what patients and insurers pay. Given this, the panel noted that the reported costs for D-dimer seem high, however this may be reflective of the U.S. setting and may differ between settings.

The panel noted that for D-dimer costs from a health system perspective are moderate.

Additionally, a diagnostic pathway starting with D-dimer would reduce costs.
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Code</th>
<th>Description</th>
<th>Facility/Non-Facility price</th>
<th>Opps Facility/Non-Facility payment amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duplex scan of lower extremities</td>
<td>93925</td>
<td>Lower extremity study</td>
<td>$37.86 - $361.27</td>
<td>$191.52 - $350.20</td>
</tr>
<tr>
<td>Venography, extremity</td>
<td>75820</td>
<td>Vein x-ray arm/leg</td>
<td>$33.34 - 149.42</td>
<td>$580.65 - 964.81</td>
</tr>
</tbody>
</table>

**References:**


38. [https://pricinghealthcare.com/prices/CenterForMedicalImaging](https://pricinghealthcare.com/prices/CenterForMedicalImaging)


42. Based on CADTH report; The cost consists of diagnostic tests costs and physician interpretation cost, and it is in Canadian dollars in 2017.

By refining the population that requires an US. However, the panel noted that when the costs of D-dimer tests are high, it is more effective to go directly to ultrasound.

---

**Moderate savings**

- Large savings
- Don't know

**Large savings**

**Don't know**

**How large are the resource requirements (costs) for Serial US?**

- Large costs
- Moderate costs
- Negligible costs and savings
- Moderate savings
- Large savings
- Don't know

**How large are the resource requirements (costs) for D-Dimer?**

- Large costs
- Moderate costs
- Negligible costs and savings
- Moderate savings
- Large savings
- Don't know
| CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES | What is the certainty of the evidence of resource requirements (costs) for Proximal CUS?  
| | | ○ Very low  
| | | ○ Low  
| | | ○ Moderate  
| | | ○ High  
| | | ○ No included studies  
| | What is the certainty of the evidence of resource requirements (costs) for Whole Leg US?  
| | | ○ Very low  
| | | ○ Low  
| | | ○ Moderate  
| | | ○ High  
| | | ○ No included studies  
| | What is the certainty of the evidence of resource requirements (costs) for Serial US?  
| | | ○ Very low  
| | | ○ Low  
| | | ○ Moderate | The panel noted uncertainty in the actual costs of the tests.
What is the certainty of the evidence of resource requirements (costs) for D-Dimer?
- High
- No included studies
- Very low
- Low
- Moderate
- High
- No included studies

<table>
<thead>
<tr>
<th>COST EFFECTIVENESS</th>
<th>Cost effectiveness of diagnostic pathways evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer:</td>
<td>No evidence identified on the cost-effectiveness of proximal compression US.</td>
</tr>
<tr>
<td>Proximal CUS:</td>
<td>No evidence identified on the cost-effectiveness of proximal compression US.</td>
</tr>
<tr>
<td>Whole Leg US:</td>
<td>No evidence identified on the cost-effectiveness of whole leg US.</td>
</tr>
</tbody>
</table>
### EQUITY

**Impact on health equity of diagnostic pathways evaluated**
The panel judged the pathways requiring the least number of tests as having the least impact, and not decreasing health equity.

- **D-Dimer:**
  Canadian provinces with larger populations tended to have a large proportion of hospitals with capability to measure D-dimer levels for VTE, whereas less populated provinces were more likely to send samples to centralized analysis facilities for D-dimer testing. (Southern 2014)

- **Proximal CUS:**
  No research evidence identified.

- **Whole Leg US:**
  No research evidence identified.

### ACCEPTABILITY

**Acceptability of diagnostic pathways evaluated to key stakeholders**
The panel considered all pathways evaluated as acceptable.

**Studies described the following regarding acceptability from key stakeholders:**

- **General (Radiology & Population):**
  In a study among nursing home patients with suspected VTE, referral for additional diagnostic investigations was withheld in almost 40%. In providers’ decisions to forgo diagnostic investigations, they incorporated the estimated relative impact of the potential disease; the potential net-benefits of diagnostic investigations and whether performing investigations agreed with established management goals in advance care planning. (Schouten 2014)

  A study among physicians who had previously referred patients for any VTE screening examination showed that physicians had a lack of basic knowledge regarding lower extremity venous anatomy, charges for the different diagnostic tests used to diagnose VTE, and current treatment standards for VTE. (Zierler 2002)

- **Proximal CUS:**
  Patient level of discomfort during point-of-care ultrasonography of the heart, lungs and deep veins for respiratory symptoms is very low and the vast majority of patients would accept being assessed by this method if the patients once again had to be examined for possible disease. (Laursen 2015)
Feasibility to implement diagnostic pathways evaluated

The panel considered all pathways as feasible, however noting specific considerations for feasibility of testing with VQ scan, D-dimer, and proximal CUS.

Studies described the following regarding feasibility and barriers to use:

**US:**

**Feasibility:**
Intensivist-performed compression ultrasonography for proximal lower extremity DVT showed high diagnostic accuracy (95%) compared with usual ultrasonography as performed by technicians and interpreted by radiologists. Time delay between ordering of ultrasonography and radiologist result was 14 hours. (Kory 2011)

**Implementation:**
Postponing after-hours venous duplex ultrasound testing for DVT to the next morning in patients who could receive LMWH, unless otherwise indicated by the vascular surgeon, was safe. After-hours ultrasound requests decreased and the rate of positive studies in off-hours increased. (Chaer 2010)

New practice guideline implementation increasing the number of duplex screening exams in trauma patients also increased the rate of DVT identification. (Haut 2007)

**D-Dimer:**

**Feasibility:**
Following at least one D-dimer test for DVT or PE, the strategy for further diagnostic testing was inappropriate in 31% with 9 out of 10 being overutilization of diagnostic imaging. (Arnason 2007)

The diagnostic work-up for DVT did not adhere to current guidelines with venous ultrasonography performed in 96%, D-dimer assay in 36% and venography in 6%. The rate of VTE at 90 days was 0.34% in patients in whom the diagnosis of DVT had been ruled out, and 2.50% in patients with inconclusive diagnostic workup. (Schellong 2009)

**Implementation:**
A policy to provide Point of Care Technology (POCT) laboratory results in the ED, including D-dimer for DVT, found no significant reduction in time to decision for patients with suspected DVT who received POCT testing. (Mogensen 2011)

Implementation of an evidence-based DVT probability scoring system as part of a clinical pathway from primary to secondary care showed that the ED waiting time decreased and initial D-dimer use increased, the latter indicating increased suspicion of DVT in primary care. Following D-dimer, ultrasound test use remained the same. (Campbell 2008)

The panel also noted that for some institutions, access to test results for ultrasound may not be quick, and that in some centres obtaining results of a D-Dimer test requires sending out to another centre for analysis, which impacts access to quick test results and feasibility.
Conclusions

In a patient population with an intermediate clinical probability of lower extremity deep vein thrombosis (LE DVT), what is the optimal diagnostic strategy to diagnose a first episode LEDVT?

<table>
<thead>
<tr>
<th>TYPE OF RECOMMENDATION</th>
<th>Strong recommendation against the intervention</th>
<th>Conditional recommendation against the intervention</th>
<th>Conditional recommendation for either the intervention or the comparison</th>
<th>Conditional recommendation for the intervention</th>
<th>Strong recommendation for the intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECOMMENDATION</td>
<td>The ASH guideline panel <strong>suggests</strong> using a strategy starting with CUS for diagnosing DVT in a population with intermediate prevalence/pretest probability (35%), followed by serial CUS if the initial CUS is negative. (<em>Conditional</em> recommendation based on <em>very low</em> certainty in the evidence about effects on clinical outcomes and <em>low</em> certainty in the evidence about diagnostic accuracy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Remarks: In intermediate prevalence/pretest probability populations where the prevalence is <35%, alternate acceptable strategies include CUS or whole leg US alone with no additional follow-up testing for negative results, or initial testing with D-dimer followed by CUS/whole leg US if D-dimer is elevated. The D-dimer strategy assumes the results will be obtained in a timely manner and that the cost of D-dimer screening is offset by avoiding unnecessary CUS.

The ASH guideline panel **recommends against** using a positive D-dimer alone to diagnose DVT in a population with intermediate prevalence/pretest probability (35%).

JUSTIFICATION

Recommendations are based on modelling a DVT prevalence of 35%. Patients may have an intermediate probability/prevalence that is less than 35% in which case, alternate strategies may be acceptable. The panel considered a strategy with D-dimer testing first to reduce cost in a population with intermediate prevalence of DVT. D-dimer alone was considered not sufficient as a rule-in test, and must be followed by another test.
Appendix 1: Modelling of Diagnostic Test Accuracy

**Note:** See diagnostic pathway diagrams on Page 1

Pathway A begins with Whole Leg US  
Pathways B-F begin with Proximal CUS  
Pathways G-I begin with D-dimer

Table 1: In a patient population with an intermediate clinical probability of lower extremity deep vein thrombosis (LEDVT), what is the optimal diagnostic strategy to diagnose a first episode LEDVT?

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F*</th>
<th>G</th>
<th>H</th>
<th>I#</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TP</strong> - patients correctly identified as having DVT and correctly anticoagulated</td>
<td>325</td>
<td>315</td>
<td>349</td>
<td>348</td>
<td>349</td>
<td>349</td>
<td>335</td>
<td>302</td>
<td>311</td>
</tr>
<tr>
<td><strong>FP</strong> - patients incorrectly identified as having DVT and receive unnecessary anticoagulation</td>
<td>16</td>
<td>10</td>
<td>424</td>
<td>11</td>
<td>11</td>
<td>10</td>
<td>421</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td><strong>TN</strong> - patients correctly identified as not having DVT and correctly not treated</td>
<td>634</td>
<td>640</td>
<td>226</td>
<td>639</td>
<td>639</td>
<td>640</td>
<td>229</td>
<td>644</td>
<td>640</td>
</tr>
<tr>
<td><strong>FN</strong> - patients incorrectly identified as not having DVT and will not receive necessary anticoagulation</td>
<td>25</td>
<td>35</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>15</td>
<td>48</td>
<td>39</td>
</tr>
</tbody>
</table>

*Venography was deemed not suitable as a follow-up test due to the use of ultrasound as the accepted reference standard for DVT diagnosis.

#Whole Leg US sensitivity and specificity estimates were used to model Pathway J.
Appendix 2: Natural Progression and Treatment Effects

When making a decision regarding which pathway to recommend for diagnosing LE DVT, one must acknowledge that there will be patients who will have negative consequences because of an incorrect test result and thus incorrect diagnosis. Patients who receive unnecessary anticoagulation (false positive) or do not receive necessary anticoagulation (false negative) are subject to the risks of bleeding, may suffer complications or may die. Tables 2 and 3 provide some insight into the frequency of these outcomes.

True positive: patients correctly identified as having LE DVT and correctly anticoagulated  
True negative: patients correctly identified as not having LE DVT and correctly not anticoagulated  
False positive: patients incorrectly identified as having LE DVT and receive unnecessary anticoagulation  
False negative: patients incorrectly identified as not having LE DVT and will not receive necessary anticoagulation

Outcomes studied include:
Lower extremity deep vein thrombosis
Pulmonary embolism
Hemorrhagic Stroke
Major Bleeding
Mortality
Recurrent LE DVT

Table 1. Clinical outcomes for LEDVT by pathway

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism</td>
<td>TOTAL: 18/407 (4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Prandoni P 2002): (36 months; untrt) 14/313 (4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Anderson et al. 1999): (with treatment within 48 hrs) 4/24 (0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Birdwell 1998): (VTE in abnormal US) 4/70 (6%)</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>TOTAL: 4/94 (4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Anderson et al. 1999): 0/24 (0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Birdwell 1998): (mortality due to PE) 4/70 (6%)</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td>TOTAL: 3/681 (0.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Bernardi 1998): (venous thromboembolic complications) 1/598 (0.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Bernardi 1998): thromboembolic complications (untreated and abnormal DD but had normal repeat US) 2/83 (2%)</td>
</tr>
<tr>
<td>Test accuracy results</td>
<td>Consequences</td>
<td>Results from published SR</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>TP</td>
<td>Mortality: all cause</td>
<td>2.0% (6m) #</td>
</tr>
<tr>
<td></td>
<td>Mortality from DVT w 3 months</td>
<td>0.4% (PE mortality)^</td>
</tr>
<tr>
<td></td>
<td>Recurrence on AC w 3 months</td>
<td>3.8% (3m)^</td>
</tr>
<tr>
<td></td>
<td>Development of PE</td>
<td>1.0% (6m)</td>
</tr>
<tr>
<td></td>
<td>Major bleeding</td>
<td>2.1% (6m)</td>
</tr>
<tr>
<td></td>
<td>Fatal major bleeding</td>
<td>0.2% (6m)</td>
</tr>
<tr>
<td></td>
<td>Hemorrhagic stroke</td>
<td></td>
</tr>
<tr>
<td>FP</td>
<td>Mortality: all cause</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Major bleeding</td>
<td>2.1% (6m)</td>
</tr>
<tr>
<td></td>
<td>Fatal major bleeding</td>
<td>0.2% (6m)</td>
</tr>
<tr>
<td>TN</td>
<td>Mortality from DVT w 3 months</td>
<td></td>
</tr>
<tr>
<td>FN</td>
<td>Mortality: all cause</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mortality from DVT w 3 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recurrence on AC w 3 months</td>
<td></td>
</tr>
</tbody>
</table>

*Mortality, DVT and PE: median event rates from included RCTs, Major bleeding rate from Carrier 2010
# Carrier 2010 reported case fatality rate of 4.9% (6m) but VTE Treatment panel did not use this
§ Carrier 2010 reported recurrent PE rate of 3.6%, but VTE Treatment panel did not use this
^ Douketis 1998
REFERENCES

References of Background:


References of Included DTA studies:


References of Clinical Outcomes Studies:
References related to prevalence:


References related to Patients Values and Preferences:


References related to Acceptability, Feasibility, Equity, Implementation:


Question 7. In a patient population with a high clinical probability of lower extremity deep vein thrombosis (LE DVT), what is the optimal diagnostic strategy to diagnose a first episode LE DVT?

**Diagnosis of Lower Extremity Deep Vein Thrombosis: Diagnostic Pathways Assessed**

a. Whole leg US
   - Positive whole leg US → anticoagulate
   - Negative whole leg US → no treatment

   ![Pathway A](image)

b. Proximal CUS
   - Positive proximal CUS → anticoagulate
   - Negative proximal CUS → no treatment

   ![Pathway B](image)
c. Proximal CUS

- Positive proximal CUS → anticoagulate
- Negative proximal CUS → D-dimer
  - Positive D-dimer → anticoagulate
  - Negative D-dimer → no treatment

---

d. Proximal CUS

- Positive proximal CUS → anticoagulate
- Negative proximal CUS → D-dimer
  - Positive D-dimer → serial US
    - Positive serial US → anticoagulate
    - Negative serial US → no treatment
  - Negative D-dimer → no treatment
e. Proximal CUS

- Positive proximal CUS → anticoagulate
- Negative proximal CUS → Serial US
  - Positive Serial US → anticoagulate
  - Negative Serial US → no treatment

f. Proximal CUS

- Positive proximal CUS → anticoagulate
- Negative proximal CUS → D-Dimer
  - Positive D-Dimer → venography
    - Positive venography → anticoagulate
    - Negative venography → No treatment
  - Negative D-Dimer → No treatment

*Venography was deemed not suitable as a follow-up test due to the use of ultrasound as the accepted reference standard for DVT diagnosis.
g. D-dimer
- Positive D-dimer → anticoagulate
- Negative D-dimer → no treatment

h. D-dimer
- Positive D-dimer → proximal CUS
  - Positive proximal CUS → anticoagulate
  - Negative proximal CUS → no treatment
- Negative D-dimer → no treatment
i. D-dimer

- Positive D-dimer → whole leg/serial US
  - Positive whole leg/serial US → anticoagulate
  - Negative whole leg/serial US → no treatment
- Negative D-dimer → no treatment

** Whole Leg US sensitivity and specificity estimates were used to model Pathway J.

Note: in the algorithms, watchful waiting will follow negative tests and low/normal probability unless stated otherwise.
Question 7. In a patient population with a high clinical probability of lower extremity deep vein thrombosis (LE DVT), what is the optimal diagnostic strategy to diagnose a first episode LE DVT?

