Appendix 2 (as supplied by the authors)
(Box 1: Definition of signs and symptoms associated with acute aortic syndrome; Table 1: Summary of results of studies informing sensitivity and specificity of tests for diagnosis of acute aortic syndrome; and 4 EtD supplemental files)

Supplementary Box 1: Definition of signs and symptoms associated with acute aortic syndrome

Risk factors

- *Connective tissue disease* - There are numerous conditions that increase a patient's risk for AAS; Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome, Turner syndrome, mutations in genes known to predispose to thoracic aortic aneurysms and dissection, such as FBN1, TGFBR1, TGFBR2, ACTA2, and MYH11. Most patients with a diagnosis of these conditions will be aware of their increased risk. In addition, some patients wear a medical alert bracelet to alert clinicians to an underlying high-risk condition. Up to 50% of those with Marfan are undiagnosed by the age of 20 and nearly 25% by age 40. Therefore, it is important that the presence or absence of physical exam features of Marfan are noted in patients <40 years of age presenting with symptoms of AAS(1). No change from AHA/ESC.
- *Aortic valve disease* – Abnormalities of the aortic valve can predispose to the development of an acute aortic syndrome. Abnormalities are defined as either surgical/endovascular repair/graft replacement for aortic valve disease or a known bicuspid aortic valve. No change from AHA/ESC.
- *Aortic aneurysms* – Any dilation of the aorta >3cm either from patient history of a known aortic aneurysm or a new suspicion based on bedside ultrasonography of visible portions aorta or a widened mediastinum on chest x-ray.

High-risk pain features

- *Migrating/radiating pain indicates pain that has changed location (migrating) or pain that has branched out from its area of origin (radiating). The pain can migrate/radiate from front (chest or abdomen) to back (thoracic or lumbar) or less commonly back to front. Pain can migrate/radiate along the aorta (chest to abdomen or abdomen to chest). Most diagnostic accuracy studies do not offer a definition of migrating/radiating pain, and it is likely that these are often confused or used interchangeably. Migrating/radiating pain was added to the AHA/ESC recommendations based on a national survey of emergency physicians deeming it important/very important in their assessment of PTP(2).*
- *Severe pain* is defined as an intensity that is described as severe or worst ever.
- *Abrupt onset/thunderclap pain* is described as sudden or unexpected pain reaching maximal intensity within seconds of onset.
- *Tearing or ripping pain* includes any pain described by the patient as tearing or ripping in character.

Appendix to: Ohle R, Yan JW, Yadav K, et al. Diagnosing acute aortic syndrome: a Canadian clinical practice guideline. *CMAJ* 2020.
doi: 10.1503/cmaj.200021.

Alternative diagnosis

- *Clinical suspicion for an alternative diagnosis refers to an unproven but suspected suspicion for an alternative diagnosis that is not feasible or unable to confirm in the emergency department. I.e. gastroesophageal reflux, musculoskeletal pain, radiculopathy. If an alternative diagnosis were confirmed in the emergency department (i.e. computed tomography evidence of a pulmonary embolism) then one would exit PTP assessment for AAS.*

Physical examination findings

- *Hypotension/pericardial effusion defined as a systolic blood pressure <90mmHg or a shock index of >1 and/or a pericardial effusion identified on point of care ultrasonography.* The shock index indicates occult shock. It is defined by heart rate divided by systolic blood pressure (normal range in heath adults 0.5-0.7). *A new pericardial effusion is often a cause of hypotension and is easily diagnosed on point of care ultrasound. The use of point of care ultrasound is meant to augment physical examination, thus if a provider is not trained in its use it is simply omitted from pre test probability assessment.*
- *Pulse deficit - A pulse deficit as a new diminution or absence in palpable pulses between either right or left carotid, brachial or femoral artery, with or without associated signs of limb malperfusion. An absent pedal pulse but a present tibial, popliteal, or femoral pulse is not consistent with a pulse deficit related to AAS. The intimal tear causing a perfusion deficit is from proximal to distal.*
- *New murmur of aortic regurgitation – A new characteristic murmur of aortic regurgitation or aortic regurgitation identified on point of care ultrasonography* ***in conjunction with pain****. If you are unsure if new or old a decision must be made to assume new and proceed with investigation as appropriate.*
- *Neurological deficit is defined by any motor, sensory, cranial nerve deficit or coma state* ***in conjunction with pain****. Patients presenting with an acute new neurological deficit should be asked about pain, as they often will not independently report this feature. The neurological deficit can be transient; therefore, in those presenting with pain, it is important to ask about any resolved neurological deficits. Rare but important neurological deficits include pain and recurrent laryngeal nerve palsy or Horner's syndrome. (Please note: isolated sensory symptoms consistent with an alternative diagnosis such as a panic attack, diabetic peripheral neuropathy, etc. should not be deemed a neurological deficit). Neurological deficits that are not new or as a result of a previous stroke do not qualify as an acute new neurological deficit.*

Supplementary Table 1: Summary of results of studies informing sensitivity and specificity of tests for diagnosis of acute aortic syndrome						
Test	Number of Participants (studies)	Sensitivity (95% CI)	Specificity (95% CI)	Quality of Evidence	Post test probability if pre test probability is 2%	
					+	–
Investigations						
CT Aorta	126(3)	1 (95% CI: 0.96 to 1)	0.98 (95% CI: 0.87 to 0.99)	High	50%	0%
D-dimer	3860 (22)	0.95 (95% CI: 0.90 to 0.99)	0.60 (95% CI: 0.48 to 0.71)	Very Low/Moderate [a]	4.6%	0.17%
Pain						
Severe pain	6039 (5)	0.72 (95% CI: 0.64 to 0.80)	0.58 (95% CI: 0.39 to 0.75)	Very Low [b, c]	3.3%	1%
Abrupt onset/Thunderclap pain	6163 (6)	0.72 (95% CI: 0.53 to 0.85)	0.60 (95% CI: 0.46 to 0.73)	Very Low [b, d]	3.4%	1%
Tearing pain	6085 (6)	0.22 (95% CI: 0.12 to 0.36)	0.89 (95% CI: 0.71 to 0.97)	Very Low [b, d]	3.6%	1.8%
Migrating/radiating pain	929 (4)	0.45 (95% CI: 0.20 to 0.73)	0.67 (95% CI: 0.40 to 0.86)	Very Low [b, i, n]	2.7%	1.7%
Clinical Suspicion	3375(12)	0.79 (95% CI: 0.70 to 0.87)	0.63 (95% CI: 0.60 to 0.65)	Very Low/Low [f]	4%	0.6%
Risk factors						
Connective tissue disease	6113 (5)	0.02 (95% CI: 0.01 to 0.09)	0.96 (95% CI: 0.84 to 0.99)	Very Low/Low [g]	-	2%
Aortic aneurysm -History of aortic aneurysm -Widened mediastinum on x-ray	6098 (4)	0.19 (95% CI: 0.14 to 0.20)	0.85 (95% CI: 0.77 to 0.91)	Low [b, n]	4.6%	1.2%
-Dilated aortic root on point of care ultrasound	659 (7)	0.79 (95% CI: 0.70 to 0.85)	0.56 (95% CI: 0.41 to 0.70)	Very Low/Low [b, n]		
	1120 (2)	0.64 (95% CI: 0.54 to 0.74)	0.81 (95% CI: 0.73 to 0.87)	Very Low [l]		
Recent aortic root manipulation	6089 (4)	0.03 (95% CI: 0.02 to 0.03)	0.97 (95% CI: 0.93 to 0.98)	Low/Moderate [h, b]	3.2%	2%
Aortic valve disease	7974 (4)	0.06 (95% CI: 0.04 to 0.09)	0.95 (95% CI: 0.93 to 0.96)	Very Low/Low [h, b, i]	1.9%	2%

Family History of AAS	6047 (4)	0.03 (95% CI: 0.02 to 0.06)	0.99 (95% CI: 0.97 to 1.00)	Low[h, b, i]	8.3%	1.9%
Physical Examination						
Hypotension/ Pericardial effusion	6085(6)	0.17 (95% CI: 0.14 to 0.20)	0.94 (95% CI: 0.91 to 0.96)	Low[k]	5.1%	1.8%
	1120(2)	0.38 (95% CI: 0.31 to 0.46)	0.91 (95% CI: 0.87 to 0.94)	Low[l]	5.6%	1.5%
Aortic regurgitation -On physical exam	6735 (10)	0.18 (95% CI: 0.11 to 0.28)	0.92 (95% CI: 0.77 to 0.97)	Very Low[b, m]	4.6%	1.7%
- Aortic insufficiency on bedside ultrasound	839(1)	0.1 (95% CI: 0.06 to 0.16)	0.93 (95% CI: 0.91 to 0.95)	Very Low/Low[l]	2.8%	1.9%
Neurological deficit	6514 (7)	0.15 (95% CI: 0.10 to 0.24)	0.95 (95% CI: 0.93 to 0.97)	Low/Moderate[p]	6.3%	1.8%
Pulse deficit	297 (3)	0.24 (95% CI: 0.13 to 0.41)	0.95 (95% CI: 0.93 to 0.97)	Low/Moderate[o]	9.3%	1.6%

a. The risk of bias was assessed using the QUADAS-2 tool. 19/22 and 11/12 of the included study had at least one domain rated as high risk. There are two other Meta analysis that only included 5 of the 22 articles, they performed a QUADAS assessment and found a low or unclear risk of bias in most domains, this led to downgrading the level of certainty. The certainty for specificity was downgraded for inconsistency and imprecision of results, with wide confidence intervals and large I squared. Sensitivity had a narrow confidence interval and low I squared therefore rated as moderate and specificity rated as very low.

b. There was significant heterogeneity between included studies indicated by an I squared >90% for both sensitivity and specificity.

c. Confidence intervals for both sensitivity and specificity are wide. The sensitivity ranges from 46-86% and the specificity ranges from 45-80%.

d. Confidence intervals for both sensitivity and specificity are wide. The sensitivity ranges from 34-88% and the specificity ranges from 23-81%.

e. Confidence intervals for both sensitivity and specificity are wide. The sensitivity ranges from 2-62% and the specificity ranges from 36-95%.

f. Risk of bias was downgraded due to variable patient population, definition of missed case, and reference standard between studies. Inconsistency was downgraded as the sensitivity ranged from 43% to 97%. Imprecision was downgraded as the 95% confidence interval ranged from 63%-84%. Indirectness was downgraded, as the study did not report what investigations were performed prior to the clinician

discharging the patient with a diagnosis other than acute aortic syndrome. Some may have performed a D-dimer or undergone other investigations. In addition the studies were not specifically testing the diagnostic accuracy of clinical judgment to rule out acute aortic syndrome.
g. Strength of evidence was downgraded secondary to a sensitivity ranging from 2% to 9% with an I squared of 93% for sensitivity and a specificity ranging from 84% to 100% with an I squared of 80%.
h. Risk of bias was downgraded due to heterogeneous inclusion criteria between trials.
i. Inconsistent and varying description of the clinical variable
k. Strength of evidence was downgraded as patient selection varied between studies with an unclear risk of bias. The confidence intervals were narrow but the I squared was 57% representing a potential for inconsistency between studies.
l. Risk of bias and indirectness were downgraded as single centre study including a convenience sample of patients.
m. The description of the index test was not adequate in most studies and it was not clear in some whether a positive result referred to a new murmur of any character or aortic regurgitation new or old. The sensitivity ranged from 5% to 49% reflected in an I squared of 95%. The specificity ranged from 45% to 99% reflected in an I squared of 95%.
n. Imprecision was downgraded due to wide confidence intervals.
o. 3 of the studies are before the year 2000; with the broader availability of CT, the characteristics of the population being investigated for acute aortic dissection may be different than the included studies.

p. Inconsistency downgraded for an unexplained range in sensitivity from 3%-30%

References

1. Groth KA, Hove H, Kyhl K, Folkestad L, Gaustadnes M, Vejlstrup N, Stochholm K, Østergaard JR, Andersen NH, Gravholt CH. Prevalence, incidence, and age at diagnosis in Marfan Syndrome. Orphanet journal of rare diseases. 2015;10(1):153.
2. Ohle R, McIsaac S, Yan J, Yadav K, Eagles D, Perry JJ. National survey of emergency physicians on the risk stratification and acceptable miss rate of acute aortic syndrome. Canadian Journal of Emergency Medicine.1-4.

