University of Sheffield

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

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

Study acronym: ASES

This document describes the ASES study, and provides information about procedures throughout the study.

Contents

Abbreviations

AAS	acute aortic syndrome
ACS	Acute coronary syndrome
ADD-RS	Aortic Dissection Detection Risk Score
AHA	American Heart Association and
CI	confidence interval
CT	computer tomography
CTA	computer tomographic angiography
DAShED	Diagnosis of Acute Aortic Syndrome in the ED
ECG	electrocardiogram
ED	emergency department
ESC	European Society of Cardiology
EVPI	expected value of perfect information
EVPPI	expected value of partial perfect information
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PE	Pulmonary embolism
PMG	Project Management Group
PROSPERO	International prospective register of systematic reviews
PSC	Project Steering Committee
QALY	quality-adjusted life-years
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
RCEM	Royal College of Emergency Medicine
RCR	Royal College of Radiologists
TERN	Trainees Emergency Research Network

General Information

Sponsor
This project is not a health/social care study so does not require a Research Governance Sponsor

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Copyright statement

Protocol amendments since Version 1.0

None

Summary of Research

Research question

What is the optimal strategy for selecting patients with suspected acute aortic syndrome (AAS) to investigation with computer tomographic angiography (CTA) and what is the most useful direction for future research?

Background

AAS is a life-threatening condition that presents with chest, abdominal, or back pain, syncope, or perfusion deficit, and requires urgent diagnosis with CTA. Diagnostic technologies, including clinical scores, models, algorithms, and biomarkers, can be used to select patients for CTA from the large population presenting with potential symptoms of AAS.

Aims and objectives

We aim to:

1. Undertake a systematic review and meta-analysis to estimate the accuracy of clinical scores, models, algorithms, and biomarkers for diagnosing AAS
2. Develop a decision analytic model to estimate the cost-effectiveness of alternative diagnostic strategies for AAS
3. Estimate the expected value of perfect information to determine whether the expected cost of future research would be valuable.

Methods

We will search key electronic databases, augmented with citation search facilities, review of reference lists, and contact with experts, to identify studies that evaluate the diagnostic accuracy of clinical scores, algorithms, models, and biomarkers for detecting AAS. We will assess methodological quality using an appropriate tool (e.g. QUADAS-2). We will report descriptive results from case-control and cohort studies, but will only include cohort studies in meta-analysis. Our scoping review suggests we will identify sufficient data to undertake meta-analysis of the Aortic Dissection Detection Risk Score (ADD-RS) and D-dimer individually and in combination.

We will develop a decision-analytic model to simulate the management of a hypothetical cohort of patients attending hospital with symptoms of AAS. We will model application to the cohort of diagnostic strategies that select patients for CTA, along with comparator strategies of CTA for all and CTA for none. We will use estimates of diagnostic accuracy from the systematic review and meta-analysis to model the consequences in terms of treated and missed AAS. We will then use estimates from existing literature and clinical experts to model the consequences of delayed AAS diagnosis and performing CTA upon survival, health utility, and health and social care costs. We will estimate the incremental cost per QALY gained by each strategy compared to the next most effective alternative on the efficiency frontier. We will also estimate the expected value of perfect information to highlight the amount health care decision makers could spend on further primary research to reduce the uncertainty.

Timelines for delivery

The project will take place over 12 months. Further details are provided below:

- Months 1-6: Literature searches, study selection, data extraction, quality assessment, clinical expert review of relevant data, data synthesis (including meta-analysis, where relevant), and development of the decision analysis model
- Months 7-12: Decision-analysis modelling, patient and clinical expert review of the emerging findings, value of information analysis, write-up and dissemination

Anticipated impact and dissemination

We anticipate our findings will lead to more consistent and rational use of diagnostic testing for AAS and more appropriately focused future research. We will engage with guideline authors, professional organisations, and patient organisations to promote awareness and ensure that guidelines, position statements, and campaigns draw upon our findings.

1.0 Introduction

1.1 Background and rationale

Acute aortic syndrome (AAS) is a life-threatening emergency condition affecting the thoracic aorta. The syndrome is an umbrella term for acute aortic dissection, intra-mural haematoma, and penetrating ulcer. Without treatment, AAS can progress to aortic rupture, with rapid deterioration and death. Early treatment improves prognosis, with mortality increasing by around 2% per hour of delay [Pape 2015].

Chest pain is the most common presenting symptom of AAS (80%) although back pain (40%) and abdominal pain often occur [Erbel 2014]. These symptoms account for over 2 million emergency department (ED) attendances per year in England [NHS Digital A&E 2021] and are overwhelmingly due to causes other than AAS. The estimated incidence of AAS is one in every 980 ED attendances with atraumatic chest pain [Alter 2015], 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 ECG-gated CTA, echocardiography, and magnetic resonance angiography, can accurately diagnose AAS [Kicska 2021] but these also require careful patient selection.

Clinical scores and biomarkers can be used to select patients with suspected AAS for CTA. The aortic dissection detection risk score (ADD-RS) uses 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 [Rogers 2011]. The Canadian clinical practice guideline uses a clinical decision aid to stratify patients into low, moderate and high risk of AAS [Ohle 2020]. The AORTA score uses six clinical features to stratify patients to low or high risk [Morello 2021]. D-dimer is the most extensively studied biomarker for AAS [Yao 2021]. A low D-dimer level in a patient with a low clinical probability of AAS could rule out AAS [Bima 2020].