<table>
<thead>
<tr>
<th>POPULATION:</th>
<th>Patients with a high clinical probability of suspected first episode lower extremity deep vein thrombosis (LE DVT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVALUATED TESTS:</td>
<td>Whole leg ultrasound (US), proximal compression ultrasound (CUS), Serial ultrasound (US), D-dimer</td>
</tr>
<tr>
<td>PURPOSE OF THE TEST:</td>
<td>Detection of lower extremity deep vein thrombosis</td>
</tr>
<tr>
<td>ROLE OF THE TEST:</td>
<td>Detection of lower extremity deep vein thrombosis</td>
</tr>
<tr>
<td>LINKED TREATMENTS:</td>
<td>Anticoagulation</td>
</tr>
<tr>
<td>ANTICIPATED OUTCOMES:</td>
<td>False Negative; False Positive; True Negative; True Positive; Mortality; Lower extremity deep vein thrombosis, Major Bleeding, Recurrent LE DVT</td>
</tr>
<tr>
<td>SETTING:</td>
<td>Inpatient and outpatient</td>
</tr>
<tr>
<td>PERSPECTIVE:</td>
<td>Clinical recommendation - population perspective</td>
</tr>
</tbody>
</table>

**BACKGROUND:**

Lower extremity DVT (LE DVT) is suspected in patients with pain, swelling and/or warmth of the lower extremity. These clinical manifestations are nonspecific, and objective tests are required to confirm the diagnosis. LE DVT is associated with significant morbidity and can lead to post-thrombotic syndrome in up to 50% of cases (Kesieme, 2011). LE DVT is also clinically important as it can result in pulmonary embolism (PE). Diagnostic modalities to identify LE DVT include D-dimer assays, compression ultrasonography, duplex ultrasonography, and contrast enhanced venography. D-dimer, a fibrin degradation product, is typically elevated in the presence of DVT. While sensitive, D-dimer is frequently elevated with systemic illness and is a nonspecific test necessitating additional methods for diagnosis. Compression ultrasonography evaluates the compressibility, or lack thereof, of a venous segment to diagnose thrombosis. With acute DVT, compressibility is lost secondary to passive distension of the vein by thrombus (Robert-Ebadi, 2017). Duplex imaging can aid in examining venous flow as well. Venography is now infrequently performed as a diagnostic test for DVT, supplanted by duplex ultrasound as the reference standard for DVT diagnosis.
**Assessment**

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
</table>
| **Is the problem a priority?** | ○ No  
○ Probably no  
○ Probably yes  
• Yes  
○ Varies  
○ Don’t know  

The exact incidence of deep venous thrombosis (DVT) of the lower extremities is unknown. One study reports an incidence of deep vein thrombosis in 48 per 100,000 patients (Anderson, 1991). However LE DVT is about 10 times more common than upper extremity DVT. (Goldhaber, 2014). Associated with significant morbidity and mortality, accurate and efficient diagnosis and treatment is important. Not only can LE DVT lead to significant pain and post-thrombotic syndrome, LE DVT can embolize to the lungs causing morbidity and mortality from PE. D-dimer, while sensitive, is not a specific test that can definitively diagnose DVT. With improvements in technology and experience, ultrasonography, has become a more reliable tool to diagnose DVT (Robert-Ebadi, 2017). |
| **How accurate is the test?**  | Proximal CUS  
Patient or population: Patients with suspected lower extremity deep vein thrombosis  
New test: Proximal CUS  
Setting: Inpatient and outpatient  
Pooled sensitivity: 0.90 (95% CI: 0.87 to 0.93)  
Pooled specificity: 0.99 (95% CI: 0.98 to 0.99)  

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the Evidence (GRADE)</th>
</tr>
</thead>
</table>
| True positives | 451 (433 to 464)  
Prevalence 50% \(^1,2\) in patients with suspected LE DVT | 676 (649 to 696) | 2889 (12)  
HIGH \(^a,b\) |
| False negatives | 49 (36 to 67)  
Prevalence 75% \(^1,2\) in patients with suspected LE DVT | 74 (54 to 101) | |

The panel noted that for proximal CUS, whole leg US, and serial US, the inconclusive results reported are low, and likely not reflective of real-world settings. The panel noted that for D-dimer, the test is not used on a standalone basis to rule in a diagnosis and patients are not treated based on a positive test result. Therefore, the rating of very inaccurate applies to the context of the diagnostic pathways being assessed. |

Draft
D-dimer

- **Very accurate**
- **Don't know**
- **Very inaccurate**
  - **Inaccurate**
  - **Accurate**
  - **Very accurate**
  - **Don't know**

<table>
<thead>
<tr>
<th>Test Results</th>
<th>Count</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>True negatives</td>
<td>493 (488 to 496)</td>
<td></td>
</tr>
<tr>
<td>False positives</td>
<td>7 (4 to 12)</td>
<td></td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Complications arising from the diagnostic test</td>
<td>Not reported</td>
<td></td>
</tr>
</tbody>
</table>

**CI:** Confidence interval

1. Fancher T et al. BMJ 2004; 329(7470):821. Clinical PTP and rapid D-dimer testing; mean prevalence of DVT in accuracy studies 11%; mean prevalence of DVT in management studies 25%

2. Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

**Explanations**

- m. Quality of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that was judged to be acceptable by the panel.
- n. Although there was minor inconsistency for sensitivity, we did not downgrade for the quality of evidence.
- o. Although there was minor inconsistency for specificity, we did not downgrade for the quality of evidence.

**Whole leg US**

**Patient or population:** Patients with suspected lower extremity deep vein thrombosis

**New test:** Whole Leg US

**Setting:** Inpatient and outpatient

**Pooled sensitivity:** 0.93 (95% CI: 0.89 to 0.96) | **Pooled specificity:** 0.98 (95% CI: 0.93 to 0.99)

The panel noted that for US tests, accuracy may differ based on the ultrasound operator (e.g., emergency department physician, ultrasound technologist).

The panel noted that whole leg US detects proximal as well as calf DVT, and overtreatment can be an issue as not all calf (distal) DVT require treatment.
<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence <strong>50%</strong>&lt;sup&gt;1,2&lt;/sup&gt; in patients with suspected LE DVT</td>
<td>Prevalence <strong>75%</strong>&lt;sup&gt;1,2&lt;/sup&gt; in patients with suspected LE DVT</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>True positives</strong></td>
<td>465 (445 to 478)</td>
<td>697 (667 to 717)</td>
<td>⬤⬤⬤⬤ HIGH&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>False negatives</strong></td>
<td>35 (22 to 55)</td>
<td>53 (33 to 83)</td>
<td></td>
</tr>
<tr>
<td><strong>True negatives</strong></td>
<td>488 (467 to 496)</td>
<td>244 (233 to 248)</td>
<td>⬤⬤⬤⬤ HIGH&lt;sup&gt;a,c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>False positives</strong></td>
<td>12 (4 to 33)</td>
<td>6 (2 to 17)</td>
<td></td>
</tr>
<tr>
<td><strong>Inconclusive test results</strong></td>
<td>8</td>
<td>1043 (7)</td>
<td></td>
</tr>
<tr>
<td><strong>Complications arising from the diagnostic test</strong></td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CI:** Confidence interval

<sup>1</sup>Fancher T et al. BMJ 2004; 329(7470):821. Clinical PTP and rapid D-dimer testing; mean prevalence of DVT in accuracy studies 11%; mean prevalence of DVT in management studies 25%

<sup>2</sup>Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

**Explanations**

p. Quality of evidence not downgraded for risk of bias, though few studies had a combination of reference standards that was judged to be acceptable by the panel.

q. Although there is minor inconsistency for sensitivity, we did not downgrade for the quality of evidence.

r. Although there is minor inconsistency for specificity, we did not downgrade for the quality of evidence.
Serial US
Patient or population: Patients with suspected lower extremity deep vein thrombosis
New test: Serial US
Setting: Inpatient and outpatient
Pooled sensitivity: 0.98 (95% CI: 0.96 to 0.99) | Pooled specificity: 0.998 (95% CI: 0.993 to 0.999)

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Prevalence 50%(^1,2) in patients with suspected LE DVT</th>
<th>Prevalence 75%(^1,2) in patients with suspected LE DVT</th>
<th>Number of participants (studies)</th>
<th>Quality of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positives</td>
<td>490 (480 to 495)</td>
<td>734 (720 to 742)</td>
<td>2415 (6)</td>
<td>⬤⬤⬤⬤ HIGH(^a,b)</td>
<td></td>
</tr>
<tr>
<td>False negatives</td>
<td>10 (5 to 20)</td>
<td>16 (8 to 30)</td>
<td>2415 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True negatives</td>
<td>499 (497 to 500)</td>
<td>250 (248 to 250)</td>
<td>2415 (6)</td>
<td>⬤⬤⬤⬤ HIGH(^a,c)</td>
<td></td>
</tr>
<tr>
<td>False positives</td>
<td>1 (0 to 3)</td>
<td>0 (0 to 2)</td>
<td>2415 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications arising from the diagnostic test</td>
<td>Not reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: Confidence interval
\(^1\)Fancher T et al. BMJ 2004; 329(7470):821. Clinical PTP and rapid D-dimer testing; mean prevalence of DVT in accuracy studies 11%; mean prevalence of DVT in management studies 25%
\(^2\)Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

Explanations
g. Quality of evidence not downgraded for risk of bias, though few studies had a combination of reference standards that was judged to be acceptable by the panel.

h. Although there is minor inconsistency for sensitivity, we did not downgrade for the quality of evidence.

i. Although there is minor inconsistency for specificity, we did not downgrade for the quality of evidence.

**D-dimer**

**Patient or population:** Patients with suspected lower extremity deep vein thrombosis

**New test:** D-dimer

**Setting:** Inpatient and outpatient

**Pooled sensitivity:** 0.96 (95% CI: 0.92 to 0.98)  |  **Pooled specificity:** 0.35 (95% CI: 0.28 to 0.43)

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positives</td>
<td>Prevalence 50% in patients with suspected LE DVT</td>
<td>Prevalence 75% in patients with suspected LE DVT</td>
<td>479 (459 to 490)</td>
</tr>
<tr>
<td>False negatives</td>
<td>21 (10 to 41)</td>
<td>32 (16 to 61)</td>
<td>4409 (14)</td>
</tr>
<tr>
<td>True negatives</td>
<td>177 (141 to 215)</td>
<td>88 (71 to 108)</td>
<td>4409 (14)</td>
</tr>
<tr>
<td>False positives</td>
<td>323 (285 to 359)</td>
<td>162 (142 to 179)</td>
<td>4409 (14)</td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>Not applicable</td>
<td></td>
<td>4409 (14)</td>
</tr>
<tr>
<td>Complications arising from the diagnostic test</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: Confidence interval
"Fancher T et al. BMJ 2004; 329(7470):821. Clinical PTP and rapid D-dimer testing; mean prevalence of DVT in accuracy studies 11%; mean prevalence of DVT in management studies 25%\(^1\)

Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

**Explanations**

g. Quality of evidence not downgraded for risk of bias, although few studies had a combination of reference standards that was judged to be acceptable by the panel.

h. Although there was minor inconsistency for sensitivity, we did not downgrade for the quality of evidence.

i. Quality of evidence was downgraded for serious unexplained inconsistency in specificity, with range from 16.3% to 92.2%. Multiple sensitivity analyses could not provide an explanation.

<table>
<thead>
<tr>
<th>CERTAINTY OF THE EVIDENCE OF TEST ACCURACY</th>
<th>Judgment</th>
<th>Research Evidence</th>
<th>Additional Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the overall certainty of the evidence of test accuracy?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Very low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Moderate (D-dimer)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ High (Proximal CUS, Whole Leg US, Serial US)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ No included studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS</td>
<td>What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Very low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ No included studies</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT</th>
<th>How certain is the link between test results and management decisions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Very low</td>
<td>The link between test results and management is unique in venous thromboembolism. With LE DVT diagnosis, all positive results will be treated with anticoagulation (regardless of the chances of false positives).</td>
</tr>
<tr>
<td>○ Low</td>
<td>The panel noted high certainty in the link between test results and management decisions. However, the panel also noted that for patients with calf DVT, the link may not be as certain.</td>
</tr>
<tr>
<td>○ Moderate</td>
<td></td>
</tr>
<tr>
<td>○ High</td>
<td></td>
</tr>
<tr>
<td>○ No included studies</td>
<td></td>
</tr>
</tbody>
</table>
### CERTAINTY OF EFFECTS

**What is the overall certainty of the evidence of effects of the test?**
- Very low
- Low
- Moderate
- High
- No included studies

The panel noted the lack of direct data on patient outcomes, and a high level of uncertainty in the consequences for patients who receive a false negative test result.

### VALUES

**Is there important uncertainty or variability in how people value different outcomes?**
- Important uncertainty or variability
- Possibly important uncertainty or variability
- Probably no important uncertainty or variability
- No important uncertainty or variability

The numbers shown below are utilities, representing the strength of an individual’s preferences for different outcomes. They are measured on a scale, with zero reflecting states of health equivalent to death/worst imaginable health and one reflecting perfect health/ best imaginable health.

**Systematic reviews found that the relative importance of the outcomes is as follows:**

- **Pulmonary embolism:** 0.63-0.93 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004)
- **Deep vein thrombosis:** 0.64-0.99 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016)
- **Deep vein thrombosis patients' own current health:** 0.95 (Time trade off) (Locadia 2004)
- **Gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off) (Hogg 2013, Locadia 2004)
- **Minor intracranial bleeding event:** 0.75 (standard gamble) (Hogg 2013)
- **Major intracranial bleeding event:** 0.15 (standard gamble) (Hogg 2013) Central nervous system bleeding: 0.29-0.60 (standard gamble) (Lenert 1997, O'Meara 1994)

**Results of Panel Utility Rating Survey:**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean Utility Rating (SD) All Panels (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>False Negative Test Result</td>
<td>0.60 (0.23)</td>
</tr>
</tbody>
</table>

The panel placed a high value on decreasing the number of false negative test results over decreasing false positive test results.

The panel also placed a high value on reducing the number of tests required in a diagnostic pathway.

The panel considered that there would not be important variability in how people value the
### Modelling of Diagnostic Test Accuracy

**Note:** See pathways on Page 1

Pathway A begins with Whole Leg US  
Pathways B-F begin with Proximal CUS  
Pathways G-I begin with D-dimer

Table 1: In a patient population with a high clinical probability of lower extremity deep vein thrombosis (LE DVT), what is the optimal diagnostic strategy to diagnose a first episode LE DVT?

<table>
<thead>
<tr>
<th>Pathways</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F*</th>
<th>G</th>
<th>H</th>
<th>I*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP</td>
<td>465</td>
<td>451</td>
<td>498</td>
<td>497</td>
<td>499</td>
<td>498</td>
<td>479</td>
<td>432</td>
<td>445</td>
</tr>
<tr>
<td>FP</td>
<td>12</td>
<td>8</td>
<td>326</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>324</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>TN</td>
<td>488</td>
<td>493</td>
<td>174</td>
<td>492</td>
<td>492</td>
<td>493</td>
<td>177</td>
<td>495</td>
<td>492</td>
</tr>
<tr>
<td>FN</td>
<td>36</td>
<td>50</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>21</td>
<td>68</td>
<td>55</td>
</tr>
</tbody>
</table>

### Desirable and undesirable effects:

The panel considered desirable effects as increasing the number of patients with true positive and true negative test result (i.e. patients accurately diagnosed and accurately treated).

The panel considered undesirable as increasing the...
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Pathways highlighted in green were judged as the top ranked pathways that provided the best balance of desirable and undesirable effects. These pathways remained below a threshold of 20 false negative results per 1000 patients tested (≤2%) and a threshold of 50 misdiagnosed results per 1000 patients tested (≤5%).

Pathways highlighted in yellow provided a less acceptable balance of desirable and undesirable effects. These pathways remained below a threshold of 50 false negative results per 1000 patients tested (≤5%) and 100 misdiagnosed results per 1000 patients tested (≤5%).

*Venography was deemed not suitable as a follow-up test due to the use of ultrasound as the accepted reference standard for DVT diagnosis.

Whole Leg US sensitivity and specificity estimates were used to model Pathway J.

### 75%

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F*</th>
<th>G</th>
<th>H</th>
<th>I*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP</td>
<td>697</td>
<td>676</td>
<td>747</td>
<td>745</td>
<td>748</td>
<td>747</td>
<td>719</td>
<td>647</td>
<td>667</td>
</tr>
<tr>
<td>FP</td>
<td>6</td>
<td>4</td>
<td>163</td>
<td>4</td>
<td>4</td>
<td>162</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>TN</td>
<td>244</td>
<td>246</td>
<td>87</td>
<td>246</td>
<td>246</td>
<td>246</td>
<td>88</td>
<td>248</td>
<td>246</td>
</tr>
<tr>
<td>FN</td>
<td>53</td>
<td>74</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>32</td>
<td>103</td>
<td>83</td>
</tr>
</tbody>
</table>

*Venography was deemed not suitable as a follow-up test due to the use of ultrasound as the accepted reference standard for DVT diagnosis.

Whole Leg US sensitivity and specificity estimates were used to model Pathway J.