QUESTION What is the optimal method to assess pre-test probability of a patient presenting with symptoms of acute aortic syndrome?

What is	
POPULATION:	Patients presenting with chest, abdominal, back, flank pain, perfusion deficit (Cerebrovascular accident/neurological deficit, acute coronary syndrome, ischemic limb, shock, BP differential >20mmHg), hypertension (systolic >180mmHg)
INTERVENTION:	History, risk factors, physical examination
PURPOSE OF THE TEST:	Risk stratification into low (<0.5%) intermediate (0.5-5%) or high (>5%) probability of AAS
ROLE OF THE TEST:	Diagnosis of AAS
LINKED TREATMENTS:	Low risk – no further testing; Intermediate risk – D-dimer, High risk – CT aorta
ANTICIPATED OUTCOMES:	False Negative; False Positive; True Negative; True Positive
SETTING:	Emergency department
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	
SUBGROUPS:	
CONFLICT OF INTERESTS:	None to declare

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes	The overall annual incidence of aortic dissection is 3-12 per 100,000. Although 60% of a recent survey respondents had seen a patient in the past year with AAS. Mortality of untreated Type A aortic dissection is 90% at 2 weeks. Miss rate ranges from 16-38%. Mortality increases 1%/hr. Improving time to diagnosis and accuracy of diagnosis is key in reducing	

● Yes ○ Varies ○ Don't know ○ Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate ○ Don't know	the overall morbidity and mortality associated with AAS. Clinicians rate AAS as the number priority in developing a clinical decision aid, in addition 98% of respondents to a national survey of emergency physicians state that we need a clinical decision aid/diagnostic algorithm to aid in the diagnostic dilemma of AAS. There are no accepted pre test probability assessment tools used in practice.	

Test accuracy

How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Severe pain **● Very inaccurate** **Abrupt onset pain** **●accurate** **Tearing/ripping** **●Accurate** **Migrating/radiating** **●Inaccurate**	**Patient or population:** Patients with suspected AAS **New test:** Severe pain **Setting:** Inpatient and outpatient **Pooled sensitivity:** 0.72 (95% CI: 0.64 to 0.80) **Pooled specificity**: 0.58 (95% CI: 0.39 to 0.75)	

Test result	Number of results per 1,000 patients tested (95% CI)	Number of participants (studies)
	Prevalence 2% in patients with suspected AAS	
True positives	14 (13 to 16)	5 studies 6039 patients
False negatives	6 (4 to 7)	
True negatives	569 (386 to 732)	4 studies 3501 patients
False positives	411 (248 to 594)	
Inconclusive test results		

Patient or population: Patients with suspected AAS

New test: Abrupt onset pain
Setting: Inpatient and outpatient
Pooled sensitivity 0.72 (95% CI: 0.53 to 0.85)
Pooled specificity: 0.60 (95% CI: 0.46 to 0.73)

Test result	Number of results per 1,000 patients tested (95% CI)	Number of participants (studies)
	Prevalence 2% in patients with suspected AAS	
True positives	14 (11 to 17)	6 studies 6163 patients
False negatives	6 (3 to 9)	
True negatives	587 (446 to 712)	5 studies 3625 patients
False positives	393 (268 to 534)	
Inconclusive test results		

Patient or population: Patients with suspected AAS
New test: Tearing pain
Setting: Inpatient and outpatient
Pooled sensitivity 0.22 (95% CI: 0.12 to 0.36) **Pooled specificity**: 0.89 (95% CI: 0.71 to 0.97)

Test result	Number of results per 1,000 patients tested (95% CI)	Number of participants (studies)
	Prevalence 2% in patients with suspected AAS	
True positives	4 (2 to 7)	6 studies 6085 patients
False negatives	16 (13 to 18)	

True negatives	874 (692 to 947)	5 studies 3502 patients
False positives	106 (33 to 288)	
Inconclusive test results		

Patient or population: Patients with suspected AAS
New test: migrating/radiating pain
Setting: Inpatient and outpatient

Pooled sensitivity 0.45 (95% CI: 0.12 to 0.36) **Pooled specificity**: 0.67 (95% CI: 0.40 to 0.86)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 2% in patients with suspected AAS	Number of participants (studies)
True positives	9 (2 to 7)	4 studies 924 patients
False negatives	11 (13 to 18)	
True negatives	657 (392 to 843)	4 studies 924 patients
False positives	323 (137 to 588)	
Inconclusive test results		

Patient or population: Patients with suspected AAS
New test: Clinical Judgment
Setting: Inpatient and outpatient
Pooled sensitivity: 0.79 (95% CI: 0.70 to 0.87)
Pooled specificity: 0.63 (95% CI: 0.60 to 0.65)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 2% in patients with suspected AAS	Number of participants (studies)
True positives	15 (13 to 17)	9 studies 7165 patients
False negatives	5 (3 to 7)	
True negatives	617 (737 to 769)	1 studies 1850 patients
False positives	363 (211 to 243)	
Inconclusive test results		

Patient or population: Patients with suspected AAS
New test: Neurological deficit
Setting: Inpatient and outpatient
Pooled sensitivity 0.15 (95% CI: 0.10 to 0.24) **Pooled specificity**: 0.95 (95% CI: 0.93 to 0.97)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 2% in patients with suspected AAS	Number of participants (studies)
True positives	3 (2 to 5)	7 studies 6514 patients
False negatives	17 (15 to 18)	
True negatives	935 (914 to 950)	6 studies 4156 patients
False positives	45 (30 to 66)	

Inconclusive test results		

Patient or population: Patients with suspected AAS
New test: Pulse deficit
Setting: Inpatient and outpatient
Pooled sensitivity 0.24 (95% CI: 0.13 to 0.41) **Pooled specificity**: 0.95 (95% CI: 0.93 to 0.97)

Test result	Number of results per 1,000 patients tested (95% CI)	Number of participants (studies)
	Prevalence 2% in patients with suspected AAS	
True positives	5 (3 to 8)	3 studies 297 patients
False negatives	15 (12 to 17)	
True negatives	931 (911 to 951)	3 studies 297 patients
False positives	49 (29 to 69)	
Inconclusive test results		

Patient or population: Patients with suspected AAS
New test: Hypotension
Setting: Inpatient and outpatient
Pooled sensitivity 0.17 (95% CI: 0.14 to 0.20) **Pooled specificity**: 0.94 (95% CI: 0.91 to 0.96)

Test result	Number of results per 1,000 patients tested (95% CI)	Number of participants (studies)
	Prevalence 2% in patients with suspected AAS	
True positives	3 (3 to 4)	9 studies 6992 patients
False negatives	17 (16 to 17)	
True negatives	924 (894 to 945)	8 studies 4454 patients
False positives	56 (35 to 86)	
Inconclusive test results		

Patient or population: Patients with suspected AAS
New test: Pericardial effusion / tamponade
Setting: Inpatient and outpatient
Pooled sensitivity 0.36 (95% CI: 0.23 to 0.51) **Pooled specificity**: 0.88 (95% CI: 0.83 to 0.92)

Test result	Number of results per 1,000 patients tested (95% CI)	Number of participants (studies)
	Prevalence 2% in patients with suspected AAS	
True positives	7 (5 to 10)	1 studies 281patients
False negatives	13 (10 to 15)	
True negatives	862 (813 to 902)	1 studies 281 patients
False positives	118 (78 to 167)	

Inconclusive test results		

Patient or population: Patients with suspected AAS
New test: Aortic insufficiency
Setting: Inpatient and outpatient
Pooled sensitivity 0.18 (95% CI: 0.11 to 0.28) **Pooled specificity**: 0.92 (95% CI: 0.77 to 0.97)

Test result	Number of results per 1,000 patients tested (95% CI)	Number of participants (studies)
	Prevalence 2% in patients with suspected AAS	
True positives	4 (2 to 6)	10 studies 6735 patients
False negatives	16 (14 to 18)	
True negatives	897 (758 to 956)	9 studies 4377 patients
False positives	83 (24 to 222)	
Inconclusive test results		

Risk factors

Patient or population: Patients with suspected AAS
New test: Marfan syndrome/connective tissue disease
Setting: Inpatient and outpatient
Pooled sensitivity 0.02 (95% CI: 0.01 to 0.09) **Pooled specificity**: 0.96 (95% CI: 0.84 to 0.99)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 2% in patients with suspected AAS	Number of participants (studies)
True positives	0 (0 to 2)	5 studies 6113 patients
False negatives	20 (18 to 20)	
True negatives	938 (828 to 969)	4 studies 3575 patients
False positives	42 (11 to 152)	
Inconclusive test results		

Patient or population: Patients with suspected AAS
New test: Aortic aneurysm
Setting: Inpatient and outpatient
Pooled sensitivity 0.19 (95% CI: 0.14 to 0.20) **Pooled specificity**: 0.85 (95% CI: 0.77 to 0.91)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 2% in patients with suspected AAS	Number of participants (studies)
True positives	4 (3 to 4)	4 studies 6098 patients
False negatives	16 (16 to 17)	
True negatives	834 (758 to 888)	3 studies 3515 patients
False positives	146 (92 to 222)	

Inconclusive test results		

Patient or population: Patients with suspected AAS
New test: Widened mediastinum
Setting: Inpatient and outpatient
Pooled sensitivity 0.79 (95% CI: 0.70 to 0.85) **Pooled specificity**: 0.56 (95% CI: 0.41 to 0.70)

Test result	Number of results per 1,000 patients tested (95% CI)	Number of participants (studies)
	Prevalence 2% in patients with suspected AAS	
True positives	16 (14 to 17)	7 studies 659 patients
False negatives	4 (3 to 6)	
True negatives	549 (402 to 686)	7 studies 659 patients
False positives	431 (294 to 578)	
Inconclusive test results		

Patient or population: Patients with suspected AAS
New test: Aortic root dilation on point of care ultrasound
Setting: Inpatient and outpatient
Pooled sensitivity 0.64 (95% CI: 0.54 to 0.74) **Pooled specificity**: 0.81 (95% CI: 0.73 to 0.87)

Test result	Number of results per 1,000 patients tested (95% CI)	Number of participants (studies)
	Prevalence 2% in patients with suspected AAS	
True positives	14 (11 to 16)	1 studies 281 patients
False negatives	6 (4 to 9)	
True negatives	735 (676 to 794)	1 studies 281 patients
False positives	245 (186 to 304)	
Inconclusive test results		

Patient or population: Patients with suspected AAS
New test: Recent aortic manipulation
Setting: Inpatient and outpatient
Pooled sensitivity 0.03 (95% CI: 0.02 to 0.03) **Pooled specificity**: 0.97 (95% CI: 0.93 to 0.98)

Test result	Number of results per 1,000 patients tested (95% CI)	Number of participants (studies)
	Prevalence 2% in patients with suspected AAS	
True positives	1 (0 to 1)	4 studies 6089 patients
False negatives	19 (19 to 20)	
True negatives	950 (915 to 965)	4 studies 6089 patients
False positives	30 (15 to 65)	