Symptoms associated with AAS are very common causes for ED attendance, with 944,204 attendances to English EDs in 2020-21 with chest pain, 1,017,601 with abdominal pain, 212,076 with back pain, and 55,875 with syncope [NHS Digital A&E 2021]. Diagnostic strategies for AAS can therefore be applied to a huge number of ED attendances, resulting in substantial health service costs and pressure on radiology services if the strategy fails to select patients for investigation with sufficient specificity.

There were 1314 emergency hospital admissions with dissection of the aorta (ICD10 code I71.0) and 494 with thoracic aortic aneurysm (I71.1 and I71.2) in England in 2020-21 [NHS Digital HES 2021]. AAS requires urgent treatment at a specialist centre, often involving inter-hospital transfer, so rapid accurate diagnosis is essential. 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 [Lovy 2013] and the misdiagnosis rate during the initial ED visit for AAS is estimated to be as high as 38% [Harris 2011]. Optimal patient selection for urgent CTA is challenging with misdiagnosis affecting between 1 in 3 to 1 in 7 AAS [Hansen 2007, Zahn 2012], leading to worse outcomes, whilst CTA over-testing leads to diagnostic yields of 2% to 3% [Lovy 2013, Ohle 2018].

NHS Resolution recently identified aortic disease, including dissection, as a common cause of fatality-related negligence claims, and noted that aortic dissection can be a challenging diagnosis to make [NHS Resolution 2022]. Problems with the diagnosis of AAS led the Healthcare Safety Investigation Branch to investigate delayed diagnosis of AAS [HSIB 2020]. The James Lind Alliance Heart Surgery and Vascular Society priority setting exercises both identified diagnosis of AAS among their research priorities [JLA PSP 2019, Lawson 2022].

1.2 Evidence explaining why this research is needed now

Recent meta-analyses have estimated the accuracy of the ADD-RS and D-dimer for AAS. Tsutsumi et al (9 studies, 26,598 patients) reported pooled sensitivity of 0.94 (95% confidence interval (CI) 0.90-0.96) and specificity of 0.40 (0.26-0.57) for ADD-RS ≥1, and sensitivity of 0.46 (0.34-0.59) and specificity 0.91 (0.79-0.96) for ADD-RS ≥2. Yao et al (16 studies, 1135 patients) reported pooled sensitivity of 0.96 (95% CI 0.91-0.98) and specificity of 0.70 (0.57-0.81) for D-dimer above the diagnostic threshold. Bima et al (4 studies, 3804 patients) reported pooled sensitivity of 0.99 (95% CI 0.993 to 1.00) for ADD-RS=0 and D-dimer<500ng/mL but did not report pooled specificity. The specificities in the primary studies ranged from 0.035 to 0.436.

Other scores have been developed but not widely evaluated to date. The AORTA score, consisting of six items, was derived using logistic regression and validated in two new (prospective and retrospective) cohorts, reporting superior accuracy to the ADD-RS [Morello 2021]. Duceau et al used machine learning to develop a prehospital prediction model for AAS [Duceau 2020] and Liu et al used a deep learning models to develop a decision support tool for diagnosis AAS [Liu 2022]. Biomarkers other than D-dimer may have potential for assisting AAS diagnosis, but these have not been systematically reviewed.

The evidence therefore identifies a number of strategies combining clinical probability scoring with D-dimer to rule out AAS with high sensitivity. However, the modest specificity of these strategies, when applied to a low prevalence cohort, are likely to result in a high rate of CTA use with a low diagnostic yield of AAS. A low positive yield from CTA may be appropriate, given the severe consequences of delayed diagnosis. Indeed, campaigns to increase awareness of acute aortic syndrome, such as the Think Aorta campaign, are intended to increase the use of CTA and reduce the risk of missed diagnosis.

Taylor and Iyer [Taylor 2013] used decision-analytic modelling of the health outcomes of AAS to compare testing strategies and determine testing thresholds for using CTA and D-dimer. 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 costs were not taken into account. The NHS would need to substantially increase capacity to deliver CTA at a low testing threshold, which would require substantial additional resources and thus evidence of cost-effectiveness. To date there has been no evaluation of the cost-effectiveness of different strategies for selecting patients with suspected AAS for CTA.

Current guidelines reflect the uncertainty in the existing evidence [Salmasi 2020]. Canadian, 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 [Ohle 2020], ESC guidelines recommend D-dimer for low-risk patients [Erbel 2014], and AHA guidelines do not identify a role for D-dimer [Hiratzka 2010]. Best Practice Guidance from the Royal College of Emergency Medicine and Royal College of Radiologists recommend CTA if any high-risk clinical features

are present and research to determine the role of D-dimer in suspected AAS [RCEM/RCR 2021].