TP - patient correctly identified as having LEDVT and anticoagulated
FP - patient incorrectly identified as having LEDVT and unnecessarily anticoagulated
TN - patient correctly identified as not having LEDVT and not anticoagulated
FN - patient incorrectly identified as not having LEDVT and will not receive needed anticoagulation

Assumptions associated with modelling:
1. Disease prevalence in a high clinical probability population was determined to be 500 per 1000 patients (50%) or 750 per 1000 patients (75%).
2. Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.
3. The panel judged the ranking of pathways with the best balance of desirable and undesirable effects based on thresholds of false negative patients and misdiagnosed patients (false negative and false positive). These rankings are depicted in the table as green being the most acceptable, yellow being less acceptable, and red being unacceptable.
4. Test accuracy for D-dimer, proximal CUS and whole leg US were derived from these tests being used as a standalone test. These sensitivity and specificity results were used when the test was the first test of the pathway. These accuracy results were also used if the test was a subsequent test in a pathway.
5. Pooled estimates from studies of high sensitivity D-dimer assays that are currently used in practice were used to model pathways.

### Balance of desirable and undesirable effects:

For this guideline question, in addition to the diagnostic test accuracy outcomes, the panel prioritized minimizing the number of tests used to establish the diagnosis.

This was considered in determining which of the pathways that met the acceptable thresholds for diagnostic test accuracy (i.e. the pathways highlighted in
results per 1000 patients (≤10%).
Pathways highlighted in red did not provide an acceptable balance of desirable and undesirable effects and were ranked lowest. These pathways were above the threshold of 50 false negative results per 1000 patients tested (>5%) and 100 misdiagnosed results per 1000 patients (>10%).

These pathways were above the threshold of 50 false negative results per 1000 patients tested (>5%) and 100 misdiagnosed results per 1000 patients (>10%).

RESOURCES REQUIRED

How large are the resource requirements (costs) for Proximal CUS?
- Large costs
- Moderate costs
- Negligible costs and savings
- Moderate savings
- Large savings
- Don’t know

Costs of diagnostic tests:

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Peer-review articles and Other sources[^3]</th>
<th>CPT (Current Procedural Terminology)-4 Codes/cost[^1,2]</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer test</td>
<td>$256 ($271 in 2017)[^4,5]</td>
<td></td>
</tr>
<tr>
<td>Lower Extremity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>Compression ultrasonography: $200 ($260 in 2017)[^6]</td>
<td>76856-144.34-192.55</td>
</tr>
<tr>
<td></td>
<td>Doppler ultrasound: $602.30[^7]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other sources: Ultrasound: leg/foot: $133-$233 abdomen/hip/pelvis: $77-$300</td>
<td></td>
</tr>
<tr>
<td>Compression ultrasound of extremity veins</td>
<td></td>
<td>93970 - Extremity study</td>
</tr>
</tbody>
</table>

[^1]: The panel noted that the data showing costs based on CPT codes do not reflect what patients are charged in different settings, and are likely an under-representation of what patients and insurers pay.

Given this, the panel noted that the reported costs

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### How large are the resource requirements (costs) for Whole Leg US?
- Large costs
- **Moderate costs**
- Negligible costs and savings
- Moderate savings
- Large savings
- Don't know

### How large are the resource requirements (costs) for Serial US?
- Large costs
- **Moderate costs**
- Negligible costs and savings
- Moderate savings
- Large savings
- Don't know

### How large are the resource requirements (costs) for D-Dimer?

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Facility/Non-Facility price:</th>
<th>Opps Facility/Non-Facility payment amount:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duplex scan of lower extremities</td>
<td>$33.34-262.08</td>
<td>$191.98-345.03</td>
</tr>
<tr>
<td>Venography, extremity</td>
<td>$37.86 - $361.27</td>
<td>$191.52 - $350.20</td>
</tr>
<tr>
<td>93925-Lower extremity study</td>
<td>$33.34-149.42</td>
<td>$580.65-964.81</td>
</tr>
<tr>
<td>75820- Vein x-ray arm/leg</td>
<td>$33.34-149.42</td>
<td>$580.65-964.81</td>
</tr>
</tbody>
</table>

### References:

45. [https://pricinghealthcare.com/prices/CenterForMedicalImaging](https://pricinghealthcare.com/prices/CenterForMedicalImaging)
47. 1 US dollar in 2012 equals to about $1.0662 in 2017 ([http://www.in2013dollars.com/](http://www.in2013dollars.com/))
49. Based on CADTH report; The cost consists of diagnostic tests costs and physician interpretation cost, and it is in Canadian dollars in 2017.

The panel noted that for D-dimer costs from a health system perspective are moderate.

Additionally, a diagnostic pathway starting with D-dimer would reduce costs by refining the population that requires an US. However, the panel noted that when the costs of D-dimer tests are high, it is more effective to go directly to US.

The panel noted that for the cost of serial US, the cost reported is usually for one more US, but that patients have to return to receive the test, creating indirect costs.
<table>
<thead>
<tr>
<th>CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES</th>
<th>What is the certainty of the evidence of resource requirements (costs) for proximal CUS?</th>
<th>What is the certainty of the evidence of resource requirements (costs) for whole leg US?</th>
<th>The panel noted uncertainty in the actual costs of the tests.</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Very low</td>
<td>○ Very low</td>
<td>○ Very low</td>
<td></td>
</tr>
<tr>
<td>○ Low</td>
<td>○ Low</td>
<td>○ Low</td>
<td></td>
</tr>
<tr>
<td>○ Moderate</td>
<td>○ Moderate</td>
<td>○ Moderate</td>
<td></td>
</tr>
<tr>
<td>○ High</td>
<td>○ High</td>
<td>○ High</td>
<td></td>
</tr>
<tr>
<td>○ No included studies</td>
<td>○ No included studies</td>
<td>○ No included studies</td>
<td></td>
</tr>
<tr>
<td>○ Don't know</td>
<td>○ Don't know</td>
<td>○ Don't know</td>
<td></td>
</tr>
</tbody>
</table>

○ Large costs
○ Moderate costs
○ Negligible costs and savings
○ Moderate savings
○ Large savings
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the certainty of the evidence of resource requirements (costs) for serial US?</td>
<td>Low</td>
</tr>
<tr>
<td>What is the certainty of the evidence of resource requirements (costs) for D-dimer?</td>
<td>Low</td>
</tr>
</tbody>
</table>

○ Very low
○ Low
○ Moderate
○ High
○ No included studies
### COST EFFECTIVENESS

**Cost effectiveness of diagnostic pathways evaluated**

The panel judged pathways starting with a d-dimer test as most cost-effective considering the lower cost of the test.

<table>
<thead>
<tr>
<th>Test</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer</td>
<td>No evidence identified on the cost-effectiveness of proximal compression US.</td>
</tr>
<tr>
<td>Proximal CUS</td>
<td>No evidence identified on the cost-effectiveness of proximal compression US.</td>
</tr>
<tr>
<td>Whole Leg US</td>
<td>No evidence identified on the cost-effectiveness of whole leg US.</td>
</tr>
</tbody>
</table>

### EQUITY

**Impact on health equity of diagnostic pathways evaluated**

The panel judged the pathways requiring the least number of tests as having the least impact, and not decreasing health equity.

We identified the following regarding impact on health equity with the different tests:

- **D-dimer:**
  
  Canadian provinces with larger populations tended to have a large proportion of hospitals with capability to measure D-dimer levels for VTE, whereas less populated provinces were more likely to send samples to centralized analysis facilities for D-dimer testing. (Southern 2014)

- **Proximal CUS:**
  
  No research evidence identified.

- **Whole Leg US:**
  
  No research evidence identified.

### ACCEPTABILITY

**Acceptability of diagnostic pathways evaluated to key stakeholders**

The panel considered all pathways.

Studies described the following regarding acceptability from key stakeholders:

- **General (Radiology & Population):**
  
  In a study among nursing home patients with suspected VTE, referral for additional diagnostic investigations was withheld in almost 40%. In providers’ decisions to forgo diagnostic investigations, they incorporated the estimated relative impact of the potential disease; the potential net-benefits of diagnostic investigations and whether performing investigations agreed with established management goals in advance care planning. (Schouten 2014)
A study among physicians who had previously referred patients for any VTE screening examination showed that physicians had a lack of basic knowledge regarding lower extremity venous anatomy, charges for the different diagnostic tests used to diagnose VTE, and current treatment standards for VTE. (Zierler 2002)

**Proximal CUS:**
Patient level of discomfort during point-of-care ultrasonography of the heart, lungs and deep veins for respiratory symptoms is very low and the vast majority of patients would accept being assessed by this method if the patients once again had to be examined for possible disease. (Laursen 2015)

<table>
<thead>
<tr>
<th>Feasibility to implement diagnostic pathways evaluated</th>
<th>Studies described the following regarding feasibility and barriers to use:</th>
</tr>
</thead>
<tbody>
<tr>
<td>US:</td>
<td>Feasibility: Intensivist-performed compression ultrasonography for proximal lower extremity DVT showed high diagnostic accuracy (95%) compared with usual ultrasonography as performed by technicians and interpreted by radiologists. Time delay between ordering of ultrasonography and radiologist result was 14 hours. (Kory 2011)</td>
</tr>
<tr>
<td>Implementation: Postponing after-hours venous duplex ultrasound testing for DVT to the next morning in patients who could receive LMWH, unless otherwise indicated by the vascular surgeon, was safe. After-hours ultrasound requests decreased and the rate of positive studies in off-hours increased. (Chaer 2010)</td>
<td>New practice guideline implementation increasing the number of duplex screening exams in trauma patients also increased the rate of DVT identification. (Haut 2007)</td>
</tr>
<tr>
<td>D-Dimer:</td>
<td>Feasibility: Following at least one D-dimer test for DVT or PE, the strategy for further diagnostic testing was inappropriate in 31% with 9 out of 10 being overutilization of diagnostic imaging. (Arnason 2007)</td>
</tr>
<tr>
<td></td>
<td>The diagnostic work-up for DVT did not adhere to current guidelines with venous ultrasonography performed in 96%, D-dimer assay in 36% and venography in 6%. The rate of VTE at 90 days was</td>
</tr>
</tbody>
</table>

The panel also noted that for some institutions, access to test results for US may not be quick, and that in some centers obtaining results of a D-dimer test requires sending out to another center for analysis, which impacts access to quick test results and feasibility.
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.34% in patients in whom the diagnosis of DVT had been ruled out, and 2.50% in patients with inconclusive diagnostic workup. (Schellong 2009)</td>
<td></td>
</tr>
<tr>
<td>Implementation:</td>
<td>A policy to provide Point of Care Technology (POCT) laboratory results in the ED, including D-dimer for DVT, found no significant reduction in time to decision for patients with suspected DVT who received POCT testing. (Mogensen 2011)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Implementation of an evidence-based DVT probability scoring system as part of a clinical pathway from primary to secondary care showed that the ED waiting time decreased and initial D-dimer use increased, the latter indicating increased suspicion of DVT in primary care. Following D-dimer, ultrasound test use remained the same. (Campbell 2008)</td>
<td></td>
</tr>
</tbody>
</table>
## Conclusions

In a patient population with a high (50%, 75%) clinical probability of lower extremity deep vein thrombosis (LE DVT), what is the optimal diagnostic strategy to diagnose a first episode LEDVT?

<table>
<thead>
<tr>
<th>TYPE OF RECOMMENDATION</th>
<th>Strong recommendation against the intervention</th>
<th>Conditional recommendation against the intervention</th>
<th>Conditional recommendation for either the intervention or the comparison</th>
<th>Conditional recommendation for the intervention</th>
<th>Strong recommendation for the intervention</th>
</tr>
</thead>
</table>
| RECOMMENDATION         | The ASH guideline panel **suggests** using a strategy starting with CUS for diagnosing DVT in a population with high prevalence/pretest probability (>50%), followed by serial CUS if the initial CUS is negative. We recommend against a strategy based on a negative single proximal CUS or whole leg US alone when the prevalence is >75%. *(Conditional recommendation based on very low certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy)*  

**Remarks:** In high prevalence/pretest probability populations where the prevalence is 50%, alternate acceptable strategies include CUS or whole leg US alone with no additional follow-up testing for negative results.  

The ASH guideline panel **recommends against** using a positive D-dimer alone to diagnose DVT in a population with high prevalence/pretest probability (>50%). |

### JUSTIFICATION

### SUBGROUP CONSIDERATIONS

### IMPLEMENTATION CONSIDERATIONS

### MONITORING AND EVALUATION

### RESEARCH PRIORITIES

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Appendix 1: Modelling of Diagnostic Test Accuracy

Note: See diagnostic pathway diagrams on Page 1

Pathway A begins with Whole Leg US
Pathways B-F begin with Proximal CUS
Pathways G-I begin with D-dimer

Table 1: In a patient population with a high clinical probability of lower extremity deep vein thrombosis (DVT) what is the optimal diagnostic strategy to diagnose a first episode DVT?

<table>
<thead>
<tr>
<th></th>
<th>50%</th>
<th>75%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pathways</td>
<td>Pathways</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>TP - patients correctly identified as having DVT and correctly anticoagulated</td>
<td>465</td>
<td>451</td>
</tr>
<tr>
<td>FP - patients incorrectly identified as having DVT and receive unnecessary anticoagulation</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>TN - patients correctly identified as not having DVT and correctly not treated</td>
<td>488</td>
<td>493</td>
</tr>
<tr>
<td>FN - patients incorrectly identified as not having DVT and will not receive necessary anticoagulation</td>
<td>36</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>697</td>
<td>676</td>
</tr>
<tr>
<td>FP - patients incorrectly identified as having DVT and receive unnecessary anticoagulation</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>
TN - patients correctly identified as not having DVT and correctly not treated

|     | 244 | 246 | 87  | 246 | 246 | 246 | 88  | 248 | 246 |

FN - patients incorrectly identified as not having DVT and will not receive necessary anticoagulation

|     | 53  | 74  | 3   | 5   | 2   | 3   | 32  | 103 | 83  |

*Venography was deemed not suitable as a follow-up test due to the use of ultrasound as the accepted reference standard for DVT diagnosis.

#Whole Leg US sensitivity and specificity estimates were used to model Pathway J.
Appendix 2: Natural Progression and Treatment Effects

When making a decision regarding which pathway to recommend for diagnosing LE DVT, one must acknowledge that there will be patients who will have negative consequences because of an incorrect test result and thus incorrect diagnosis. Patients who receive unnecessary anticoagulation (false positive) or do not receive necessary anticoagulation (false negative) are subject to the risks of bleeding, may suffer complications or may die. Tables 2 and 3 provide some insight into the frequency of these outcomes.

True positive: patients correctly identified as having LE DVT and correctly anticoagulated
True negative: patients correctly identified as not having LE DVT and correctly not anticoagulated
False positive: patients incorrectly identified as having LE DVT and receive unnecessary anticoagulation
False negative: patients incorrectly identified as not having LE DVT and will not receive necessary anticoagulation

Outcomes studied include:
- Lower extremity deep vein thrombosis
- Pulmonary embolism
- Hemorrhagic Stroke
- Major Bleeding
- Mortality
- Recurrent LE DVT

Table 1. Clinical outcomes for LEDVT by pathway

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary embolism</strong></td>
<td><strong>TOTAL: 18/407 (4%)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Prandoni P 2002): (36 months; untreated) 14/313 (4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Anderson et al. 1999): (with treatment within 48 hrs) 4/24 (0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Birdwell 1998): (VTE in abnormal US) 4/70 (6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td><strong>TOTAL: 4/94 (4%)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Anderson et al. 1999): 0/24 (0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Birdwell 1998): (mortality due to PE) 4/70 (6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Major bleeding</strong></td>
<td></td>
<td><strong>TOTAL: 3/681 (0.4%)</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Bernardi 1998): (venous thromboembolic complications) 1/598 (0.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Bernardi 1998): (thromboembolic complications (untreated and abnormal DD but had normal repeat US) 2/83 (2%)</td>
</tr>
<tr>
<td>Test accuracy results</td>
<td>Consequences</td>
<td>Results from published SR</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>TP</td>
<td>Mortality: all cause</td>
<td>2.0% (6m) #</td>
</tr>
<tr>
<td></td>
<td>Mortality from DVT w 3 months</td>
<td>0.4% (PE mortality) ^</td>
</tr>
<tr>
<td></td>
<td>Recurrence on AC w 3 months</td>
<td>3.8% (3m) ^</td>
</tr>
<tr>
<td></td>
<td>Development of PE</td>
<td>1.0% (6m)</td>
</tr>
<tr>
<td></td>
<td>Major bleeding</td>
<td>2.1% (6m)</td>
</tr>
<tr>
<td></td>
<td>Fatal major bleeding</td>
<td>0.2% (6m)</td>
</tr>
<tr>
<td></td>
<td>Hemorrhagic stroke</td>
<td>2.0 (ICH; 1y)</td>
</tr>
<tr>
<td>FP</td>
<td>Mortality: all cause</td>
<td>2.1% (6m)</td>
</tr>
<tr>
<td></td>
<td>Major bleeding</td>
<td>2.1% (6m)</td>
</tr>
<tr>
<td></td>
<td>Fatal major bleeding</td>
<td>0.2% (6m)</td>
</tr>
<tr>
<td>TN</td>
<td>Mortality from DVT w 3 months</td>
<td>0%</td>
</tr>
<tr>
<td>FN</td>
<td>Mortality: all cause</td>
<td>18.4% (1y)</td>
</tr>
<tr>
<td></td>
<td>Mortality from DVT w 3 months</td>
<td>10.5% (1y)</td>
</tr>
<tr>
<td></td>
<td>Recurrence on AC w 3 months</td>
<td>11.0% (1y)</td>
</tr>
</tbody>
</table>

* Mortality, DVT and PE: median event rates from included RCTs, Major bleeding rate from Carrier 2010
# Carrier 2010 reported case fatality rate of 4.9% (6m) but VTE Treatment panel did not use this
§ Carrier 2010 reported recurrent PE rate of 3.6%, but VTE Treatment panel did not use this
^ Douketis 1998
REFERENCES

References of Background:

References of Included DTA studies:


References of Clinical Outcomes Studies:


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References related to prevalence:

References related to Patients Values and Preferences:


References related to Acceptability, Feasibility, Equity, Implementation:


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Question 8. In patients with a prior history of deep vein thrombosis (DVT), what is the optimal diagnostic strategy to diagnose recurrent DVT?

