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Synopsis

Diagnostic strategies for suspected acute aortic syndrome: systematic review, meta-analysis, decision-analytic modelling and value of information analysis

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Abstract

Background: Acute aortic syndrome is a life-threatening condition that requires urgent diagnosis with computed tomographic angiography. Diagnostic technologies, including clinical scores and biomarkers, can be used to select patients presenting with potential symptoms of acute aortic syndrome for computed tomographic angiography.

Objectives: We aimed to estimate the accuracy of clinical scores and biomarkers for diagnosing acute aortic syndrome, the cost-effectiveness of alternative diagnostic strategies and the expected value of future research.

Methods: We searched online databases from inception to February 2024, reference lists of included studies and existing systematic reviews. We included cohort studies evaluating the accuracy of clinical scores or biomarkers for diagnosing acute aortic syndrome compared with a reference standard. Two authors independently selected and extracted data. Risk of bias was appraised using the quality assessment of diagnostic accuracy studies-2 tool. Data were synthesised using either a multinomial or a bivariate normal meta-analysis model.

We developed a decision-analytic model to simulate the management of a hypothetical cohort of patients attending hospital with possible acute aortic syndrome. We modelled diagnostic strategies that used the Aortic Dissection Detection Risk Score and D-dimer to select patients for computed tomographic angiography. We used estimates from our meta-analysis, existing literature and clinical experts to model the consequences of diagnostic strategies upon survival, health utility and healthcare costs. We estimated the incremental cost per quality-adjusted life-year gained by each strategy compared to the next most effective alternative on the efficiency frontier, and the expected value of perfect information.

Results: Primary meta-analysis included 12 studies of Aortic Dissection Detection Risk Score alone, 6 studies of Aortic Dissection Detection Risk Score with D-dimer and 18 studies of D-dimer using the 500 ng/ml threshold. Sensitivities and specificities (95% credible intervals) were: Aortic Dissection Detection Risk Score > 0 94.6% (90% to 97.5%) and 34.7% (20.7% to 51.2%), Aortic Dissection Detection Risk Score > 1 43.4% (31.2% to 57.1%) and 89.3% (80.4% to 94.8%); Aortic Dissection Detection Risk Score > 0 or D-dimer > 500 ng/ml 99.8% (98.7% to 100%)

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and 21.8% (12.1% to 32.6%); Aortic Dissection Detection Risk Score > 1 or D-dimer > 500 ng/ml 98.3% (94.9% to 99.5%) and 51.4% (38.7% to 64.1%); Aortic Dissection Detection Risk Score > 1 or Aortic Dissection Detection Risk Score = 1 with D-dimer > 500 ng/ml 93.1% (87.1% to 96.3%) and 67.1% (54.4% to 77.7%); and D-dimer alone 96.5% (94.8% to 98%) and 56.2% (48.3% to 63.9%). We identified 11 cohort studies of other biomarkers, but accuracy estimates were limited and inconsistent.
Decision-analytic modelling showed that applying diagnostic strategies to an unselected population (acute aortic syndrome prevalence 0.26%) resulted in high rates of computed tomographic angiography, and only the strategy selecting patients with Aortic Dissection Detection Risk Score > 1 for computed tomographic angiography was cost-effective. If clinicians can select a population for investigation with higher acute aortic syndrome prevalence (0.61%), then using a strategy of Aortic Dissection Detection Risk Score > 1 or Aortic Dissection Detection Risk Score = 1 with D-dimer > 500 ng/ml or a strategy of Aortic Dissection Detection Risk Score > 1 or D-dimer > 500 ng/ml to select patients for computed tomographic angiography is cost-effective and deliverable. At a threshold of £20,000/quality-adjusted life-year, population expected value of perfect information was around £17.75M.
Limitations: Studies included in the meta-analysis showed substantial heterogeneity in estimates of specificity. In the modelling, there was substantial uncertainty around what constitutes suspected acute aortic syndrome and the effect of delayed diagnosis.
Conclusions: The Aortic Dissection Detection Risk Score and D-dimer provide useful diagnostic information and may offer cost-effective strategies for selecting patients for computed tomographic angiography, but their role depends upon how clinicians identify suspected acute aortic syndrome.
Future work: Primary research is required to compare different combinations of Aortic Dissection Detection Risk Score with D-dimer in practice, explore how suspected acute aortic syndrome is identified and evaluate alternative biomarkers.
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Introduction

Rationale for research and background

Acute aortic syndrome (AAS) is a life-threatening emergency condition affecting the thoracic aorta. The 'syndrome' is an umbrella term for acute aortic dissection (including type A, involving the ascending aorta; and type B, limited to the descending aorta), intramural haematoma and penetrating ulcer. Without treatment, AAS can progress to aortic rupture, with rapid deterioration and death.

Chest pain is the most common presenting symptom of AAS (80%), although back pain (40%) and abdominal pain often occur.[5] These symptoms account for over 2 million emergency department (ED) attendances per year in England[6] and are overwhelmingly due to causes other than AAS. The incidence of AAS has been estimated as one in every 980 ED attendances with atraumatic chest pain,[7] thus creating a substantial diagnostic challenge.

Computed tomographic angiography (CTA) scanning of the aorta has high sensitivity and specificity for diagnosing AAS but incurs significant costs and risks of ionising radiation. Clinicians therefore need to use CTA selectively in patients presenting to the ED with symptoms that could be due to AAS. Imaging techniques other than CTA, such as electrocardiogram (ECG)-gated CTA, echocardiography and magnetic resonance angiography, can accurately diagnose AAS,[8] but these also require careful patient selection. Our analysis focuses on CTA as the imaging modality recommended in UK and international guidelines.[5,9–11]

Patients with successful treatment for AAS can have good life expectancy and return to full health, while misdiagnosis can lead to avoidable death. Around 25% of patients with AAS are not diagnosed with the condition until 24 hours after presenting to the ED,[12] and the misdiagnosis rate during the initial ED visit for AAS is estimated to be as high as 38%.[13] Optimal patient selection for urgent CTA is challenging with misdiagnosis affecting between one in three and one in seven patients with AAS,[14,15] leading to worse outcomes, while CTA overtesting leads to diagnostic yields of 2–3%.[12,16]

Clinical scores and biomarkers can be used to select patients with suspected AAS for CTA. The Aortic Dissection Detection Risk Score (ADD-RS) uses information on high-risk conditions (such as Marfan syndrome or known aortic disease), pain features (abrupt onset, severe intensity or ripping/tearing) or examination features (perfusion deficit, new aortic insufficiency murmur or hypotension/shock) to identify patients at risk of AAS.[17] The Canadian clinical practice guideline uses a clinical decision aid to stratify patients into low, moderate and high risk of AAS.[9] The AORTA score uses six clinical features to stratify patients to low or high risk.[18] D-dimer is the most extensively studied biomarker for AAS.[19] A low D-dimer level in a patient with a low clinical probability of AAS could rule out AAS.[20]

Current guidelines reflect the uncertainty in the existing evidence.[10] Canadian Heart Association, American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines all recommend estimating clinical probability of AAS, but there are inconsistencies in the clinical features used. All recommend CTA for high-risk patients but provide different recommendations for low- and intermediate-risk patients. The Canadian guidelines recommend D-dimer for intermediate-risk patients,[9] ESC guidelines recommend D-dimer for low-risk patients[5] and AHA guidelines do not identify a role for D-dimer.[21] Best Practice Guidance from the Royal College of Emergency Medicine (RCEM) and Royal College of Radiologists (RCR) recommend CTA if any high-risk clinical features are present and further research to determine the role of D-dimer in suspected AAS.[11]

Objectives

We aimed to identify an optimal diagnostic strategy for suspected AAS and measure the expected value of information from future primary research. Our specific objectives were:

1. To estimate the accuracy of clinical scores, models or algorithms, and/or biomarkers (including D-dimer) for diagnosing AAS.
2. To estimate the effectiveness [in terms of quality-adjusted life-year (QALY) gained], cost-effectiveness (in terms of net benefit and incremental cost per QALY gained) and practical implications (in terms of the burden of radiological investigations) of using alternative diagnostic strategies for AAS.
3. To estimate the expected value of perfect information (EVPI) to highlight the amount healthcare decision-makers could spend on future primary research to reduce the uncertainty in diagnostic strategies for AAS.

Methods for data collection and analysis

We undertook a systematic review, meta-analysis, decision analysis modelling and value of information analysis. The systematic review identified studies of index tests evaluating the accuracy of clinical scores, models, algorithms or biomarkers for a reference standard diagnosis of AAS in patients attending the ED with symptoms suggesting AAS (new-onset chest, back, or abdominal pain, syncope or symptoms related to perfusion deficit). Meta-analysis was used to generate summary estimates of accuracy for AAS for index tests evaluated with sufficient data of acceptable quality. We then developed a decision-analytic model to estimate the cost-effectiveness and practical implications of using alternative diagnostic strategies based on index tests identified in the systematic review to select patients with suspected AAS for CTA. The model was also used to estimate the EVPI associated with future research into diagnostic strategies for suspected AAS.

Full details of our methods and findings have been published.[1–4] This synopsis provides an overview of the methods and results.

Systematic review and meta-analysis

We undertook a systematic review to identify studies estimating the diagnostic accuracy of clinical scores and biomarkers for detecting AAS. The systematic review was undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[22] the guidelines published by Cochrane Screening and Diagnostic Test Methods Group[23] and was prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42022252121).

We identified potentially relevant studies through electronic searches of key electronic databases, including MEDLINE (OvidSP from 1946), EMBASE (OvidSP from 1974) and the Cochrane Library (www.cochranelibrary.com). All database searches were conducted from inception to February 2024. Searches were supplemented by hand-searching the reference lists of all relevant studies (including existing systematic reviews), forward citation searching of relevant articles, contacting key experts in the field (including professional and academic research groups) and undertaking targeted searches of the World Wide Web using the Google (Google Inc., Mountain View, CA, USA) search engine. No date or language restrictions were applied on any database.

We included all cohort studies that evaluated the diagnostic accuracy of clinical scores (including models

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and algorithms), and biomarkers against a reference standard for AAS in a population with suspected AAS. The reference standard used a definitive imaging modality (CTA, ECG-gated CTA, echocardiography or magnetic resonance angiography), operation or autopsy to confirm AAS. Studies including people with AAS following major trauma or as incidental findings were excluded. Studies using a case-control design (i.e. studies in which patients were selected on the basis of the results of their reference standard test) were also excluded due to the potential for design-related bias which tend to lead to overestimation of diagnostic accuracy[24,25] and are not generally representative of a test's accuracy in a clinical setting[24,25] (a post hoc change – for further details, see *Changes from the proposed project*).

Potentially relevant articles were selected using a two-step process. (1) One reviewer examined all titles and excluded any citations that clearly did not meet the inclusion criteria (i.e. non-human, unrelated to AAS). (2) All abstracts and full-text articles were then examined independently by a minimum of two reviewers. Any disagreements in the selection process were resolved through discussion or, if necessary, arbitration by a third reviewer and included by consensus. Data were extracted by one reviewer and independently checked for accuracy by a second. Where we identified multiple publications of the same study, we extracted and reported data as a single study, seeking clarification from the study authors where appropriate. We assessed the methodological quality of each included study using the quality assessment of diagnostic accuracy studies-2 (QUADAS-2) tool.[26]

We planned to undertake meta-analysis of studies evaluating the diagnostic accuracy of clinical scores and biomarkers (e.g. the ADD-RS alone, D-dimer alone and the ADD-RS in combination with D-dimer) and to present descriptive results for any index tests with insufficient data for meta-analysis. In each meta-analysis of tests using a single threshold, the diagnostic test data were analysed using a bivariate hierarchical model,[27] where, at a lower level, sensitivities and specificities of each study are modelled using binomial distributions and, at a higher level, logit-transformed sensitivities and specificities are modelled using a normal distribution to allow for possible (negative) correlation, as suggested in Deeks *et al.*[23] For multiple threshold, we estimated the accuracy of the ADD-RS at thresholds of > 0 point and > 1 point using a multinomial meta-analysis model of Jones *et al.*[28] As heterogeneity between studies was generally expected in studies of diagnostic test accuracy, a random-effects model was used to allow for the heterogeneity beyond chance between studies. Model descriptions and prior specifications can be found in *Appendix 1*.

All the analyses were conducted using a Bayesian framework via Markov chain Monte Carlo simulation and implemented in the R software (R Foundation, Vienna, Austria) environment using JAGs and rjags package.[29] Different options of prior distributions were explored. Convergence to the target posterior distributions was assessed using the Gelman–Rubin convergence statistic.[30] A total of 1,000,000 iterations with a burn-in of 100,000 and thinning of 10 were used to estimate the model parameters. Results were presented as forest plots and receiver operating characteristic (ROC) plots of sensitivity versus 1 – specificity. Estimates of sensitivity and specificity with 95% credible intervals (CrIs, also known as Bayesian confidence intervals) were plotted individually against each threshold to illustrate the variations among the synthesised studies. Ninety-five per cent prediction intervals (PrIs) were also reported, illustrating the between-study heterogeneity and a range of values that might be expected in a future study.

We estimated the accuracy of D-dimer at the 500 ng/ml threshold, where this was reported. We also undertook a sensitivity analysis of D-dimer that also included studies that did not report the 500 ng/ml threshold, using the threshold reported in the study that was closest to 500 ng/ml. Moreover, we identified six studies[18,31–35] that reported the accuracy of the ADD-RS and D-dimer. We contacted the authors who agreed to share data to allow analysis of multiple alternative combinations of ADD-RS with D-dimer. We selected combinations for analysis that have previously been reported as potential strategies for selecting patients with suspected AAS for computed tomography (CT) scanning. This resulted in the analysis of the following index tests: ADD-RS > 0; ADD-RS > 1; ADD-RS > 0 or D-dimer > 500 ng/ml; ADD-RS > 1 or D-dimer > 500 ng/ml; and a strategy combining the ADD-RS with D-dimer based on the Canadian guideline (ADD-RS > 1 or ADD-RS = 1 with D-dimer > 500 ng/ml). We also performed sensitivity analysis for ADD-RS > 0 and ADD-RS > 1 limited to studies that also evaluated D-dimer to assess the impact of study selection.