2.0 Aims and objectives

The aim of the research project is to identify an optimal diagnostic strategy for suspected AAS and the expected value of information from future primary research. The specific objectives will be:

1. To systematically review existing primary and secondary research to estimate the accuracy of clinical scores, models or algorithms, and/or biomarkers (including D-dimer) for diagnosing AAS
2. To develop a decision analytic model to estimate the effectiveness (in terms of quality-adjusted life years (QALYs) 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 on a typical acute hospital) of using alternative diagnostic strategies for AAS
3. To estimate the expected value of perfect information to highlight the amount health care decision makers could spend on future primary research to reduce the uncertainty in diagnostic strategies for AAS

PICO definition of the research question

Population: People presenting to the ED with symptoms of AAS

Interventions: Diagnostic strategies using a clinical score and/or biomarker measurement to select patients for CTA or an alternative gold standard imaging technique

Comparators: (1) CTA for all patients; (2) CTA for none

Outcomes: Diagnostic accuracy for detecting AAS on CTA (including aortic dissection, intra-mural haematoma, penetrating aortic ulcer, and aortic rupture), QALYs, incremental cost per QALY gained and incremental net monetary benefit

3.0 Research plan

3.1 Design

We will undertake a systematic review, meta-analysis, decision analysis modelling, and value of information analysis. The systematic review and meta-analysis are intended to generate the best available estimates of the accuracy of diagnostic tests for AAS in people presenting to hospital with suspected AAS. The decision-analytic modelling then simulates what would happen if diagnostic strategies were applied to a typical population attending an NHS hospital with suspected AAS. The model then uses estimates of the outcomes following AAS from the existing literature, along with estimates of survival, health utility, and health and social care costs, to model the costs and QALYs that would be accrued if each potential strategy were used. Strategies are then compared to each other to estimate their relative cost-effectiveness and determine the most cost-effective strategy for the NHS. We can then use the model to identify the areas of greatest uncertainty and the cost-effectiveness of future research to reduce uncertainty.

Members of our research team will also be undertaking the Diagnosis of Acute Aortic Syndrome in the ED (DAShED) study between 1 June and 30 November 2022, which will

provide data to inform parameter estimates in the decision-analytic modelling. DAShED is an observational cohort study of people attending the ED with symptoms consistent with AAS, funded through a £8821 grant from the Royal College of Emergency Medicine. The study will involve clinical collaborators collecting presenting data from all ED attendances with possible AAS in at least five EDs over a 4-week period to determine the prevalence of AAS across the unselected cohort and within selected cohorts, specifically those identified by the attending clinician as having suspected AAS. This will inform a sensitivity analysis exploring variation in strategy application in practice.

3.2 Health technologies being assessed

We will evaluate any diagnostic strategy that ED clinicians could use to select patients with suspected AAS for CTA and has sufficient supporting data to estimate its accuracy for detecting AAS. Strategies will include clinical scores, models, or algorithms that use clinical features to stratify patients according to their risk of AAS, and blood tests used to detect AAS. Strategies may consist of a single technology (clinical score, model, algorithm, or blood test alone) or a combination (such as a diagnostic strategy in which a clinical score selects patients for a blood test, CTA, or no further investigation).

The ADD-RS and D-dimer (separately and in combination) are the most widely studied technologies. Clinicians already use these technologies in practice and they are included in a number of national guidelines (see page 3). Clinicians can easily calculate the ADD-RS at the bedside without using additional technology but it is available on the popular MDCalc website and app if a reminder is needed (https://www.mdcalc.com/aortic-dissection-detection-risk-score-add-rs). Other clinical scores, models or algorithms are more difficult to calculate and require supporting technology to facilitate their use. However, emergency clinicians are generally familiar with calculating clinical scores using apps or websites, such as MDCalc, so the need for supporting technology is an addressable barrier. D-dimer is a routine blood test in all EDs, usually as a central laboratory test with a turnaround time of 1-2 hours, but it can also be measured using point-of-care technology, with a much shorter turnaround time. Some other (novel) biomarkers are not currently routinely available. We will consider the NHS implications of implementing novel biomarkers if our analysis suggests they could form part of a cost-effective diagnostic strategy.

The existing literature often lacks clarity regarding the target population for the technologies. AAS can present in many ways, so clinicians need to suspect AAS in a wide range of ED presentations to avoid missed diagnosis. However, technologies are often developed and evaluated in selected groups of patients, typically on the basis of receiving a reference standard test, with unclear description of the selection process. To provide consistency and clarity, we will assume in this project that technologies will be applied to all patients presenting to the ED with symptoms of possible AAS but have planned a sensitivity analysis to explore the impact of selective application.

3.3 Target population

People attending the ED with symptoms of AAS, including those with new-onset chest, back, or abdominal pain, syncope, or symptoms related to perfusion deficit.

3.4 Exclusion criteria

We anticipate that the following groups will be excluded from studies identified in the literature review and from the hypothetical modelling population:

- Participants with AAS following major trauma or as incidental findings.

We will also exclude case reports and case series, and studies that do not report primary data

3.5 Setting/context
NHS acute hospital EDs

3.6 Outcomes
The key outcomes of interest will include diagnostic accuracy for detecting AAS on CTA (including aortic dissection, intra-mural haematoma, penetrating aortic ulcer, and aortic rupture), QALYs, incremental cost per QALY gained and incremental net monetary benefit

4.0 Systematic review and meta-analysis
4.1 Search strategy
We will undertake a systematic review to identify studies estimating the diagnostic accuracy of clinical scores, models, algorithms, and biomarkers for detecting AAS. We will undertake the systematic review in accordance with guidelines published by the Centre for Reviews and Dissemination [Centre for Reviews and Dissemination 2009] and report in accordance with the PRISMA statement [Moher 2015]. We will register the protocol with the PROSPERO register (National Institute for Health Research, PROSPERO 2012). We will refine the search strategy used for our scoping review (see https://figshare.shef.ac.uk/articles/report/Scoping_review_Diagnostic_tests_for_acute_aortic_syndrome/19658535/1) to identify studies with terms for acute aortic syndrome AND clinical scores, risk scores, models, algorithms or biomarkers (including specific names, such as ADD-RS and D-dimer) AND methodological filters for diagnostic accuracy studies.