**Diagnosis of Recurrent DVT: Diagnostic Pathways Assessed**
- Clinical probability
  - Low clinical probability → D-dimer
    - Positive D-dimer → CUS
      - Positive CUS → anticoagulate
      - Negative CUS → no treatment
    - Negative D-dimer → no treatment
  - High clinical probability → CUS
    - Positive CUS → anticoagulate
    - Negative CUS → D-dimer
      - Negative D-dimer → no treatment
      - Positive D-dimer → serial US
        - Positive CUS → anticoagulate
        - Negative CUS → no treatment
<table>
<thead>
<tr>
<th>POPULATION:</th>
<th>Patients with suspected recurrent lower extremity deep vein thrombosis (LE DVT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVALUATED TESTS:</td>
<td>D-dimer, proximal compression ultrasound (CUS), whole leg ultrasound (US)</td>
</tr>
<tr>
<td>PURPOSE OF THE TEST:</td>
<td>Detection of recurrent lower extremity deep vein thrombosis</td>
</tr>
<tr>
<td>ROLE OF THE TEST:</td>
<td>Detection of recurrent lower extremity deep vein thrombosis</td>
</tr>
<tr>
<td>LINKED TREATMENTS:</td>
<td>Anticoagulation</td>
</tr>
<tr>
<td>ANTICIPATED OUTCOMES:</td>
<td>False Negative; False Positive; True Negative; True Positive; Mortality; Pulmonary Embolism, Major Bleed, Recurrent Lower Extremity DVT</td>
</tr>
<tr>
<td>SETTING:</td>
<td>Inpatient and outpatient</td>
</tr>
<tr>
<td>PERSPECTIVE:</td>
<td>Clinical recommendation - population perspective</td>
</tr>
</tbody>
</table>

**BACKGROUND:** Lower extremity DVT (LE DVT) is suspected in patients with pain, swelling and/or warmth of the lower extremity. These clinical manifestations are nonspecific, and objective tests are required to confirm the diagnosis. LE DVT is associated with significant morbidity and can lead to post-thrombotic syndrome in up to 50% of cases (Kesieme, 2011). LE DVT is also clinically important as it can result in pulmonary embolism (PE). Diagnostic modalities to identify LE DVT include D-dimer assays, compression ultrasonography, duplex ultrasonography, and contrast enhanced venography. D-dimer, a fibrin degradation product, is typically elevated in the presence of DVT. While sensitive, D-dimer is frequently elevated with systemic illness and is a nonspecific test necessitating additional methods for diagnosis. Compression ultrasonography evaluates the compressibility, or lack thereof, of a venous segment to diagnose thrombosis. With acute DVT, compressibility is lost secondary to passive distension of the vein by thrombus (Robert-Ebadi, 2017). Duplex imaging can aid in examining venous flow as well. Venography is now infrequently performed as a diagnostic test for DVT, supplanted by duplex ultrasound as the reference standard for DVT diagnosis.
Assessment

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Is the problem a priority?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Probably no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Probably yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Varies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Don’t know</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The exact incidence of deep venous thrombosis (DVT) of the lower extremities is unknown. One study reports an incidence of deep vein thrombosis in 48 per 100,000 patients (Anderson, 1991). However, LE DVT is about 10 times more common than upper extremity DVT. (Goldhaber, 2014). Associated with significant morbidity and mortality, accurate and efficient diagnosis and treatment is important. Not only can LE DVT lead to significant pain and post-thrombotic syndrome, LE DVT can embolize to the lungs causing morbidity and mortality from PE. D-dimer, while sensitive, is not a specific test that can definitively diagnose DVT. With improvements in technology and experience, ultrasonography, has become a more reliable tool to diagnose DVT (Robert-Ebadi, 2017).

**How accurate is the pathway?**

**D-dimer for low PTP, CUS for low PTP with positive D-dimer and high PTP**

○ Very inaccurate
○ Inaccurate
○ Accurate
○ Very accurate
○ Don’t know

**Proximal CUS**

Patient or population: patients suspected of having recurrent LEDVT

New test: D-dimer

Setting: Inpatient and outpatient

Pooled sensitivity: 0.95 (95% CI: 0.91 to 0.97) | Pooled specificity: 0.44 (95% CI: 0.35 to 0.53)

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence 15% in low-risk patients suspected of having recurrent LE DVT</td>
<td>Prevalence 40% in low-risk patients suspected of having recurrent LE DVT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True positives (patients with lower extremity DVT)</td>
<td>143 (137 to 146)</td>
<td>381 (364 to 390)</td>
<td>4902 (16)</td>
</tr>
<tr>
<td>False negatives (patients incorrectly classified as not having lower extremity DVT)</td>
<td>7 (4 to 13)</td>
<td>19 (10 to 36)</td>
<td></td>
</tr>
<tr>
<td>True negatives (patients without lower extremity DVT)</td>
<td>374 (299 to 453)</td>
<td>264 (211 to 320)</td>
<td>4902 (16)</td>
</tr>
<tr>
<td>False positives (patients incorrectly</td>
<td>476 (397 to 551)</td>
<td>336 (280 to 389)</td>
<td></td>
</tr>
</tbody>
</table>

The panel noted that for proximal CUS, whole leg US, and serial US, the inconclusive results reported are low, and likely not reflective of real-world settings.

The panel noted that for D-dimer, the test is not used on a standalone basis to rule in a diagnosis and patients are not treated based on a positive test result. Therefore, the rating of very inaccurate applies to the context of the diagnostic pathways being assessed.

The panel noted that for US tests, accuracy may differ based on the ultrasound operator (e.g. emergency department physician, ultrasound technologist).
### Whole Leg US

<table>
<thead>
<tr>
<th>Quality</th>
<th>Inaccurate</th>
<th>Accurate</th>
<th>Very accurate</th>
<th>Don’t know</th>
</tr>
</thead>
</table>

#### Inconclusive test results

<table>
<thead>
<tr>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence 15%(^{1,2,3}) in low-risk patients suspected of having recurrent LE DVT</td>
<td>138 (129 to 144)</td>
<td>![MODERATE]^{a,b,d,e}</td>
</tr>
<tr>
<td>Prevalence 40%(^{1,2,3}) in low-risk patients suspected of having recurrent LE DVT</td>
<td>369 (345 to 383)</td>
<td>3301 (8)</td>
</tr>
</tbody>
</table>

#### Complications arising from the diagnostic test

The panel noted that whole leg US detects proximal as well as calf DVT, and overtreatment can be an issue as not all calf (distal) DVT require treatment.

---

**Quality of evidence not downgraded for risk of bias, though few studies had a combination of reference standards that was judged to be acceptable by the panel.**

**Although there is minor inconsistency for sensitivity, we did not downgrade for the quality of evidence.**

**Quality of evidence was downgraded for serious unexplained inconsistency in specificity, with range from 16.3% to 92.2%. Multiple sensitivity analyses could not provide an explanation.**

**Quality of evidence downgraded for indirectness because of lack of data on accuracy in recurrent pulmonary embolism. Sensitivity and specificity used for modeling are for mixed populations of patients.**

**Quality of evidence downgraded for indirectness because of lack of data on the accuracy of this test following a previous test in a pathway. Sensitivity and specificity used for modeling are based on the test accuracy of the individual test rather than in an algorithm.**

---

**Patient or population:** patients suspected of having recurrent LEDVT

**New test:** Proximal CUS

**Setting:** Inpatient and outpatient

**Pooled sensitivity:** 0.92 (95% CI: 0.86 to 0.96) | **Pooled specificity:** 0.99 (95% CI: 0.98 to 0.99)

---

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| True negatives (patients without lower extremity DVT) | **839** (830 to 844) | **592** (586 to 596) | 3301 (8) | ⨁⨁⨁◯ | MODERATE |
| False positives (patients incorrectly classified as having lower extremity DVT) | **11** (6 to 20) | **8** (4 to 14) | - | - | - |
| Inconclusive test results | **20** | - | 3321 (8) | - |
| Complications arising from the diagnostic test | - | - | - | - |

**CI:** Confidence interval

1Heit J. Nat Rev Cardiol 2015;12(8):464
2Aguilar C et al. Am J Hematol 2007; 82:41-44. Clinical PTP and D-dimer used to evaluate patients with suspected recurrent DVT, prevalence 44.8% (40% used in table).
3Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

**Explanations**

a. Quality of evidence not downgraded for risk of bias, though few studies had a combination of reference standards that was judged to be acceptable by the panel.
b. Although there is minor inconsistency for sensitivity, we did not downgrade for the quality of evidence.
c. Although there is minor inconsistency for specificity, we did not downgrade for the quality of evidence.
d. Quality of evidence downgraded for indirectness because of lack of data on accuracy in recurrent pulmonary embolism. Sensitivity and specificity used for modeling are for mixed populations of patients.
e. Quality of evidence downgraded for indirectness because of lack of data on the accuracy of this test following a previous test in a pathway. Sensitivity and specificity used for modeling are based on the test accuracy of the individual test rather than in an algorithm.

**Patient or population:** patients suspected of having recurrent LEDVT

**New test:** Whole Leg US

**Setting:** Inpatient and outpatient

**Pooled sensitivity:** 0.93 (95% CI: 0.89 to 0.89) | **Pooled specificity:** 0.98 (95% CI: 0.93 to 0.99)
<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positives (patients with lower extremity DVT)</td>
<td>Prevalence 15%(^1,2,3) in low-risk patients suspected of having recurrent LE DVT</td>
<td><strong>139</strong> (133 to 133)</td>
<td>1035 (7)</td>
</tr>
<tr>
<td>False negatives (patients incorrectly classified as not having lower extremity DVT)</td>
<td>Prevalence 40%(^1,2,3) in low-risk patients suspected of having recurrent LE DVT</td>
<td><strong>372</strong> (356 to 356)</td>
<td></td>
</tr>
<tr>
<td>True negatives (patients without lower extremity DVT)</td>
<td>Prevalence 15%(^1,2,3) in low-risk patients suspected of having recurrent LE DVT</td>
<td><strong>830</strong> (793 to 843)</td>
<td>1035 (7)</td>
</tr>
<tr>
<td>False positives (patients incorrectly classified as having lower extremity DVT)</td>
<td>Prevalence 40%(^1,2,3) in low-risk patients suspected of having recurrent LE DVT</td>
<td><strong>586</strong> (560 to 595)</td>
<td></td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td></td>
<td><strong>8</strong></td>
<td>1035 (7)</td>
</tr>
<tr>
<td>Complications arising from the diagnostic test</td>
<td></td>
<td></td>
<td>1043</td>
</tr>
</tbody>
</table>

**Notes:**
- **CI:** Confidence interval
- \(^1\)Heit J. Nat Rev Cardiol 2015;12(8):464
- \(^2\)Aguilar C et al. Am J Hematol 2007; 82:41-44. Clinical PTP and D-dimer used to evaluate patients with suspected recurrent DVT, prevalence 44.8% (40% used in table).
- \(^3\)Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.

**Explanations**
- a. Quality of evidence not downgraded for risk of bias, though few studies had a combination of reference standards that was judged to be acceptable by the panel.
- b. Although there is minor inconsistency for sensitivity, we did not downgrade for the quality of evidence.
- c. Although there is minor inconsistency for specificity, we did not downgrade for the quality of evidence.
- d. Quality of evidence downgraded for indirectness because of lack of data on accuracy in recurrent pulmonary embolism. Sensitivity and specificity used for modeling are for mixed populations of patients.
Quality of evidence downgraded for indirectness because of lack of data on the accuracy of this test following a previous test in a pathway. Sensitivity and specificity used for modeling are based on the test accuracy of the individual test rather than in an algorithm.

<table>
<thead>
<tr>
<th>CERTAINTY OF THE EVIDENCE OF TEST ACCURACY</th>
<th>What is the overall certainty of the evidence of test accuracy?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>○ Very low (D-dimer)</td>
</tr>
<tr>
<td></td>
<td>○ Low (D-dimer with CUS)</td>
</tr>
<tr>
<td></td>
<td>○ Moderate (CUS)</td>
</tr>
<tr>
<td></td>
<td>○ High (Whole leg US)</td>
</tr>
<tr>
<td></td>
<td>○ No included studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS</th>
<th>What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the pathway?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>○ Very low</td>
</tr>
<tr>
<td></td>
<td>○ Low</td>
</tr>
<tr>
<td></td>
<td>○ Moderate</td>
</tr>
<tr>
<td></td>
<td>○ High</td>
</tr>
<tr>
<td></td>
<td>○ No included studies</td>
</tr>
</tbody>
</table>
### CERTAINTY OF THE EVI
DENCE OF TEST RESULT/MANAGEMENT

<table>
<thead>
<tr>
<th>How certain is the link between pathway results and management decisions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Very low</td>
</tr>
<tr>
<td>- Low</td>
</tr>
<tr>
<td>- Moderate</td>
</tr>
<tr>
<td>- High</td>
</tr>
<tr>
<td>- No included studies</td>
</tr>
</tbody>
</table>

The link between test results and management is unique in venous thromboembolism. With LE DVT diagnosis, all positive results are generally treated with anticoagulation (regardless of the chances of false positives).

### CERTAINTY OF EFFECTS

<table>
<thead>
<tr>
<th>What is the overall certainty of the evidence of effects of the pathway?</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Very low</td>
</tr>
<tr>
<td>- Low</td>
</tr>
<tr>
<td>- Moderate</td>
</tr>
<tr>
<td>- High</td>
</tr>
<tr>
<td>- No included studies</td>
</tr>
</tbody>
</table>

The panel noted high certainty in the link between test results and management decisions. However, the panel also noted that for patients with calf DVT, the link may not be as certain.

### VALUES

<table>
<thead>
<tr>
<th>Is there important uncertainty or variability in how people value different outcomes?</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Important uncertainty or variability</td>
</tr>
<tr>
<td>- Possibly important uncertainty or variability</td>
</tr>
<tr>
<td>- Probably no important uncertainty or variability</td>
</tr>
<tr>
<td>- No important uncertainty or variability</td>
</tr>
</tbody>
</table>

**Systematic reviews found that the relative importance of the outcomes is as follows:**

- Pulmonary embolism: 0.63-0.93 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004)
- Deep vein thrombosis: 0.64-0.99 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016)
- Deep vein thrombosis patients’ own current health: 0.95 (Time trade off) (Locadia 2004)
- Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg 2013, Locadia 2004)
- Minor intracranial bleeding event: 0.75 (standard gamble) (Hogg 2013)
- Major intracranial bleeding event: 0.15 (standard gamble) (Hogg 2013) Central nervous system bleeding: 0.29-0.60 (standard gamble) (Lenert 1997, O'Meara 1994)

**Studies additionally described the following regarding the relative importance of outcomes and patients’ preferences:**

The panel noted that there was a lack of information on value of outcomes specifically for recurrent DVT patients. The judgment is based on data from patients with first episode LE DVT.

The panel placed a high value on first decreasing false negative test results, and second decreasing false positive test results.
In a survey study (Geyer 2014) based on a shared decision-making model, the researchers provided patients with a standardized description of the diagnostic workup for PE, described the risks of computed tomography in low pretest probability patients and the risks of deferring imaging assuming a D-dimer was less than twice the value normally considered positive. With the decision aid, of the 203 patients in the study, 63% of patients favored undergoing CTPA; while seventy-four patients (37%) elected to defer CTPA. The mostly frequent reasons for decline include risk of malignancy, contrast-induced nephropathy, or allergy. Other than those common reasons, 20 patients deferred CTPA testing because they believed it was unnecessary. Patients with a previous PE diagnosis were less likely to defer CTPA testing. Most patients (n=109 [85%]) who accepted CTPA testing, had concerns about missing a PE.