We were unable to perform meta-analysis of biomarkers other than D-dimer due to the limited number of studies per biomarker and variable reporting of items. As a result, a narrative synthesis approach was undertaken, with data

being summarised in tables with accompanying narrative summaries that included a description of the included variables, statistical methods and performance measures (e.g. sensitivity, specificity).[36,37]

Decision-analytic modelling

We developed a decision analysis model in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) that applied diagnostic strategies to a hypothetical population of 1000 patients attending hospital with symptoms suggesting AAS. Cost-effectiveness of the diagnostic strategies, measured as the incremental cost per QALY gained by each strategy compared with the next most effective alternative, was estimated using a lifetime horizon and NHS healthcare perspective. Probabilistic analysis incorporated uncertainty in the parameter estimates to provide more robust estimates of the mean costs and QALYs.

The structure of the model is shown in *Figure 1*. Each diagnostic strategy is applied to the patient cohort to determine the proportions classified as true positive (TP), false positive (FP), true negative (TN) or false negative (FN), depending upon the prevalence of AAS and sensitivity or specificity of the diagnostic strategy. We assume that true and FNs would not receive further testing for AAS, while true and FPs would receive confirmatory testing using CTA as the reference standard for AAS (with TPs receiving treatment for AAS).

Tables 1 and *2* show the parameters used in the model. The prevalence of AAS was estimated from the Diagnosis of Acute Aortic Syndrome in the Emergency Department (DAShED) study,[33] and the mean age of the patients, the proportion of type A and type B AAS and the proportion of males were estimated from the International Registry of Acute Aortic Dissection (IRAD).[38] We assume that the population excludes patients whose frailty and/or comorbidities preclude surgery or thoracic endovascular aortic repair (TEVAR), because this would substantially increase the complexity of the model and reduce applicability to the population most likely to benefit from investigation for AAS. The base-case analysis used the estimate of AAS prevalence from the total DAShED population presenting with any possible symptoms of AAS (0.26%). Secondary analyses used AAS prevalence estimates for populations in the DAShED study selected on the basis of clinician estimates of AAS likelihood being greater than zero, > 1/10 and > 2/10 (0.61%, 1.0% and 1.74%, respectively) and the population in the DAShED study who received CTA (2.95%). The QALYs for those without AAS are estimated based on life expectancy of general population from the Office of National Statistics, and the general population utilities estimated from Ara *et al.*[49]

We evaluated strategies that use ADD-RS and/or D-dimer to select patients for CTA, including strategies recommended in guidelines. Current UK guidance

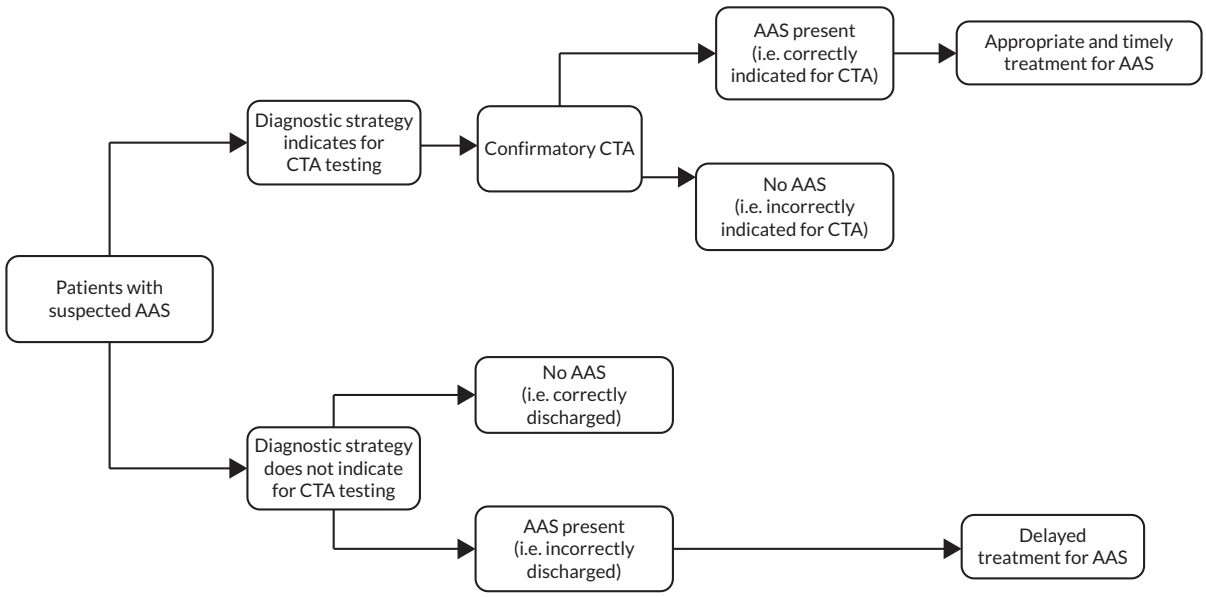

FIGURE 1 Structure of the decision-analytic model. Reproduced from Thokala *et al.*[3] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

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TABLE 1 Prevalence of AAS and diagnostic accuracy and costs of the strategies tested in the model

Parameter	Value	Distribution	Source
Epidemiology			
Prevalence of AAS:			
Primary analysis	0.26%	Beta (14, 5339)	DAShED study[33]
Secondary (AAS likelihood > 0)	0.61%		
Secondary (AAS likelihood > 1/10)	1.0%		
Secondary (AAS likelihood > 2/10)	1.74%		
Secondary (currently receive CTA)	2.95%		
Proportion of type A patients	66.67%	Beta (2952, 1476)	IRAD[38]
Proportion of type B patients	33.33%	Beta (1476, 2952)	IRAD[38]
Proportion male	66.93%	Beta (2964, 1464)	IRAD[38]
Diagnostic accuracy and costs of the strategies tested in the model[a]			
	Sensitivity	**Specificity**	**Cost**
ADD-RS > 1	41.6 (24.8 to 59.1)	91.7 (81.7 to 97)	£3.77
Modified Canadian guidelines (ADD-RS > 1 or if ADD-RS = 1 and D-dimer > 500 ng/l)	93.1 (87.1 to 96.3)	67.1 (54.4 to 77.7)	£7.69
ADD-RS > 0	95.1 (88.5 to 98.4)	38 (20.1 to 59.1)	£3.77
D-dimer > 500 ng/ml	96.4 (94.9 to 97.7)	56.6 (49.5 to 63.4)	£7.30
ADD-RS > 1 or D-dimer > 500 ng/ml	98.3 (94.9 to 99.5)	51.4 (38.7 to 64.1)	£10.46
ADD-RS > 0 or D-dimer > 500 ng/ml	99.8 (98.7 to 100)	21.8 (12.1 to 32.6)	£6.54

a Estimated from meta-analysis.

recommends CTA for any patient who has risk features for AAS, which is similar to the ADD-RS > 0 strategy. Sensitivity and specificity of the diagnostic strategies were estimated by meta-analysis of diagnostic cohort studies. We also tested two hypothetical diagnostic strategies in the model: no investigation for AAS (0% sensitivity, 100% specificity) and CTA for all (100% sensitivity, 0% specificity). The costs of applying each strategy were estimated assuming 2 minutes of consultant time to calculate the ADD-RS and a reference cost for D-dimer.

We assumed that the diagnostic strategy only influenced outcomes among patients with AAS. Patients with TP type A AAS received surgical treatment, with 80% survival at 2 months estimated from IRAD data,[38] while FN patients were assumed to die or have delayed treatment, with 50% survival at 2 months estimated from studies by Matthews *et al.*[39] and Pourafkari *et al.*[40] Patients with TP type B AAS received TEVAR (10%) or medical management (90%) with overall survival of 87.4% at 2 months estimated from IRAD data,[38] while FN patients did not benefit from blood pressure control, resulting in 74.8% survival at 2 months, based on the relative risk for blood pressure control.[50] The estimated annual mortality risk was 2.5% for type A AAS patients,[38] 5.5% for type B patients managed medically and 3.8% for those receiving TEVAR, based on data from Sa *et al.*[41]

The model included costs of diagnostic strategies, CTA, CT for incidental findings, treatment for AAS, costs of death in ED and long-term costs associated with AAS management. The costs of CTA, open repair and TEVAR were estimated from the NHS reference costs,[46] while the costs of medical management for type B AAS were estimated using expert clinical opinion. The annual costs assumed to be the same for all AAS survivors.

TABLE 2 Mortality, cost and utility data used in the model

Parameter	Value	Distribution	Source
Short-term survival of type A patients			
Patients identified and treated surgically	80% at 2 months	Normal (0.8, 0.08)	IRAD[38]
Misdiagnosed type A patients	50% at 2 months	Normal (0.5, 0.05)	Matthews *et al.*[39] and Pourafkari *et al.*[40]
Short-term survival of type B patients			
Type B patients identified promptly	87.4% at 2 months	Normal (0.87, 0.087)	Calculations
Misdiagnosed type B patients	74.8% at 6 months	Normal (0.748, 0.0748)	Calculations
Annual mortality risk of survivors			
Annual mortality risk of type A patients	2.5%	Normal (0.025, 0.0025)	IRAD[38]
Annual mortality risk of type B patients managed medically	5.5%	Normal (0.055, 0.0055)	Sa *et al.*[41]
Annual mortality risk of type B patients receiving TEVAR	3.8%	Normal (0.038, 0.0038)	Sa *et al.*[41]
Annual probability of reintervention			
Type A patients	0.77%	Beta (97, 2413)	Isselbacher *et al.* 2016[42]
Type B patients	1.62%	Beta (101, 1211)	Isselbacher *et al.* 2016[42]
Utilities			
Type A patients	0.792	Normal (0.792, 0.04)	Bojko *et al.*,[43] Ara *et al.*[44]
Type B patients medically managed	0.783	Normal (0.783, 0.039)	Meccanici *et al.* 2023,[45] Ara *et al.*[44]
Type B patients receiving TEVAR	0.862	Normal (0.862, 0.043)	Meccanici *et al.* 2023,[45] Ara *et al.*[44]
Costs			
Cost of CTA	£154.5	Normal (154.5, 15.45)	NHS reference costs[46]
Cost of CT for incidental findings	£117	Normal (117, 11.70)	NHS reference costs[46]
Cost of D-dimer	£7.30	Normal (7.30, 0.73)	Cost of lab test (£6.79 in 2020 costs)
Cost of ADD-RS	£3.77	Normal (3.77, 0.377)	2 minutes of consultant time
Costs of open repair	£34,553	Normal (34,553, 3455)	NHS reference costs[46]
Cost of TEVAR	£13,973	Normal (13,973, 1397)	NHS reference costs[46]
Costs of medical management for type B patients (first year)	£4887.70	Normal (4887.7, 488.70)	NHS reference costs[46]
Annual costs for AAS survivors who received TEVAR or medical management	£411.20	Normal (411.2, 41.12)	NHS reference costs[46]
Annual costs of AAS survivors who received open surgery	£517.78	Normal (517.78, 51.78)	NHS reference costs[46]
Costs of ED death	£885.27	Normal (885.27, 88.52)	NHS reference costs[46]
Cancer due to CTA			
Risk of cancer due to CTA	0.15%	Normal (0.0015, 0.00015)	Huang *et al.*[47]
Costs of cancer[a]	£18,248.57	Normal (18,248.57, 1824.86)	Goodacre *et al.*[48]
QALY loss due to cancer[a]	−0.12	−Normal (0.12, 0.006)	Goodacre *et al.*[48]

a Applied at 12 years, that is, mid-point of life expectancy.

In the long term, all survivors had an annual probability of reintervention which was estimated based on IRAD data,[38] and it was assumed that all reinterventions are TEVAR. The model also included a small risk of cancer associated with CTA based on the study by Huang *et al.*,[47] and modelled the impact of cancer as one-off lifetime cost and QALY loss estimated from Goodacre *et al.*,[48] at the mid-point of life expectancy estimated from UK life tables.

The utilities for patients with AAS were sourced from studies identified in the recent systematic review by Carbone *et al.*[51]

Results summary

Systematic review

Figure 2 shows the PRISMA flow chart for the systematic review. We screened 2017 titles, 767 abstracts and 117 full-text articles, and included 39 studies in the review: 13 studies of the ADD-RS,[18,31–35,52–58] 25 studies of D-dimer,[18,31–35,54,59–76] 13 studies of other biomarkers[52,63,68,69,73,76–83] and 3 studies of other clinical scores[18,33,84] (several studies evaluated more than one index test).

Studies of Aortic Dissection Detection Risk Score alone and in combination with D-dimer

We included 13 studies[18,31–35,52–58] investigating ADD-RS alone or ADD-RS in combination with D-dimer. Of these, 12 studies[18,31–33,35,53–58] contributed to the meta-analysis for ADD-RS alone (one reported the same data as another included study) and 6 studies[18,31–35] contributed to the meta-analysis for ADD-RS in combination with D-dimer (sample size $N = 162$ to $N = 22{,}075$, prevalence of AAS 0.26–64%). The range of prevalence across the studies reflects variation in patient selection. Studies that used clinical presentation (e.g. symptoms suggesting AAS) to select patients tended to have lower prevalence than those that selected patients who received imaging for AAS. The methodological quality of the included studies was variable, with most studies having low or unclear risk of bias and applicability concerns in at least one item of the QUADAS-2 tool (see *Figure 3*). The proportion of patients receiving reference standard imaging varied between studies.