Inconclusive test results		

Patient or population: Patients with suspected AAS
New test: aortic valve disease
Setting: Inpatient and outpatient
Pooled sensitivity 0.06 (95% CI: 0.04 to 0.09) **Pooled specificity** 0.95 (95% CI: 0.93 to 0.96)

Test result	Number of results per 1,000 patients tested (95% CI)	Number of participants (studies)
	Prevalence 2% in patients with suspected AAS	
True positives	1 (1 to 2)	4 studies 7974 patients
False negatives	19 (18 to 19)	
True negatives	928 (907 to 943)	3 studies 3546 patients
False positives	52 (37 to 73)	
Inconclusive test results		

Patient or population: Patients with suspected AAS
New test: Family history of AAS
Setting: Inpatient and outpatient
Pooled sensitivity 0.03 (95% CI: 0.02 to 0.06) **Pooled specificity** 0.99 (95% CI: 0.97 to 1.00)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 2% in patients with suspected AAS	Number of participants (studies)
True positives	1 (0 to 1)	4 studies 6047 patients
False negatives	19 (19 to 20)	
True negatives	969 (951 to 976)	3 studies 3508 patients
False positives	11 (4 to 29)	
Inconclusive test results		

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	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).	An absence of any high risk pain features, risk factors or physical exam findings and a negative chest x-ray increased the number of true positives but also decreased the number of true negatives. Using only clinical features and not routine chest x-ray increased the number of true negatives but also decreased the number of true positives. The panel felt that routine use of chest x-ray in risk stratification for AAS is not required, i.e. in those presenting with abdominal, flank, low back pain. But where clinically indicated can be useful to establish an alternatives diagnosis or if a widened mediastinum/absence of an aortic notch is found. Incorporating clinical judgment was

		deemed important by emergency physicians and the panel. Those with either 1 or 2 high risk pain features and a suspicion for an alternative diagnosis are likely low risk.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	The panel considered undesirable as increasing the number of patients with false positive and false negative test results (i.e. morbidity/mortality from missed diagnosis). The panel noted False positives. Physical exam findings	The panel noted there is no direct benefit for any of the diagnostic pathways.

Certainty of the evidence of test accuracy

What is the overall certainty of the evidence of test accuracy?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
●Very low ○ Low ○ Moderate ○ High ○ No included studies		

Outcome	№ of studies (№ of patients)	Factors that may decrease certainty of evidence					Test accuracy CoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives **False negatives**	6 studies 6163 patients	not serious	not serious	very serious [a]	very serious [b]	none	⨁◯◯◯ VERY LOW
True negative	5 studies	not serious	Not serious	very serious [a]	very serious [b]	none	

s **False positives**	3625 patients						⊕◯◯◯ VERY LOW

Abrupt onset pain

a. There was significant heterogeneity between included studies indicated by an I squared >90% for both sensitivity and specificity.
b. Confidence intervals for both sensitivity and specificity are wide. The sensitivity ranges from 34-88% and the specificity ranges from 23-81%.

Severe Pain

Outcome	№ of studies (№ of patients)	Factors that may decrease certainty of evidence					Test accuracy CoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives **False negative**	5 studies 6039 patients	not serious	not serious	very serious [a]	very serious [b]	none	⊕◯◯◯ VERY LOW

s							
True negatives **False positives**	4 studies 3501 patients	not serious	Not serious	very serious [a]	very serious [b]	none	⨁◯◯◯ VERY LOW

a. There was significant heterogeneity between included studies indicated by an I squared >90% for both sensitivity and specificity.
b. Confidence intervals for both sensitivity and specificity are wide. The sensitivity ranges from 46-86% and the specificity ranges from 45-80%.

Migrating/radiating pain

Outcome	№ of studies (№ of patients)	Factors that may decrease certainty of evidence					Test accuracy CoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives **False negatives**	4studies 924 patients	serious [a]	not serious	serious [b]	not serious	none	⨁⨁◯◯ LOW
True negatives **False positives**	4studies 924 patients	serious [a]	not serious	serious [c]	not serious	none	⨁⨁◯◯ LOW

a. There was significant heterogeneity between included studies indicated by an I squared >90% for both sensitivity and specificity.
b. Wide confidence intervals

Tearing/ripping pain

Outcome	№ of studies (№ of patients)	Factors that may decrease certainty of evidence					Test accuracy CoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives **False negatives**	6 studies 6085 patients	not serious	not serious	very serious [a]	very serious [b]	none	⊕◯◯◯ VERY LOW
True negatives **False positives**	5 studies 3502 patients	not serious	Not serious	very serious [a]	very serious [b]	none	⊕◯◯◯ VERY LOW

a. There was significant heterogeneity between included studies indicated by an I squared >90% for both sensitivity and specificity.
b. Confidence intervals for both sensitivity and specificity are wide. The sensitivity ranges from 2-62% and the specificity ranges from 36-95%.

Clinical Judgement

Outcome	№ of studies (№ of patients)	Factors that may decrease certainty of evidence					Test accuracy CoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives **False negatives**	9 studies 3433 patients	serious [a]	serious [a]	serious [b]	serious [c]	none	⊕◯◯◯ VERY LOW
True negatives	1 studies	serious	serious [d]	not serious	not serious	none	⊕⊕◯◯ LOW

False positives	1850 patients						

a. Risk of bias was downgraded due to variable patient population, definition of missed case, and reference standard between studies
b. Inconsistency was downgraded as the sensitivity ranged from 43% to 97%
c. Imprecision was downgraded as the 95% confidence interval ranged from 63%-84%
d. Indirectness was downgraded as the study did not report what investigations were performed prior to the clinician discharging the patient with a diagnosis other than acute aortic dissection. Some may have performed a D-dimer or undergone other investigations. In addition the study was not specifically testing the diagnostic accuracy of clinical judgment to rule out acute aortic dissection.

PHYSICAL EXAMINATION

Hypotension

Outcome	№ of studies (№ of patients)	Factors that may decrease certainty of evidence					Test accuracy CoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives	6 studies 6085 patients	serious [a]	not serious	serious [b]	not serious	none	⊕⊕◯◯ LOW
False negatives							
True negatives	5 studies 3502 patients	serious [a]	not serious	serious [c]	not serious	none	⊕⊕◯◯ LOW
False positives							

a. Strength of evidence was downgraded as patient selection varied between studies with an unclear risk of bias.
b. The confidence intervals were narrow but the I squared was 57% representing a potential for inconsistency between studies.
c. The confidence intervals were narrow but the I squared was 82% representing a potential for inconsistency between studies.

Pericardial effusion/ tamponade

Outcome	№ of studies (№ of patients)	Factors that may decrease certainty of evidence					Test accuracy CoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives **False negatives**	1studies 281patients	Serious [a]	serious [a]	not serious	serious [b]	none	⊕◯◯◯ VERY LOW
True negatives **False positives**	1 studies 281 patients	serious [a]	serious [a]	not serious	serious [b]	none	⊕◯◯◯ VERY LOW

a. risk of bias and indirectness were downgraded as single centre study including a convenience sample of patients only with Type A aortic dissection
b. Imprecision was downgraded due to wide confidence intervals

Neurological deficits

Outcome	№ of studies (№ of patients)	Factors that may decrease certainty of evidence					Test accuracy CoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives **False negatives**	7 studies 6514 patients	serious	not serious	not serious [a]	not serious	none	⊕⊕⊕◯ MODERATE
True negatives	6 studies	serious	not serious	serious [a]	not serious	none	⊕⊕◯◯ LOW

False positives	4156 patients						
False positives							

a. Inconsistency downgraded for an unexplained range in sensitivity from 3%-30%

Murmur of aortic insufficiency

Outcome	№ of studies (№ of patients)	Factors that may decrease certainty of evidence					Test accuracy CoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives **False negatives**	10 studies 6735 patients	serious [a]	not serious	very serious [b]	very serious [b]	none	⨁◯◯◯ VERY LOW
True negatives **True negatives**	9 studies 4377 patients	serious [a]	not serious	very serious [c]	very serious [c]	none	⨁◯◯◯ VERY LOW

a. The description of the index test was not adequate in most studies and it was not clear in some whether a positive result referred to a new murmur of any character or aortic regurgitation new or old.
b. The sensitivity ranged from 5% to 49% reflected in an I squared of 95%.
c. The specificity ranged from 45% to 99% reflected in an I squared of 95%.

Aortic insufficiency on point of care ultrasound

Outcome	№ of studies (№ of patients)	Factors that may decrease certainty of evidence					Test accuracy CoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives **False negatives**	1 studies 281 patients	serious [a]	serious [a]	not serious	serious [b]	none	⨁◯◯◯ VERY LOW
True negatives **True negatives**	1 studies 281 patients	serious [a]	serious [a]	not serious	serious [b]	none	⨁◯◯◯ VERY LOW

a. Risk of bias and indirectness were downgraded for a single centre convenience sample of patients who underwent echocardiography.
b. Imprecision was downgraded due to wide confidence intervals

Pulse deficit

Outcome	№ of studies (№ of patients)	Factors that may decrease certainty of evidence					Test accuracy CoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives **False negatives**	3 studies 297 patients	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW
True negatives	3 studies	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE

False positives	297 patients						

a. 3 of the studies are before the year 2000, with the broader availability of CT the characteristics of the population being investigated fro acute aortic dissection may be different to the included studies.
b. There was minimal statistical heterogeneity between studies with an I squared of 0, however strength of evidence was marked down due to a sensitivity ranging from 12-49%.

RISK FACTORS

Marfans syndrome/connective tissue disease

Outcome	№ of studies (№ of patients)	Factors that may decrease certainty of evidence					Test accuracy CoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives	5 studies 6113 patients	not serious	not serious	very serious [a]	serious [a]	none	⊕◯◯◯ VERY LOW
False negatives							
True negatives	4 studies 3575 patients	not serious	not serious	serious [b]	serious [b]	none	⊕⊕◯◯ LOW
False positives							

a. Strength of evidence was downgraded secondary to a sensitivity ranging from 2% to 9% with an I squared of 93%.
b. Strength of evidence was downgraded secondary to a specificity ranging from 84% to 100% with an I squared of 80%.

Aortic aneurysm

Outcome	№ of studies (№ of patients)	Factors that may decrease certainty of evidence					Test accuracy CoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives **False negatives**	4 studies 6098 patients	not serious	not serious	serious [a,b]	serious [a]	none	⨁⨁◯◯ LOW
True negatives **False positives**	3 studies 3515 patients	not serious	not serious	serious [a,b]	serious [a]	none	⨁⨁◯◯ LOW

a. Confidence intervals for both sensitivity and specificity are wide. The sensitivity ranges from 46-86% and the specificity ranges from 45-80%.
b. There was significant heterogeneity between included studies indicated by an I squared >90% for both sensitivity and specificity.