**Results of Panel Utility Rating Survey:**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean Utility Rating (SD) All Panels (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>False Negative Test Result</td>
<td>0.60 (0.23)</td>
</tr>
<tr>
<td>False Positive Test Result</td>
<td>0.62 (0.21)</td>
</tr>
<tr>
<td>True Negative Test Result</td>
<td>0.91 (0.15)</td>
</tr>
<tr>
<td>True Positive Test Result</td>
<td>0.76 (0.19)</td>
</tr>
<tr>
<td>Inconclusive Test Result</td>
<td>0.69 (0.18)</td>
</tr>
<tr>
<td>Radiation Exposure</td>
<td>0.84 (0.14)</td>
</tr>
<tr>
<td>Contrast Induced Nephropathy</td>
<td>0.56 (0.20)</td>
</tr>
<tr>
<td>Pulmonary Embolism – Moderate Marker State</td>
<td>0.42 (0.15)</td>
</tr>
<tr>
<td>Proximal DVT – Moderate Marker State</td>
<td>0.58 (0.14)</td>
</tr>
<tr>
<td>Distal DVT – Moderate Marker State</td>
<td>0.64 (0.16)</td>
</tr>
<tr>
<td>Upper Extremity DVT – Moderate Marker State</td>
<td>0.61 (0.16)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>0.33 (0.23)</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>0.12 (0.10)</td>
</tr>
<tr>
<td>Chronic Thrombotic Pulmonary Hypertension</td>
<td>0.34 (0.15)</td>
</tr>
</tbody>
</table>

* Utility rating by panel members from 0 (dead) to 1 (full health)

The panel also placed a high value on reducing the number of tests required in a diagnostic pathway. The panel considered that there would not be important variability in how people value the different outcomes.
### BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favor the diagnostic pathway?
- **Favors pathway**
- **Probably favors pathway**
- **Does not favor pathway or no pathway**
- **Probably favors no pathway**
- **Favors no pathway**

The panel considered desirable effects as increasing the number of patients with true positive and true negative test result (i.e. patients accurately diagnosed and accurately treated).

### RESOURCES REQUIRED

How large are the resource requirements (costs) for D-dimer?
- **Large costs**
- **Moderate costs**
- **Negligible costs and savings**
- **Large savings**
- **Don’t know**

How large are the resource requirements (costs) for proximal CUS?
- **Large costs**
- **Moderate costs**
- **Negligible costs and savings**
- **Large savings**
- **Don’t know**

Costs of diagnostic tests:

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Peer-review articles and Other sources</th>
<th>CPT (Current Procedural Terminology)-4 Codes/cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer test</td>
<td>$256 ($271 in 2017)</td>
<td></td>
</tr>
<tr>
<td>Lower Extremity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compression ultrasound of extremity veins</td>
<td>93970 - Extremity study Facility/Non-Facility price: $33.34-262.08 Opps Facility/Non-Facility payment amount: $191.98-345.03</td>
<td></td>
</tr>
<tr>
<td>Duplex scan of lower extremities</td>
<td>93925-Lower extremity study Facility/Non-Facility price: $37.86 - $361.27 Opps Facility/Non-Facility payment amount: $191.52 - $350.20</td>
<td></td>
</tr>
<tr>
<td>Venography, extremity</td>
<td>75820-Vein x-ray arm/leg Facility/Non-Facility price: $33.34-149.42 Opps Facility/Non-Facility payment amount: $580.65-964.81</td>
<td></td>
</tr>
</tbody>
</table>

The panel noted that the data showing costs based on CPT codes do not reflect what patients are charged in different settings, and are likely an under-representation of what patients and insurers pay.

Given this, the panel noted that the reported costs for D-dimer seem high, however this may be reflective of the U.S. setting and may differ between settings.

The panel noted that for D-dimer costs from a health system perspective are moderate.

Additionally, a diagnostic pathway starting with D-dimer would reduce costs by refining the population that requires an US. However, the...
### How large are the resource requirements (costs) for whole leg US?

- Large costs
- **Moderate costs**
- Negligible costs and savings
- Moderate savings
- Large savings
- Don't know

### How large are the resource requirements (costs) for serial US?

- Large costs
- **Moderate costs**
- Negligible costs and savings
- Moderate savings
- Large savings
- Don't know

### References:

52. [https://pricinghealthcare.com/prices/CenterForMedicalImaging](https://pricinghealthcare.com/prices/CenterForMedicalImaging)
56. Based on CADTH report; The cost consists of diagnostic tests costs and physician interpretation cost, and it is in Canadian dollars in 2017.

### CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES

### What is the certainty of the evidence of resource requirements (costs) for D-dimer?

- Very low
- **Low**
- Moderate
- High
- No included studies

The panel noted that when the costs of D-dimer tests are high, it is more effective to go directly to US.

The panel noted that for the cost of serial US, the cost reported is usually for one more US, but that patients have to return to receive the test, creating indirect costs.
<table>
<thead>
<tr>
<th>What is the certainty of the evidence of resource requirements (costs) for proximal CUS?</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Very low</td>
</tr>
<tr>
<td><strong>Low</strong></td>
</tr>
<tr>
<td>○ Moderate</td>
</tr>
<tr>
<td>○ High</td>
</tr>
<tr>
<td>○ No included studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What is the certainty of the evidence of resource requirements (costs) for whole leg US?</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Very low</td>
</tr>
<tr>
<td><strong>Low</strong></td>
</tr>
<tr>
<td>○ Moderate</td>
</tr>
<tr>
<td>○ High</td>
</tr>
<tr>
<td>○ No included studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COST EFFECTIVENESS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost effectiveness of diagnostic pathways evaluated</strong></td>
</tr>
<tr>
<td>The panel judged a pathway of d-dimer and compression ultrasound as cost-effective.</td>
</tr>
<tr>
<td><strong>D-dimer:</strong></td>
</tr>
<tr>
<td>No evidence identified on the cost-effectiveness of proximal compression US for recurrent DVT.</td>
</tr>
<tr>
<td><strong>Proximal CUS:</strong></td>
</tr>
<tr>
<td>No evidence identified on the cost-effectiveness of proximal compression US for recurrent DVT.</td>
</tr>
<tr>
<td><strong>Whole Leg US:</strong></td>
</tr>
<tr>
<td>No evidence identified on the cost-effectiveness of whole leg US for recurrent DVT.</td>
</tr>
</tbody>
</table>
## Impact on health equity of diagnostic pathways evaluated

The panel judged the pathways requiring the least number of tests as having the least impact, and not decreasing health equity. We identified the following regarding impact on health equity with the different tests:

**D-dimer:**
Canadian provinces with larger populations tended to have a large proportion of hospitals with capability to measure D-dimer levels for VTE, whereas less populated provinces were more likely to send samples to centralized analysis facilities for D-dimer testing. (Southern 2014)

**Proximal CUS:**
No research evidence identified.

**Whole Leg US:**
No research evidence identified.

## Acceptability of diagnostic pathways evaluated to key stakeholders

The panel considered a pathway of d-dimer with compression ultrasound as acceptable. Studies described the following regarding acceptability from key stakeholders:

**General (Radiology & Population):**
In a study among nursing home patients with suspected VTE, referral for additional diagnostic investigations was withheld in almost 40%. In providers’ decisions to forgo diagnostic investigations, they incorporated the estimated relative impact of the potential disease; the potential net-benefits of diagnostic investigations and whether performing investigations agreed with established management goals in advance care planning. (Schouten 2014)

A study among physicians who had previously referred patients for any VTE screening examination showed that physicians had a lack of basic knowledge regarding lower extremity venous anatomy, charges for the different diagnostic tests used to diagnose VTE, and current treatment standards for VTE. (Zierler 2002)

**Proximal CUS:**
Patient level of discomfort during point-of-care ultrasonography of the heart, lungs and deep veins for respiratory symptoms is very low and the vast majority of patients would accept being assessed by this method if the patients once again had to be examined for possible disease. (Laursen 2015)

## Feasibility to implement diagnostic pathways evaluated

The panel considered a pathway of d-dimer with compression ultrasound as feasible. Studies described the following regarding feasibility and barriers to use:

**US:**

**Feasibility:**

The panel also noted that for some institutions, access to test results for US may not be quick, and that in some centers obtaining results of a D-dimer test
Specific considerations for D-dimer and CUS.

Intensivist-performed compression ultrasonography for proximal lower extremity DVT showed high diagnostic accuracy (95%) compared with usual ultrasonography as performed by technicians and interpreted by radiologists. Time delay between ordering of ultrasonography and radiologist result was 14 hours. (Kory 2011)

Implementation:
Postponing after-hours venous duplex ultrasound testing for DVT to the next morning in patients who could receive LMWH, unless otherwise indicated by the vascular surgeon, was safe. After-hours ultrasound requests decreased and the rate of positive studies in off-hours increased. (Chaer 2010)

New practice guideline implementation increasing the number of duplex screening exams in trauma patients also increased the rate of DVT identification. (Haut 2007)

D-Dimer:

Feasibility:
Following at least one D-dimer test for DVT or PE, the strategy for further diagnostic testing was inappropriate in 31% with 9 out of 10 being overutilization of diagnostic imaging. (Arnason 2007)

The diagnostic work-up for DVT did not adhere to current guidelines with venous ultrasonography performed in 36%, D-dimer assay in 36% and venography in 6%. The rate of VTE at 90 days was 0.3% in patients in whom the diagnosis of DVT had been ruled out, and 2.5% in patients with inconclusive diagnostic workup. (Schellong 2009)

Implementation:
A policy to provide Point of Care Technology (POCT) laboratory results in the ED, including D-dimer for DVT, found no significant reduction in time to decision for patients with suspected DVT who received POCT testing. (Mogensen 2011)

Implementation of an evidence-based DVT probability scoring system as part of a clinical pathway from primary to secondary care showed that the ED waiting time decreased and initial D-dimer use increased, the latter indicating increased suspicion of DVT in primary care. Following D-dimer, ultrasound test use remained the same. (Campbell 2008)

requires sending out to another center for analysis, which impacts access to quick test results and feasibility.
Conclusions

In patients with a prior history of deep vein thrombosis (DVT), what is the optimal diagnostic strategy to diagnose recurrent DVT?

<table>
<thead>
<tr>
<th>TYPE OF RECOMMENDATION</th>
<th>Strong recommendation against the intervention</th>
<th>Conditional recommendation against the intervention</th>
<th>Conditional recommendation for either the intervention or the comparison</th>
<th>Conditional recommendation for the intervention</th>
<th>Strong recommendation for the intervention</th>
</tr>
</thead>
</table>
| RECOMMENDATION         | The ASH guideline panel suggests using a strategy starting with D-dimer for diagnosing recurrent DVT in patients with a prior history of DVT and low prevalence/pretest probability. Patients with a negative D-dimer do not undergo further testing and all other patients (positive D-dimer, non-low pretest probability) undergo compression ultrasound. *(Conditional recommendation for D-dimer and CUS based on low certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy studies).*  
Remarks:  
- If clinical suspicion remains high following a negative initial ultrasound, serial compression ultrasound could be considered.  
- The clinical decision rule used to assess clinical probability of suspected recurrent DVT was the modified Wells score. |
| JUSTIFICATION          | The panel considered a strategy with D-dimer testing first to reduce cost in a population with low prevalence of DVT. D-dimer alone was not considered sufficient as a rule-in test, and must be followed by another test. |
| SUBGROUP CONSIDERATIONS| Noted importance of promoting D-dimer first strategy in low clinical probability patients. |
| IMPLEMENTATION CONSIDERATIONS | Noted importance of promoting D-dimer first strategy in low clinical probability patients. |
| MONITORING AND EVALUATION | |
| RESEARCH PRIORITIES    | |
Appendix 1: Natural Progression and Treatment Effects

When making a decision regarding which pathway to recommend for diagnosing DVT, one must acknowledge that there will be patients who will have negative consequences because of an incorrect test result and thus an incorrect diagnosis. Patients who receive unnecessary anticoagulation (false positive) or do not receive necessary anticoagulation (false negative) are subject to the risks of bleeding, may suffer complications or may die. Tables 1 provides some insight into the frequency of these outcomes.

**True positive**: patients correctly identified as having DVT and correctly anticoagulated

**True negative**: patients correctly identified as not having DVT and correctly not anticoagulated

**False positive**: patients incorrectly identified as having DVT and receive unnecessary anticoagulation

**False negative**: patients incorrectly identified as not having DVT and will not receive necessary anticoagulation

Outcomes studied include:
- Hemorrhagic Stroke
- Major Bleeding
- Mortality
- Pulmonary Embolism
- Recurrent DVT

Table 1: Outcomes by Test Result

<table>
<thead>
<tr>
<th>Outcomes at 3 months</th>
<th>Aguilar 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT – after negative D-dimer and Compression US in high clinical probability patients</td>
<td>1/18</td>
</tr>
</tbody>
</table>
REFERENCES.

References of Background:


References of Included accuracy and outcome studies:


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References of included outcome studies:


References related to prevalence:


References related to values and preferences:


**References related to cost and cost effectiveness:**


Sauders RJ, Ozols AA. Cost burden of venous thromboembolism and its prophylaxis in the United States. ISPOR 21st Annual International Meeting; 2016; Washington DC.


Del Rio Sola ML, Fajardo JAG, Pedrosa MM, Gutierrez V, Carrera S, Puerta CV. Clinical evaluation of D-Dimer in the diagnosis of thromboembolic disease. [Spanish]


**References related to Acceptability, Feasibility, Equity, Implementation:**

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Question 9. In a patient population with a low clinical probability of upper extremity deep vein thrombosis (UE DVT) what is the optimal diagnostic strategy to diagnose UE DVT?

**Diagnosis of Upper Extremity DVT: Diagnostic Pathways Assessed**

a. Duplex US

- Positive duplex US → anticoagulate
- Negative duplex US → no treatment

b. Duplex US

- Positive duplex US → anticoagulate
- Negative duplex US → serial US
  - Positive serial US → anticoagulate
  - Negative serial US → no treatment
c. Duplex US

- Positive duplex US → anticoagulate
- Negative duplex US → D-dimer
  - Positive D-dimer → anticoagulate
  - Negative D-dimer → no treatment

---

d. Duplex US

- Positive duplex US → anticoagulate
- Negative duplex US → D-dimer
  - Positive D-dimer → serial US
    - Positive serial US → anticoagulate
    - Negative serial US → no treatment
  - Negative D-dimer → no treatment
e. D-dimer

- Positive D-dimer → anticoagulate
- Negative D-dimer → no treatment

f. D-dimer

- Positive D-dimer → duplex US
  - Positive duplex US → anticoagulate
  - Negative duplex US → no treatment
- Negative D-dimer → no treatment
g. D-dimer

- Positive D-dimer → duplex US
  - Positive duplex US → anticoagulate
  - Negative duplex US → serial US
    - Positive serial US → anticoagulate
    - Negative serial US → no treatment
- Negative D-dimer → no treatment

h. D-dimer

- Positive D-dimer → anticoagulate
- Negative D-dimer → duplex US
  - Positive duplex US → anticoagulate
  - Negative duplex US → no treatment

Note: in the algorithms, watchful waiting will follow negative tests unless stated otherwise.

**Legend**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>deep vein thrombosis</td>
</tr>
<tr>
<td>PTP</td>
<td>pretest probability</td>
</tr>
<tr>
<td>US</td>
<td>ultrasound</td>
</tr>
</tbody>
</table>
Question 9. In a patient population with a low clinical probability of upper extremity deep vein thrombosis (UE DVT) what is the optimal diagnostic strategy to diagnose UE DVT?

| POPULATION: | Patients with a low clinical probability of suspected upper extremity deep vein thrombosis (UE DVT) |
| EVALUATED TESTS: | D-dimer, duplex ultrasound |
| PURPOSE OF THE TEST: | Detection of upper extremity deep vein thrombosis |
| ROLE OF THE TEST: | Detection of upper extremity deep vein thrombosis |
| LINKED TREATMENTS: | Anticoagulation |
| ANTICIPATED OUTCOMES: | False Negative; False Positive; True Negative; True Positive; Mortality; Pulmonary Embolism, Major Bleed, Recurrent Upper Extremity DVT |
| SETTING: | Inpatient and outpatient |
| PERSPECTIVE: | Clinical recommendation - population perspective |

**BACKGROUND:**
Upper extremity DVT (UEDVT) is suspected in patients with pain, swelling, and functional impairment of the upper extremity. These clinical manifestations are highly nonspecific, and objective tests are required to confirm the diagnosis (Prandoni 1997). UEDVT is clinically important since it can result in pulmonary embolism (PE) although the prevalence of PE developing from UEDVT is uncertain (Kroger 1998, Baxter 1991). In patients with low clinical probability of UEDVT, prevalence of disease was determined to be 10% (Kleinjan 2014).