Figure 4 shows the summary plots for ADD-RS alone in panels A and B, and the summary plots for ADD-RS with D-dimer in panels C and D. Individual sensitivity and specificity from the same study are linked with lines. In panels A and C, ROC plots are displayed. In panels B and D, pooled sensitivity and specificity, along with the 95% CrI and 95% PrI, are plotted. The 95% CrI are marked by the shaded areas around the summary estimates, showing the range of likely values for average diagnostic accuracy. The 95% PrI are marked by the wider and lighter-shaded areas around the summary estimates, indicating a range of values that might be expected in a future study. *Figure 5* shows the pooled estimates and 95% CrI for each strategy. Details on the exploration of different prior distributions can be found in *Appendix 1*.

Table 3 shows the results of meta-analysis, each with a 95% CrI and PrI. ADD-RS > 0 has high sensitivity and low specificity, while ADD-RS > 1 has low sensitivity and high specificity. Combinations of ADD-RS with D-dimer provide a range of trade-offs between sensitivity and specificity. There is a large amount of heterogeneity between studies, as illustrated by the wide 95% PrI. A sensitivity analysis of ADD-RS > 0 and ADD-RS > 1 limited to the six studies that also evaluated D-dimer showed very similar estimates to the base-case analysis with 10 studies.

Studies of D-dimer

We included 25 studies of D-dimer[18,31–35,54,59–76] (sample size $N = 41$ to $N = 1848$, prevalence of AAS 0.9% to 64.8%). The methodological quality of the included studies was variable, with most studies having low or unclear risk of bias and applicability concerns in at least one item of the QUADAS-2 tool (see *Figure 6*). The diagnostic threshold was pre-specified, apart from the studies of Fan *et al.*,[62] Peng *et al.*[69] and Zhang *et al.*,[76] where they were determined from the study data, and thus had an uncertain risk of bias in quality assessment. A D-dimer threshold of 500 ng/ml was reported in 17 studies,[18,31–35,59,63–68,71–74] and the threshold of 490 ng/ml reported by Fan *et al.*[62] was considered equivalent to 500 ng/ml, so 18 studies[18,31–35,59,62–68,71–74] were included in the base-case analysis and 25 studies[18,31–35,54,59–76] in the sensitivity analysis.

Figure 7 shows the forest plot and *Figure 8* shows the summary plot for the 18 studies reporting data for the 500 ng/ml threshold. *Table 4* shows the summary estimates for the base-case meta-analysis and the sensitivity analysis. The wide PrI, especially for summary specificity, reflects substantial heterogeneity in the results from individual studies. Specificity varied markedly from 33%[63] to 86%.[71] The summary estimates for the sensitivity analysis were similar to the base-case analysis, suggesting that inclusion of studies with alternative thresholds did not markedly change our estimates of accuracy. A non-informative prior distribution is used for the analysis. Details on the prior specifications can be found in *Appendix 1*.

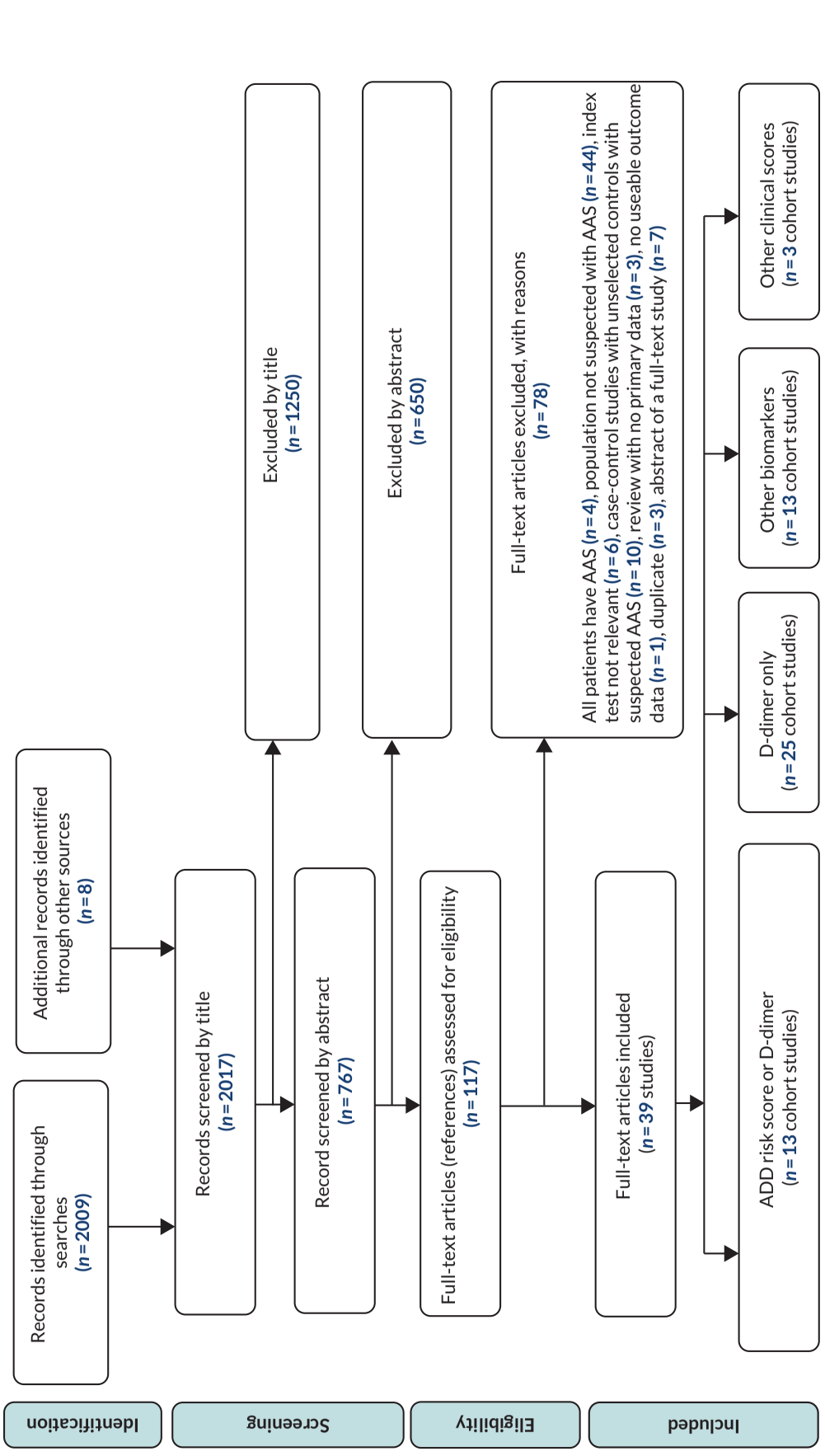

FIGURE 2 The PRISMA flow chart for each review. Reproduced from Ren *et al.*[2] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

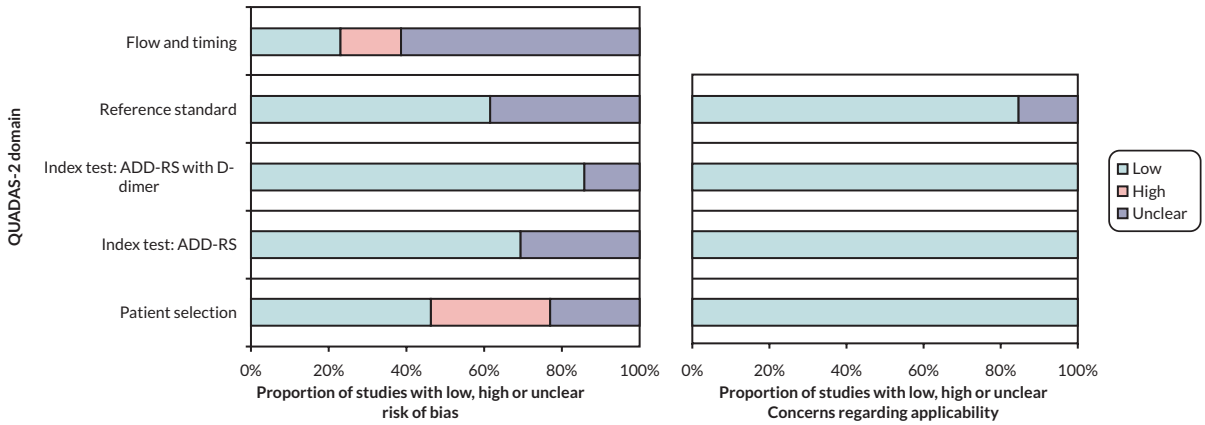

FIGURE 3 Quality assessment of diagnostic accuracy studies-2 assessment summary graph for studies of ADD-RS. Reproduced from Ren *et al.*[2] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

Studies of biomarkers other than D-dimer

We included 13 cohort studies of other biomarkers[52,63,68,69,73,76–83] (sample size $N = 76$ to $N = 999$, prevalence of AAS 1–51%). A team of researchers in Italy undertook five of the studies, evaluating the following biomarkers in consecutive cohorts: matrix metalloproteinases 8 and 9,[63] lactate dehydrogenase,[81] white blood cell count, platelet count, fibrinogen,[79] copeptin[80] and soluble suppression of tumourigenicity-2 (sST2).[78] The other studies were undertaken in China (three studies),[69,73,76] Germany,[83] Japan[82] and Canada,[68] evaluating the following biomarkers: troponin,[68,73] alpha-smooth muscle actin,[69] smooth muscle myosin heavy chain,[69] soluble elastin fragments in serum,[69] polycystin-1,[69] acidic and basic calponin at six and 24 hours after presentation,[82] sST2,[73] neutrophil-lymphocyte ratio[76] and leukocyte count.[83] The methodological quality of the included studies was variable, with most studies having unclear or high risk of bias and applicability concerns in at least one item of the QUADAS-2 tool.

The area under the receiver operating characteristic (AUROC) for the biomarkers was generally modest, with sensitivity sufficient to rule out AAS only when a threshold was used that resulted in low specificity. The exception was the study of Wang *et al.*,[73] reporting 99.1% sensitivity, 84.9% specificity and AUROC 0.97 for sST2, which differed markedly from the findings reported by Morello *et al.*[78] for sST2 (sensitivity 58%, specificity 70.8%, AUROC 0.675). Accuracy improved when the biomarkers were combined with D-dimer but was not clearly superior to D-dimer alone.

We excluded 38 case-control studies[85–122] that evaluated a wide variety of biomarkers using a variety of different control groups. Only three used control groups consisting of patients presenting with suspected AAS.[103,104,115] Case-control studies may identify biomarkers for future research but do not provide reliable estimates of accuracy to inform clinical practice.[24,25]

We identified three studies[18,33,84] that reported clinical scores, models or algorithms other than the ADD-RS. Morello *et al.*[18] developed the AORTA score based on six clinical features (thoracic aortic aneurysm, severe pain, sudden pain, pulse deficit, neurologic deficit, hypotension) and reported an area under the curve (AUC) of 0.729. McLatchie *et al.*[33] evaluated the AORTA score and reported an AUC of 0.689. McLatchie *et al.*[33] also evaluated the Canadian guidelines (results reported above) and the Sheffield score, which was developed through clinical expertise (AUC 0.628). Duceau *et al.*[84] used machine learning to develop an algorithm for pre-hospital triage of suspected AAS with AUC of 0.73 in a validation cohort.

Decision-analytic modelling

Table 5 shows the number of CTA performed and number of cases of AAS detected and missed in the base-case analysis at a typical hospital with 3281 cases of possible AAS per year, based on extrapolating from the incidence of cases in the DAShED study,[33] and across the NHS, based on extrapolation from the incidence of AAS across the NHS in England and Wales (https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics). The low prevalence of AAS in this unselected population means that most strategies result in numbers of CTA that would markedly exceed current rates of CTA at a typical hospital, estimated to be 298 per year by extrapolation from the DAShED study. The exceptions (no testing, CTA if ADD-RS > 1) resulted in high rates of missed AAS.

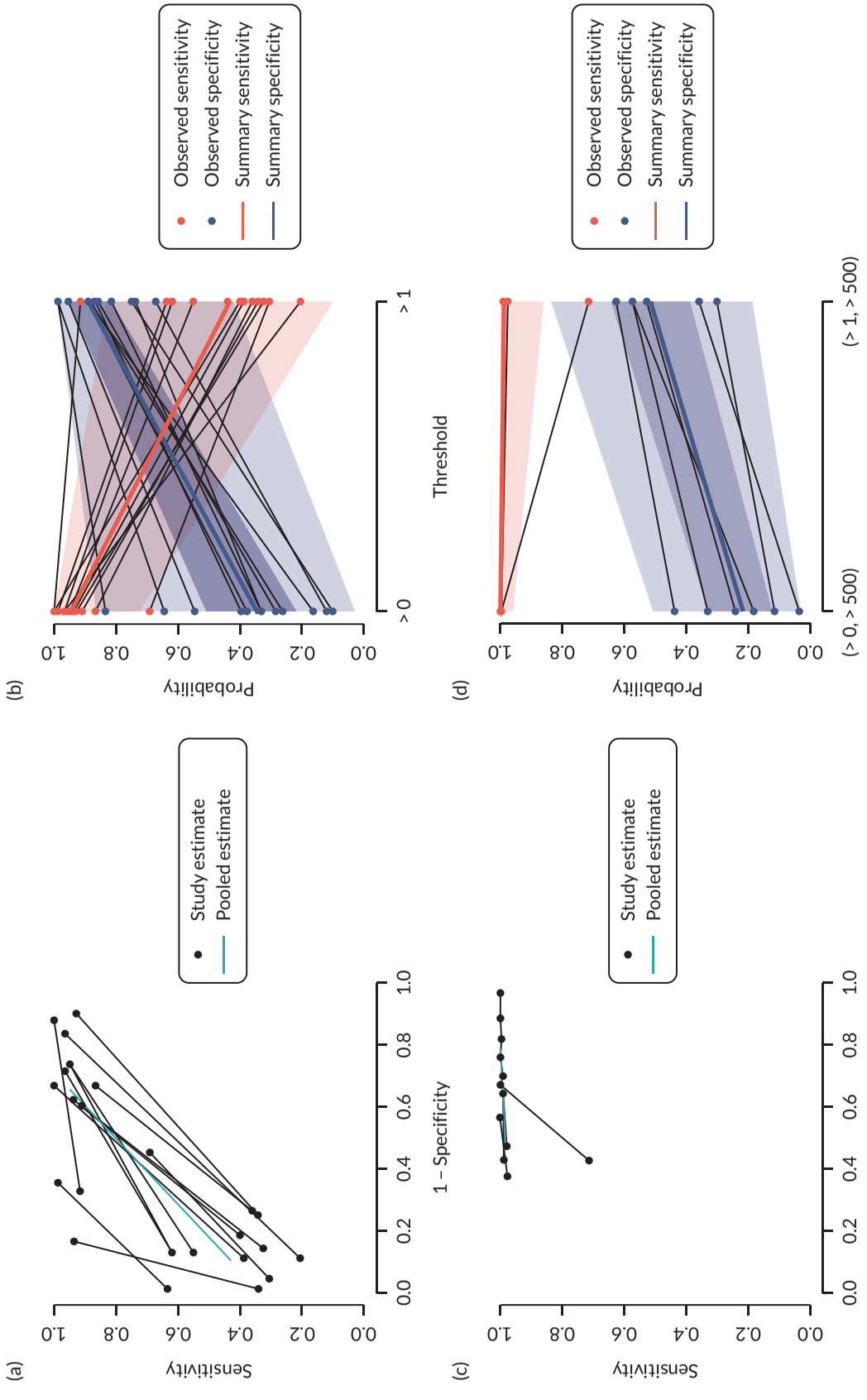

FIGURE 4 Summary plots for ADD-RS and ADD-RS in combination with D-dimer. Reproduced from Ren *et al.*[2] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