Relevant studies will be identified through electronic searches of key electronic databases including MEDLINE, EMBASE and all databases in the Cochrane Library (including the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials and NHS Economic Evaluations Database). References will also be located through review of reference lists for relevant articles and through use of citation search facilities through the Web of Knowledge. In addition, systematic searches of trial registries and the Internet using the Google search engine will be used to identify unpublished materials and work in progress. Key authors and professional and academic research groups will also be contacted and asked for unpublished material.

4.2 Study selection
Studies will be included if they evaluate the diagnostic accuracy of any of the health technologies outlined above against a reference standard for AAS, in a population with suspected AAS. Case-control studies will be identified and reported descriptively, but will not be included in meta-analysis due to the risk of bias [Lijmer 1999]. Studies will be included if the participants (cohort, cases, or controls) presented with suspected non-traumatic AAS, and excluded if they presented following major trauma or as incidental findings. We will exclude case reports and case series, and studies that do not report primary data.

The inclusion of potentially relevant articles will be undertaken using a two-step process:

1. One reviewer will examine all titles and exclude any citations that clearly do not meet the inclusion criteria (i.e. non-human, unrelated to AAS).
2. One reviewer will examine all abstracts and full text articles, with a second reviewer independently examining a random subset of at least 20% [Garritty 2017, Taylor-Phillips 2017]. We will resolve any disagreements in the selection process through discussion and arbitration by a third reviewer if necessary.

4.3 Data collection
Data will be extracted independently by one reviewer using a standardised data extraction form and independently checked for accuracy by a second. Uncertainties will be resolved by

discussion. Those that cannot be resolved will be referred to the rest of the project team. Where we identify multiple publications of the same study we will extract and report data as a single study, seeking clarification from the study author where appropriate. We will extract the following standardised data from each eligible study: date, setting, design, population characteristics (age, sex, prevalence and types of AAS), patient selection criteria, index test characteristics, reference standard definitions, and results (numbers of true and false positives and negatives). If appropriate, we will contact the authors of the primary studies for missing data.

4.4 Assessment of methodological quality

Methodological quality of primary studies will be assessed using a quality assessment tool developed for diagnostic accuracy studies (e.g. QUADAS-2) [Whiting 2011]. For the patient selection domain, we will identify a high risk of bias if the sample selection was based on receipt of the reference standard test rather than presentation with possible AAS. For the reference standard domain, we will identify a high risk of bias if more than 10% of the study sample did not receive definitive investigation for AAS or adequate follow-up to detect missed AAS. We will determine whether the study derived the index test (including the threshold for positivity) using data that the study then used to estimate accuracy.

4.5 Data analysis

We anticipate that there will be sufficient data to undertake meta-analysis of studies evaluating the diagnostic accuracy of the ADD-RS alone, D-dimer alone, and the ADD-RS in combination with D-dimer. We will present descriptive results for any index tests with insufficient data for meta-analysis.

The ADD-RS meta-analysis will estimate accuracy at thresholds of >0 points and >1 point, since these are the key decision-making thresholds. The D-dimer meta-analysis will estimate accuracy using the diagnostic threshold reported in the primary study. Where studies report multiple thresholds, we will select a standard threshold, such as the manufacturer's recommended threshold or the threshold used in clinical practice. We will also analyse sensitivity and specificity at multiple thresholds, and obtain a summary receiver operating characteristic curve, to explore the trade-off between sensitivity and specificity [Steinhauser 2016]. We will undertake secondary analysis limited to studies reporting a standard threshold. The meta-analysis of combined ADD-RS and D-dimer will estimate the accuracy of four combinations based on ADD-RS above 0 points or above 1 point, alongside D-dimer below a standard threshold (expected to be 500ng/mL based on the scoping review) or below an age-adjusted threshold. The combined test is negative if both results are below the threshold and positive if either test is above the threshold.

The primary analysis will include all eligible studies with usable data. We will undertake sensitivity analyses in which studies are included in the analysis on the basis of key determinants of methodological quality, outlined in the methodological quality section above. This is likely to result in three analysis: (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).

A previous systematic review [Bima, 2020] suggested a higher prevalence of intramural haematoma in studies from Japan and Asia. If we identify potentially important differences between studies in the prevalence of different types of AAS, we will undertake separate analyses limited to studies with similar prevalence profiles of different types of AAS.

In each meta-analysis, the diagnostic test data will be analysed using a bivariate normal model for the log odds of the sensitivities and specificities in each study to allow for possible

(negative) correlation between sensitivity and specificity within studies [Reitsma 2005]. As heterogeneity between studies is generally expected in studies of diagnostic test accuracy, a random effects model will be used to allow for the heterogeneity beyond chance between studies. All the analyses will be conducted using a Bayesian framework via Markov chain Monte Carlo simulation, because it has the following advantages over a classical approach: (1) it allows us to analyse complex models exactly, (2) it is able to incorporate external evidence in addition to sample data, (3) it can make probabilistic statements about parameters. Results will be presented as a 95% credible interval for the population sensitivities and specificities, and a 95% prediction interval for a new study.