Diagnostic modalities to identify UEDVT include venography, duplex ultrasonography (US), contrast-enhanced computed tomography and magnetic resonance imaging. Duplex US, a non-invasive and widely available technique, has become the first-line diagnostic tool (Baarslag 2002) and has largely replaced contrast venography in this indication, even though it has not been formally validated in this application (Merminod 2006).

**Assessment**

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROBLEM</strong> Is the problem a priority?</td>
<td>The exact incidence of deep venous thrombosis (DVT) of the upper extremities is unknown. A prevalence of 2 cases per 1000 hospital admissions has been reported. Upper extremity DVT (UEDVT) is increasingly recognized as a cause of high mortality and morbidity, similar to DVT of the leg. Traditionally regarded as a rare entity, UEDVT is now diagnosed more frequently due to the widespread use of intravenous catheters, often in relation with cancer</td>
<td></td>
</tr>
<tr>
<td>○ No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Probably no</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
treatment (Kommareddy 2002; Verso 2003; van Rooden 2005). Other causes include thoracic outlet syndrome, trauma, malignancy, thrombophilic states, or stasis from extrinsic obstruction. Pulmonary embolism related to upper limb thrombosis is a rare but serious complication. The diagnosis is suspected clinically and confirmed traditionally with contrast venography. Noninvasive duplex ultrasonography is now used as the primary imaging modality in evaluating suspected UEDVT (Chao 2001). There are few published prospective studies on diagnosis and management of UEDVT (Baarslag 2002).

<table>
<thead>
<tr>
<th>How accurate is the test?</th>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duplex US</strong></td>
<td>True positives (patients with upper extremity DVT)</td>
<td>87 (73 to 95)</td>
<td>465 (7)</td>
<td>MODERATE a,b</td>
</tr>
<tr>
<td></td>
<td>False negatives (patients incorrectly classified as not having upper extremity DVT)</td>
<td>13 (5 to 27)</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td>True negatives (patients without upper extremity DVT)</td>
<td>764 (646 to 833)</td>
<td>465 (7)</td>
<td>MODERATE a,b</td>
</tr>
<tr>
<td></td>
<td>False positives (patients incorrectly classified as having upper extremity DVT)</td>
<td>136 (67 to 254)</td>
<td>Not reported</td>
<td></td>
</tr>
</tbody>
</table>

The panel noted that for D-dimer, a negative result in patients with low clinical probability may assist in ruling out PE. However, a positive D-dimer result cannot be used as a standalone test to diagnose PE and initiate anticoagulant treatment. Therefore, the rating of very inaccurate applies to the diagnostic pathways where D-dimer is being used as an individual test.
Complications arising from the diagnostic test

<table>
<thead>
<tr>
<th>CI: Confidence interval</th>
</tr>
</thead>
</table>

**Explanations**

a. Not downgraded for risk of bias, although few studies had unclear information on the standard reference test.

b. One study (Haire 1993) had wide confidence interval for sensitivity and specificity, not overlapping with other studies. Given the inconsistency and imprecision, we downgraded by one level.

**D-Dimer:**

**Patient or population:** Patients with suspected upper extremity deep vein thrombosis

**Setting:** Inpatient and outpatient

**New test:** D-dimer; Cut-off value: 500 ng/mL

**Pooled sensitivity:** 0.96 (95% CI: 0.87 to 0.99) | **Pooled specificity:** 0.47 (95% CI: 0.43 to 0.52)

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positives (patients with upper extremity DVT)</td>
<td>96 (87 to 99)</td>
<td>482 (3)</td>
<td>★★★ ○○ LOW abc</td>
</tr>
<tr>
<td>False negatives (patients incorrectly classified as not having upper extremity DVT)</td>
<td>4 (1 to 13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True negatives (patients without upper extremity DVT)</td>
<td>425 (384 to 467)</td>
<td>482 (3)</td>
<td>★★★ ○○ LOW abc</td>
</tr>
<tr>
<td>False positives (patients incorrectly classified as having upper extremity DVT)</td>
<td>475 (433 to 516)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Complications arising from the diagnostic test

<table>
<thead>
<tr>
<th>CI: Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not reported</td>
</tr>
</tbody>
</table>

**Explanations**


### CERTAINTY OF THE EVIDENCE OF TEST ACCURACY

<table>
<thead>
<tr>
<th>Judgment</th>
<th>Research Evidence</th>
<th>Additional Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>What is the overall certainty of the evidence of test accuracy?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Very low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Low (D-dimer)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Moderate (Duplex US)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ No included studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS</td>
<td>What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?</td>
<td>The panel noted uncertainty in the clinical consequences related to UE DVT, as well as the natural history of UE DVT in patients with catheters with and without cancer.</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>☐ Very low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ No included studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT</td>
<td>How certain is the link between test results and management decisions?</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ Very low</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ Low</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ Moderate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ High</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ No included studies</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CERTAINTY OF EFFECTS</th>
<th>What is the overall certainty of the evidence of effects of the pathway?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>○ Very low</td>
</tr>
<tr>
<td></td>
<td>○ Low</td>
</tr>
<tr>
<td></td>
<td>○ Moderate</td>
</tr>
<tr>
<td></td>
<td>○ High</td>
</tr>
<tr>
<td></td>
<td>○ No included studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VALUES</th>
<th>Is there important uncertainty or variability in how people value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The numbers shown below are utilities, representing the strength of an individual’s preferences for different outcomes. They are measured on a scale, with zero reflecting states of health equivalent to death/worst imaginable health and one reflecting perfect health/best imaginable health.</td>
</tr>
</tbody>
</table>

The panel noted that the distinction between the deep and superficial veins in the upper extremity are less clear.

The consequences of PE arising from an UE DVT are generally less severe compared to lower extremity DVT.

The anticoagulant management (duration, dose) of UE DVT is less clear.
**Systematic reviews found that the relative importance of the outcomes is as follows:**

- Pulmonary embolism: 0.63-0.93 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004)
- Deep vein thrombosis: 0.64-0.99 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016)
- Deep vein thrombosis patients' own current health: 0.95 (Time trade off) (Locadia 2004)
- Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg 2013, Locadia 2004)
- Minor intracranial bleeding event: 0.75 (standard gamble) (Hogg 2013)
- Major intracranial bleeding event: 0.15 (standard gamble) (Hogg 2013)
- Central nervous system bleeding: 0.29-0.60 (standard gamble) (Lenert 1997, O'Meara 1994)

**Results of Panel Utility Rating Survey:**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean Utility Rating (SD)</th>
<th>All Panels (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>False Negative Test Result</td>
<td>0.60 (0.23)</td>
<td></td>
</tr>
<tr>
<td>False Positive Test Result</td>
<td>0.62 (0.21)</td>
<td></td>
</tr>
<tr>
<td>True Negative Test Result</td>
<td>0.91 (0.15)</td>
<td></td>
</tr>
<tr>
<td>True Positive Test Result</td>
<td>0.76 (0.19)</td>
<td></td>
</tr>
<tr>
<td>Inconclusive Test Result</td>
<td>0.69 (0.18)</td>
<td></td>
</tr>
<tr>
<td>Radiation Exposure</td>
<td>0.84 (0.14)</td>
<td></td>
</tr>
<tr>
<td>Contrast Induced Nephropathy</td>
<td>0.56 (0.20)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Embolism – Moderate Marker State</td>
<td>0.42 (0.15)</td>
<td></td>
</tr>
<tr>
<td>Proximal DVT – Moderate Marker State</td>
<td>0.58 (0.14)</td>
<td></td>
</tr>
<tr>
<td>Distal DVT – Moderate Marker State</td>
<td>0.64 (0.16)</td>
<td></td>
</tr>
<tr>
<td>Upper Extremity DVT – Moderate Marker State</td>
<td>0.61 (0.16)</td>
<td></td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>0.33 (0.23)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>0.12 (0.10)</td>
<td></td>
</tr>
<tr>
<td>Chronic Thrombotic Pulmonary Hypertension</td>
<td>0.34 (0.15)</td>
<td></td>
</tr>
</tbody>
</table>

* Utility rating by panel members from 0 (dead) to 1 (full health)

The panel considered that there would not be important variability in how people value the different outcomes.

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BALANCE OF DESIRABLE AND UNDESIRABLE EFFECTS

Rank the top pathways in order of which provides the best balance of desirable and undesirable effects to which provides the least balance.

The panel judged the ranking of the pathways based on a threshold of false negative patients and a threshold of misdiagnosed patients (combination of false negative and false positive results).

Pathways highlighted in green were judged as the top ranked pathways that provided the best balance of desirable and undesirable effects. These pathways highlight in green were judged as the top ranked pathways that provided the best balance of desirable and undesirable effects. These

Modelling of Diagnostic Test Accuracy

Note: See pathways on Page 1
Pathways A-D begin with Duplex Ultrasound
Pathways E-H begin with D-dimer

Table 1: In a patient population with a low clinical probability (10%) of upper extremity deep vein thrombosis (UE DVT), what is the optimal diagnostic strategy to diagnose a first episode UE DVT?

<table>
<thead>
<tr>
<th>Pathway</th>
<th>TP</th>
<th>FP</th>
<th>TN</th>
<th>FN</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>87</td>
<td>135</td>
<td>765</td>
<td>13</td>
</tr>
<tr>
<td>B</td>
<td>98</td>
<td>250</td>
<td>650</td>
<td>2</td>
</tr>
<tr>
<td>C</td>
<td>99</td>
<td>540</td>
<td>360</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>98</td>
<td>196</td>
<td>704</td>
<td>2</td>
</tr>
<tr>
<td>E</td>
<td>96</td>
<td>477</td>
<td>423</td>
<td>4</td>
</tr>
<tr>
<td>F</td>
<td>84</td>
<td>72</td>
<td>828</td>
<td>16</td>
</tr>
<tr>
<td>G</td>
<td>94</td>
<td>132</td>
<td>768</td>
<td>6</td>
</tr>
<tr>
<td>H</td>
<td>99</td>
<td>540</td>
<td>360</td>
<td>1</td>
</tr>
</tbody>
</table>

TP: patient correctly identified as having UE DVT and anticoagulated
FP: patient incorrectly identified as having UE DVT and unnecessarily anticoagulated
TN: patient correctly identified as not having UE DVT and not anticoagulated
FN: patient incorrectly identified as not having UE DVT and will not receive needed anticoagulation

Assumptions associated with modelling:
1. Disease prevalence in a moderate clinical probability population was determined be 100 per 1000 patients (10%).
2. Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.
3. The panel judged the ranking of pathways with the best balance of desirable and undesirable effects based on thresholds of false negative patients and misdiagnosed patients (false negative and false positive). These rankings are depicted in the table as green being the most acceptable, yellow being less acceptable, and red being unacceptable.
4. Due to the lack of data on accuracy of serial ultrasound, the sensitivity and specificity for proximal compression ultrasound was used to represent serial ultrasound. In addition, serial ultrasound was determined to be one follow-up test after initial ultrasound.
5. Test accuracy for D-dimer and Duplex US was derived from these tests being used as a standalone test. These sensitivity and specificity results were used when the test was the first test of the pathway. These accuracy results were also used if the test was a subsequent test in a pathway.

Desirable and undesirable effects:

The panel considered desirable effects as increasing the number of patients with true positive and true negative test results (i.e. patients accurately diagnosed and accurately treated).

The panel considered undesirable as increasing the number of patients with false positive and false negative test results (i.e. receive unnecessary anticoagulation or face mortality from missed diagnosis).

The panel noted that for UE DVT a higher threshold for false negative and misdiagnosed (FN+FP) results can be considered, given the decreased severity of clinical consequences and general uncertainty in the natural history.
Pathways remained below a threshold of 50 false negative results per 1000 patients tested (5%) and a threshold of 100 misdiagnosed results per 1000 patients tested (10%).

Pathways highlighted in yellow provided a less acceptable balance of desirable and undesirable effects. These pathways remained below a threshold of 100 false negative results per 1000 patients tested (10%) and 200 misdiagnosed results per 1000 patients (20%).

Pathways highlighted in red did not provide an acceptable balance of desirable and undesirable effects: For this guideline question, in addition to the diagnostic test accuracy outcomes, the panel considered that complications of PE and chronic thromboembolic pulmonary hypertension are likely to be small, given that emboli arising from UE DVT are generally smaller and less likely to result in fatal PE.

These criteria were considered in determining which of the pathways that met the acceptable thresholds for diagnostic test accuracy (i.e. the pathways highlighted in green), provided the best balance of effects.
acceptable balance of desirable and undesirable effects and were ranked lowest. These pathways were above the threshold of 100 false negative results per 1000 patients tested (>10%) and 200 misdiagnosed results per 1000 patients (>20%).

### RESOURCES REQUIRED

**How large are the resource requirements (costs) for Duplex Ultrasound?**
- Large costs
- Moderate costs
- Negligible costs and savings
- Moderate savings
- Large savings
- Don’t know

### Costs of diagnostic tests:

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Peer-review articles and Other sources³</th>
<th>CPT (Current Procedural Terminology)-4 Codes/cost ¹²</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer test</td>
<td>$256 ($271 in 2017)⁴ ⁵</td>
<td>-</td>
</tr>
</tbody>
</table>
| Ultrasonography          | Compression ultrasonography: $200 ($260 in 2017)⁶\nDoppler ultrasound: $602.30⁷\nOther sources:
Ultrasound: arm/hand: $133-$200 | -                                                  |

### References:

58. [https://pricinghealthcare.com/prices/CenterForMedicalImaging](https://pricinghealthcare.com/prices/CenterForMedicalImaging)

The panel noted that the reported costs for D-dimer seem high, however this may be reflective of the U.S. setting and may differ between settings.

Considering a health system perspective, D-dimer costs are moderate. A diagnostic pathway starting with D-dimer would reduce cost compared to...
### How large are the resource requirements (costs) for D-Dimer?

- **Large costs**
- **Moderate costs**
  - Negligible costs and savings
  - Moderate savings
  - Large savings
- **Don't know**

### CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60. 1 US dollar in 2012 equals to about $1.0662 in 2017 (<a href="http://www.in2013dollars.com/">http://www.in2013dollars.com/</a>)</td>
</tr>
<tr>
<td></td>
<td>62. Based on CADTH report; The cost consists of diagnostic tests costs and physician interpretation cost, and it is in Canadian dollars in 2017.</td>
</tr>
</tbody>
</table>

**The panel noted uncertainty in the actual costs of the tests and variability in costs between different settings.**
<table>
<thead>
<tr>
<th>COST EFFECTIVENESS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>of resource requirements (costs) for D-Dimer?</td>
<td></td>
</tr>
<tr>
<td>☐ Very low</td>
<td></td>
</tr>
<tr>
<td>☐ Low</td>
<td></td>
</tr>
<tr>
<td>☐ Moderate</td>
<td></td>
</tr>
<tr>
<td>☐ High</td>
<td></td>
</tr>
<tr>
<td>☐ No included studies</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COST EFFECTIVENESS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost effectiveness of diagnostic pathways evaluated</td>
<td>No research evidence identified on cost effectiveness for diagnosis of upper extremity DVT</td>
</tr>
<tr>
<td></td>
<td>with ultrasound or D-dimer.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EQUITY</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Impact on health equity of diagnostic pathways evaluated</td>
<td>No research evidence identified.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Acceptability**

**Acceptability of diagnostic pathways evaluated to key stakeholders**
The panel considered all pathways evaluated as acceptable.

No research evidence identified.

---

**Feasibility**

**Feasibility to implement diagnostic pathways evaluated**
The panel considered all pathways as feasible, however noting specific considerations for feasibility of testing with D-dimer and proximal Duplex US.

Studies described the following regarding feasibility and barriers to use:

**Ultrasound and D-Dimer**

**Feasibility:**

A diagnostic algorithm combining clinical probability, D-dimer testing and ultrasonography for suspected UE DVT was found to be feasible and safely and effectively excluded upper extremity DVT. (Kleinjan 2014) Intensivist-performed compression US showed high diagnostic accuracy (95%) compared with usual US as performed by technicians and interpreted by radiologists. Time delay between ordering of US and radiologist result was 14 hours. (Kory 2011)

The panel also noted that for some institutions, access to test results for US may not be quick, and that in some centers obtaining results of a D-dimer test requires sending out to another center for analysis, which impacts access to quick test results and feasibility.
Conclusions

In a patient population with a low clinical probability (10%) of upper extremity deep vein thrombosis (UE DVT), what is the optimal diagnostic strategy to diagnose a first episode UE DVT?

**RECOMMENDATION**

The ASH guideline panel **suggests** a strategy starting with D-dimer for diagnosing UE DVT in a population with low prevalence/pretest probability (10%), followed by Duplex US if D-dimer is positive. If D-dimer is not readily available, performing a Duplex US is acceptable. *(Conditional recommendation for D-dimer based on low certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy studies).*

**Remarks:**
- If the D-dimer strategy is followed, a highly sensitive D-dimer assay is required. In the D-dimer strategy, a negative D-dimer rules out PE and no additional testing or anticoagulation is provided.
- The clinical decision rule used to assess clinical probability of suspected UE DVT was a dichotomized Constans score where score ≤1 is unlikely and ≥2 is likely.