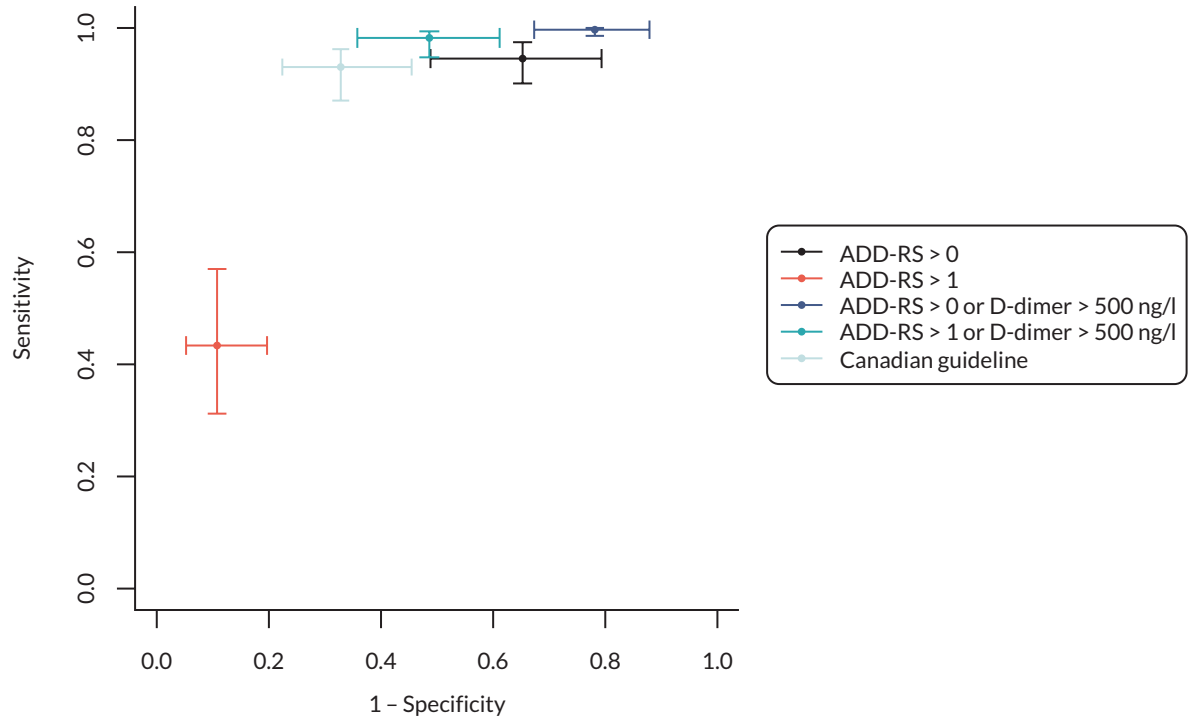

FIGURE 5 Pooled estimates and 95% CrI for each strategy. Reproduced from Ren *et al.*[2] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

TABLE 3 Summary estimates from each analysis of ADD-RS and D-dimer

Strategy	Threshold	Number of studies	Sensitivity (95% CrI)	Specificity (95% CrI)	Sensitivity (95% PrI)	Specificity (95% PrI)
ADD-RS analysis	ADD-RS > 0	12	94.6% (90 to 97.5)	34.7% (20.7 to 51.2)	94.6% (72.7 to 99.7)	34.7% (3.3 to 86.9)
	ADD-RS > 1	12	43.4% (31.2 to 57.1)	89.3% (80.4 to 94.8)	43.4% (9.9 to 83.3)	89.3% (41.1 to 99.5)
ADD-RS with D-dimer analysis	ADD-RS > 0 or D-dimer > 500	6	99.8% (98.7 to 100)	21.8% (12.1 to 32.6)	99.8% (96.1 to 100)	21.8% (2.6 to 50.7)
	ADD-RS > 1 or D-dimer > 500	6	98.3% (94.9 to 99.5)	51.4% (38.7 to 64.1)	98.3% (86.4 to 100)	51.4% (18.5 to 83.5)
	ADD-RS > 1 or ADD-RS = 1 with D-dimer > 500	6	93.1% (87.1 to 96.3)	67.1% (54.4 to 77.7)	93.1% (74.1 to 98.3)	67.1% (33.4 to 89.3)
ADD-RS sensitivity analysis	ADD-RS > 0	6	95.1% (88.5 to 98.4)	38% (20.1 to 59.1)	95.1% (72.9 to 99.8)	38% (4.5 to 86.8)
	ADD-RS > 1	6	41.6% (24.8 to 59.1)	91.7% (81.7 to 97)	41.6% (8.1 to 82.5)	91.7% (53.7 to 99.6)

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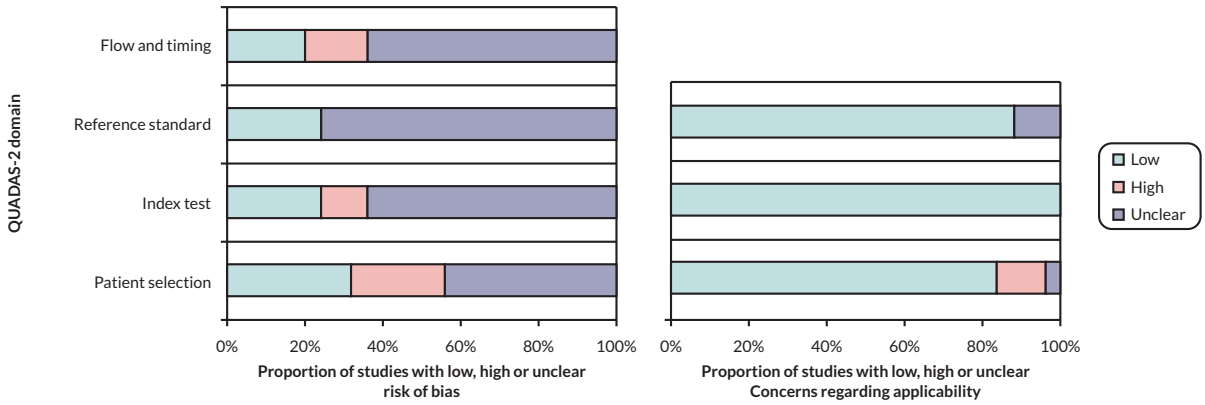

FIGURE 6 The QUADAS-2 assessment summary graph for studies of D-dimer. Reproduced from Essat *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

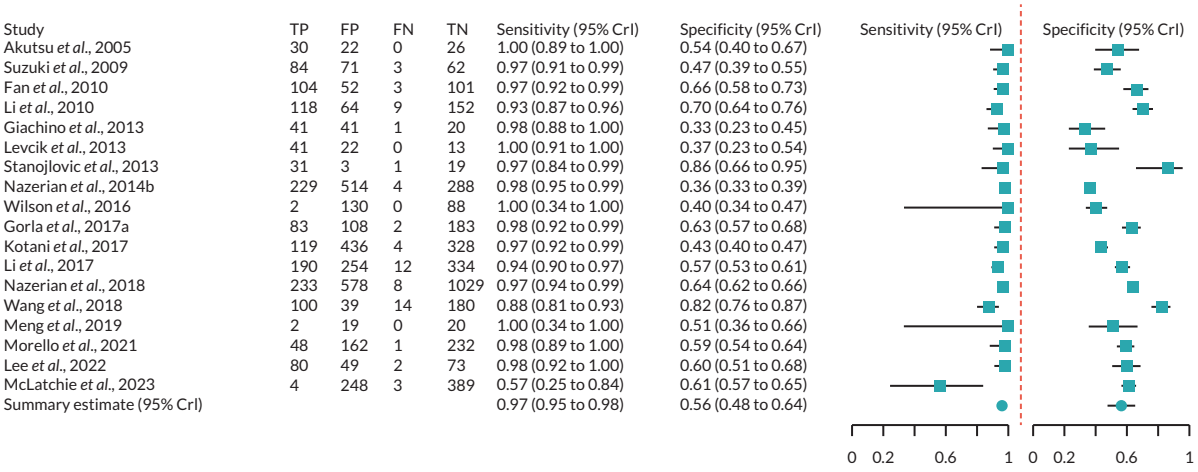

FIGURE 7 Forest plot for studies of D-dimer using the 500 ng/ml threshold (*N* = 18). Reproduced from Essat *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

Table 6 shows the deterministic results for the base-case analysis. CTA for those with ADD-RS > 1 was cost-effective at the £20,000/QALY threshold, although *Table 3* suggests that over half of cases of AAS would be missed. CTA for those with ADD-RS > 1 or ADD-RS = 1 with D-dimer > 500 ng/ml was cost-effective at the £30,000/QALY threshold, although *Table 3* suggests this would require tripling or quadrupling CTA capacity.

Figure 9 shows the cost-effectiveness acceptability curves from the base-case probabilistic sensitivity analysis. It shows that as the maximum acceptable incremental cost-effectiveness ratio (MAICER) increases, the strategy with the greatest probability of being cost-effective changes from no testing to ADD-RS > 1 and then ADD-RS > 1 or ADD-RS = 1 with D-dimer > 500 ng/ml.

Table 7 shows the results of secondary analysis assuming 0.61% prevalence of AAS, as seen in the DAShED cohort when patients with a clinician-estimated probability of AAS of zero were excluded. If clinicians can use their judgement to exclude patients they consider to have zero risk of AAS, then CTA for those with ADD-RS > 1 or ADD-RS = 1 with D-dimer > 500 ng/ml is cost-effective at the £20,000/QALY and 30,000/QALY thresholds, and would require 465 CTA per year in a typical hospital (≈60% increase).

Table 8 shows the results of sensitivity analysis assuming 2.95% prevalence of AAS, as seen in the DAShED study cohort who received CTA. This suggests that CTA for all is not cost-effective compared to strategies using ADD-RS and D-dimer. CTA for those with ADD-RS > 1 or D-dimer > 500 ng/ml is cost-effective at the £20,000/QALY or £30,000/QALY threshold and would approximately halve the number of CTA required compared to CTA all.

The EVPI analysis showed that at a threshold of £20,000/QALY, the individual EVPI was £4.46 per patient.

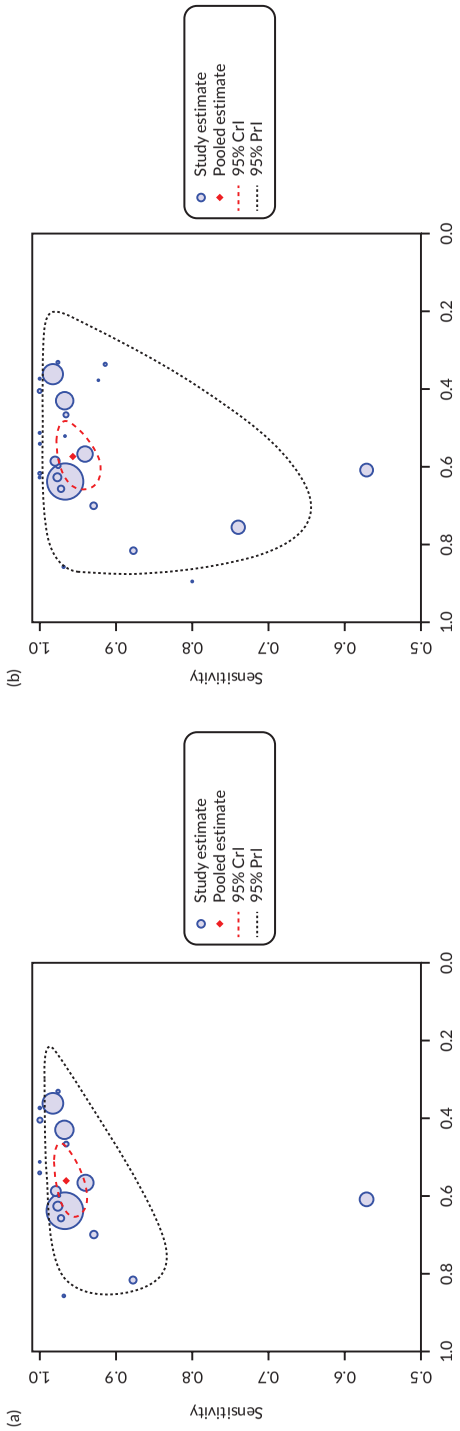

FIGURE 8 Summary plot for studies reporting D-dimer using the 500 ng/ml threshold (N = 18). Reproduced from Essat *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

TABLE 4 Summary estimates from the base-case and sensitivity analyses of D-dimer

Strategy (*N*, threshold)	Sensitivity (95% CrI) (95% PrI)	Specificity (95% CrI) (95% PrI)	Between-study SD for sensitivity and specificity (95% CrI)	Correlation coefficient between logit sensitivity and specificity (95% CrI)
D-dimer main analysis (*N* = 18, > 500 ng/ml)	96.5% (94.8 to 98) (86.1 to 99.3)	56.2% (48.3 to 63.9) (25.3 to 83.1)	Sensitivity: 0.65 (0.30 to 1.33) Specificity: 0.62 (0.43 to 0.96)	−0.75 (−0.99 to −0.10)
D-dimer sensitivity analysis (*N* = 25 to > 500 ng/ml or any other threshold used)[a]	95.7% (93.2 to 97.5) (73 to 99.5)	57.5% (50.1 to 64.6) (24 to 85.3)	Sensitivity: 0.99 (0.65 to 1.57) Specificity: 0.69 (0.50 to 1.00)	−0.57 (−0.85 to −0.09)

N, number of studies; SD, standard deviation.
a Any other D-dimer thresholds included the following: 240 ng/ml,[60] 246 ng/ml,[61] 300 ng/ml,[70] 400 ng/ml,[75] 1000 ng/ml,[54] 2110 ng/ml[69] and the Youden's index 0.51.[76]

TABLE 5 Results for a typical hospital and the NHS (AAS prevalence of 0.26%)

	Typical hospital Number of suspected AAS = 3281			NHS Number of suspected AAS = 796,538		
	Number of CTA	Number of cases of AAS detected	Number of cases of AAS missed	Number of CTA	Number of cases of AAS detected	Number of cases of AAS missed
No testing or CTA	0.00	0.00	8.53	0	0	2071
ADD-RS > 1	275.16	3.55	4.98	66,802	862	1209
ADD-RS > 1 or ADD-RS = 1 with D-dimer > 500	1084.58	7.94	0.59	263,308	1928	143
ADD-RS > 0	2037.04	8.11	0.42	494,539	1970	101
D-dimer > 500 ng/ml	1428.48	8.22	0.31	346,795	1996	75
ADD-RS > 1 or D-dimer > 500 ng/ml	1598.81	8.39	0.15	388,147	2036	35
ADD-RS > 0 or D-dimer > 500 ng/ml	2567.58	8.51	0.02	623,340	2067	4
CTA all	3289.53	8.53	0.00	798,609	2071	0

Using a population size of 796,538 suspected AAS patients to the NHS each year and a 5-year horizon, the population EVPI was estimated as £17.75M.

Discussion/interpretation

Principal findings

Our systematic review and meta-analyses provide estimates of the accuracy of ADD-RS and D-dimer for AAS based upon cohort studies using consistent thresholds for positivity. The sensitivity and specificity (95% CrI) of ADD-RS greater than zero were 94.6% (90% to 97.5%) and 34.7% (20.7% to 51.2%), and of ADD-RS greater than one were 43.4% (31.2% to 57.1%) and 89.3% (80.4% to 94.8%). The sensitivity and specificity of D-dimer using the 500 ng/ml threshold for positivity were 96.5% (94.8% to 98%) and 56.2% (48.3% to 63.9%). Sensitivity analyses of ADD-RS limited to the six studies evaluating combinations of ADD-RS with D-dimer, and of D-dimer including studies with alternative thresholds for positivity showed similar estimates to the base-case analysis.

TABLE 6 Base-case cost-effectiveness results (AAS prevalence 0.26%)

	Total costs	Total QALYs	ICER (cost/QALY gained)
CTA all	£255.62	11.10741	Dominated
ADD-RS > 0 or D-dimer > 500 ng/ml	£222.88	11.10743	£1,812,565
ADD-RS > 1 or D-dimer > 500 ng/ml	£173.56	11.10741	£137,338
D-dimer > 500 ng/ml	£160.46	11.10732	Extendedly dominated
ADD-RS > 0	£189.58	11.10722	Extendedly dominated
ADD-RS > 1 or ADD-RS = 1 with D-dimer > 500	£140.97	11.10717	£25,789
ADD-RS > 1	£74.81	11.10460	£15,990
No testing or CTA	£41.37	11.10251	–

ICER, incremental cost-effectiveness ratio.

The sensitivities and specificities of ADD-RS greater than zero or D-dimer > 500 ng/ml were 99.8% (98.7% to 100%) and 21.8% (12.1% to 32.6%), ADD-RS greater than one or D-dimer > 500 ng/ml were 98.3% (94.9% to 99.5%) and 51.4% (38.7% to 64.1%) and the Canadian guideline-based strategy (ADD-RS > 1 or ADD-RS = 1 with D-dimer > 500 ng/ml) were 93.1% (87.1% to 96.3%) and 67.1% (54.4% to 77.7%).

These findings indicate that ADD-RS and D-dimer provide potentially useful information in the diagnostic assessment of AAS, and combinations of ADD-RS and D-dimer could be used to rule out AAS, albeit with a risk of missed diagnosis.

Our systematic review of biomarkers other than D-dimer produced much more limited data and no reliable estimates of diagnostic accuracy for use in clinical practice. We identified 38 case-control studies[85–122] of biomarkers but only 13 cohort studies[52,63,68,69,73,76–83] for inclusion in our review. Biomarker accuracy was generally modest, with sensitivity sufficient to rule out AAS only when a threshold was used that resulted in low specificity. An exception was the study of Wang *et al.*,[73] reporting 99.1% sensitivity, 84.9% specificity for sST2, but this differed markedly from the findings reported by Morello *et al.*[78] (sensitivity 58%, specificity 70.8%). No biomarkers, other than D-dimer, can currently be recommended for clinical use.

Decision-analytic modelling showed that if strategies were applied unselectively to all patients with possible AAS, then CTA for those with ADD-RS > 1 would be cost-effective at the £20,000/QALY threshold but would result in more than half of cases of AAS being missed. CTA for those with ADD-RS > 1 or ADD-RS = 1 with D-dimer > 500 ng/ml would be cost-effective at the £30,000/QALY threshold but would require a three- to fourfold increase in current CTA use, which is unlikely to be deliverable. If clinicians are able to use their judgement to exclude patients considered to have a zero risk of AAS, then a strategy of CTA for patients with ADD-RS > 1 or ADD-RS = 1 with D-dimer > 500ng/ml would be cost-effective and require a more modest (≈60%) increase in CTA capacity. A strategy of ADD-RS > 1 or D-dimer > 500 ng/ml is cost-effective at 2.95% prevalence of AAS, which is the prevalence of AAS in patients receiving CTA in the DAShED study.

At a threshold of £20,000/QALY, the individual EVPI was £4.46 per patient, and the population EVPI for patients presenting to the NHS with suspected AAS over 5 years was estimated as £17.75M, suggesting that further research to reduce the uncertainty would be valuable.

Contribution to existing knowledge

Our summary estimates of accuracy for ADD-RS (alone and with D-dimer) are similar to previous meta-analyses,[20,123] although we report slightly lower sensitivity. We also evaluated a strategy based on the Canadian clinical practice guideline (ADD-RS > 1 or ADD-RS = 1 with D-dimer > 500 ng/ml), which has lower sensitivity but higher specificity than other strategies combining the ADD-RS with D-dimer. This offers an alternative strategy to patients who wish to avoid overinvestigation and populations with a low prevalence of AAS, where a strategy with low specificity would generate an acceptably low yield of positive imaging.

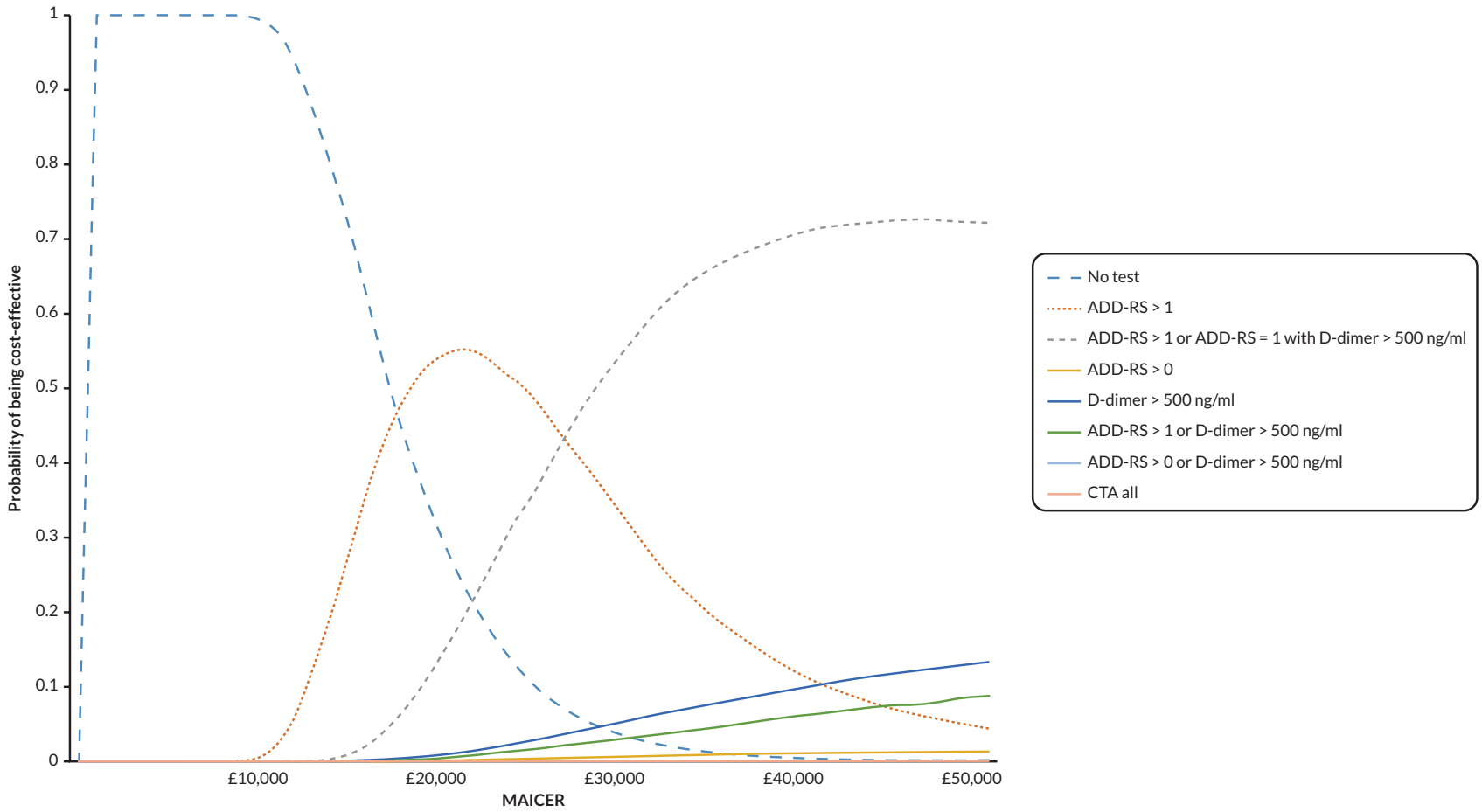

FIGURE 9 Cost-effectiveness acceptability curves from the base-case probabilistic sensitivity analysis. Reproduced from Thokala *et al.*[3] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

This synopsis should be referenced as follows: Goodacre S, Pandor A, Thokala P, Ren S, Essat M, Ren S, *et al.* Diagnostic strategies for suspected acute aortic syndrome: Systematic review, meta-analysis, decision-analytic modelling and value of information analysis. *Health Technol Assess* 2025;**29**(45). https://doi.org/10.3310/GGOP6363

TABLE 7 Secondary cost-effectiveness results (AAS prevalence 0.61%)

	Total costs	Total QALYs	ICER (cost/QALY gained)	Number of CTA (typical hospital)	Number of CTA (NHS)
CTA all	£359.43	11.09010	Dominated	1406.53	341,579
ADD-RS > 0 or D-dimer > 500 ng/ml	£326.19	11.09011	£384,837	1095.08	265,943
ADD-RS > 1 or D-dimer > 500 ng/ml	£276.33	11.08998	£59,159	683.67	166,030
D-dimer > 500 ng/ml	£262.35	11.08977	Extendedly dominated	611.25	148,444
ADD-RS > 0	£290.72	11.08958	Extendedly dominated	869.58	211,180
ADD-RS > 1 or ADD-RS = 1 with D-dimer > 500	£241.34	11.08939	£14,955	465.08	112,945
ADD-RS > 1	£150.51	11.08332	£10,851	118.87	28,869
No testing or CTA	£97.07	11.07840	–	0.00	0

ICER, incremental cost-effectiveness ratio.

TABLE 8 Secondary cost-effectiveness results (AAS prevalence 2.95%)

	Total costs	Total QALYs	ICER (cost/QALY gained)	Number of CTA (typical hospital)	Number of CTA (NHS)
CTA all	£1053.49	10.97441	£457,862	297.53	72,274
ADD-RS > 0 or D-dimer > 500 ng/ml	£1016.89	10.97433	£65,685	227.84	55,346
ADD-RS > 1 or D-dimer > 500 ng/ml	£963.44	10.97351	£17,262	144.69	35,148
D-dimer > 500 ng/ml	£943.55	10.97243	Extendedly dominated	129.94	31,566
ADD-RS > 0	£966.96	10.97165	Extendedly dominated	182.00	44,211
ADD-RS > 1 or ADD-RS = 1 with D-dimer > 500	£912.34	10.97055	£8662	100.21	24,344
ADD-RS > 1	£656.58	10.94103	£7841	26.83	6516
No testing or CTA	£469.43	10.91716	–	0.00	0

ICER, incremental cost-effectiveness ratio.

Previous meta-analyses of D-dimer for AAS have produced conflicting estimates of specificity. Yao *et al.*[19] reported sensitivity and specificity of 96% and 70%, respectively, but included many case-control studies; while Asha *et al.*[124] reported 98% and 42%, respectively, but included only four studies (1557 participants).[34,59,62,72] Our base-case analysis included 18 cohort studies[18,31–35,59,62–68,71–74] with 7978 participants and reported sensitivity and specificity of 96.5% and 56.2%, respectively. This is likely to be a more robust and reliable estimate of D-dimer accuracy than previous studies, by being based on a large number of cohort studies.

Our study is, to our knowledge, the first systematic review of biomarkers for AAS other than D-dimer. The conclusions were limited by the quality of the primary data, with 38

case-control studies excluded and only 13 cohort studies eligible for inclusion. We have, therefore, highlighted the need for more robust studies of biomarkers but are unable to identify any current biomarkers that are suitable for clinical practice, other than D-dimer.

Our decision-analytic modelling is, to our knowledge, the first to examine the cost-effectiveness of strategies for selecting patients with suspected AAS for CTA. Taylor and Iyer[125] used decision-analytic modelling to compare testing strategies for AAS in terms of health outcomes but not costs. Their model suggested using low testing thresholds of 0.03% probability of AAS for CTA compared to no testing and 0.013% for D-dimer compared to no testing. These findings suggest that the benefits of accurate diagnosis substantially outweigh the risks of testing but do not take costs into account. Our analysis suggests that CTA for all is not cost-effective compared to alternative strategies when costs are considered rather than health outcomes alone. Furthermore, our base-case analysis showed that even if strategies are cost-effective, they may require an increase in CTA capacity that is unlikely to be deliverable in a typical hospital or across the NHS.

Strengths and weakness of the study/in relation to other studies

Our meta-analysis of ADD-RS and D-dimer only included cohort studies, thus avoiding the risk of bias associated with case-control studies, yet still included sufficient primary data to provide reasonably accurate and precise estimates of diagnostic accuracy. We were also able to use data shared by the primary study teams to estimate the accuracy of an additional strategy combining ADD-RS with D-dimer that was based on the Canadian clinical practice guideline.

There was potentially important heterogeneity between studies in both meta-analyses, especially in estimates of specificity, which increases the uncertainty around these estimates. This is discussed in detail in the primary publications.[1,2] The heterogeneity may reflect differences in study design, particularly patient selection, with studies varying between those reporting populations with a low rate of imaging for the reference standard and AAS prevalence to those reporting populations with a higher rate of imaging and AAS prevalence. The wide range of prevalence in the primary studies limit our ability to generalise the findings from meta-analysis to specific groups, particularly low-prevalence populations, including many patients who would not normally receive imaging.

As noted previously, the biomarker systematic review was substantially limited by the quality of the primary data. We were unable to recommend any biomarkers for clinical use, other than D-dimer, and could not include biomarkers other than D-dimer in the decision-analytic modelling.

Our decision-analytic modelling is the first to examine the cost-effectiveness of alternative strategies for selecting patients with possible AAS to CTA. It is based upon robust estimates from our meta-analysis of the accuracy of the strategies and draws upon clinical expertise to ensure a model that reflects the complexities of the clinical problem while retaining transparency.

A key limitation in our understanding of AAS diagnosis relates to how clinicians determine whether a patient presenting with symptoms compatible with AAS is considered to require investigation for AAS. Our base-case analysis included all patients whose symptoms were compatible with AAS. However, the DAShED study[33] showed that clinicians considered a substantial proportion of these patients to have a low or zero likelihood of AAS and only used CTA to investigate a minority for AAS. Our analysis showed that strategies involving the ADD-RS and D-dimer are cost-effective if limited to selected patients in whom clinical judgement suggests a meaningful risk of AAS. The limitation with this finding is that we do not know how clinicians make this judgement and whether their assessment of AAS risk is accurate.

A related limitation is that we did not compare the strategies to using unstructured clinical judgement to select patients for CTA or consider how clinical judgement could be used alongside the strategies. If we conclude that clinical judgement is required to select patients for diagnostic investigation with the ADD-RS and D-dimer, then we should consider whether the selection for CTA should be based on clinical judgement alone (or informed by ADD-RS and D-dimer). There is little evidence available to estimate the accuracy of unstructured clinical judgement for diagnosing AAS, so we were unable to evaluate it in our analysis.

It is also important to note that we assumed that the population for the modelling excluded patients whose frailty and/or comorbidities meant that they would not be eligible for surgery or endovascular repair if AAS were detected. We made this assumption because including such patients would increase the complexity and uncertainty in the analysis, while reducing the applicability of findings to the population most likely to benefit from AAS diagnosis. We felt that this assumption reflected clinical practice, which involves assessing the potential implications for treatment before ordering a diagnostic test. Our findings are, therefore, not applicable to patients with frailty or

comorbidities that limit the treatment options to medical treatment alone. The decision to investigate such patients is likely to be individualised and involve consideration (and discussion with the patients) of whether extensive investigation is in the patient's best interests.

Other limitations relate to uncertainties in the assumptions and estimates used in the model:

1. Estimates of the effect of delayed treatment are inevitably based on limited observational data.
2. We were unable to include any credible estimates of the benefits and harms arising from non-AAS diagnoses and incidental findings identified on CTA due to the variety of findings identified and uncertainty over their clinical significance.

Changes from the proposed project

We planned to include case-control studies and report their characteristics and findings but exclude them from the meta-analyses due to the potential high risk of bias of such studies.[24,25] We also specified that studies would only be included if participants (cohort, cases or controls) presented with suspected AAS. We found that the reporting of case-control studies was often insufficient to determine whether the control group presented with suspected AAS or not, and therefore whether such studies should be included. We, therefore, made a post hoc decision to exclude case-control studies from the review. We reported the number and characteristics of case-control studies of alternative biomarkers to provide readers of this review with an insight into the large number of such studies but did not attempt to draw conclusions from the findings of these studies.

We made some changes to the proposed methods for meta-analysis:

1. We planned to use the method of Steinhauser *et al.*[126] but, instead, used the method of Jones *et al.* 2019.[28] The Jones' model has advantages over Steinhauser's model in the following areas: it models the exact multinomial likelihoods of the spread of test results across thresholds, rather than requiring the normal approximations; it automatically accounts for within-study correlations resulting from studies reporting at more than one threshold; and it performs better with small counts.
2. We planned to analyse sensitivity and specificity at multiple thresholds for D-dimer, but we found insufficient data to support this analysis. Most studies only reported one threshold, usually the 500 ng/ml threshold. The few studies that reported more than one threshold only reported a few variable thresholds, which were insufficient to support detailed analysis.
3. We proposed to perform sensitivity analysis and listed the likely analyses as (1) studies with a sample based on suspicion of AAS rather than receipt of a reference standard test, (2) studies with > 90% of the sample receiving a definitive reference standard or adequate follow-up and (3) studies that evaluated a fully derived index test (including the threshold for positivity). We were unable to undertake analyses (1) and (2) because the primary study reporting of sample selection and reference standard testing was limited and inconsistent, and could not therefore support categorisation for sensitivity analysis. We were unable to undertake analysis (3) because most studies used the pre-specified 500 ng/ml threshold. We, therefore, used this threshold for the primary analysis and used sensitivity analysis to explore, including studies with other thresholds.

We made the following changes to the planned decision-analytic modelling:

1. In accordance with the meta-analysis, we found insufficient data reporting D-dimer sensitivity and specificity at thresholds other than the 500 ng/ml threshold, so we did not explore the cost-effectiveness of using D-dimer at alternative thresholds for positivity.
2. The systematic review identified no biomarkers (other than D-dimer) with sufficient robust evidence of accuracy to support clinical use, so we did not evaluate any strategies using alternative biomarkers in the decision-analytic modelling.
3. We estimated the accuracy of strategies included in the modelling using data from cohort studies that reported ADD-RS and D-dimer in combination. We, therefore, did not need to undertake the planned exploratory analyses using indirect estimates of accuracy (estimates based on combining an estimate of ADD-RS accuracy with a combination of D-dimer accuracy) or estimates from case-control studies.
4. We reviewed studies reporting the diagnostic yield of CTA for non-AAS pathology, along with data from the DAShED study[33] and a single-centre study of CTA results.[127] These showed that CTA identify a wide range of non-AAS pathology. For example, the 407 CTA reported in the DAShED study[33] showed 201 non-AAS findings involving 61 different pathologies. We decided that it would not be possible to include any credible estimates of benefit or harm from these findings in the modelling, so we

acknowledged this uncertainty and limitation of the model. Similarly, we were unable to include any estimate of benefit or harm from incidental CTA findings in the model but included a cost for the proportion of patients who would require a repeat CT scan for pulmonary nodules or similar equivocal findings.

Take-home messages

The ADD-RS and D-dimer, alone and in combination, provide useful diagnostic information, but their use in the diagnostic pathway for AAS (specifically ruling out AAS) depends upon how clinical suspicion of AAS is determined. D-dimer below 500 ng/ml in a patient with low clinical risk (ADD-RS zero) effectively rules out AAS (sensitivity 99.8%), but unselective application of this rule will lead to a high rate of negative CTA.

Clinical scores other than the ADD-RS and biomarkers other than D-dimer currently lack sufficient evidence of diagnostic accuracy for AAS to be recommended for clinical use.

In an unselected population with possible symptoms of AAS, current validated strategies struggle to achieve an acceptable balance between overinvestigation and risk of missed AAS. A strategy based on the Canadian guideline (CTA if ADD-RS > 1 or if ADD-RS = 1 with D-dimer > 500 ng/ml) appears cost-effective but would require over a quarter of a million CTAs and result in over 100 missed AAS across the NHS in England and Wales, if applied to an unselected population.

If clinicians can select a population with a higher prevalence of AAS without missing cases, then the strategy based on the Canadian guidelines or a strategy of CTA if ADD-RS > 1 or D-dimer > 500 ng/ml would be cost-effective and potentially deliverable without a substantial increase in CTA capacity. Further research is needed to determine how clinicians select this population.

For patients currently receiving CTA, the strategy of ADD-RS > 1 or D-dimer > 500 ng/ml could halve the number of CTA undertaken and would be cost-effective according to National Institute for Health and Care Excellence (NICE) thresholds for willingness to pay but would result in 143 additional missed cases of AAS per year across the NHS.

Patient and public involvement

The Aortic Dissection Charitable Trust (https://aorticdissectioncharitabletrust.org/) aims to improve the diagnosis of aortic dissection and bring consistency of treatment across the patient pathway. It developed from a national campaign by the family of Tim Fleming, who died after a missed diagnosis of AAS. The trust involves people who have survived AAS and relatives of people who have died from AAS. It promotes education and awareness of AAS and supports research into the detection, prevention, treatment and cure for aortic dissection.

Our research team included two members of the Aortic Dissection Charitable Trust. Valerie Lechene has lived experience of AAS, having received successful treatment for AAS despite delayed diagnosis. She brought her experience of delayed diagnosis to the project and provided a powerful patient perspective of the diagnostic process. Catherine Fowler experienced the loss of her father to AAS in 2015. She brought her insights as a bereaved relative due to AAS and acted as a powerful advocate for victims of AAS who did not survive. Valerie Lechene and Catherine Fowler helped to develop the study proposal, attended project meetings, facilitated contact with other members of the trust, assisted with the development of the decision-analytic model and reviewed emerging findings from the study.

The Aortic Dissection Charitable Trust organised a webinar during project development that 23 of their members attended. The participants shared their experience of AAS diagnosis and identified important issues around interpretation of the risk scores; patient knowledge of risk variables; the importance of family history, gender and ethnicity; the involvement of ambulance services and hospital recording of missed/delayed diagnosis.

We created a patient and public involvement (PPI) group for the project that included 10 survivors of AAS and five relatives of people who had AAS, from members of the Aortic Dissection Charitable Trust and patients identified by clinical investigators involved in the project. The group met quarterly throughout the project to share their experiences of AAS, review diagnostic strategies evaluated in the study, consider assumptions in the decision-analytic modelling, review emerging findings, assist with interpretation of the findings and assist with dissemination.

The Aortic Dissection Charitable Trust assisted with dissemination of the findings to the public through a public webinar on 5 February 2024 and through posting findings on their website and social media.

Equality, diversity and inclusion

The role of personal characteristics in diagnosis and management of AAS has not been extensively studied.

This synopsis should be referenced as follows:
Goodacre S, Pandor A, Thokala P, Ren S, Essat M, Ren S, *et al*. Diagnostic strategies for suspected acute aortic syndrome: Systematic review, meta-analysis, decision-analytic modelling and value of information analysis. *Health Technol Assess* 2025;**29**(45). https://doi.org/10.3310/GGOP6363

AAS tends to occur in older people, due to association with uncontrolled hypertension, but can occur in younger people with connective tissue diseases. The few studies of sex-related differences suggest that AAS tends to occur in women at an older age but with little evidence of differences in treatment or outcomes.[128] Studies of ethnicity suggest that African Americans are more likely than other ethnicities to present with type B aortic dissection[129] and are more likely to present at a younger age and with risk factors, but treatment and outcomes are similar.[130]

None of the studies included in the systematic review reported ethnicity characteristics for the study population. Mean or median age was reported in 7/13 studies[18,31–33,35,52,53] of ADD-RS (ranging from 55[33] to 70 years)[32] and 8/25 studies[18,31,35,59,64,71,73,74] of D-dimer (ranging from 53[73] to 68 years[59]). The percentage of male or female patients was reported in 11/13 studies[18,31–35,52,53,55–57] of ADD-RS (ranging from 32%[32] to 53%[33] females) and 18/25 studies[18,31,32,34,35,59,61–65,67,70–74,76] of D-dimer (ranging from 23%[67] to 57%[74] females). The studies, therefore, suggest that women may be under-represented. Age was not reported by sex, so we are unable to determine whether under-representation of women may reflect exclusion of older people from studies. Inadequate reporting means that we are unable to determine whether people of different ethnicities are appropriately represented in the studies.

We recommend that future studies should record the ethnicity of participants to determine whether the study population is representative of the wider population and allow exploration of whether there are differences in diagnostic accuracy between people of different ethnicity. Future studies should also provide complete reporting of age and sex characteristics, along with details of any relevant exclusion criteria and characteristics of those excluded, so readers can determine whether specific patient groups are under-represented and gain a more granular understanding of the research.

We requested equality monitoring data from our PPI group members to determine whether the group reflected the characteristics of the wider population. We only received 5 replies from the 16 PPI group members, with responses indicating some diversity in gender (3 females, 2 males) and ethnicity (2 Black or Black British Caribbean, 3 White people).

We also requested equality monitoring data from our research team and received 10 replies from the 14 research team members. The replies indicated that the team included more males than females (three females, seven males) and some diversity in ethnicity (three Asian or Asian British Indian, five White, two Chinese people).

Impact and learning

The publications listed in the *Additional information* are the main outputs and form the basis for impact and learning arising from the study. We plan to present our findings at professional meetings, including the RCEM Annual Scientific Meeting, the European Society for Emergency Medicine Annual Conference, and the Society for Medical Decision Making.

We will share summaries of our findings, supported by peer-reviewed publications, with professional organisations involved in delivering clinical care for suspected AAS (RCEM, RCR, Vascular Society of Great Britain and Ireland, British Society of Interventional Radiology). We will share plain language summaries of our findings with patient organisations involved in improving care for suspected AAS (Aortic Dissection Awareness, the Aortic Dissection Charitable Trust).

The main UK guidelines for the diagnosis of AAS are the RCEM/RCR Best Practice Guidelines. We will draw upon our contacts with the guideline authors to ensure that they are aware of our findings. We will provide tailored information showing how the guidelines might develop in the light of our findings and offer to work with the guideline authors to help them to draw upon our findings.

We will also share our findings with the developers of the ESC guidelines,[5] the European Society for Vascular Surgery guidelines (https://esvs.org/guidelines/) and the AHA/American College of Cardiology guidelines.[21]

We will use our contacts with the Aortic Dissection Charitable Trust and Aortic Dissection Awareness to ensure awareness of our findings. We will provide tailored information to show how information provided by each organisation and relevant campaigns, such as the Think Aorta campaign, could be developed in the light of our findings.

We produce plain language information summarising our findings and work with the Aortic Dissection Charitable Trust, using mainstream media and social media, to promote public awareness of our findings.

The impact of this evidence synthesis project will largely be achieved through future primary research, as identified in the research recommendations. The James Lind Alliance

Emergency Medicine Priority Setting Partnership Refresh 2022 identified diagnosis of AAS in the ED as the seventh top priority (https://rcem.ac.uk/research-priorities/), and diagnosis of AAS is also currently the third top priority in the James Lind Alliance Aortic Priority Setting Partnership (www.jla.nihr.ac.uk/priority-setting-partnerships/vascular-conditions/aortic-top-10-priorities.htm). Our findings will feed into research proposals developing from these prioritisations.

We will share the research recommendations outlined in *Research recommendations* with research funders, including National Institute for Health and Care Research (NIHR), UK Research and Innovation Medical Research Council (MRC), British Heart Foundation and Heart Research UK, and feed our findings into research priority setting exercises.

The RCEM funded Aortic Syndrome Evidence Synthesis (ASES) coinvestigators Matthew Reed and Sarah Wilson to undertake the DAShED study[33] alongside our study. This multicentre observational cohort study of 5548 patients, with potential symptoms of AAS attending 27 hospitals across the UK, showed that 0.3% (14 patients) had AAS, while 7% received CTA. The findings were included in our systematic reviews, used to populate our decision-analytic model and will inform future research proposals around AAS diagnosis.

The DAShED study[33] provided essential data to develop our model, put our findings into context and understand the problem of suspected AAS. The involvement of 27 hospitals and the Trainee Emergency Research Network, along with support from the RCEM and Aortic Dissection Charitable Trust, provide a valuable network for developing future research proposals.

The Aortic Dissection Charitable Trust has funded the Rapid Acute Aortic Syndrome Diagnosis using Artificial Intelligence study,[131] led by Jim Zhong and involving ASES coinvestigators Matthew Reed, Graham Cooper, Sarah Wilson and Steve Goodacre. This study aims to use the DAShED data to develop a machine learning decision support system to assist AAS diagnosis in the ED.

In response to the James Lind Alliance prioritisation of AAS diagnosis, the RCEM Research Engagement and NIHR Emergency Care Incubator meetings have included sessions on developing research into AAS diagnosis. Matthew Reed facilitated these sessions and is developing a research network based on the DAShED study to undertake future multicentre research into AAS diagnosis. We plan to build upon the links we made with international researchers while undertaking the meta-analysis of ADD-RS and D-dimer to develop international collaborative research into AAS diagnosis.

Implications for decision-makers

Our findings have implications for guideline developers, clinicians, service managers and research funders.

Guideline developers

The ADD-RS and D-dimer, alone and in combination, provide useful diagnostic information and could be included in guidelines, but specific guidance needs to take into account the role of clinical judgement in determining whether AAS is suspected in people presenting with possible symptoms. Using the ADD-RS and/or D-dimer to select patients for CTA from an unselected population is likely to lead to high rates or CTA.

If clinical judgement can identify patients with higher AAS prevalence, then a strategy based on the Canadian guideline or a strategy of CTA if ADD-RS is greater than zero or D-dimer > 500 ng/ml appears to be cost-effective and could be recommended in guidelines. These strategies could also be used in guidelines to reduce the number of CTA performed, albeit with a small increase in the risk of missed AAS. The role of clinical judgement emphasises the need for clinician training and awareness of AAS. Our findings suggest no role for clinical scores other than the ADD-RS or for biomarkers other than D-dimer in guidelines.

Clinicians

The ADD-RS and D-dimer, alone and in combination, provide useful diagnostic information. Clinicians can use the estimates of diagnostic accuracy from our meta-analysis in their diagnostic assessment of suspected AAS. These estimates are based on reasonably robust evidence for cohort studies.

The main problem with using the ADD-RS and D-dimer in diagnostic assessment is that they are likely to generate a high rate of FPs if used indiscriminately in patients with a very low risk of AAS, which will presumably then require potential unnecessary CTA. Clinicians should, therefore, not use the ADD-RS and D-dimer in diagnostic assessment unless they consider there to be a realistic possibility of AAS. In these circumstances, the ADD-RS and D-dimer can be used to select patients for CTA. Using the ADD-RS and D-dimer is also inappropriate when the diagnosis of AAS is obvious or the patient is critically ill and urgent definitive diagnostic assessment is required.

We have published a *British Medical Journal* 'Easily missed' paper that describes how clinicians can use the findings reported in this synopsis to improve their diagnostic assessment of suspected AAS.[132]

Service managers

The base-case analysis suggested that applying the strategies to an unselected population would miss more than half of AAS cases or would require a three- to fourfold increase in CTA capacity (from 298 to 1079 CTA per year), which is unlikely to be deliverable. To provide some context, in 2023, 17,491 patients received 20,378 CT scans at the Royal Infirmary of Edinburgh, while 15,399 CT scans were requested from the Northern General Hospital Emergency Department in Sheffield. Most of these were non-contrast CT scans of the brain, so unselective implementation of the strategies would markedly increase requirements for CT with contrast.

If clinicians can select a population with higher prevalence, then cost-effective strategies using ADD-RS and D-dimer would be potentially deliverable, albeit with a potential increase in demand for CTA. A strategy using ADD-RS > 1 or D-dimer > 500 ng/ml could be cost-effective and reduce CTA use among those currently receiving CTA, but would be difficult to implement without also being applied to patients who do not currently receive CTA.

Research funders

Diagnosis of AAS is currently the seventh top priority in the James Lind Alliance Emergency Medicine Priority Setting Partnership (https://rcem.ac.uk/research-priorities/) and third top priority in the James Lind Alliance Aortic Priority Setting Partnership (www.jla.nihr.ac.uk/priority-setting-partnerships/vascular-conditions/aortic-top-10-priorities.htm). Our evidence synthesis has identified areas of uncertainty in current knowledge and informed the research recommendations outlined in *Research recommendations*.

Research recommendations

This project has identified the following priority areas for future research:

1. Evaluation of implementation of strategies using the ADD-RS and D-dimer test in clinical practice.

We identified two strategies that use the ADD-RS and D-dimer to select patients for CTA and could be cost-effective in the NHS. However, our conclusions were limited by uncertainty around how the strategies would be implemented in practice, specifically in terms of how clinicians would select patients with a significant probability of AAS and how the strategies would be used alongside clinical judgement to influence decision-making. We, therefore, recommend evaluation to determine the effects of using these strategies upon CTA ordering, AAS diagnosis, patient outcomes and healthcare costs.

2. Research into how clinicians use their judgement to determine whether to suspect AAS.

As above, clinical judgement needs to be used to determine whether patients have suspected AAS and need investigation. We currently know very little about how clinicians make this judgement, whether their judgements are accurate and what factors influence their judgement. Research is, therefore, required to improve our knowledge of clinical judgement in the assessment of AAS and potentially to determine how clinicians can identify patients requiring investigation for AAS. Research could also explore how clinicians incorporate information from the ADD-RS and D-dimer into their decision-making.

3. Evaluation of the diagnostic accuracy of biomarkers other than D-dimer.

We identified many low-quality studies evaluating a wide range of biomarkers. Only 11 cohort studies were identified for inclusion in our review, and most of the excluded case-control studies used selected control groups that are likely to bias estimates of diagnostic accuracy. The findings from the 11 cohort studies were limited and inconsistent. We, therefore, recommend that future research should evaluate potential biomarkers for AAS in a large cohort study with a sufficient number of cases of AAS to estimate sensitivity with acceptable precision. This is likely to require a multicentre study and potentially international collaboration. The study should also record the ADD-RS and D-dimer so that analysis can determine how biomarkers add to current assessment with the ADD-RS and D-dimer.

4. Research into diagnostic pathways for people with previous AAS or known aneurysm.

This research recommendation did not arise directly from our study but was identified as a priority by our PPI group. They noted that people with previous AAS or known thoracic aortic aneurysm are at increased risk of AAS but may also have concerns about symptoms that make them more likely to present to hospital. We identified very little evidence relevant to this population. We noted that D-dimer measurement could be helpful in identifying a new or recurrent AAS, whereas the ADD-RS may have a more limited role in clinical probability estimation than

in the general population. We, therefore, recommend further research to determine how diagnostic strategies for suspected AAS apply to people with previous AAS or known thoracic aortic aneurysm.

Conclusions

The ADD-RS and D-dimer, alone or in combination, provide useful diagnostic information that can assist clinical decision-making, specifically the selection of patients for CTA. ADD-RS > 0, D-dimer > 500 ng/ml and combinations of ADD-RS and D-dimer have high sensitivity (> 90%) with variable specificity (22% to 67%). The combination of ADD-RS of zero and D-dimer < 500 ng/ml effectively rules out AAS (sensitivity 99.8%). However, unselective use of ADD-RS or D-dimer in patients with very low prevalence of AAS will result in a high rate of FP cases requiring CTA.

Clinical scores other than the ADD-RS and biomarkers other than D-dimer currently lack sufficient evidence of accuracy to be recommended for clinical use in diagnosing AAS. Further research using an appropriate design and sample size is required to determine the accuracy of alternative biomarkers for AAS.

Decision-analytic modelling showed that a strategy based on the Canadian guideline (CTA if ADD-RS > 1 or if ADD-RS = 1 with D-dimer > 500 ng/ml) is cost-effective but, if applied unselectively to any patient whose symptoms were compatible with AAS, would require CTA capacity to be tripled or quadrupled.

Secondary analysis suggested that if the diagnostic strategies were only applied to patients that clinicians considered to have a non-zero probability of AAS, then the strategy based on the Canadian guidelines would be cost-effective and deliverable with only a 60% increase in CTA capacity. A strategy of CTA if ADD-RS > 1 or D-dimer > 500 ng/ml could also be cost-effective and deliverable if clinical judgement were used to select a higher prevalence cohort. Research is required to determine how these strategies would be delivered in practice and how an appropriate population would be selected for investigation.

For patients currently receiving CTA, the strategy of ADD-RS > 1 or D-dimer > 500 ng/ml could halve the number of CTA undertaken and would be cost-effective according to NICE thresholds for willingness to pay but would result in an estimated 143 cases of missed AAS per year across the NHS in England and Wales.

Additional information

CRediT contribution statement

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

No ethical approval was needed as all included data were from secondary published sources.

Information governance statement

The study was undertaken in accordance with University of Sheffield information governance procedures, General Data Protection Regulations (EU GDPR) 2016/679 and the Data Protection Act (2018). The study did not involve using sensitive data. Steve Goodacre is the data controller. Steve Goodacre Abdullah Pandor, Munira Essat and Sarah Ren were data processors.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GGOP6363.

Primary conflicts of interest: Steve Goodacre was member of HTA Board recruitment, HTA Remit and Competitiveness Group, HTA Prioritisation Committee B Methods Group, HTA Prioritisation Committee A Methods Group, HTA Post-Funding Committee teleconference, HTA Funding Committee Policy Group and HTA Commissioning Committee until 2020, and was chair of the NIHR HTA Clinical Trials Unit Standing Advisory Committee until 2023.

Abdullah Pandor is a member of the NIHR HTA Programme Funding Committee (General).

Matthew J Reed is supported by an NHS Research Scotland Career Researcher Clinician award.

Graham Cooper has received personal payment for expert testimony, support (airfare/accommodation) from Cleveland Clinic for attending a symposium meeting and is a Trustee of The Aortic Dissection Charitable Trust.

Catherine Fowler is a Trustee of The Aortic Dissection Charitable Trust.

All other authors declare no competing interests.

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This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Study registration

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Award publications

This synopsis provided an overview of the research award *Diagnostic strategies for suspected acute aortic syndrome (AAS): Systematic review, meta-analysis, decision-analytic modelling, and value of information analysis*. Other articles published as part of this thread are:

Thokala P, Goodacre S, Cooper G, Hinchliffe R, Reed MJ, Thomas S, *et al*. Decision-analytic modelling of strategies for investigating suspected acute aortic syndrome. *Emerg Med J* 2024;**41**:728–35. https://doi.org/10.1136/emermed-2024-214222

Wren J, Goodacre S, Pandor A, Essat M, Clowes M, Cooper G, *et al*. Diagnostic accuracy of alternative biomarkers for acute aortic syndrome: a systematic review. *Emerg Med J* 2024;**41**:678–85. https://doi.org/10.1136/emermed-2023-213772

Essat M, Goodacre S, Pandor A, Ren S, Ren S, Clowes M. Diagnostic accuracy of D-dimer for acute aortic syndromes: systematic review and meta-analysis. *Ann Emerg Med* 2024;**84**:409–21. https://doi.org/10.1016/j.annemergmed.2024.05.001

Ren S, Essat M, Pandor A, Goodacre S, Ren K, Clowes M, *et al*. Diagnostic accuracy of the aortic dissection detection risk score alone or with D-dimer for acute aortic syndromes: systematic review and meta-analysis. *PLOS ONE* 2024;**19**:e0304401. https://doi.org/10.1371/journal.pone.0304401

For more information about this research please view the award page (www.fundingawards.nihr.ac.uk/award/NIHR151853).

Additional outputs

Goodacre S, Lechene V, Cooper G, Wilson S, Zhong J. Easily missed? Acute aortic syndrome. *BMJ* 2024;**386**:e080870. https://doi.org/10.1136/bmj-2024-080870

About this synopsis

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List of abbreviations

AAS	acute aortic syndrome
ADD-RS	Aortic Dissection Detection Risk Score
AHA	American Heart Association
ASES	Aortic Syndrome Evidence Synthesis
AUC	area under the curve
AUROC	area under the receiver operating characteristic
CT	computed tomography
CTA	computed tomographic angiography
DAShED	Diagnosis of Acute Aortic Syndrome in the Emergency Department
DIC	deviance information criterion
ECG	electrocardiogram
ED	emergency department
ESC	European Society of Cardiology
EVPI	expected value of perfect information
FN	false negative
FP	false positive
IRAD	International Registry of Acute Aortic Dissection
MAICER	maximum acceptable incremental cost-effectiveness ratio
MRC	Medical Research Council
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PPI	patient and public involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	quality-adjusted life-year
QUADAS-2	quality assessment of diagnostic accuracy studies-2
RCEM	Royal College of Emergency Medicine
RCR	Royal College of Radiologists
ROC	receiver operating characteristic
sST2	soluble suppression of tumourigenicity-2
TEVAR	thoracic endovascular aortic repair
TN	true negative
TP	true positive

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Appendix 1 Statistical models for the meta-analysis

Model for a single threshold

A bivariate model is used for analysing sensitivity and specificity jointly by allowing for correlation between them.[23] In particular, the observed number of TPs in study i, TP_i, is assumed to be binomially distributed with parameter, π_{Ai} , representing the study-specific sensitivity given the total number of positives on the reference test such that:

$$TP_i \sim \text{Binomial}\ ((TP_i + FN_i),\ \pi_{Ai}).$$

Similarly, the observed number of TNs in study i, TN_i, is assumed to be binomially distributed with parameter, π_{Bi}, representing the study-specific specificity given the total number of negatives on the reference test such that:

$$TN_i \sim \text{Binomial}\ ((TN_i + FP_i),\ \pi_{Bi}).$$

The probabilities are transformed to a logit scale:

$$\mu_{Ai} = \text{logit}\,(\pi_{Ai}),$$

$$\mu_{Bi} = \text{logit}\,(\pi_{Bi}).$$

The study-specific sensitivity and specificity are jointly modelled using a bivariate normal distribution:

$$\begin{pmatrix}\mu_{Ai}\\ \mu_{Bi}\end{pmatrix} \sim N\begin{pmatrix}m_A\\ m_B\end{pmatrix}, \Sigma_{AB}\Bigg),$$

$$\Sigma_{AB} = \begin{pmatrix}\sigma_A^2 & \sigma_{AB}\\ \sigma_{AB}\sigma_B^2\end{pmatrix},$$

where m_A and m_B represent the population mean for logit sensitivity and specificity; σ_A^2 represents the variability in the logit sensitivity between studies, σ_B^2 represents the variability in the logit specificity between studies and σ_{AB} represents the covariance of the logit sensitivity and logit specificity. Specifically, we rewrite the covariance as $\sigma_{AB} = \rho\sigma_A\sigma_B$, with ρ being the correlation coefficient and we place prior distributions over ρ, σ_A, σ_B in the Bayesian analysis.

Model for multiple thresholds

The ADD-RS can take value between zero and three, with multiple thresholds commonly used in practice. In order to accommodate the estimates of sensitivity and specificity at multiple thresholds from each study, we adopted a multinomial meta-analysis model developed by Jones *et al.*[28] The model is briefly described as follows.

For each study i, we have the number of healthy patients N_i, the number of diseased patients P_i, and the number of thresholds T_i. Test results above a given threshold are considered positive. The number of FPs and TPs at threshold $C_{i,t}$ are denoted by $(FP_{i,t},\ TP_{i,t})$, with $t = 1, 2, \ldots, T_i$.

Jones *et al.*[28] proposed to model the dependency between different threshold values by linking the results from different thresholds using conditional distributions. Specifically, the observed count data $(FP_{i,t},\ TP_{i,t})$ at threshold $C_{i,t}$ are modelled using the following formula,

$$FP_{i,1} \sim \text{Binomial}\ (N_i,\ FPR_{i,1}),$$

$$FP_{i,t}|FP_{i,t-1} \sim \text{Binomial}\ (FP_{i,t-1},\ FPR_{i,t}/FPR_{i,t-1}),$$

$$TP_{i,1} \sim \text{Binomial}\ (P_i,\ TPR_{i,1}),$$

$$TP_{i,t}|TP_{i,t-1} \sim \text{Binomial}\ (TP_{i,t-1},\ TPR_{i,t}/TPR_{i,t-1}).$$

Here, $FPR_{i,t}$ and $TPR_{i,t}$ represent the FP rates and TP rates of study i at threshold t, respectively.

In the multinomial meta-analysis model, $FPR_{i,t}$ and $TPR_{i,t}$ depend on the individual mean and scale parameters μ_{Ai}, μ_{Bi}, $\log(\sigma_{Ai})$, $\log(\sigma_{Bi})$, and the specific threshold $C_{i,t}$ by the following specification,

$$\text{logit}\left(FPR_{i,t}\right) = \frac{\mu_{Ai} - g\left(C_{i,t}\right)}{\sigma_{Ai}},$$

$$\text{logit}\left(TPR_{i,t}\right) = \frac{\mu_{Bi} - g\left(C_{i,t}\right)}{\sigma_{Bi}}.$$

For the transformation $g()$, we use a natural logarithm, $g() = \log()$ for computational convenience. More details about a flexible form of transformation can be found in Jones *et al.*[28]

The individual parameters μ_{Ai}, μ_{Bi}, $\log(\sigma_{Ai})$, $\log(\sigma_{Bi})$ are assumed to be normally distributed with mean parameters m_A, m_B, s_A, s_B and a four-dimensional variance-covariance matrix Σ,

$$\begin{pmatrix} \mu_{Ai} \\ \mu_{Bi} \\ \log(\sigma_{Ai}) \\ \log(\sigma_{Bi}) \end{pmatrix} \sim \text{MVN}\left(\begin{pmatrix} m_A \\ m_B \\ s_A \\ s_B \end{pmatrix}, \Sigma \right).$$

Correlations are generally expected across the four sets of random effects μ_{Ai}, μ_{Bi}, $\log(\sigma_{Ai})$, $\log(\sigma_{Bi})$, and the correlation matrix can be pre-specified accordingly. Different correlation structures are described in Jones *et al.*[28] including a full correlation matrix which allows for all possible between-study correlations, a structured correlation matrix and an independence model that assumes independence of the random effects.

Prior specification

Prior distributions are required for the hyperparameters. For the D-dimer main analysis with 18 studies and sensitivity analysis with 25 studies, a non-informative prior was used for the bivariate model. Specifically, a normal distribution $N\ (0,\ 100)$ is used as the prior for the mean parameters m_A, m_B, a uniform distribution $U\,(0,\ 5)$ is used as the prior for the SD of the random effects σ_A, σ_B and a uniform distribution $U\,(-1, 1)$ is used as prior over the correlation coefficient ρ.

For the ADD-RS main analysis with 12 studies, we adopted a reference prior for the hyperparameters as recommended by Jones *et al.*[28] Specifically, a normal distribution $N\ (0,\ 100)$ is used as the prior for the mean parameters m_A, m_B, s_A, s_B, and a uniform distribution $U\,(0,\ 5)$ is used as the prior for the SD of the random effects μ_{Ai}, μ_{Bi}, $\log(\sigma_{Ai})$, $\log(\sigma_{Bi})$. For the correlation structure, we explored using an independent correlation matrix with the four sets of parameters assumed to be independent of each other, and a structured correlation matrix with a uniform distribution $U\,(-1, 1)$ used as prior over the correlation coefficient.

After a total 1,000,000 iterations with a burn-in of 100,000 and thinning of 10, the deviance information criterion (DIC) is 239.51 with an independent reference prior and the DIC is 239.54 with the structured reference prior. Including additional parameters for between-study correlations did not improve the model fit according to the DIC. Therefore, the simpler independence model was used in the ADD-RS main analysis. The point estimates of the pooled sensitivity and the specificity of the two different priors are quite similar, and the CrIs and the PrI are slightly wider for the structure prior compared to the independent prior, as presented in *Table 9*.

For the ADD-RS sensitivity analysis, ADD-RS with D-dimer analysis, and Canadian guideline analysis, we used informative priors for the SD as there are only limited number of studies available for analysis. The use of informative prior can help to incorporate external information into the model so that a better estimation can be obtained for the between-study correlation matrix. An informative prior is obtained by fitting a parametric distribution to the posterior samples from the ADD-RS main analysis. We found that the gamma distribution has a good fit to the posterior samples and a good convergence, compared to the log-normal distribution and the normal distribution. Specifically, we selected gamma distributions $\Gamma\ (13.2,\ \ 44.7)$, $\Gamma\ (7.4,\ \ 38.3)$, $\Gamma\ (9.3,\ \ 38.1)$, $\Gamma\ (4.4,\ \ 15.2)$ as the prior distribution over the SD.

We also explored using a reference prior with an independent correlation structure for the ADD-RS sensitivity analysis and ADD-RS with D-dimer analysis, which means that a normal distribution $N\ (0,\ 100)$ is used as the prior distribution over the mean parameters m_A, m_B, s_A, s_B, and a uniform distribution $U(0,\ 5)$ is used as the prior over the SD of the random effects. Results of the ADD-RS sensitivity analysis, ADD-RS with D-dimer analysis, and Canadian guideline analysis with different priors are presented in *Table 9*. The point estimates of the pooled sensitivity and the specificity of the two different priors are quite similar. The PrI and the CrI are wider with the reference prior compared to the informative prior.

TABLE 9 Pooled estimates for each analysis

Strategy	Threshold	Prior specification	Sensitivity (%) (95% CrI) (95% PrI)	Specificity (%) (95% CrI) (95% PrI)
ADD-RS main analysis	ADD-RS > 0	Independent reference prior (preferred)	94.6 (90 to 97.5) (72.6 to 99.7)	34.7 (20.7 to 51.2) (3.3 to 86.9)
		Structured reference prior	94.6 (89.8 to 97.6) (69.7 to 99.8)	34.6 (19.7 to 52.8) (2.5 to 89.6)
	ADD-RS > 1	Independent reference prior (preferred)	43.4 (31.2 to 57.1) (9.9 to 83.3)	89.3 (80.4 to 94.8) (41.9 to 99.5)
		Structured reference prior	43.5 (30.5 to 58.2) (8.5 to 85.8)	89.3 (79.2 to 95.1) (36.2 to 99.6)
ADD-RS with D-dimer analysis	ADD-RS > 0 or D-dimer > 500	Informative gamma prior (preferred)	99.8 (98.7 to 100) (96.1 to 100)	21.8 (12.1 to 32.6) (2.6 to 50.7)
		Reference prior	99.7 (96.9100) (74.1 to 100)	22.1 (6.6 to 39.9) (0.1 to 69.1)
	ADD-RS > or D-dimer > 500	Informative gamma prior (preferred)	98.3 (94.9 to 99.5) (86.4 to 100)	51.4 (38.7 to 64.1) (18.5 to 83.5)
		Reference prior	98.3 (89.2 to 99.8) (44 to 100)	51.4 (31.6 to 71.8) (4.6 to 96.5)
	ADD RS > 1 to ADD RS = 1 and D-dimer > 500	Informative gamma prior (preferred)	93.1 (87.1 to 96.3) (74.1 to 98.3)	67.1 (54.4 to 77.7) (33.4 to 89.3)
		Reference prior	93.1 (81.8 to 97) (50 to 99.3)	67.1 (47.5 to 82.3) (19.2 to 94.7)
ADD-RS sensitivity analysis	ADD-RS > 0	Informative gamma prior (preferred)	95.1 (88.5 to 98.4) (72.9 to 99.8)	38 (20.1 to 59.1) (4.5 to 86.8)
		Reference prior	95.1 (86.1 to 98.8) (64.4 to 99.9)	38 (20.1 to 58.7) (4 to 86.7)
	ADD-RS > 1	Informative gamma prior (preferred)	41.6 (24.8 to 59.1) (8.1 to 82.5)	91.7 (81.7 to 97) (53.7 to 99.6)
		Reference prior	41.7 (21.9 to 61.8) (4.9 to 87.7)	91.7 (81.1 to 97.4) (54.5 to 99.8)