Dilated aortic root on bedside ultrasonography

Outcome	№ of studies (№ of patients)	Factors that may decrease certainty of evidence					Test accuracy CoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives **False negatives**	1 studies 281 patients	serious [a]	serious [a]	not serious	serious [b]	none	⨁◯◯◯ VERY LOW
True negatives	1 studies	serious [a]	serious [a]	not serious	serious [b]	none	⨁◯◯◯ VERY LOW

True negatives	281 patients						

a. Risk of bias and indirectness were downgraded for a single centre convenience sample of patients who underwent echocardiography.
b. Imprecision was downgraded due to wide confidence intervals

Widened mediastinum/absence of aortic notch

Outcome	№ of studies (№ of patients)	Factors that may decrease certainty of evidence					Test accuracy CoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives **False negatives**	7 studies 659 patients	not serious	serious [a]	serious [b]	none	not serious	⨁⨁◯◯ LOW
True negatives **False positives**	7 studies 659 patients	not serious	serious [a]	very serious [c]	none	not serious	⨁◯◯◯ VERY LOW

a. High level of statistical heterogeneity led to downgrading of the recommendation
b. Sensitivity ranging from 76%-94% led to downgrading of recommendation
c. specificity ranging from 24%-78% led to downgrading of recommendation

Recent aortic manipulation

Outcome	№ of studies (№ of patients)	Factors that may decrease certainty of evidence					Test accuracy CoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives **False negatives**	4 studies 6089 patients	serious	not serious	serious	not serious	none	⊕⊕◯◯ LOW
True negatives **Fa F FaFalse positives alse positives lse positives**	4 studies 6089 patients	serious	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE

a. Risk of bias was downgraded due to heterogeneous inclusion criteria between trials.
b. Inconsistency was downgraded for large I squared

Family history of AAS

Outcome	№ of studies (№ of patients)	Factors that may decrease certainty of evidence					Test accuracy CoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives **False negatives**	4 studies 6047 patients	serious [a]	not serious	serious [b]	not serious	none	⊕⊕◯◯ LOW

True negatives	3 studies 3508 patients	serious [a]	not serious	serious [b]	not serious	none	⊕⊕◯◯ LOW
False positives							
False positives							

a. Inclusion criteria was clinical suspicion for AAS, they did not follow up amongst those not included for missed cases
b. Downgraded for I squared >70%

a. Inconsistency downgraded for an unexplained range in sensitivity from 3%-30%

Aortic valve disease

Outcome	№ of studies (№ of patients)	Factors that may decrease certainty of evidence					Test accuracy CoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives	4 studies 7974 patients	serious [a]	serious [a]	serious [a]	not serious	none	⊕◯◯◯ VERY LOW
False negatives							

True negatives **False positives**	3 studies 3546 patients	serious [a]	not serious	serious [a]	not serious	none	⊕⊕◯◯ LOW

a. Evidence downgraded for inconsistent and varying description of aortic valve disease, large I squared and wide confidence intervals

There was significant heterogeneity between included studies indicated by an I squared >90% for both sensitivity and specificity. Indirectness was downgraded as one study only included history of aortic valve replacement and not bicuspid aortic valve.

Point of care ultrasound aortic root dilation

Outcome	№ of studies (№ of patients)	Factors that may decrease certainty of evidence					Test accuracy CoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives **False negatives**	1 studies 281 patients	serious	not serious	not serious	very serious	none	⨁◯◯◯ VERY LOW
True negatives **False positives**	1 studies 281 patients	serious	not serious	not serious	very serious	none	⨁◯◯◯ VERY LOW

a. Risk of bias was downgraded due convenience sample including all those who underwent ultrasonography
b. Imprecision was downgraded due to wide 95% confidence intervals

Certainty of the evidence of test's effects

What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No direct evidence.	Performing the test itself should have a low burden as it is largely clinical.

Certainty of the evidence of management's effects

What is the overall certainty of the evidence of effects of the management that is guided by the test results?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● Varies ○ No included studies	The panel considered management effects as; no testing, D-dimer and CT aorta. There are no studies looking at certain management options at risk levels defined by the panel. Prevalence of AAS in studies looking at miss rates support that a lower threshold for imaging is necessary. Comparing studies in which the threshold for imaging led to a prevalence of 25% versus studies with a prevalence of 2-3% the miss rate was considerably lower in the lower prevalence studies. This evidence is indirect, retrospective and observational in nature thus certainty would be low. Evidence of the effects of the management. Management is further testing, effects of the management effects of further testing.	The panel felt that a patient defined as high risk should undergo advanced imaging. Although there were 0 studies looking at the effect of advanced imaging for those specifically at high risk, all included studies assessing diagnostic accuracy patients underwent imaging if there was a suspicion for AAS.

Certainty of the evidence of test result/management

How certain is the link between test results and management decisions?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ●Low ○ Moderate ○ High ○ No included studies	There is low certainty of the link between management decisions at any risk level with a variation in the literature on the prevalence of those with AAS in a population undergoing advanced imaging.	The certainty of evidence that high risk patients should undergo CT is high, however the evidence for what to do at a risk level is limited.

Certainty of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PTP low ○ Very low ○ Low ● Moderate ○ High ○ No included studies PTP intermediate ○ Very low ○ Low	The panel considered the effects of the test as successfully risk stratifying into a low moderate and high risk group. There are 3 studies looking at the effect of using absence of high risk pain, risk factor and physical exam findings to define a low risk group. Rogers at al that absence of all high risk clinical features identified 95% of cases of AAS. Nazerian et al., in a retrospective and prospective studies, found an absence of all risk factors missed 5% of cases. The prevalence of AAS in this low risk population was 2.7%. The pre test probability in this population was 13% is far higher than a Canadian population that is being risk stratified for AAS. These studies indirectly assess a portion of the PTP assessment that resulted from modelling. The certainty of evidence at low risk was downgraded for risk of bias, but not for consistency as rogers and Nazerian study supports a consistent sensitivity, and not for imprecision as confidence intervals around both study estimates are narrow. So certainty for low risk is moderate.	

○ Moderate ○ High ● No included studies PTP high ○ Very low ○ Low ○ Moderate ○ High ● No included studies	Studies included in the diagnostic accuracy review do not provide sufficient data to extrapolate the prevalence of AAS in those with isolated pulse deficit, hypotension, neurological deficit or new murmur of aortic insufficiency, therefore certainty of evidence for prevalence of AAS at a risk level defined by these variables is low/no included studies. At an intermediate risk level included diagnostic accuracy studies do not allow for calculation of prevalence of AAS with each of the variables used to define an intermediate risk level in the proposed PTP tool. Therefore certainty is low/no included studies	

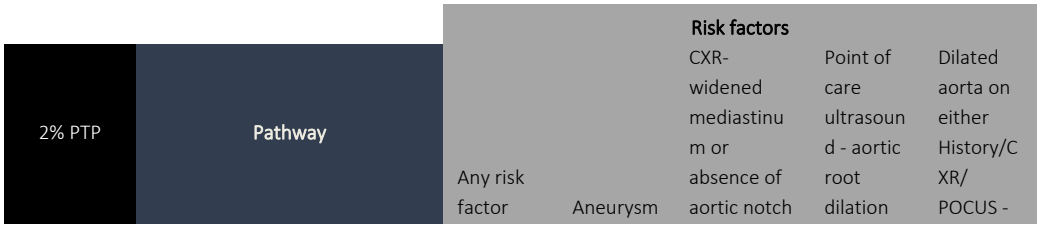
Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	91% of respondents deemed ruling out AAS (TN) important. 37% deemed the ability to rule in the diagnosis (TP) important. 88% deemed reducing false negatives or missed cases as a priority. 71% deemed priority be to reduce unnecessary imaging or False positives. A patient led priority setting initiative found that diagnosis of AAS including reducing missed cases was the number 1 priority for research.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know **which provides the least balance.**	**Table 1: What is the optimal criteria in assessing PTP for those presenting with symptoms suggestive of AAS.** 	**Highlighted in green are either pathways that meet threshold for low risk (<0.5%) or high risk (>5%)** The panel discussed that history of an aortic aneurysm only slightly increased the probability of AAS, however all panel members felt that a patient presenting with abdominal or chest pain and a known aortic aneurysm should undergo advanced imaging even though threshold values for imaging were not met **Pain features**

The panel judged the ranking of the pathways based on the probability of AAS if positive and negative. Pathways highlighted in green were judged as the top ranked pathways that reached the predefined threshold for low or high risk. 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 5 false negative results per 1000 patients tested (<0.5%) or above a threshold of 50 true positives per 1000 patients tested (>5%) Pathways highlighted in red did not meet threshold of <0.5% or >5% and thus were deemed intermediate risk

	TP	6	4	16	12	
	FN	14	16	4	8	
	TN	843	834	549	833	
	FP	137	146	431	147	
	Misdaignosis(FP+FN/1000)	15.10%	16.20%	43.50%	15.50%	
	Probability of AAS if negative	1.634%	1.882%	0.723%	0.951%	
	Probability of AAS if positive	4.20%	2.67%	3.58%	7.55%	4.6%
	Percentage of missed AAS(False negative rate)	70.00%	80.00%	20.00%	40.00%	
	Percentage of CT that will be negative (False positive rate)	95.80%	97.33%	96.42%	92.45%	
	Number of CT that would be performed per 1000 patients screened	143	150	447	159	

		Physical exam				
	Pathway	Hypotension	Neurological deficit	Pulse deficit	Aortic insufficiency	Pericardial Effusion on POCUS
2% PTP	TP	3	3	5	4	7
	FN	17	17	15	16	13
	TN	924	935	931	897	862
	FP	56	45	49	83	118
	Misdaignosis(FP+FN/1000)	7.30%	6.20%	6.40%	9.90%	13.10%
	Probability of AAS if negative	1.807%	1.786%	1.586%	1.752%	1.486%

The panel agreed using Bayesian modeling(serial application of pain features to a PTP) to assess the sequential probability of AAS with multiple pain features was inappropriate given that features such as severe and tearing are likely related. However the panel agreed that a patient with severe, tearing and abrupt onset pain should undergo advanced imaging. The multiple pain features modelling was from sensitivity and specificity from studies looking at only severe, tearing and abrupt onset pain, if multiple pain features were present 80% of the time it was for 2 and not three high risk pain features. Therefore 2 high risk pain features did not meet threshold for high risk.

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. morbidity/mortality from missed diagnosis). The panel noted that for CT aorta, alternate diagnoses may be revealed which would be a desirable effect

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.

	Probability of AAS if positive	5.08%	6.25%	9.26%	4.60%	5.60%	2.82%
	Percentage of missed AAS(False negative rate)	85.00%	85.00%	75.00%	80.00%	65.00%	90.00%
	Percentage of CT that will be negative (False positive rate)	94.92%	93.75%	90.74%	95.40%	94.40%	97.18%
	Number of CT that would be performed per 1000 patients screened	59	48	54	87	Effusion	AI

Pain features

	Pathway	Tearing	Severe	Migrating	Abrupt onset /thunder clap pain	Multiple pain features(>1)
2% PTP						
	TP	4	14	9	14	18
	FN	16	6	11	6	2
	TN	874	569	657	587	392
	FP	106	411	320	393	588
	Misdaignosis(FP+FN/1000)	12.20%	41.70%	34.30%	39.90%	59.00%
	Probability of AAS if negative	1.798%	1.043%	1.374%	1.012%	0.508%
	Probability of AAS if positive	3.64%	3.29%	3.19%	3.44%	2.97%
	Percentage of missed AAS(False negative rate)	80.00%	30.00%	45.00%	30.00%	10.00%
	Percentage of CT that will be negative (False positive rate)	96.36%	96.71%	96.81%	96.56%	97.03%
	Number of CT that would be performed per 1000 patients screened	110	425	345	407	606

Combination

	Pathway	Risk factor + pain feature	Absence of pain features, risk factors, physical exam features	Clinical judgement applied to those with multiple pain features	ADDRS 0 Vs >0
2% PTP					
	TP	5	19	16	19
	FN	16	1	4	1
	TN	894	213	845	213
	FP	86	767	135	767
	Misdaignosis(FP+FN/1000)	10.20%	76.80%	13.90%	76.80%
	Probability of AAS if negative	1.758%	0.467%	0.471%	0.467%
	Probability of AAS if positive	5.49%	2.42%	10.60%	2.42%
	Percentage of missed AAS(False negative rate)	76.19%	5.00%	20.00%	5.00%
	Percentage of CT that will be negative (False positive rate)	94.51%	97.58%	89.40%	97.58%
	Number of CT that would be performed per 1000 patients screened	91	786	151	786

Assumptions associated with modelling:

1. Disease prevalence in a population with a suspicion for AAS was determined to be 20 per 1000 patients (2%).
2. Disease prevalence applies to the index test in each pathway. We did not model multiple clinical symptoms as they are likely linked.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ●Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No direct evidence of costs, chest x-ray and point of care ultrasound are optional components of risk stratification.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No included studies	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○Probably favors the intervention ○ Favors the intervention ○ Varies ●No included studies	No direct evidence, intervention is risk stratification not linked to further testing.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Not including any blood tests and optional chest x-ray and point of care ultrasound will likely reduce health inequity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	A survey of 455 ED physicians stated that likelihood of an alternative diagnosis and likelihood of AAS were important or very important. All the included variables were rated as important or very important in the survey and therefore likely acceptable.	Hypertension was not included as a variable and this was a point of discussion between cardiac surgeons and emergency physicians, cardiac surgeons noted that patients with AAS present with a systolic >180mmHg, however emergency physicians noted that a large number of patients per year present with uncontrolled hypertension and do not have an AAS. The discussion was resolved with adding a systolic >180mmHg to the set

		of clinical signs and symptoms that should initiate your suspicion for AAS

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There are no direct studies.	The panel discussed that it is likely feasible to use a PTP assessment tool to risk stratify for AAS. The only concern was the inclusion criteria for a population that is being risk stratified. Implementing in a population that has PTP <2% would likely effect the number of false positives and limit the usability of any such tool

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		**Varies**	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF THE EVIDENCE OF TEST ACCURACY	Very low	**Low**	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	Very low	**Low**	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	Very low	Low	**Moderate**	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT	Very low	Low	**Moderate**	High			No included studies
CERTAINTY OF EFFECTS	Very low	Low	Moderate	High			**No included studies**

	JUDGEMENT						
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either **the intervention or the comparison**	**Probably favors the** intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
◯	◯	◯	x	◯

CONCLUSIONS

Recommendation

Recommendation 1a. The panel *recommends* providers routinely evaluate any patient presenting with complaints that may represent AAS to establish a pretest risk of disease that can then be used to guide diagnostic decisions. This process should include specific questions about risk factors and pain features, as well as a focused examination to identify findings that are associated with AAS. Risk factors (e.g., connective tissue disease, aortic valve disease, Recent aortic manipulation, Aortic aneurysm [thoracic or

abdominal, on chest x-ray, history or bedside echocardiography], family history of AAS); High-risk pain features (e.g., abrupt onset/thundercap pain, severe/worst ever pain, tearing or ripping pain, migrating pain); High-risk physical exam findings (e.g., new aortic regurgitation [auscultated murmur or bedside echocardiography], pulse deficit, neurological deficit, hypotension or pericardial effusion on bedside echocardiography). (*Strong* recommendation based on *low* certainty in the evidence of effects on clinical outcomes and *moderate* certainty in the evidence of diagnostic accuracy studies.)

Recommendation 1.b The panel *suggests* using historical pain, risk factors and physical exam findings to define a patient as low (≤0.5%), moderate (0.5-5%) or high (>5%) probability for AAS (Figure 1.) (*conditional* recommendation based on *low* certainty in the evidence of effects on clinical outcomes and *low* certainty in the evidence of diagnostic accuracy studies.)

Technical Remarks:

- *An absence of any high-risk historical, risk factor or physical exam findings places the patient in a population with a very low prevalence for AAS.*
- *The panel recognised that different clinical features have different strengths of association with AAS; in addition.*
- *Clinical suspicion for an alternative diagnosis or for AAS is important in assessment of pre-test probability.*
- *For patients with a low risk of AAS and no alternative diagnosis, if clinicians do not suspect AAS, they are still considered low risk*.

Justification

The panel suggests using a pre test probability assessment tool. The evidence to support the tool was low quality but the panel felt that the benefits and unintended consequences are likely balanced, minimal impact on equity, and the tool was deemed to be acceptable and feasible to implement.

Subgroup considerations

n/a

Implementation considerations

Noted importance of promoting alternative diagnosis first strategy.

Monitoring and evaluation

A comprehensive implementation strategy needs to be developed in order to monitor the diagnostic accuracy and uptake of the pathway. IN addition to pre planned analysis to assess for need for modification of the assessment tool.

Research priorities

Validating pre test probability assessment

Table A-1. Search strategy for MEDLINE

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:	

1	Aneurysm, Dissecting/ or dissecting.tw.
2	aortic aneurysm/ or aortic aneurysm, thoracic/
3	1 and 2
4	aortic dissection.tw.
5	dissecting aorta.tw.
6	**3 or 4 or 5**
7	medical history taking/ or history taking.tw.
8	Observer Variation/
9	Bayes Theorem/ or (Bayes or Bayesian).tw.
10	exp "sensitivity and specificity"/
11	"Reproducibility of Results"/

12	physical examination/ or physical exam$.tw.
13	clinical exam$.tw.
14	Diagnostic Tests, Routine/
15	diagnostic test$.tw.
16	**or/7-15**
17	**6 and 16**
18	**limit 17 to yr="1966 -Current"**

QUESTION In a patient population with a *Low* clinical probability of AAS, what is the optimal diagnostic strategy to evaluate for suspected AAS?

What is	
POPULATION:	Patients with a low clinical probability for acute aortic syndrome(AAS)
INTERVENTION:	D-dimer, CT aorta
PURPOSE OF THE TEST:	Diagnosis of AAS
ROLE OF THE TEST:	Diagnosis of AAS
LINKED TREATMENTS:	Appropriate surgical or medical management
ANTICIPATED OUTCOMES:	False Negative; False Positive; True Negative; True Positive; Mortality;
SETTING:	Emergency department
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	
SUBGROUPS:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The overall annual incidence of aortic dissection is 3-12 per 100,000. Although 60% of a recent survey respondents had seen a patient in the past year with AAS. Mortality of untreated Type A aortic dissection is 90% at 2 weeks. Miss rate ranges from 16-38%. Mortality increases 1%/hr. Improving time to diagnosis and accuracy of diagnosis is key in reducing the overall morbidity and mortality associated with AAS. Clinicians rate AAS as the number priority in developing a clinical decision aid, in addition 98% of respondents to a national survey of emergency physicians state that we need a clinical decision aid/diagnostic algorithm to aid in the diagnostic dilemma of AAS.	

Test accuracy

How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

CT-Aorta
○ Very inaccurate
○ Inaccurate
○ Accurate
•**Very accurate**
○ Don't know

D-dimer to rule in AAS
• **Very inaccurate**
○ Inaccurate
○ Accurate
○ Very accurate
○ Don't know

D-dimer to rule out AAS
○ Very inaccurate
○ Inaccurate
•**Accurate**
○ Very accurate
○ Don't know

D-dimer
Patient or population: Patients with suspected AAS
New test: D-dimer
Setting: Inpatient and outpatient
Pooled sensitivity: 0.95 (95% CI: 0.90 to 0.99)| **Pooled specificity**: 0.60 (95% CI: 0.48 to 0.71)

Test result	Number of results per 1,000 patients tested (95% CI)	Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 0.5% in patients with suspected PE		
True positives	4 (4 to 5)	3860 (22)	⊕⊕⊕◯ **MODERATE** [a,b]
False negatives	1 (0 to 1)		
True negatives	601 (483 to 709)	2827 (12)	⊕◯◯◯ **Very Low** [a,b]
False positives	394 (286 to 512)		
Inconclusive test results			-
Complications arising from the diagnostic test	Not reported		

a. The risk of bias was assessed using the QUADAS-2 tool. 19/22 and 11/12 of the included study had at least one domain rated as high risk. There are two other meta analysis that only included 5 of the 22 articles, they performed a QUADAS assessment and found a low or unclear risk of bias in most domains.
b. The I squared demonstrated significant statistical heterogeneity in the results of specificity between included studies. This is reflected in the specificity ranging from 25 to 95%.

CT
Patient or population: Patients with suspected acute aortic dissection

New test: CT
Setting: Inpatient and outpatient
Pooled sensitivity: 1 (95% CI: 0.92 to 1) | **Pooled specificity**: 0.98 (95% CI: 0.96 to 0.99)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 0.5% in patients with suspected AAD	Number of participants (studies)	Certainty of the Evidence (GRADE)
True positives	5 (5 to 5)	3 studies 126 patients	⨁⨁⨁⨁ HIGH
False negatives	0 (0 to 0)		
True negatives	975 (866 to 985)	3 studies 126 patients	⨁⨁⨁⨁ HIGH
False positives	20 (10 to 129)		
Inconclusive test results		4159	-
Complications arising from the diagnostic test	Not reported		

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	There are no implementation studies exploring management strategies at a low pre test probability. However indirect evidence for implementation of a no testing strategy at a low probability for AAS has shown a potential reduction in imaging ranging from 9-30%.	system vs patient effects were considered

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Potential undesirable effects are an increased in D-dimer ordering with this pathway and consequently an increase in false positives and an increase in imaging. In the trial educational study at a single site, offering a diagnostic pathway for AAS did increase D-dimer ordering but did not increase imaging.	,

Certainty of the evidence of test accuracy

What is the overall certainty of the evidence of test accuracy?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	There are no direct studies exploring the accuracy of a diagnostic pathway using D-dimer or CT in a low prevalence population.	

Certainty of the evidence of test's effects

What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Varies depending on components	delaying diagnosis, IMH miss, burden on healthcare system - unknonw evidence of the effects, radiation....

Certainty of the evidence of management's effects

What is the overall certainty of the evidence of effects of the management that is guided by the test results?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Multiple studies looking at the reduction in mortality with surgery for Type A dissections and in type B that require surgical intervention. The evidence for surgical management of type IMH and PAU is unclear. Medical management of type b aortic dissections there is weak evidence to support heart rate and blood pressure control.	

Certainty of the evidence of test result/management

How certain is the link between test results and management decisions?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Does this vary? Although the link between diagnosis and management is certain, the exact management varies with the diagnosis Type A vs B, the co-morbidities and complications.	The panel noted high certainty in the link between test results and management decisions. However, the panel also noted that for patients with IMH or PAU the link may not be as certain.

Certainty of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	91% of respondents deemed ruling out acute aortic(TN) syndrome important. 37% deemed the ability to rule in the diagnosis (TP) important. 88% deemed reducing false negatives or missed cases as a priority. 71% deemed priority be to reduce unnecessary imaging or False positives.	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.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know		**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

	Pathway	D-dimer	CT	Clinical Judgment
0.5% PTP	TP	4	5	5
	FN	1	0	0
	TN	601	975	765
	FP	394	20	230
	Misdiagnosis(FP+FN/1000)	39.50%	2.00%	23.00%
	Probability of AAS if negative	0.166%	0.000%	0.000%
	Probability of AAS if positive	1.01%	20.00%	2.13%
	Percentage of missed AAS(False negative rate)	20.00%	0.00%	0.00%
	Percentage of CT that will be negative (False positive rate)	98.99%	80.00%	97.87%

	Number of CT that would be performed per 1000 patients screened	398	1000	235	test results (i.e. morbidity/mortality from missed diagnosis). The panel noted that for CT aorta, alternate diagnoses may be revealed which would be a desirable effect **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. Using a no further testing strategy unless clinical judgment dictates

		resulted in the most desirable balance of decreasing number of investigations and reducing false negative and false positive. The panel however noted that depending on the clinical situation shared decision making may factor into a discussion with individual patient.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	CT first pathway would result in an increase in advanced imaging resources, but there is no direct evidence to support this assumption. D-dimer first pathway could theoretically reduce number of advanced imaging however would increase resource utilization compared to a no investigation strategy at a low probability level. There is no direct evidence to indicate what impact on resources of a no testing strategy at a low pre test probability threshold.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	CT or a d-dimer first strategy could potentially increase resources in lower use areas, possibly no impact on high use areas ie in emergency departments with a high rate of advanced imaging or d-dimer use. A d-dimer first strategy could reduce imaging if implemented in a high use area. There is no direct evidence on resources required	The panel noted uncertainty in the actual costs of the tests.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ●Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	There was only one study assessing cost of screening with either D-dimer or CT aorta for all those admitted to a chest pain monitoring unit for investigation. It found that screening for AAS with either D-dimer or CT aorta would increase costs without any proven impact on morbidity related to AAS(1).	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We identified the following regarding the impact on health equity with the different tests: **CTA:** 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(2)	**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.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	A survey of 455 ED physicians stated a rule incorporating a pretest probability assessment would be acceptable . The same survey found that a miss rate of <1% was acceptable and therefore if probability is below this then a pathway suggesting no further testing would likely be acceptable.	It was noted by the panel that acceptability to physicians was assessed through a survey but there was no evidence of acceptability of any of the suggested pathways by patients. Patient representatives on the panel felt that no further testing at a PTP <0.5% was acceptable.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**General (Radiology & Population):** Feasibility: A retrospective chart review showed that there was substantial variation in utilization and diagnostic yield of advanced radiography for AAD(Ohle 2018) Implementation: A prospective implementation of a diagnostic algorithm which included no further testing at a PTP <0.5% showed an increase in uptake with an education intervention involving an educational video, posters, website/calculator. (Ohle 2018)	The panel noted that in terms of feasibility, some institutions do not offer 24h CT scanning or have access to a CT scanner. Therefore having CT as first line in pathway requires all patiesnt to be transferred. For CT 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 or be transferred to another institution. The panel also noted 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.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		**Varies**	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF THE EVIDENCE OF TEST ACCURACY	Very low	**Low**	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	Very low	**Low**	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	Very low	Low	**Moderate**	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT	Very low	Low	**Moderate**	High			No included studies
CERTAINTY OF EFFECTS	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know

	JUDGEMENT						
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

Recommendation 2. The panel *suggests* no further testing in a population with a prevalence of AAS of ≤0.5%. (*Conditional* recommendation based on *low* certainty in the evidence of effects on clinical outcomes and *moderate* certainty in the evidence of diagnostic accuracy studies.

Remarks:

- There are no prospectively validated clinical decision rules to assess for a pre- test probability of ≤0.5%. Estimates are based on modelling of moderate quality observational studies.
- AAS is a rare but serious diagnosis in the emergency department. An absence of any high risk historical, risk factor or physical exam findings places the patient in a population with a very low prevalence of AAS.
- There are no validated clinical decision aids to define pre test probability ≤0.5%. However, multiple observational studies support that an absence of any high-risk features establishes the patient as being in a low prevalence population.
- Advanced imaging is not required in a population with a probability below 0.5%

Justification

Overall justification

The panel considered a strategy of no further testing in a population with a PTP <0.5%. Use of D-dimer could reduce the miss rate further but would increase the number of fale positive CT aorta. Starting with a strategy involving CT aorta first would drastically increase the number of false positive CT aorta.

Subgroup considerations

n/a

Implementation considerations

Noted importance of promoting alternative diagnosis first strategy.

Monitoring and evaluation

A comprehensive implementation strategy needs to be developed in order to monitor the diagnostic accuracy and uptake of the pathway.

Research priorities

Validating pre test porbability assessment

References

1. Moysidis T, Lohmann M, Lutkewitz S, Kemmeries G, Kroger K**.** Cost associated with D-Dimer screening for acute aortic dissection. Advances in therapy. 2011;28(11):1038-44.
2. Southern DA, Poole J, Patel A, Waters N, Pilote L, Hull RD, et al. Health system capacity and infrastructure for adopting innovations to care for patients with venous thromboembolic disease. Open Medicine. 2014;8(2):e46.

QUESTION In a patient population with a *moderate* clinical probability of AAS, what is the optimal diagnostic strategy to evaluate for suspected AAS?

What is	
POPULATION:	Patients with a moderate clinical probability for acute aortic syndrome (AAS)

INTERVENTION:	D-dimer, CT aorta
PURPOSE OF THE TEST:	Diagnosis of AAS
ROLE OF THE TEST:	Diagnosis of AAS
LINKED TREATMENTS:	Appropriate surgical or medical management
ANTICIPATED OUTCOMES:	False Negative; False Positive; True Negative; True Positive
SETTING:	Emergency department
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	
SUBGROUPS:	
CONFLICT OF INTERESTS:	None to declare

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The overall annual incidence of aortic dissection is 3-12 per 100,000. Although 60% of a recent survey respondents had seen a patient in the past year with AAS. Mortality of untreated Type A aortic dissection is 90% at 2 weeks. Miss rate ranges from 16-38%. Mortality increases 1%/hr. Improving time to diagnosis and accuracy of diagnosis is key in reducing the overall morbidity and mortality associated with AAS. Clinicians rate AAS as the number priority in developing a clinical decision aid, in addition 98% of respondents to a national survey of emergency physicians state that we need a clinical decision aid/diagnostic algorithm to aid in the diagnostic dilemma of AAS.	

Test accuracy

How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
CT-Aorta ○ Very inaccurate ○ Inaccurate	**D-dimer** **Patient or population:** Patients with suspected AAS **New test:** D-dimer **Setting:** Inpatient and outpatient **Pooled sensitivity**: 0.95 (95% CI: 0.90 to 0.99)| **Pooled specificity**: 0.60 (95% CI: 0.48 to 0.71)	

○ Accurate ●Very accurate ○ Don't know D-dimer to rule in AAS ● Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate ○ Don't know D-dimer to rule out AAS ○ Very inaccurate ○ Inaccurate ●Accurate ○ Very accurate ○ Don't know		

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 3% in patients with suspected AAS	Number of participants (studies)	Certainty of the Evidence (GRADE)
True positives	28 (27 to 30)	3860 (22)	⊕⊕⊕◯ MODERATE [a]
False negatives	2 (0 to 3)		
True negatives	586 (470 to 691)	2827 (12)	⊕◯◯◯ Very Low [a,b]
False positives	384 (279 to 500)		
Inconclusive test results			-
Complications arising from the diagnostic test	Not reported		

a. The risk of bias was assessed using the QUADAS-2 tool. 19/22 and 11/12 of the included study had at least one domain rated as high risk. There are two other meta analysis that only included 5 of the 22 articles, they performed a QUADAS assessment and found a low or unclear risk of bias in most domains, this led to downgrading the level of certainty to moderate.
b. The certainty was downgraded for inconsistency and imprecision of results. The I squared demonstrated significant statistical heterogeneity in the results of specificity between included studies. This is reflected in the specificity ranging from 25 to 95%.

CT
Patient or population: Patients with suspected acute aortic dissection
New test: CT
Setting: Inpatient and outpatient
Pooled sensitivity: 1 (95% CI: 0.92 to 1) | **Pooled specificity**: 0.98 (95% CI: 0.96 to 0.99)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 3% in patients with suspected AAS	Number of participants (studies)	Certainty of the Evidence (GRADE)
True positives	30 (29 to 30)	3 studies 126 patients	⨁⨁⨁⨁ HIGH
False negatives	0 (0 to 1)		
True negatives	975 (866 to 985)	3 studies 126 patients	⨁⨁⨁⨁ HIGH
False positives	20 (10 to 129)		
Inconclusive test results			-
Complications arising from the diagnostic test	Not reported		

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Pathways at an intermediate pre test probability involve either CT first or D-dimer first strategies. Desirable effects of a D-dimer first strategy involve a reduction in use of CT. Desirable effects of CT first pathway is a reduction in false negative results and reduction in the number of steps in a given pathway and therefore potentially reduction in time to diagnosis. There is no direct evidence substantiating the desired effects of either pathway.	The panel spent time discussing patient versus system desirable effects. From a system point of view if a patient requires transport for CT then less resources would be used in a d-dimer first pathway. Most centres who do not have access to d-dimer testing 24hrs a day will also not have access to CT. From a system point of view D-dimer first strategy may have a larger effect in a setting without access to CT. However from a patient perspective desired effects of either pathway may vary, ie greater weight places on not having to be transferred for a CT/ration exposure, or desire to undergo the gold standard investigation.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Potential undesirable effects are an increased in D-dimer ordering with this pathway and consequently an increase in false positives and an increase in imaging. CT first pathway potential undesirable effects are an increase in CT ordering. In a pilot implementation study-suggesting D-dimer at an intermediate pre test probability resulted in an increase in D-dimer ordering but no increase in the number of CT ordered. Incidental findings on CT can result in further imaging, increase stress and over testing. A retrospective study looking at all those who underwent CT to rule out AAS found a 16% incidental finding rate. A CT first pathway will have different results at different centres depending on current CT rate.	The panel noted there is no direct benefit for any of the diagnostic pathways.

Certainty of the evidence of test accuracy

What is the overall certainty of the evidence of test accuracy?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
D-dimer to rule in AAS ○ Very low ● Low ○ Moderate ○ High ○ No included studies **D-dimer to rule out AAS** ○ Very low ○ Low ●Moderate ○ High ○ No included studies **CT to rule in or rule out AAS** ○ Very low ○ Low ○ Moderate ●High ○ No included studies	CT has a high level for certainty of evidence. However this is based on a small number of studies and small number of patients. The international registry for acute aortic dissection states that CT is the most commonly used diagnostic modality for AAS therefore is accepted as a gold standard investigation for AAS. D-dimer has a high level of certainty for sensitivity, with consistent results across a large number of diagnostic accuracy studies. However certainty around specificity is low, there is large statistical and clinical heterogeneity in diagnostic accuracy studies. This limits its use in ruling in the diagnosis of AAS.	

Certainty of the evidence of test's effects What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	There is low certainty of level of evidence of D-dimer or CT use in an intermediate pre test probability population. There are no studies looking at the effects of the undesirable effects of CT, One retrospective study that found an incidental finding rate of 16% reported that more patients underwent further imaging but not the full 16%. Evidence of direct benefits of CT Evidence for burden of the test Evidence for adverse effects of the test A single centre retrospective review of all patients undergoing imaging for AAS with a prevalence of 3% found incidental findings requiring further testing in 16% of patients. There was no assessment of time in emergency department. A multi centre prospective observational study using D-dimer in a population with a prevalence of >5% found a false negative rate of 3%.	There a multiple concerns with using D-dimer as an investigation at any risk level. This is based on the potential for false negatives with a delay in presentation, intramural hematomas may not have connection with the circulation and therefore d-dimer will be falsely negative. The panel noted that there is no direct evidence of test effects but some indirect evidence of a high false positive rate with d-dimer testing in a high prevalence population.
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the test results?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Multiple studies looking at the reduction in mortality with surgery for Type A dissections and in type B that require surgical intervention. The evidence for surgical management of type IMH and PAU is unclear. There is weak evidence supporting the effects of medical management of type b aortic dissections.	
Certainty of the evidence of test result/management How certain is the link between test results and management decisions?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	There is moderate level of certainty between diagnosis of AAS and management decisions. This is based on apparent practice variation between centres for the different subtypes of AAS.	The panel noted high certainty in the link between test results and management decisions for Type A aortic dissection. The panel downgraded the judgment from high to moderate as

		there is not as high a certainty for management links with PAU and IMH.

Certainty of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	91% of respondents deemed ruling out AAS(TN) important. 37% deemed the ability to rule in the diagnosis (TP) important. 88% deemed reducing false negatives or missed cases as a priority. 71% deemed priority be to reduce unnecessary imaging or False positives.	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 patient representatives on the panel agreed they reiterated that values are patient dependant, however they believed that there is unlikely to be a significant variation in values across the majority of a patient population.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know		**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. morbidity/mortality from missed diagnosis). The panel noted that for CT aorta, alternate diagnoses may be revealed which would be a desirable effect **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. D-dimer first pathway followed by CT had the most desirable effects, reducing probability of AAS <0.5% and decreasing the overall CT needed and increasing the number of true positives. This was at the expense of an increased false negative rate.

	Pathway	D-dimer	CT	D-dimer then CT
5% PTP				
	TP	47	50	47
	FN	3	0	3
	TN	574	931	943
	FP	376	19	8
	Misdiagnosis (FP+FN/1000)	37.90%	1.90%	1.10%
	Probability of AAS if negative	0.520%	0.000%	0.317%
	Probability of AAS if positive	11.11%	72.46%	85.45%
	Percentage of missed AAS(False negative rate)	6.00%	0.00%	6.00%
	Percentage of tests that will be negative (False positive rate)	88.89%	95 %	14.55%
	Number of CT that would be performed per 1000 patients screened	423	1000	423

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	.Cost of CT vary depending on province. There is limited direct cost to patient in regards either pathway unless transport is needed and indirect costs related to family travelling to the referral centre. However current practice is transfer for imaging in suspected cases.	A dimer first pathway would likely increase use of D-dimer as this is not routinely used in patients with a intermediate probability for the diagnosis.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies		The panel noted that the costs for CT aorta are large, but vary based on setting. This is a system cost and not a patient cost. 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

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○Probably favors the intervention ○ Favors the intervention ○ Varies ●No included studies	There were no cost effectiveness studies for either CT or D-dimer. There was one study assessing cost of screening with either D-dimer or CT aorta for all those admitted to a chest pain monitoring unit for investigation. It found that screening for AAS with either D-dimer or CT aorta would increase costs without any proven impact on morbidity related to AAS and therefore some risk stratification is required(1).	Cost of D-dimer and CT varies by centre and province. The panel discussed that D-dimer cost less than CT, but only if it reduces the number of CT. If a d-dimer first strategy would increase the number of D-dimer tests ordered without decreasing the number of CT then this might have a net increase in costs. Physicians and patients discussed the cost of a missed case of AAS both in morbidity and mortality. An increase in D-dimer use would be cost effective also if it reduced missed cases.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We identified the following regarding the impact on health equity with the different tests: **CT:** 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, whereas less populated provinces were more likely to send samples to centralized analysis facilities for D-dimer testing(2)	**Impact on health equity of diagnostic pathways evaluated** There was no direct evidence to inform the discussion however the panel felt that there are likely to be more centres without CT than access to D-dimer, therefore a d-dimer first pathway is likely to have the least effect on equity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	A survey of 455 ED physicians stated that use of d-dimer for risk stratification would be acceptable to 82.9% of respondents	It was noted by the panel that acceptability to physicians was assessed through a survey but there was no evidence of acceptability of any of the suggested pathways by patients. Patient representatives on the panel discussed

		that values may vary from patient to patient and this may impact on the acceptability of either a d-dimer or CT first pathway.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**General (Radiology & Population):** Feasibility: A retrospective chart review showed that there was substantial variation in utilization and diagnostic yield of advanced radiography for AAD(Ohle 2018) Implementation: A prospective implementation of a diagnostic algorithm which included D-dimer testing at a intermediate probability level showed an increase in D-dimer usage but no increase in number of CT ordered. (Ohle 2018)	The panel noted that in terms of feasibility, some institutions do not offer 24h CT scanning or have access to a CT scanner. Therefore having CT as first line in pathway requires all patients to be transferred. For CT 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 or be transferred to another institution. The panel also noted 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.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		**Varies**	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF THE EVIDENCE OF TEST ACCURACY	Very low	**Low**	Moderate	High			No included studies

	JUDGEMENT						
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	Very low	**Low**	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	Very low	Low	**Moderate**	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT	Very low	Low	**Moderate**	High			No included studies
CERTAINTY OF EFFECTS	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

Recommendation 3a. The panel *suggests* using a strategy starting with D-dimer for excluding AAS in a population with intermediate PTP/prevalence (approximately 0.5-5%), followed by computed tomography (CT) in patients requiring additional testing. If D-dimer is not readily available, an alternate acceptable strategy includes performing CT alone. (*Conditional* recommendation for D-dimer based on *low* certainty in the evidence of effects on clinical outcomes and *moderate* certainty in the evidence about diagnostic accuracy studies; *Conditional* recommendation for CT based on *moderate* certainty in the evidence of effects on clinical outcomes and *moderate* certainty in the evidence from diagnostic accuracy studies).

Remarks:

- There are no prospectively validated clinical decision rules to assess for a PTP of 0.5-5%. Estimates are based on modelling of moderate quality observational studies.
- 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 CT in patients at intermediate PTP for AAS. If the D-dimer strategy is followed, a highly sensitive D-dimer assay is required. A negative D-dimer (i.e., <500mcg/L) rules out AAS and no additional testing is required. D-dimer has limited utility in certain patient populations (e.g., post-surgical or pregnant women) due to the high frequency of positive D-dimer results with standard thresholds.
- D-dimer should be used with caution in those presenting with symptoms for >24 hours as it can be falsely negative.

Justification

Overall justification

Subgroup considerations

n/a

Implementation considerations

Noted importance of promoting alternative diagnosis first strategy.

Monitoring and evaluation

A comprehensive implementation strategy needs to be developed in order to monitor the diagnostic accuracy and uptake of the pathway.

Research priorities

Validating pre test probability assessment

References

1. Moysidis T, Lohmann M, Lutkewitz S, Kemmeries G, Kroger K. Cost associated with D-Dimer screening for acute aortic dissection. Advances in therapy. 2011;28(11):1038-44.
2. Southern DA, Poole J, Patel A, Waters N, Pilote L, Hull RD, et al. Health system capacity and infrastructure for adopting innovations to care for patients with venous thromboembolic disease. Open Medicine. 2014;8(2):e46.

QUESTION In a patient population with a *High* clinical probability of AAS, what is the optimal diagnostic strategy to evaluate for suspected AAS?

What is	
POPULATION:	Patients with a high clinical probability for acute aortic syndrome(AAS)
INTERVENTION:	D-dimer, CT aorta

PURPOSE OF THE TEST:	Diagnosis of AAS
ROLE OF THE TEST:	Diagnosis of AAS
LINKED TREATMENTS:	Appropriate surgical or medical management
ANTICIPATED OUTCOMES:	False Negative; False Positive; True Negative; True Positive
SETTING:	Emergency department
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	
SUBGROUPS:	
CONFLICT OF INTERESTS:	None to declare

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The overall annual incidence of aortic dissection is 3-12 per 100,000. Although 60% of a recent survey respondents had seen a patient in the past year with AAS. Mortality of untreated Type A aortic dissection is 90% at 2 weeks. Miss rate ranges from 16-38%. Mortality increases 1%/hr. Improving time to diagnosis and accuracy of diagnosis is key in reducing the overall morbidity and mortality associated with AAS. Clinicians rate AAS as the number priority in developing a clinical decision aid, in addition 98% of respondents to a national survey of emergency physicians state that we need a clinical decision aid/diagnostic algorithm to aid in the diagnostic dilemma of AAS.	

Test accuracy

How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
CT-Aorta ○ Very inaccurate ○ Inaccurate ○ Accurate	**D-dimer** **Patient or population:** Patients with suspected AAS **New test:** D-dimer **Setting:** Inpatient and outpatient **Pooled sensitivity**: 0.95 (95% CI: 0.90 to 0.99)| **Pooled specificity**: 0.60 (95% CI: 0.48 to 0.71)	

•Very accurate
○ Don't know

D-dimer to rule in AAS
• Very inaccurate
○ Inaccurate
○ Accurate
○ Very accurate
○ Don't know

D-dimer to rule out AAS
○ Very inaccurate
○ Inaccurate
•Accurate
○ Very accurate
○ Don't know

Test result	Number of results per 1,000 patients tested (95% CI)	Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 5% in patients with suspected AAS		
True positives	47 (45 to 50)	3860 (22)	⊕⊕⊕◯ **MODERATE** [a]
False negatives	3 (0 to 5)		
True negatives	574 (461 to 676)	2827 (12)	⊕◯◯◯ **Very Low** [a,b]
False positives	376 (274 to 489)		
Inconclusive test results			-
Complications arising from the diagnostic test	Not reported		

a. The risk of bias was assessed using the QUADAS-2 tool. 19/22 and 11/12 of the included study had at least one domain rated as high risk. There are two other meta analysis that only included 5 of the 22 articles, they performed a QUADAS assessment and found a low or unclear risk of bias in most domains, this led to downgrading the level of certainty.
b. The certainty was downgraded for inconsistency and imprecision of results. The I squared demonstrated significant statistical heterogeneity in the results of specificity between included studies. This is reflected in the specificity ranging from 25 to 95%.

CT
Patient or population: Patients with suspected acute aortic dissection
New test: CT
Setting: Inpatient and outpatient
Pooled sensitivity: 1 (95% CI: 0.92 to 1) | **Pooled specificity**: 0.98 (95% CI: 0.96 to 0.99)

Test result	Number of results per 1,000 patients tested (95% CI)	Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 5% in patients with suspected AAS		
True positives	50 (48 to 50)	3 studies 126 patients	⨁⨁⨁⨁ HIGH
False negatives	0 (0 to 2)		
True negatives	931 (827 to 941)	3 studies 126 patients	⨁⨁⨁⨁ HIGH
False positives	19 (9 to 123)		
Inconclusive test results		4159	-
Complications arising from the diagnostic test	Not reported		

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Pathways at a high pre test probability involve either CT first or D-dimer first strategies. Desirable effects of a D-dimer first strategy involve a reduction in use of CT. Desirable effects of CT first pathway is a reduction in false negative results and reduction in the number of steps in a given pathway and therefore potentially reduction in time to diagnosis. There is no direct evidence substantiating the desired effects of either pathway.	The panel spent time discussing patient versus system desirable effects. From a system point of view if a patient requires transport for CT then less resources would be used in a d-dimer first pathway. Most centres who do not have access to d-dimer testing 24hrs a day will also not have access to CT. From a system point of view D-dimer first strategy may have a larger effect in a setting without access to CT. However from a patient perspective desired effects of either pathway may vary, ie greater weight places on not having to be transferred for a CT/ration exposure, or desire to undergo the gold standard investigation.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Potential undesirable effects are an increased in D-dimer ordering with this pathway and consequently an increase in false positives and an increase in imaging. CT first pathway potential undesirable effects are an increase in CT ordering. In a pilot implementation study-suggesting CT at a high pre test probability did not result in an increase in CT ordering(1). Incidental findings on CT can result in further imaging, increase stress and over testing. A retrospective study looking at all those who underwent CT to rule out AAS found a 16% incidental finding rate(2). A CT first pathway is not expected to increase advanced imaging however there is no direct evidence to dictate the anticipated undesirable effects.	

Certainty of the evidence of test accuracy

What is the overall certainty of the evidence of test accuracy?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
CT ○ Very low ○ Low ● Moderate ○ High ○ No included studies D-dimer ○ Very low ●Low ○ Moderate ○ High ○ No included studies	CT has a high level for certainty of evidence. However this is based on a small number of studies and small number of patients(3). The international registry for acute aortic dissection states that CT is the most commonly used diagnostic modality for AAS therefore is accepted as a gold standard investigation for AAS(4). D-dimer has a high level of certainty for sensitivity, with consistent results across a large number of diagnostic accuracy studies. However certainty around specificity is low, there is a large statistical and clinical heterogeneity in diagnostic accuracy studies. This limits its use in diagnosis of AAS(5-7).	

Certainty of the evidence of test's effects

What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate	There is low certainty of level of evidence of D-dimer or CT use in a high pre test probability population. A multi centre prospective observational study using D-dimer in a population with a prevalence of >5% found a false negative rate of 3%(8). Therefore indirect evidence would suggest a direct benefit of the CT first pathway of reducing false negatives. A single centre	There a multiple concerns with using D-dimer as an investigation at any risk level. This is based on the potential for

○ High ○ No included studies	retrospective review of all patients undergoing imaging for AAS with a prevalence of 3% found incidental findings requiring further testing in 16% of patients, there are no large/long term studies that could comment on direct adverse outcomes of CT ie anaphylaxis or radiation induced carcinoma(2).	false negatives with a delay in presentation, intramural hematomas may not have connection with the circulation and therefore d-dimer will be falsely negative. The panel noted that there is no direct evidence of test effects but some indirect evidence of a high false positive rate with d-dimer testing even in a high prevalence population. Standard of care currently is CT for those at high probability for AAS therefore a CT first pathway should not significantly increase the burden of the test. However currently physicians may actually have a far higher threshold for what constitutes high PTP, therefore defining a high PTP as >5% may increase the number of CT and therefore increase burden of the test.

Certainty of the evidence of management's effects

What is the overall certainty of the evidence of effects of the management that is guided by the test results?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Multiple studies looking at the reduction in mortality with surgery for Type A dissections and in type B that requires surgical intervention. The evidence for surgical management of type IMH and PAU is unclear. Medical management of type b aortic dissections there is weak evidence to support heart rate and blood pressure control(4, 9).	

Certainty of the evidence of test result/management

How certain is the link between test results and management decisions?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High	There is moderate level of certainty between diagnosis of AAS and management decisions. This is based on apparent practice variation between centres for the different subtypes of AAS(4, 9).	The panel noted high certainty in the link between test results and management decisions for Type A and Type B aortic dissection. However, the

○ No included studies		panel also noted that for patients with IMH or PAU the link may not be as certain.

Certainty of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies		The effects of the test

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	91% of respondents deemed ruling out AAS(TN) important. 37% deemed the ability to rule in the diagnosis (TP) important. 88% deemed reducing false negatives or missed cases as a priority. 71% deemed priority be to reduce unnecessary imaging or False positives.	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.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● **Probably favors the intervention** ○ Favors the intervention ○ Varies	5% PTP **Pathway** / D-dimer / CT **TP** 47 50 **FN** 3 0 **TN** 574 931 **FP** 376 19	**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

○ Don't know			

Misdiagnosis(FP+FN/1000)	37.90%	1.90%
Probability of AAS if negative	0.520%	0.000%
Probability of AAS if positive	11.11%	72.46%
Percentage of missed AAS(False negative rate)	6.00%	0.00%
Percentage of CT that will be negative (False positive rate)	88.89%	95 %
Number of CT that would be performed per 1000 patients screened	423	1000

TP-patient correctly identified as having AAS
FP-patient incorrectly identified as having AAS
TN- patient correctly identified as not having AAS
FN - patient incorrectly identified as not having AAS

Assumptions associated with modelling:
1. Disease prevalence in a HIGH clinical probability population was determined be greater than 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 and red being unacceptable.

results (i.e. morbidity/mortality from missed diagnosis).
The panel noted that for CT aorta, alternate diagnoses may be revealed which would be a desirable effect

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.

The CT first pathway had the most desirable balance of effects however this does not take into account effects of the need to transfer a patient for investigation. In limited resource environment where transfer depletes resources to a potentially unsafe level for the remainder of patients in an emergency department their may be a role for shared decision making on an individual patient basis.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	There is no direct evidence for resources required. Cost of CT vary depending on province. There is limited direct cost to patient in regards either pathway unless transport is needed and indirect costs related to family travelling to the referral centre. However current practice is transfer for imaging in suspected cases.	A D-dimer first pathway would likely increase use of D-dimer as this is not routinely used in patients with a high probability for the diagnosis.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	CT or a D-dimer first strategy could potentially increase resources in lower use areas, possibly no impact on high use areas ie in emergency departments with a high rate of advanced imaging or d-dimer use. A D-dimer first strategy could reduce imaging if implemented in a high use area. There is no direct evidence on resources required	The panel noted uncertainty in the actual costs of the tests.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	There was only one study assessing cost of screening with either D-dimer or CT aorta for all those admitted to a chest pain monitoring unit for investigation. It found that screening for AAS with either D-dimer or CT aorta would increase costs without any proven impact on morbidity related to AAS(10).	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We identified the following regarding the impact on health equity with the different tests: **CTA:** 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, whereas less populated provinces were more likely to send samples to centralized analysis facilities for D-dimer testing(11)	**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.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	A survey of 455 ED physicians stated a rule incorporating a pretest probability assessment would be acceptable . The same survey found that a miss rate of <1% was acceptable and therefore if probability is below this then a pathway suggesting no further testing would likely be acceptable.	It was noted by the panel that acceptability to physicians was assessed through a survey but there was no evidence of acceptability of any of the suggested pathways by patients. Patient representatives on the panel felt CT first in a high PTP population was more acceptable than D-dimer given its limitations..

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**General (Radiology & Population):** Feasibility: A retrospective chart review showed that there was substantial variation in utilization and diagnostic yield of advanced radiography for AAS(2). Implementation: A prospective implementation of a diagnostic algorithm which suggested CT for those with a high PTP of >5% showed an increase in uptake with an education intervention involving an educational video, posters, website/calculator(1).	The panel noted that in terms of feasibility, some institutions do not offer 24h CT scanning or have access to a CT scanner. Therefore having CT as first line in pathway requires all patients to be transferred. For CT 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 or be transferred to another institution. The panel also noted 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.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		**Varies**	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF THE EVIDENCE OF TEST ACCURACY	Very low	**Low**	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	Very low	**Low**	Moderate	High			No included studies

	JUDGEMENT						
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	Very low	Low	**Moderate**	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT	Very low	Low	**Moderate**	High			No included studies
CERTAINTY OF EFFECTS	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	○	●

CONCLUSIONS

Recommendation

Recommendation 4a. The panel *recommends* using a strategy starting with ECG-gated CT for assessing patients suspected of having AAS in a population with high PTP/prevalence ≥5%. (*Strong* recommendation for CT based on *moderate* certainty in the evidence of effects on clinical outcomes and *moderate* certainty in the evidence of diagnostic accuracy studies).

Technical remarks:

- *There are no prospectively validated clinical decision rules to assess for a pre test probability of >5%. Estimates are based on modelling of low/moderate quality observational studies.*
- *CT should always be performed with ECG gating unless gating technology is not available.*
- *The strategy assumes that test results are obtained under optimal conditions. Suboptimal CT results, due to improper technique (no gating, only unenhanced study or venous phase scanning), may require repeat testing.*
- *If CT is not feasible (e.g., contrast media allergy, severe renal impairment, or unavailability), magnetic resonance imaging (MRI) or transesophageal echocardiography (TEE) may be acceptable.*
- *In cases where clinical suspicion for AAS remains high with a negative initial CT, repeat ECG gated CT should be considered. If repeat CT with proper technique is not feasible, additional testing with TEE or MRI may be considered.*

Recommendation 4b. The panel *suggests* not using a D-dimer in a population with high PTP/prevalence ≥5%. (*Conditional* recommendation against D-dimer based on *low* certainty in the evidence of effects on clinical outcomes and *moderate* certainty in the evidence of diagnostic accuracy studies).

Justification

Overall justification

The panel recommends starting with an ECG gated CT. The panel recognised the evidence of effects or certainty are low. The original recommendation was for a conditional recommendation for a CT first pathway, however the feedback after the draft document was disseminated for external review by over 300 emergency physicians, surgeons and radiologists was that a strong recommendation was more acceptable.

Subgroup considerations

n/a

Implementation considerations

Noted importance of promoting alternative diagnosis first strategy.

Monitoring and evaluation

A comprehensive implementation strategy needs to be developed in order to monitor the diagnostic accuracy and uptake of the pathway.

Research priorities

Validating pre test probability assessment

References

1. Ohle R, Fortino N, Montpellier O, Ludgate M, McIsaac S, Bota G**.** P096: Prospective pilot implementation of a clinical decision aid for acute aortic syndrome. Canadian Journal of Emergency Medicine. 2019;21(S1):S98-S.
2. Ohle R, Anjum O, Bleeker H, Wells G, Perry JJ**.** Variation in emergency department use of computed tomography for investigation of acute aortic dissection. Emergency radiology. 2018:1-6.
3. Shiga T, Wajima Zi, Apfel CC, Inoue T, Ohe Y**.** Diagnostic accuracy of transesophageal echocardiography, helical computed tomography, and magnetic resonance imaging for suspected thoracic aortic dissection: systematic review and meta-analysis. Archives of internal medicine. 2006;166(13):1350-6.
4. Evangelista A, Isselbacher EM, Bossone E, Gleason TG, Eusanio MD, Sechtem U, et al. Insights from the International Registry of Acute Aortic Dissection: a 20-year experience of collaborative clinical research. Circulation. 2018;137(17):1846-60.
5. Asha SE, Miers JW**.** A Systematic Review and Meta-analysis of D-dimer as a Rule-out Test for Suspected Acute Aortic Dissection. Annals of emergency medicine. 2015;66(4):368-78.
6. Fan Qk, Wang Ww, Zhang Zl, Liu Zj, Yang J, Zhao Gs, et al. Evaluation of D-dimer in the diagnosis of suspected aortic dissection. Clinical chemistry and laboratory medicine : CCLM / FESCC. 2010;48(12):1733-7.
7. Watanabe H, Horita N, Shibata Y, Minegishi S, Ota E, Kaneko T**.** Diagnostic test accuracy of D-dimer for acute aortic syndrome: systematic review and meta-analysis of 22 studies with 5000 subjects. Scientific reports. 2016;6:26893.

8. Nazerian P, Mueller C, de Matos Soeiro A, Leidel BA, Salvadeo SAT, Giachino F, et al. Diagnostic accuracy of the aortic dissection detection risk score plus D-dimer for acute aortic syndromes: the ADvISED Prospective Multicenter Study. Circulation. 2017:CIRCULATIONAHA. 117.029457.
9. Pape LA, Awais M, Woznicki EM, Suzuki T, Trimarchi S, Evangelista A, et al. Presentation, diagnosis, and outcomes of acute aortic dissection: 17-year trends from the International Registry of Acute Aortic Dissection. Journal of the American College of Cardiology. 2015;66(4):350-8.
10. Moysidis T, Lohmann M, Lutkewitz S, Kemmeries G, Kroger K**.** Cost associated with D-Dimer screening for acute aortic dissection. Advances in therapy. 2011;28(11):1038-44.
11. Southern DA, Poole J, Patel A, Waters N, Pilote L, Hull RD, et al. Health system capacity and infrastructure for adopting innovations to care for patients with venous thromboembolic disease. Open Medicine. 2014;8(2):e46.