The ASH guideline panel **recommends against** using a positive D-dimer alone to diagnose UE DVT in a population with low prevalence/pretest probability (10%).

**JUSTIFICATION**

The panel considered a strategy with D-dimer testing first to reduce cost. D-dimer alone was considered not sufficient as a rule-in test, and should be followed by another test.

**SUBGROUP CONSIDERATIONS**

**IMPLEMENTATION CONSIDERATIONS**

**MONITORING AND EVALUATION**

**RESEARCH PRIORITIES**

Further research and validation of clinical decision rules to determine pretest probability assessment for UE DVT are needed. The natural history and consequences of UE DVT, both catheter and non-catheter related require further study.
Appendix 1: Modelling of Diagnostic Test Accuracy

Note: See pathways on Page 1
Pathways A-D begin with Duplex Ultrasound
Pathways E-H begin with D-dimer

Table 1: In a patient population with a low clinical probability (10%) of upper extremity deep vein thrombosis (UE DVT), what is the optimal diagnostic strategy to diagnose a first episode UE DVT?

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Pathway</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP</td>
<td></td>
<td>87</td>
<td>98</td>
<td>99</td>
<td>98</td>
<td>96</td>
<td>84</td>
<td>94</td>
<td>99</td>
</tr>
<tr>
<td>FP</td>
<td></td>
<td>135</td>
<td>250</td>
<td>540</td>
<td>196</td>
<td>477</td>
<td>72</td>
<td>132</td>
<td>540</td>
</tr>
<tr>
<td>TN</td>
<td></td>
<td>765</td>
<td>650</td>
<td>360</td>
<td>704</td>
<td>423</td>
<td>828</td>
<td>768</td>
<td>360</td>
</tr>
<tr>
<td>FN</td>
<td></td>
<td>13</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>16</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

TP - patient correctly identified as having UE DVT and anticoagulated
FP - patient incorrectly identified as having UE DVT and unnecessarily anticoagulated
TN - patient correctly identified as not having UE DVT and not anticoagulated
FN - patient incorrectly identified as not having UE DVT and will not receive needed anticoagulation
Appendix 2: Natural Progression and Treatment Effects

When making a decision regarding which pathway to recommend for diagnosing UE DVT, one must acknowledge that there will be patients who will have negative consequences because of an incorrect test result and thus incorrect diagnosis. Patients who receive unnecessary anticoagulation (false positive) or do not receive necessary anticoagulation (false negative) are subject to the risks of bleeding, may suffer complications or may die. Tables 2 and 3 provide some insight into the frequency of these outcomes.

**True positive**: patients correctly identified as having UE DVT and correctly anticoagulated  
**True negative**: patients correctly identified as not having UE DVT and correctly not anticoagulated  
**False positive**: patients incorrectly identified as having UE DVT and receive unnecessary anticoagulation  
**False negative**: patients incorrectly identified as not having UE DVT and will not receive necessary anticoagulation

**Outcomes studied include:**  
Pulmonary Embolism  
Hemorrhagic Stroke  
Major Bleeding  
Mortality  
Recurrent UE DVT  
Progression of UE DVT

### Table 2: Outcomes by Test Result

<table>
<thead>
<tr>
<th>Test accuracy results</th>
<th>Consequences</th>
<th>Results from published SR</th>
<th>Results from treatment guideline</th>
<th>Targeted search of primary studies</th>
<th>Panel survey results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TP</strong></td>
<td>Mortality: all cause</td>
<td></td>
<td>22%</td>
<td></td>
<td>14% (1y)</td>
</tr>
<tr>
<td></td>
<td>Mortality from DVT w 3 months</td>
<td>Not reported</td>
<td></td>
<td></td>
<td>10.4% (1y)</td>
</tr>
<tr>
<td></td>
<td>Recurrent Upper Extremity DVT</td>
<td>6.7%</td>
<td>3.0% (1y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Development of PE</td>
<td>0%</td>
<td>3.0% (1y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Major bleeding</td>
<td>6.0%</td>
<td>4.0% (1y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fatal major bleeding</td>
<td>Not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemorrhagic stroke</td>
<td>Not Reported</td>
<td></td>
<td></td>
<td>1.4% (ICH; 1y)</td>
</tr>
<tr>
<td><strong>FP</strong></td>
<td>Mortality: all cause</td>
<td>Not Reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Major bleeding</td>
<td>Not Reported</td>
<td></td>
<td></td>
<td>4.0% (1y)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
<td>E</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Fatal major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TN</td>
<td>Mortality from DVT w 3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FN</td>
<td>Mortality: all cause</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mortality from DVT w 3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recurrence on AC w 3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Table 2. Outcomes by Diagnostic Pathway</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
<td>E</td>
</tr>
<tr>
<td>PE</td>
<td>Prandoni 1997 – 1/58 (2%)</td>
<td>Not found</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chao – 1/17 (6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>Not found</td>
<td>Not found</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>Not found</td>
<td>Not found</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>Prandoni 1997 – 1/58 (2%)</td>
<td>Not found</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent UE DVT</td>
<td>Prandoni 1997 - 2/58 (3%)</td>
<td>Not found</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression of UE DVT</td>
<td>Not found</td>
<td>Not found</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
REFERENCES

References of Background:


References regarding Priority:


References of Included DTA studies:


References of clinical outcomes studies:


References for treatment effect and natural progression:


extremity deep vein thrombosis (The Catheter Study).” Journal of Thrombosis and Haemostasis; 5.8: 1650-653.


References related to prevalence:


References related to Patients values and preferences:


References related to cost and cost effectiveness:

Sauders; RJ, Ozols AA. Cost burden of venous thromboembolism and its prophylaxis in the United States. ISPOR 21st Annual International Meeting; 2016; Washington DC.


Del Rio Sola ML, Fajardo JAG, Pedrosa MM, Gutierrez V, Carrera S, Puerta CV. Clinical evaluation of D-Dimer in the diagnosis of thromboembolic disease. [Spanish]


References related to Acceptability, Feasibility, Equity, Implementation:


Question 10. In a patient population with a high clinical probability of upper extremity deep vein thrombosis (UE DVT) what is the optimal diagnostic strategy to diagnose UE DVT?

**Diagnosis of Upper Extremity DVT: Diagnostic Pathways Assessed**

a. Duplex US
   - Positive duplex US → anticoagulate
   - Negative duplex US → no treatment

b. Duplex US
   - Positive duplex US → anticoagulate
   - Negative duplex US → serial US
     - Positive serial US → anticoagulate
     - Negative serial US → no treatment
c. Duplex US

- Positive duplex US → anticoagulate
- Negative duplex US → D-dimer
  - Positive D-dimer → anticoagulate
  - Negative D-dimer → no treatment

![Pathway C](image)

---

d. Duplex US

- Positive duplex US → anticoagulate
- Negative duplex US → D-dimer
  - Positive D-dimer → serial US
    - Positive serial US → anticoagulate
    - Negative serial US → no treatment
  - Negative D-dimer → no treatment

![Pathway D](image)
e. D-dimer

- Positive D-dimer → anticoagulate
- Negative D-dimer → no treatment

f. D-dimer

- Positive D-dimer → duplex US
  - Positive duplex US → anticoagulate
  - Negative duplex US → no treatment
- Negative D-dimer → no treatment
g. D-dimer
- Positive D-dimer $\rightarrow$ duplex US
  - Positive duplex US $\rightarrow$ anticoagulate
  - Negative duplex US $\rightarrow$ serial US
    - Positive serial US $\rightarrow$ anticoagulate
    - Negative serial US $\rightarrow$ no treatment
- Negative D-dimer $\rightarrow$ no treatment

h. D-dimer
- Positive D-dimer $\rightarrow$ anticoagulate
- Negative D-dimer $\rightarrow$ duplex US
  - Positive duplex US $\rightarrow$ anticoagulate
  - Negative duplex US $\rightarrow$ no treatment

Note: in the algorithms, watchful waiting will follow negative tests unless stated otherwise.

<table>
<thead>
<tr>
<th>Legend</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>deep vein thrombosis</td>
</tr>
<tr>
<td>PTP</td>
<td>pretest probability</td>
</tr>
<tr>
<td>US</td>
<td>ultrasound</td>
</tr>
</tbody>
</table>

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Question 10. In a patient population with a high clinical probability of upper extremity deep vein thrombosis (UE DVT) what is the optimal diagnostic strategy to diagnose UE DVT?

<table>
<thead>
<tr>
<th>POPULATION:</th>
<th>Patients with a high clinical probability of suspected upper extremity deep vein thrombosis (UE DVT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVALUATED TESTS:</td>
<td>D-dimer, duplex ultrasound</td>
</tr>
<tr>
<td>PURPOSE OF THE TEST:</td>
<td>Detection of upper extremity deep vein thrombosis</td>
</tr>
<tr>
<td>ROLE OF THE TEST:</td>
<td>Detection of upper extremity deep vein thrombosis</td>
</tr>
<tr>
<td>LINKED TREATMENTS:</td>
<td>Anticoagulation</td>
</tr>
<tr>
<td>ANTICIPATED OUTCOMES:</td>
<td>False Negative; False Positive; True Negative; True Positive; Mortality; Pulmonary Embolism, Major Bleed, Recurrent Upper Extremity DVT</td>
</tr>
<tr>
<td>SETTING:</td>
<td>Inpatient and outpatient</td>
</tr>
<tr>
<td>PERSPECTIVE:</td>
<td>Clinical recommendation - population perspective</td>
</tr>
</tbody>
</table>

**BACKGROUND:**
Upper extremity DVT (UEDVT) is suspected in patients with pain, swelling, and functional impairment of the upper extremity. These clinical manifestations are highly nonspecific, and objective tests are required to confirm the diagnosis (Prandoni 1997). UEDVT is clinically important since it can result in pulmonary embolism (PE) although the prevalence of PE developing from UEDVT is uncertain (Kroger 1998, Baxter 1991). In patients with high clinical probability of UEDVT, prevalence of disease was determined to be 40% (Kleinjan 2014).

Diagnostic modalities to identify UEDVT include venography, duplex ultrasonography (US), contrast-enhanced computed tomography and magnetic resonance imaging. Duplex US, a non-invasive and widely available technique, has become the first-line diagnostic tool (Baarslag 2002) and has largely replaced contrast venography in this indication, even though it has not been formally validated in this application (Merminod 2006).

**Assessment**

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Is the problem a priority?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ No</td>
<td>The exact incidence of deep venous thrombosis (DVT) of the upper extremities is unknown. A prevalence of 2 cases per 1000 hospital admissions has been reported. Upper extremity DVT (UEDVT) is increasingly recognized as a cause of high mortality and morbidity, similar to DVT of the leg. Traditionally regarded as a rare entity, UEDVT is now diagnosed more frequently due to the widespread use of intravenous catheters, often in relation with cancer treatment (Kommareddy 2002; Verso 2003; van Rooden 2005). Other causes include thoracic outlet syndrome, trauma, malignancy, thrombophilic states, or stasis from extrinsic obstruction. Pulmonary embolism related to upper limb thrombosis is a rare but serious complication. The diagnosis is suspected clinically and confirmed traditionally with contrast venography. Noninvasive duplex ultrasonography is now used as the primary imaging modality in evaluating suspected UEDVT (Chao 2001). There are few published prospective studies on diagnosis and management of UEDVT (Baarslag 2002).</td>
<td></td>
</tr>
</tbody>
</table>
### How accurate is the test?

**Duplex US**
- **Patient or population:** Patients with suspected upper extremity deep vein thrombosis
- **New test:** Duplex ultrasound
- **Setting:** Inpatient and outpatient
- **Pooled sensitivity:** 0.87 (95% CI: 0.73 to 0.94) | **Pooled specificity:** 0.85 (95% CI: 0.72 to 0.93)

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positives (patients with upper extremity DVT)</td>
<td>349 (292 to 378)</td>
<td>465 (7)</td>
<td>⨁⨁⨁◯ MODERATE (^{a,b})</td>
</tr>
<tr>
<td>False negatives (patients incorrectly classified as not having upper extremity DVT)</td>
<td>51 (22 to 108)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True negatives (patients without upper extremity DVT)</td>
<td>509 (431 to 556)</td>
<td>465 (7)</td>
<td>⨁⨁⨁◯ MODERATE (^{a,b})</td>
</tr>
<tr>
<td>False positives (patients incorrectly classified as having upper extremity DVT)</td>
<td>91 (44 to 169)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inconclusive test results</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The panel noted that for D-dimer, a negative result in patients with low clinical probability may assist in ruling out PE. However, a positive D-dimer result cannot be used as a standalone test to diagnose PE and initiate anticoagulant treatment. Therefore, the rating of very inaccurate applies to the diagnostic pathways where D-dimer is being used as an individual test.
### Complications arising from the diagnostic test

Not reported

---

**CI:** Confidence interval


**Explanations**

- Not downgraded for risk of bias, although few studies had unclear information on the standard reference test.
- One study (Haire 1993) had wide confidence intervals for sensitivity and specificity, not overlapping with other studies. Given the inconsistency and imprecision, we downgraded by one level.

### D-Dimer:

**Patient or population:** Patients with suspected upper extremity deep vein thrombosis  
**Setting:** Inpatient and outpatient  
**New test:** D-dimer; Cut-off value: 500 ng/mL  
**Pooled sensitivity:** 0.96 (95% CI: 0.87 to 0.99)  
**Pooled specificity:** 0.47 (95% CI: 0.43 to 0.52)

<table>
<thead>
<tr>
<th>Test result</th>
<th>Number of results per 1,000 patients tested (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the Evidence (GRADE)</th>
</tr>
</thead>
</table>
| **True positives**  
(patients with upper extremity DVT) | 385 (348 to 396) | 482 (3) | ☑️☑️◯◯ LOW a,b,c |
| **False negatives**  
(patients incorrectly classified as not having upper extremity DVT) | 15 (4 to 52) | | |
| **True negatives**  
(patients without upper extremity DVT) | 284 (256 to 312) | 482 (3) | ☑️☑️◯◯ LOW a,b,c |
| **False positives**  
(patients incorrectly classified as having upper extremity DVT) | 316 (288 to 344) | | |
| Inconclusive test results | | Not reported | |

---

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<table>
<thead>
<tr>
<th>Complications arising from the diagnostic test</th>
<th>Not reported</th>
</tr>
</thead>
</table>

CI: Confidence interval

Explanations
a. Not downgraded for risk of bias, although few studies had unclear information on the standard reference test
b. Downgraded for indirectness as data are from studies evaluating D-dimer only, not D-Dimer following a negative Duplex US.
c. Small number of patients included in studies

<table>
<thead>
<tr>
<th>Judgment</th>
<th>Research Evidence</th>
<th>Additional Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CERTAINTY OF THE EVIDENCE OF TEST ACCURACY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What is the overall certainty of the evidence of test accuracy?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Very low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Low (D-dimer)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Moderate (Duplex US)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ No included studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS</td>
<td>What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>○ Very low</td>
<td>Panel noted uncertainty in the clinical consequences related to UE DVT, as well as the natural history of UE DVT in patients with catheters with and without cancer.</td>
<td></td>
</tr>
<tr>
<td>○ Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ No included studies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT</th>
<th>How certain is the link between test results and management decisions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Very low</td>
<td>The panel noted that the distinction between the deep and superficial veins in the upper extremity are less clear.</td>
</tr>
<tr>
<td>○ Low</td>
<td>The consequences of PE arising from an UE DVT are generally less severe compared to lower extremity DVT.</td>
</tr>
<tr>
<td>○ Moderate</td>
<td>The anticoagulant management (duration, dose) of UE DVT is less clear.</td>
</tr>
<tr>
<td>○ High</td>
<td></td>
</tr>
<tr>
<td>○ No included studies</td>
<td></td>
</tr>
</tbody>
</table>
### CERTAINTY OF EFFECTS

What is the overall certainty of the evidence of effects of the pathway?
- Very low
- Low
- Moderate
- High
- No included studies

### VALUES

Is there important uncertainty or variability in how people value different outcomes?
- Important uncertainty or variability
- Possibly important uncertainty or variability
- Probably no important uncertainty or variability
- No important uncertainty or variability

The numbers shown below are utilities, representing the strength of an individual’s preferences for different outcomes. They are measured on a scale, with zero reflecting states of health equivalent to death/worst imaginable health and one reflecting perfect health/best imaginable health.