5.0 Decision-analytic modelling

Decision-analytic modelling of cost-effectiveness analyses will use a lifetime horizon and NHS health and social care perspective, and follow the good practice guidance outlined in the NICE methods guide for technology appraisals [NICE 2013].

5.1 Model overview

We will simulate the management of a hypothetical cohort of patients attending the ED with symptoms of AAS. The model will simulate what would happen if we used alternative diagnostic strategies to select patients for CTA, compared to using CTA for all, or using CTA for none. We will assume that true positive cases receive appropriate timely treatment for AAS while the false negative cases receive delayed treatment for AAS. We will assume that all patients without AAS (true negatives and false positives) are the same as the general population.

Clinical experts in the research team will review the results of the systematic review and meta-analysis, and identify up to 12 diagnostic strategies that could be used to select patients for CTA and are supported by reasonably robust estimates of diagnostic accuracy from the available literature. In doing this they will take into account the quality of the data and applicability to a typical NHS population, given evidence of differences in clinical features of AAS between populations [Wang 2014].

5.2 Data inputs

- *Patient cohort*

We will assume that the cohort has the age and sex profile of a population of patients attending an NHS ED with symptoms of AAS. We will estimate age and sex characteristics, along with the prevalence of AAS in the cohort, using routine data sources (NHS Digital), audit data from clinical members of the team, and data from the DAShED study.

- *Diagnostic accuracy*

We will use estimates of diagnostic accuracy from primary studies identified in our systematic review or our meta-analyses to model the consequences in terms of strategy true positives (CTA shows AAS), false positives (CTA shows no AAS), false negatives (missed AAS – no CTA performed), and true negatives (no AAS and no CTA).

The base-case analysis will only include strategies with direct estimates of accuracy from cohort study data. Our scoping review suggests this will include strategies based on the ADD-RS, D-dimer, the ADD-RS and D-dimer combined, and several other biomarkers. We will also analyse sensitivity and specificity at multiple thresholds, and obtain a summary receiver operating characteristic curve, to explore the trade-off between sensitivity and specificity [Steinhauser 2016].

Exploratory analyses will include:

1. Strategies involving combinations of tests with indirect estimates of accuracy based on using a Bayesian model to integrate the tests and estimate an overall accuracy [Baez 2017]. This assumes no correlation between the tests. If any of these strategies are cost-effective compared to strategies with direct estimates of accuracy, we will undertake sensitivity analysis to explore the impact of varying the assumption of no correlation between tests.
2. Strategies with estimates of accuracy from a case-control study. This will explore whether further research to produce more robust estimates of accuracy might be worthwhile.

- *Long term modelling*

We will assume that true positive cases receive appropriate timely treatment for AAS. Their short-term survival, rate of complications, subsequent life expectancy, long-term disabilities, health utility, and health and social care costs will be estimated from existing data, including registries, such as the International Registry of Acute Aortic Dissection [Evangelista 2018], cohort studies, such as the Oxford Vascular Study [Howard 2013], and studies of administrative datasets [Ianuzzi 2018, Scaffer 2015]. We will assume that false negative cases receive delayed treatment for AAS and use existing literature to estimate the impact of delay upon survival and complications [Matthews 2021, Pourafkari 2017, Hirata 2015, Harris 2011, Kurabayashi 2011]. We will use existing literature and relevant health economic evaluations to estimate long-term survival, health utility, and costs after disabling complications of AAS.

Type A and type B aortic dissection have different treatment, prognosis, and rates of complication, and are therefore reported separately in most of the relevant literature [Pape 2015]. We will model the outcomes of type A and type B aortic dissection separately but assume in the base case analysis that all diagnostic strategies have the same sensitivity for detecting different types of AAS. If the systematic review identifies evidence of any tests having differential sensitivity for type A and type B aortic dissection, we will undertake sensitivity analysis to explore the impact of differential sensitivity upon the cost-effectiveness of relevant strategies.

We will assume that all patients without AAS (true negatives and false positives) will have normal age and sex adjusted life expectancy, health utility, and health and social care costs (other than the QALY decrement associated with CTA – see next paragraph).

Clinical experts in the team will review estimates of key parameters in the model, such as the effect of delay upon survival, rate of complications, subsequent life expectancy, and long-term disabilities, to assess their credibility and applicability to the study population and the NHS. If required, they will facilitate surveys of clinician opinion, through organisations such as the Vascular Society of Great Britain and Ireland, and the Royal College of Emergency Medicine.

- *Quality of life impact of CTA and incidental findings*

We will assume that all patients who receive CTA (true and false positives) will suffer a QALY decrement determined by the risks of intravenous contrast media (hypersensitivity reaction, extravasation) and of radiation-related malignancy, which will be estimated from existing literature [American College of Radiology 2018], and additional costs associated with incidental findings (e.g. interval CT scans for lung nodules).

Investigation for AAS may identify alternative causes for chest pain that may benefit from diagnosis and treatment, such as acute coronary syndrome (ACS) and pulmonary embolism (PE). These diagnoses are usually identified through clinical assessment and a diagnostic work-up focused on the relevant pathology, but some may only be identified as incidental

findings in diagnostic assessment for AAS. Other incidental findings may be entirely unrelated to the presenting complaint but could still provide benefit through early treatment, or incur harm through unnecessary investigation. We will undertake a literature search for studies reporting the diagnostic yield of investigations for AAS, e.g. Meng at el and Hayter et al [Meng 2019, Hayter 2006], and review studies included in our systematic review, to determine the incidence and nature of additional diagnoses. We will then ask our clinical experts to review these data and determine whether there is sufficient evidence to estimate a QALY increment or decrement associated with incidental findings occurring with investigations for AAS.

We will undertake literature searches for evidence relating to the benefits and harms of incidental findings, and if we identify appropriate evidence, we will use it to adjust the QALY decrement associated with CTA. We will also look for any evidence that CTA or elements of the diagnostic strategies (such as D-dimer) can usefully identify alternative causes of chest pain, such as PE, and thus provide benefits unrelated to AAS. If we find evidence, we will amend the model accordingly.

- *Utilities*

We will perform focused literature review to identify the utility estimates for AAS patients and expert clinical input would be used to understand the impact of delayed treatment on the quality of life of AAS patients. Patients without AAS (true negatives and false positives) will have normal age and sex adjusted health utility estimated using the equation "General population utility = 0.9508566 + 0.0212126*male - 0.0002587*age - 0.0000332*age^2" specified in Ara et al 2010.

- *Resource use and costs*

We will estimate the following costs using previous literature or NHS reference costs:

1. Collecting relevant information and calculating a clinical score, assuming this takes 5 minutes of clinician time
2. Blood tests
3. CTA and interval scans to follow-up incidental findings
4. Treatment for any complications of CTA (hypersensitivity reaction, extravasation, radiation-induced malignancy)
5. Treatment for AAS
6. Long-term follow-up for AAS
7. Lifetime costs of care for complications of AAS

5.3 Model outputs

We will thus estimate the number of CTA undertaken, the number of AAS detected and missed, the QALYs accrued, and the costs accrued, if we were to apply each strategy to the relevant population in a typical hospital and for the whole NHS. We will then estimate the incremental cost per QALY gained by each strategy compared to the next most effective alternative on the efficiency frontier.

We will also estimate the resource impacts, especially in terms of number of CTA undertaken to understand the feasibility of implementing different diagnostic strategies [Thokala 2015].

- *Sensitivity and scenario analyses*

Probabilistic sensitivity analyses will use Monte-Carlo simulation to incorporate the uncertainty in the accuracy (i.e. sensitivity and specificity) of diagnostic strategies, costs, utilities, life expectancy, and other parameters. The results will be estimated as the average of 10,000 model runs, each time with different values for the input parameters. Probabilistic distributions will be used to capture the uncertainty in the input parameters where

appropriate, and samples will be used directly for other parameters (e.g. we anticipate that the sensitivity and specificity for diagnostic strategies would be input into the model as sampled values estimated from the Bayesian meta-analysis). Cost effectiveness acceptability curves will be plotted to identify the probability of different strategies being cost effective for a range of threshold values for an additional QALY.

Once the optimal strategies are identified, the impact of key parameters on the cost-effectiveness will be identified using deterministic one-way sensitivity analyses, where one parameter is varied at a time. Tornado plots would be presented to understand the key parameters that affect the cost-effectiveness results.

We will also perform specific scenario analyses as outlined above, which include:

1. Exploratory analysis including strategies with estimates of accuracy based on modelled data and/or case-control data.
2. Exploratory analysis of strategies with differential sensitivity for type A and type B aortic dissection.

Analyses will also be performed using sensitivity and specificity at multiple thresholds from the summary receiver operating characteristic curve [Steinhauser 2016], to identify the sensitivity and specificity at which the diagnostic strategy achieves optimal cost-effectiveness.

- *Sensitivity analysis to explore variation in strategy application in practice*

A major, and often unrecognised, source of uncertainty in AAS diagnosis relates to the application of risk stratification in practice. The high incidence of ED presentations with chest, abdominal, or back pain, and the relatively low incidence of AAS, suggests a very low prevalence of AAS in the cohort of patients in which AAS might be suspected (1 in 980 [Alter 2015]). However, prospective cohort studies evaluating diagnostic strategies for suspected AAS [Nazerian 2014, Nazerian 2018, Morello 2020, Morello 2021] report a much higher prevalence of AAS (10-30%). This suggests that clinicians may apply diagnostic strategies for AAS to a selected population from those with symptoms that are associated with AAS. We currently know very little about how clinicians suspect AAS in practice and decide to apply diagnostic strategies, but the available data suggests that variation in practice results in substantial variation in the prevalence of AAS in the clinically relevant population. Furthermore, campaigns to raise awareness of AAS, such as “Think Aorta”, encourage clinicians to suspect AAS more frequently and would therefore be expected to reduce the prevalence of AAS in the clinically relevant population.

We therefore plan a key sensitivity analysis to explore how the cost-effectiveness of the most cost-effective strategies in the base-case analysis varies with the prevalence of AAS in the clinically relevant cohort. We will vary the estimated prevalence of AAS in the hypothetical cohort and then determine the probability of each strategy being cost-effective at each prevalence. We will use administrative data, audit data, and data from the DAShED study to estimate the prevalence of AAS in selected and unselected populations. This will allow us to determine how the optimal strategy changes as prevalence increases and determine what the most cost-effective strategy would be if clinicians applied the strategy to selected population with a higher prevalence of AAS.

This sensitivity analysis could inform consideration of what constitutes an appropriate rate of CTA positivity for AAS within an organisation or across the NHS, which is currently uncertain and subject to substantial variation. We surveyed NHS hospitals regarding prevalence of AAS in those referred for CTA and received estimates from 26 hospitals ranging from 0.5% to 20% (median 5%). The sensitivity analysis could identify the threshold at which CTA for all becomes the optimal strategy (assuming that CTA for all will be more effective and

expensive that the alternatives). If an institution has missed diagnoses of AAS and has a CTA positivity rate above the threshold prevalence, then our analysis would suggest that CTA is being used too selectively.

6.0 Value of information analysis

We will estimate the expected value of perfect information to highlight the amount health care decision makers could spend on further primary research to reduce the uncertainty [Strong 2015]. Expected value of perfect information (EVPI) will be estimated to identify whether the expected cost of future research would be valuable. Expected value of partial perfect information (EVPPI) will also be estimated to identify the critical areas of uncertainty where future research would produce most benefit. Value of information analyses (EVPI and EVPPI) provide an estimate of the monetary value of further research to reduce uncertainty and, in particular, an estimate of how much we should be prepared to pay for a trial to reduce uncertainty.

7.0 Summary of patients/service users/carers/public as research participants

Our proposed evidence synthesis project does not involve patients/service users/carers/public as research participants. Details of our patient and public involvement are outlined in Section 14.0.

8.0 Dissemination, Outputs and anticipated impact

This study can influence health care policy and practice, through findings of systematic reviews and cost-effectiveness analysis, and future research, through findings from the value of information analysis. We therefore aim to promote dissemination and impact through clinical and research communities, as well as raising awareness among patients and the public.

We anticipate producing the following outputs at the end of the project:

- Open access peer reviewed publications describing the findings of the systematic review and the health economic modelling
- Presentations at professional meetings, such as the Royal College of Emergency Medicine (RCEM) Annual Scientific Meeting, the European Society for Emergency Medicine Annual Conference, and the Society for Medical Decision Making.
- Presentations at meetings organised by the Aortic Dissection Charitable Trust

We will share our findings with professional organisations involved in delivering clinical care for suspected AAS (RCEM, Royal College of Radiologists (RCR), Vascular Society of Great Britain and Ireland, British Society of Interventional Radiology) and patient organisations involved in improving care for suspected AAS (Aortic Dissection Awareness, the Aortic Dissection Charitable Trust). We will share scientific and plain language summaries of our findings with these organisations, supported by the outputs described above.

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 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.

We will use our value of information analysis, with input from clinicians and public/patient representatives, to identify priorities for research. We will produce a summary of the research priorities, with supporting rationale from our findings, to feed into research priority setting exercises and share with research funders, including NIHR, UKRI Medical Research Council, British Heart Foundation and Heart Research UK. We will present our findings at research development meetings, such as the RCEM Research Engagement Meeting.

Co-applicant Matt Reed has developed a research network around the DAShED study that aims to take forward primary research into the diagnosis of AAS. He will share our findings with DAShED collaborators and use the findings to develop future collaborative research and funding applications.

The possible barriers to generating impact depend upon the findings of the study. The ADD-RS is simple to use and D-dimer is readily available across the NHS, so any strategy based on the ADD-RS or D-dimer would not face significant practical barriers. We are not aware of any intellectual property restrictions around the use of the ADD-RS, which can be accessed on the MDCalc app - https://www.mdcalc.com/aortic-dissection-detection-risk-score-add-rs

Biomarkers that are not routinely available across the NHS would face substantial barriers to implementation. If our analysis suggested they could improve care and be cost-effective, then this would create a case for further research evaluating how they could be implemented in a cost-effective manner.

Our analysis could suggest that the most cost-effective strategy involves more liberal use of CTA than current practice. Implementation of such a strategy may face logistical barriers due to limited capacity of CT facilities or radiology expertise. In this situation, our findings would provide a case for greater investment in facilities or expertise, and our analysis of resource implications could guide service planning.

Implementation of research priorities may be limited by practical considerations around undertaking research of a low prevalence condition and undertaking research in the busy and unpredictable setting of emergency care. We will address these barriers through our wider work developing emergency care research, such as through the DAShED research group, the NIHR emergency care incubator, the RCEM research committee, and the Trainees Emergency Research Network (TERN). We will draw upon our clinical experts to ensure that research recommendations are practical and draw upon our patient representatives, and links with the Aortic Dissection Charitable Trust, to ensure that future research would be acceptable to patients.

Ultimately, we anticipate that our research will lead to greater clarity in guidelines for suspected AAS, more consistent and rational use of CTA, fewer diagnostic delays, and fewer cases of missed AAS.

9.0 Project timetable

The GANTT below shows the scheduling of the key stages in the project and their expected durations. We will submit a progress report at six months with the results of the systematic review and a final report at 12 months.

	Project month											
	1	2	3	4	5	6	7	8	9	10	11	12
PMG meetings	■		■		■		■		■		■	
PSC meetings		■				■					■	
PPI webinars		■					■					■
Report to funder						■						■
Literature searches	■	■										
Study selection		■	■									
Data extraction			■	■								
Quality assessment			■	■								
Expert and PPI review				■	■	■						
Meta-analysis					■	■						
Development of model					■	■	■	■				
Model analysis							■	■	■	■	■	
VoI analysis									■	■	■	
Expert and PPI review										■	■	
Writing up										■	■	■
Dissemination											■	■

PMG: project management group, PSC: Project Steering Committee, PPI: Patient and Public Involvement, VoI: Value of information

10.0 Study Supervision

The University of Sheffield will act as Sponsor for the project. A Project Steering Committee (PSC) and a Project Management Group (PMG) will be established to govern the conduct of the project.

10.1 Project Management Group

The Chief Investigator (SG) will take overall responsibility for delivering project. AP will be the study manager and responsible for the day-to-day delivery of the project with help from a clerical assistant. The Project Management Group, consisting of the co-applicants, will meet bi-monthly. A core group consisting of the Chief Investigator, Study Manager and key individuals will meet at least monthly to provide day to day management of the study. The composition of the core group will vary depending on the phase of the study.

10.2 Project Steering Committee

A Project Steering Committee will provide independent oversight to the project. This will consist of the Chief Investigator and Study Manager, alongside an independent chair, independent experts in emergency care, cardiac surgery, vascular surgery, vascular radiology, statistics, heath economics, and representatives from patient and public groups.

11.0 Funding and role of the funder

This study has been funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme. The funder has reviewed the research protocol but will have no role in data collection, analysis, data interpretation, report writing or in the decision to submit the report for publication.

12.0 Ethics

This project does not require Research Ethics Committee review, according to the Health Research Authority decision tool (http://www.hra-decisiontools.org.uk/ethics/). There are no research participants, the research does not collect information from individual patients, carers or the public, and does not involve processing confidential information.

We have not identified any significant ethical risks specific to this research. We have based the design on using aggregate data that is already in the public domain, so there are no significant data protection issues. We may need to contact authors to clarify issues around missing data, but we have no plans to request data sharing. If we do require individual patient data for any reason, we will only request anonymised data and will follow University of Sheffield information governance standard operating procedures. If the clinical co-investigators use any data from their NHS institution to inform the modelling, they will collect the data within their NHS institution, following local procedures, and will only share aggregate data with the study team.

13.0 Research expertise

The project will be undertaken in the School of Health and Related Research (ScHARR) in the University of Sheffield. It will involve collaboration between clinical experts in emergency medicine (SG, MR, SW), vascular radiology (ST), cardiothoracic surgery (GC), and vascular surgery (RH), methodological experts in systematic reviewing (AP, ME, MC), statistics (KR) and health economic modelling (PT), and patient/public representatives (CF, VL).

ScHARR is a leading centre for evidence synthesis that hosts an NIHR technology appraisal group (ScHARR-TAG) and evidence synthesis teams for the HS&DR and Public Health Research programmes. ScHARR has world-leading expertise in systematic reviewing and decision-analytic modelling, especially in emergency care.

14.0 Patient and public involvement

Our research team includes two members of the Aortic Dissection Charitable Trust. 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 promotes education and awareness of AAS, and supports research into the detection, prevention, treatment and cure for aortic dissection.

We will also identify additional patients with lived experience from outside the existing patient advocacy groups through two routes: (1) Patients identified as receiving investigation for suspected acute aortic syndrome in the DAShED study; (2) Patients who were treated for AAS at centres where our surgical co-applicants work. We will provide information about the study and invite these additional patients to join a PPI group.

Our PPI representatives will provide regular patient involvement through the project management group. The PPI group will meet every two months during the study to provide PPI as outlined below. We will arrange webinars to engage the wider Aortic Dissection Charitable Trust membership at the beginning, midway through, and the end of the project. We can also email members of the Trust to survey perspectives on any specific issues that arise during the project, if the PPI group considers this to be helpful.

The key specific areas of anticipated involvement are:

1. Reviewing diagnostic strategies for inclusion in the evaluation. Patient representatives will consider the feasibility and acceptability of using each strategy in practice.

2. Development of the decision-analytic model. Patient representatives will consider the key assumptions and parameter estimates in the model. They will consider whether the model reflects patient and public values, and whether the implications of assumptions in the model would be acceptable to the public.
3. Reviewing study outputs. Patient representatives will review the study conclusions, implications for practice and research recommendations, and will consider whether these reflect the needs, preferences and values or patients and the public. They will participate in redrafting study outputs and will be included as co-authors on the final report.
4. Co-production of any patient or public facing material. The study does not involve patients as research participants, so there are no information sheets, consent forms or questionnaires. However, we plan to disseminate findings to the public through social media, mainstream media and key interest groups. Patient representatives and researchers will work together to develop these materials.
5. In all of the above, the patient representatives will consider whether there are any implications for equity, such as in relation to age, gender, ethnicity, or socio-economic status.

15.0 Success criteria and barriers to proposed work

We are confident that we will deliver the work outlined in this proposal to time and budget. Our team has the expertise to deliver the work and we have planned to project carefully to ensure the work is deliverable. ScHARR is one of the largest centres for evidence synthesis in this UK, which ensures we will have the capacity to deliver the project if individual members of the team face difficulties. We have previously successfully delivered many similar projects to time and budget, so our confidence in our ability to deliver this project is based on experience.

Our ability to deliver the anticipated outputs and impact depends upon the findings of our analysis. We will be using established methods and following methodological guidance, so our outputs should be judged as scientifically valid and thus publishable, but whether they achieve high impact publication will depend upon the novelty and clinical acceptability of the findings. Similarly, although we expect our work to have impact, the findings will determine whether the impact involves policy and practice (if clear conclusions can be drawn about the cost-effectiveness of diagnostic strategies) or future research (if we identify important uncertainty that needs to be resolved).

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