**Systematic reviews found that the relative importance of the outcomes is as follows:**

- **Pulmonary embolism:** 0.63-0.93 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004)
- **Deep vein thrombosis:** 0.64-0.99 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016)
- **Deep vein thrombosis patients’ own current health:** 0.95 (Time trade off) (Locadia 2004)
- **Gastrointestinal tract bleeding event:** 0.65 (standard gamble and time trade off) (Hogg 2013, Locadia 2004)
- **Minor intracranial bleeding event:** 0.75 (standard gamble) (Hogg 2013)
- **Major intracranial bleeding event:** 0.15 (standard gamble) (Hogg 2013)
- **Central nervous system bleeding:** 0.29-0.60 (standard gamble) (Lenert 1997, O’Meara 1994)

**Results of Panel Utility Rating Survey:**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean Utility Rating (SD) All Panels (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>False Negative Test Result</td>
<td>0.60 (0.23)</td>
</tr>
<tr>
<td>False Positive Test Result</td>
<td>0.62 (0.21)</td>
</tr>
<tr>
<td>True Negative Test Result</td>
<td>0.91 (0.15)</td>
</tr>
<tr>
<td>True Positive Test Result</td>
<td>0.76 (0.19)</td>
</tr>
<tr>
<td>Inconclusive Test Result</td>
<td>0.69 (0.18)</td>
</tr>
</tbody>
</table>

The panel placed a high value on first decreasing false negative test results, and second decreasing false positive test results.

The panel considered that there would not be important variability in how people value the different outcomes.
### Rank the top pathways in order of which provides the best balance of desirable and undesirable effects to which provides the least balance.

The panel judged the ranking of the pathways based on a threshold of false negative patients and a threshold of misdiagnosed patients (combination of false negative and false positive results).

Pathways highlighted in green were judged as the top ranked pathways that provided the best balance of desirable and undesirable effects. These pathways remained below a threshold of 50 false negative and misdiagnosed (FN+FP) results.

### Balancing Desirable and Undesirable Effects

The panel considered desirable effects as increasing the number of patients with true positive and true negative test results (i.e. patients accurately diagnosed and treated).

The panel considered undesirable as increasing the number of patients with false positive and false negative test results (i.e. receive unnecessary anticoagulation or morbidity/mortality from missed diagnosis).

The panel noted that for UE DVT a higher threshold for false negative and misdiagnosed (FN+FP) results can be considered, given the

### Modelling of Diagnostic Test Accuracy

**Note:** See pathways on Page 1
Pathways A-D begin with Duplex Ultrasound
Pathways E-H begin with D-dimer

**Table 1:** In a patient population with a high clinical probability (40%) of upper extremity deep vein thrombosis (UE DVT), what is the optimal diagnostic strategy to diagnose a first episode UE DVT?

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP</td>
<td>348</td>
<td>393</td>
<td>398</td>
<td>391</td>
<td>384</td>
<td>334</td>
<td>378</td>
<td>398</td>
</tr>
<tr>
<td>FP</td>
<td>90</td>
<td>167</td>
<td>360</td>
<td>131</td>
<td>318</td>
<td>48</td>
<td>88</td>
<td>360</td>
</tr>
<tr>
<td>TN</td>
<td>510</td>
<td>434</td>
<td>240</td>
<td>469</td>
<td>282</td>
<td>552</td>
<td>512</td>
<td>240</td>
</tr>
<tr>
<td>FN</td>
<td>52</td>
<td>7</td>
<td>2</td>
<td>9</td>
<td>16</td>
<td>66</td>
<td>22</td>
<td>2</td>
</tr>
</tbody>
</table>

TP - patient correctly identified as having UE DVT and anticoagulated
FP - patient incorrectly identified as having UE DVT and unnecessarily anticoagulated
TN - patient correctly identified as not having UE DVT and not anticoagulated
FN - patient incorrectly identified as not having UE DVT and will not receive needed anticoagulation
negative results per 1000 patients tested (5%) and a threshold of 100 misdiagnosed results per 1000 patients tested (10%).

Pathways highlighted in yellow provided a less acceptable balance of desirable and undesirable effects. These pathways remained below a threshold of 100 false negative results per 1000 patients tested (10%) and 200 misdiagnosed results per 1000 patients (20%).

Pathways highlighted in red did not provide an acceptable balance of desirable and undesirable effects and were ranked lowest. These pathways were above the threshold of 100 false negative results per 1000 patients tested (10%) and 200 misdiagnosed results per 1000 patients (20%).

Assumptions associated with modelling:
1. Disease prevalence in a moderate clinical probability population was determined be 400 per 1000 patients (40%).
2. Disease prevalence applies to the index test in each pathway. Prevalence applied to the accuracy of each subsequent test depends on the result of the previous test in the pathway.
3. The panel judged the ranking of pathways with the best balance of desirable and undesirable effects based on thresholds of false negative patients and misdiagnosed patients (false negative and false positive). These rankings are depicted in the table as green being the most acceptable, yellow being less acceptable, and red being unacceptable.
4. Due to the lack of data on accuracy of serial ultrasound, the sensitivity and specificity for proximal compression ultrasound was used to represent serial ultrasound. In addition, serial ultrasound was determined to be one follow-up test after initial ultrasound.
5. Test accuracy for D-dimer and Duplex US was derived from these tests being used as a standalone test. These sensitivity and specificity results were used when the test was the first test of the pathway. These accuracy results were also used if the test was a subsequent test in a pathway.

Balance of desirable and undesirable effects:
For this guideline question, in addition to the diagnostic test accuracy outcomes, the panel considered that complications of PE and chronic thromboembolic pulmonary hypertension are likely to be small, given that emboli arising from UE DVT are generally smaller and less likely to result in fatal PE.

These criteria were considered in determining which of the pathways that met the acceptable thresholds for diagnostic test accuracy (i.e. the pathways highlighted in green), provided the best balance of effects.

decreased severity of clinical consequences and general uncertainty in the natural history.
How large are the resource requirements (costs) for Duplex Ultrasound?

○ Large costs
○ Moderate costs
○ Negligible costs and savings
○ Moderate savings
○ Large savings
○ Don’t know

How large are the resource requirements (costs) for D-Dimer?

○ Large costs
○ Moderate costs
○ Negligible costs and savings
○ Moderate savings
○ Large savings
○ Don’t know

How large are the resource requirements (costs) for Duplex Ultrasound?

Costs of diagnostic tests:

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Peer-review articles and Other sources(^3)</th>
<th>CPT (Current Procedural Terminology)-4 Codes/cost (^{1,2})</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer test</td>
<td>$256 ($271 in 2017) (^4,5)</td>
<td></td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>Compression ultrasonography: $200 ($260 in 2017) (^6)</td>
<td>Doppler ultrasound: $602.30 (^7)</td>
</tr>
<tr>
<td></td>
<td>Other sources:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ultrasound: arm/hand: $133-$200</td>
<td></td>
</tr>
</tbody>
</table>

References:

65. [https://pricinghealthcare.com/prices/CenterForMedicalImaging](https://pricinghealthcare.com/prices/CenterForMedicalImaging)
69. Based on CADTH report; The cost consists of diagnostic tests costs and physician interpretation cost, and it is in Canadian dollars in 2017.

The panel noted that the reported costs for D-dimer seem high, however this may be reflective of the U.S. setting and may differ between settings.

Considering a health system perspective, D-dimer costs are moderate. A diagnostic pathway starting with D-dimer would reduce cost compared to the other alternatives.

Additionally, a diagnostic pathway starting with D-dimer would reduce cost compared to the other alternatives.
<table>
<thead>
<tr>
<th>COST EFFECTIVENESS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost effectiveness of diagnostic pathways evaluated</strong></td>
<td>No research evidence identified on cost effectiveness for diagnosis of UE DVT with US or D-dimer.</td>
</tr>
<tr>
<td>The panel judged pathways starting with a D-dimer test as most cost-effective considering the lower cost of the test.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EQUITY</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Impact on health equity of diagnostic pathways evaluated</strong></td>
<td>No research evidence identified.</td>
</tr>
<tr>
<td>The panel judged the pathways requiring the least number of tests as having the least impact, and not decreasing health equity.</td>
<td></td>
</tr>
<tr>
<td>ACCEPTABILITY</td>
<td>Acceptability of diagnostic pathways evaluated to key stakeholders</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>The panel considered all pathways evaluated as acceptable.</td>
</tr>
</tbody>
</table>

| No research evidence identified. |

<table>
<thead>
<tr>
<th>FEASIBILITY</th>
<th>Feasibility to implement diagnostic pathways evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The panel considered all pathways as feasible, however noting specific considerations for feasibility of testing with D-dimer and proximal Duplex US.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Studies described the following regarding feasibility and barriers to use:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound and D-Dimer</td>
</tr>
<tr>
<td><strong>Feasibility:</strong></td>
</tr>
<tr>
<td>A diagnostic algorithm combining clinical probability, D-dimer testing and ultrasonography for suspected UE DVT was found to be feasible and safely and effectively excluded upper extremity DVT. (Kleinjan 2014) Intensivist-performed compression US showed high diagnostic accuracy (95%) compared with usual US as performed by technicians and interpreted by radiologists. Time delay between ordering of US and radiologist result was 14 hours. (Kory 2011)</td>
</tr>
</tbody>
</table>

| The panel also noted that for some institutions, access to test results for US may not be quick, and that in some centers obtaining results of a D-dimer test requires sending out to another center for analysis, which impacts access to quick test results and feasibility. |
Conclusions

In a patient population with a high clinical probability (40%) of upper extremity deep vein thrombosis (UE DVT), what is the optimal diagnostic strategy to diagnose a first episode of UE DVT?

| RECOMMENDATION | The ASH guideline panel suggests a strategy of either D-dimer followed by duplex US/serial duplex US, or duplex US/serial duplex US for diagnosing UE DVT in a population with high prevalence/pretest probability (40%). (Conditional recommendation based on low certainty in the evidence about effects on clinical outcomes and low certainty in the evidence about diagnostic accuracy studies).
Remarks:
  o If the D-dimer strategy is followed, a highly sensitive D-dimer assay is required. In the D-dimer strategy, a negative D-dimer rules out PE and no additional testing or anticoagulation is provided.
  o The clinical decision rule used to assess clinical probability of suspected UE DVT was a dichotomized Constans score where score ≤1 is unlikely and ≥2 is likely.

The ASH guideline panel recommends against using a positive D-dimer alone to diagnose UE DVT in a population with high prevalence/pretest probability (40%).

| JUSTIFICATION | The ASH Guideline panel considered a strategy with D-dimer testing first to reduce cost and ensure feasibility. D-dimer alone was considered not sufficient as a rule-in test, and should be followed by another test.

| SUBGROUP CONSIDERATIONS |

| IMPLEMENTATION CONSIDERATIONS | The panel considered a strategy with D-dimer testing first to reduce cost. D-dimer alone was considered not sufficient as a rule-in test, and should be followed by another test. The panel acknowledged that the evidence supporting a negative D-dimer to rule out UE DVT in patients at high probability was weak.

| MONITORING AND EVALUATION |

| RESEARCH PRIORITIES | Further research and validation of clinical decision rules to determine pretest probability assessment for UE DVT are needed. The natural history and consequences of UE DVT, both catheter and non-catheter related require further study.
**Appendix 1: Modelling of Diagnostic Test Accuracy**

*Note:* See pathways on Page 1  
Pathways A-D begin with Duplex Ultrasound  
Pathways E-H begin with D-dimer

**Table 1:** In a patient population with a *high* clinical probability (40%) of upper extremity deep vein thrombosis (UE DVT), what is the optimal diagnostic strategy to diagnose a first episode UE DVT?

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TP</strong></td>
<td>348</td>
<td>393</td>
<td>398</td>
<td>391</td>
<td>384</td>
<td>334</td>
<td>378</td>
<td>398</td>
</tr>
<tr>
<td><strong>FP</strong></td>
<td>90</td>
<td>167</td>
<td>360</td>
<td>131</td>
<td>318</td>
<td>48</td>
<td>88</td>
<td>360</td>
</tr>
<tr>
<td><strong>TN</strong></td>
<td>510</td>
<td>434</td>
<td>240</td>
<td>469</td>
<td>282</td>
<td>552</td>
<td>512</td>
<td>240</td>
</tr>
<tr>
<td><strong>FN</strong></td>
<td>52</td>
<td>7</td>
<td>2</td>
<td>9</td>
<td>16</td>
<td>66</td>
<td>22</td>
<td>2</td>
</tr>
</tbody>
</table>

TP - patient correctly identified as having UE DVT and anticoagulated  
FP - patient incorrectly identified as having UE DVT and unnecessarily anticoagulated  
TN - patient correctly identified as not having UE DVT and not anticoagulated  
FN - patient incorrectly identified as not having UE DVT and will not receive needed anticoagulation
Appendix 2: Natural Progression and Treatment Effects

When making a decision regarding which pathway to recommend for diagnosing UE DVT, one must acknowledge that there will be patients who will have negative consequences because of an incorrect test result and thus incorrect diagnosis. Patients who receive unnecessary anticoagulation (false positive) or do not receive necessary anticoagulation (false negative) are subject to the risks of bleeding, may suffer complications or may die. Tables 2 and 3 provide some insight into the frequency of these outcomes.

**True positive**: patients correctly identified as having UE DVT and correctly anticoagulated  
**True negative**: patients correctly identified as not having UE DVT and correctly not anticoagulated  
**False positive**: patients incorrectly identified as having UE DVT and receive unnecessary anticoagulation  
**False negative**: patients incorrectly identified as not having UE DVT and will not receive necessary anticoagulation

Outcomes studied include:  
- Pulmonary Embolism  
- Hemorrhagic Stroke  
- Major Bleeding  
- Mortality  
- Recurrent UE DVT  
- Progression of UE DVT

### Table 2: Outcomes by Test Result

<table>
<thead>
<tr>
<th>Test accuracy results</th>
<th>consequences</th>
<th>Results from published SR</th>
<th>Results from treatment guideline</th>
<th>Targeted search of primary studies</th>
<th>Panel survey results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TP</strong></td>
<td>Mortality: all cause</td>
<td></td>
<td>22%</td>
<td></td>
<td>14% (1y)</td>
</tr>
<tr>
<td></td>
<td>Mortality from DVT w 3 months</td>
<td></td>
<td>Not reported</td>
<td></td>
<td>10.4% (1y)</td>
</tr>
<tr>
<td></td>
<td>Recurrent Upper Extremity DVT</td>
<td></td>
<td>6.7%</td>
<td></td>
<td>3.0% (1y)</td>
</tr>
<tr>
<td></td>
<td>Development of PE</td>
<td></td>
<td>0%</td>
<td></td>
<td>3.0% (1y)</td>
</tr>
<tr>
<td></td>
<td>Major bleeding</td>
<td></td>
<td>6.0%</td>
<td></td>
<td>4.0% (1y)</td>
</tr>
<tr>
<td></td>
<td>Fatal major bleeding</td>
<td></td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemorrhagic stroke</td>
<td></td>
<td>Not Reported</td>
<td></td>
<td>1.4% (ICH; 1y)</td>
</tr>
<tr>
<td><strong>FP</strong></td>
<td>Mortality: all cause</td>
<td></td>
<td>Not Reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
<td>E</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>PE</td>
<td>Prandoni 1997 – 1/58 (2%)</td>
<td>Not found</td>
<td>Sartori -0/180 (0%)</td>
<td>Kleinjen – 0/203 (0%)</td>
<td>Not found</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>Not found</td>
<td>Not found</td>
<td>Not found</td>
<td>Not found</td>
<td>Not found</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>Not found</td>
<td>Not found</td>
<td>Not found</td>
<td>Not found</td>
<td>Not found</td>
</tr>
<tr>
<td>Mortality</td>
<td>Prandoni 1997 – 1/58 (2%)</td>
<td>Not found</td>
<td>Not found</td>
<td>Not found</td>
<td>Not found</td>
</tr>
<tr>
<td>Recurrent UE DVT</td>
<td>Prandoni 1997 - 2/58 (3%)</td>
<td>Not found</td>
<td>Not found</td>
<td>Not found</td>
<td>Not found</td>
</tr>
<tr>
<td>Progression of UE DVT</td>
<td>Not found</td>
<td>Not found</td>
<td>Not found</td>
<td>Not found</td>
<td>Not found</td>
</tr>
</tbody>
</table>

**Table 2. Outcomes by Diagnostic Pathway**
REFERENCES

References of Background:


References regarding Priority:


References of Included DTA studies:


References of clinical outcomes studies:


References for treatment effect and natural progression:


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References related to prevalence:


References related to Patients values and preferences:


**References related to cost and cost effectiveness:**


Sauders; RJ, Ozols AA. Cost burden of venous thromboembolism and its prophylaxis in the United States. ISPOR 21st Annual International Meeting; 2016; Washington DC.


Del Rio Sola ML, Fajardo JAG, Pedrosa MM, Gutierrez V, Carrera S, Puerta CV. Clinical evaluation of D-Dimer in the diagnosis of thromboembolic disease. [Spanish]


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References related to Acceptability, Feasibility, Equity, Implementation:

