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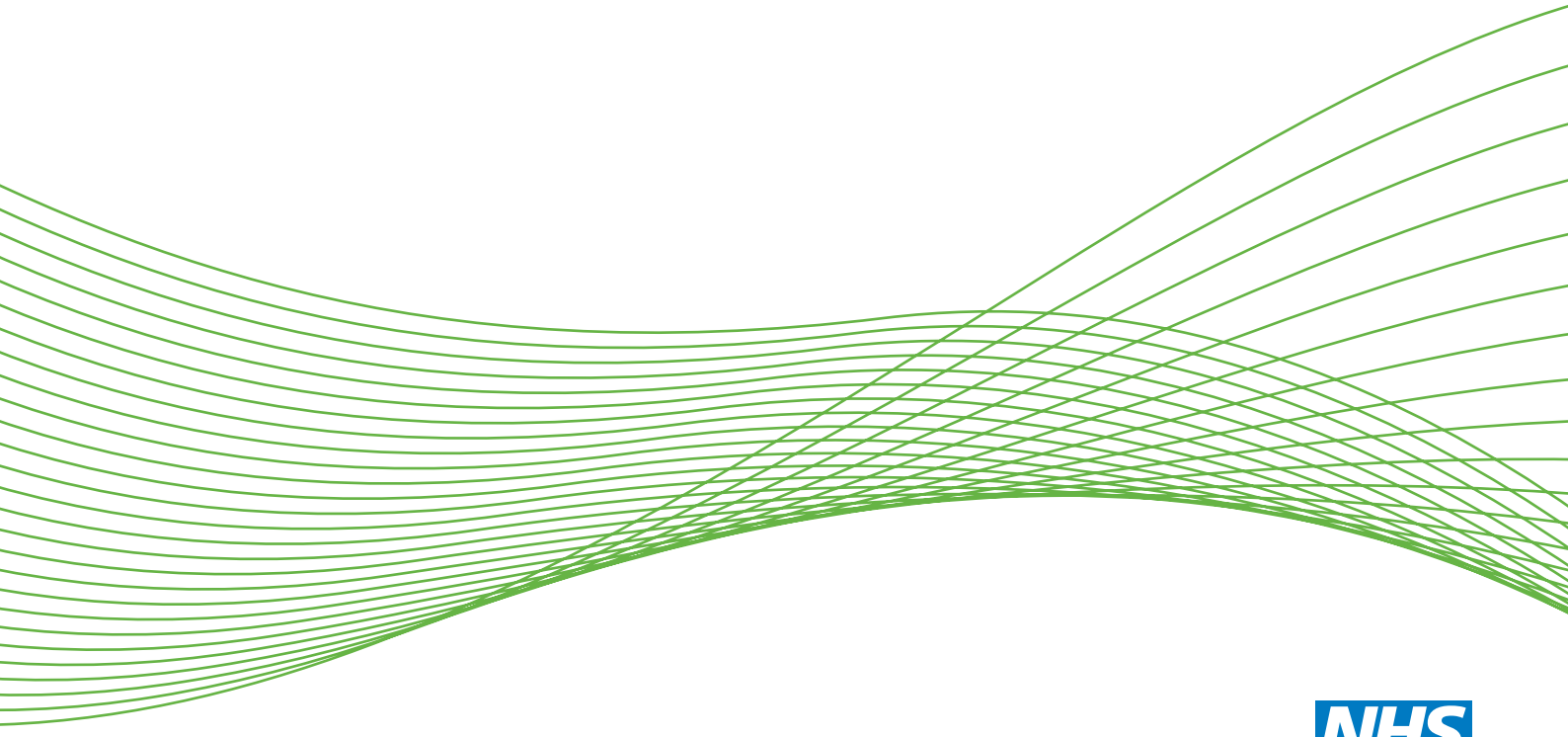

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Abstract

Routine echocardiography in the management of stroke and transient ischaemic attack: a systematic review and economic evaluation

Michael Holmes,* John Rathbone, Chris Littlewood, Andrew Rawdin, Matt Stevenson, John Stevens, Rachel Archer, Pippa Evans and Jenny Wang

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Background: Identification of the underlying cause of stroke and transient ischaemic attack (TIA) is important so that preventative therapy can be used to reduce the risk of recurrence. Transthoracic echocardiography (TTE) and transoesophageal echocardiography (TOE) are diagnostic tools used to identify those cardiac sources of stroke that may respond to treatment.

Objectives: (1) Undertake systematic reviews to determine (a) the prevalence of cardiac sources of stroke and TIA and (b) the diagnostic accuracy of echocardiography; (2) undertake a survey to ascertain which guidelines and management strategies are used by UK stroke centres; and (3) evaluate the cost-effectiveness of the addition of TTE to the routine assessment of patients who have had a first-episode diagnosed stroke or TIA in the UK.

Data sources: Bibliographic databases including MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature, PsycINFO and the NHS Economic Evaluation Database were searched from inception to December 2010 (prevalence) or September 2011 (diagnostic accuracy). Bibliographies of related papers were screened and experts were contacted to identify additional published and unpublished references.

Review methods: The systematic reviews were undertaken according to the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A decision-analytic model was developed to estimate the costs and quality-adjusted life-years accrued by each potential echocardiography strategy in the management of stroke and TIA for patients aged 45, 55 and 65 years. The model took a lifetime horizon and a NHS perspective. Costs and health benefits were discounted at an annual rate of 3.5%. Evidence to enable modelling was found for left atrial thrombus only. The cost-effectiveness of echocardiography is therefore based on all stroke patients being tested but only those with a left atrial thrombus receiving the benefits and harms of treatment. To describe current NHS stroke management practice we provided a questionnaire to the lead clinician of all stroke units in the UK.

Results: The searches identified 17,278 citations for the systematic review of the prevalence of potential cardiac sources of stroke and TIA, of which 65 studies were included. Patent foramen ovale was the most frequently reported pathology, followed by atrial septal aneurysm and mitral valve prolapse, with prevalence ranging from 0.25% to 73%, from 0.4% to 28% and from 0% to 31.6% respectively. For the systematic review of the diagnostic accuracy of echocardiography, 16,504 citations were identified, of which 51 studies were included. The pooled sensitivity to detect left atrial thrombus in three studies using transthoracic echocardiography in second harmonic imaging mode (TTEh) was 0.79 [95% credible interval

(CrI) 0.47 to 0.94], with a pooled specificity of 1.00 (95% CrI 0.99 to 1.00) compared with TOE. Differences in the diagnostic accuracy of tests occurred mostly in their sensitivity to detect cardiac sources of stroke. No adverse events data were reported. Our principal economic finding is that TTEh is a cost-effective use of NHS resources compared with TOE when clinicians deem it the most appropriate test. The survey showed that the decision-making process for the management of stroke and TIA is very complex and varies considerably by site. It is clear that to accurately describe current management practice a very sophisticated questionnaire would be required.

Limitations: The prevalence review highlights the difficulties that clinicians face when identifying the cause of cardioembolic stroke (the limitations of the tests, the confounding comorbidities and the inherent mobility of blood clots). The diagnostic accuracy review was limited by the small number of studies reporting data or because studies included too few participants with a cardiac pathology, leaving a large degree of uncertainty about the underlying diagnostic accuracy. The economic model has limitations because of the limited data available for important parameters such as the efficacy of treatment in reducing stroke recurrence.

Conclusion: The economic analysis indicates that, in those cases in which TTEh is deemed the most appropriate test, it is a cost-effective use of NHS resources. However, this analysis has highlighted a lack of evidence in several areas and the results of the economic evaluation should therefore be treated with caution. There is a need for further evaluation of current echocardiography technologies, the causal associations between potential risk factors and stroke and whether or not anticoagulation therapies prevent recurrent stroke. Studies attempting to establish the prevalence of cardiac sources of stroke should identify all potential risk factors, rule out those that are not relevant and grade the findings according to risk. Research is also needed to reduce the uncertainty around the estimates of the sensitivity and specificity of TTEh and TOE, singly and in combination, in detecting treatable cardiac abnormalities compared with the 'gold standard' in each pathology.

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Contents

List of tables xi

List of figures xiii

Glossary xv

List of abbreviations xvii

Scientific summary xix

Chapter 1 Background 1
Description of the health problem 1
Stroke 1
Transient ischaemic attack 1
Risk factors 1
Aetiology 2
Cardiac embolism 2
Diagnosis 2
Current service provision 3
Description of technology under assessment 3

Chapter 2 Definition of the decision problem 5
Decision problem 5
Population 5
Intervention (diagnostic index test) 5
Relevant comparators 5
Outcomes 5
Overall aims and objectives of the assessment 6

Chapter 3 Assessment of prevalence of cardiac sources of stroke and transient ischaemic attack 7
Methods for reviewing prevalence 7
Identification of studies 7
Inclusion and exclusion criteria 7
Data extraction strategy 8
Critical appraisal strategy 8
Methods of data synthesis 8
Results 8
Quantity of research available 8
Study characteristics 8
Discussion 9

Chapter 4 Assessment of diagnostic accuracy 13
Methods for reviewing diagnostic accuracy 13
Identification of studies 13
Inclusion and exclusion criteria 14
Data extraction 14

Critical appraisal strategy 14
Methods of data synthesis 14
Results of the review of diagnostic accuracy 15
Results of the search 15
Included studies 16
Excluded studies 21
Study quality 21
Analysis of diagnostic accuracy data: transthoracic echocardiography studies 26
Discussion of clinical effectiveness 35
Patent foramen ovale 35
Atrial thrombi 35
Left ventricular thrombi 35
Atrial septal defect 35
Atrial septal aneurysm 35
Left atrial appendage thrombi 36
Spontaneous echo contrast 36
Left ventricular aneurysm 36
Aortic valve stenosis 36
Cardiac vegetations 36
Mitral valve disorders 36
Atrial myxoma 36
Adverse effects and contraindications 36
Discussion 37

Chapter 5 Survey of relevant comparators **39**
Discussion of survey results 41

Chapter 6 Assessment of cost-effectiveness **43**
Systematic review of existing cost-effectiveness evidence 43
Identification of studies 43
Inclusion and exclusion criteria 43
Quality assessment strategy 44
Results of the cost-effectiveness review 44
Independent economic assessment 46
Methods 47
Definition of cost-effectiveness terms 55
Results 56
Deterministic results 56
Univariate sensitivity results 57
Probabilistic sensitivity analysis results 58
Probabilistic sensitivity analysis assuming correlation between tests when carried out in sequence 59
Results of the individual patient-level model (model 1) 61
Cost-effectiveness of warfarin 62
Expected value of perfect information analysis 63
Discussion of the economic analysis 63
Summary of key results 64

Chapter 7 Assessment of factors relevant to the NHS and other parties **67**

Chapter 8 Discussion **69**
Statement of principal findings 69
Prevalence 69

Diagnostic accuracy studies 69
Survey of relevant comparators 70
Economic evaluation 70
Strengths and limitations of the assessment 70
Clinical evaluation 70
Survey of relevant comparators 70
Economic evaluation 71
Uncertainties 71

Chapter 9 Conclusions **73**
Implications for service provision 73
Suggested research priorities 73
Economic analysis 73

Acknowledgements **75**

References **77**

Appendix 1 Cardiac sources of stroke and transient ischaemic attack **89**

Appendix 2 MEDLINE search strategy for the systematic review of prevalence studies **91**

Appendix 3 List of excluded studies (studies all excluded as no relevant data were identified) **93**

Appendix 4 Prevalence of cardiac sources of stroke by study **115**

Appendix 5 MEDLINE search strategy for the systematic review of diagnostic accuracy studies **119**

Appendix 6 Description of included studies **121**

Appendix 7 Diagnostic accuracy excluded studies **141**

Appendix 8 Summary of results **151**

Appendix 9 Cost-effectiveness review: literature search strategies, a MEDLINE example **155**

Appendix 10 Cost-effectiveness review: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (adapted) flow chart **157**

Appendix 11 Economic evaluation checklist **159**

Appendix 12 Stroke survey **161**

Appendix 13 Clinicians' comments **163**

Appendix 14 Protocol **165**

List of tables

TABLE 1 Calculation of sensitivity and specificity 6

TABLE 2 Prevalence of cardiac pathologies 10

TABLE 3 Characteristics of the included studies 17

TABLE 4 Responses to the question 'How often are the following tests used to investigate ischaemic stroke or TIA?' 40

TABLE 5 Responses to the question 'What guidelines do you use to investigate and manage ischaemic stroke or TIA?' (England and Wales) 40

TABLE 6 Responses to the question 'What guidelines do you use to investigate and manage ischaemic stroke or TIA?' (Scotland) 40

TABLE 7 Classification of patients after testing with TTEh 50

TABLE 8 The TTEh –ve TOE strategy results 50

TABLE 9 The TTEh +ve TOE strategy results 50

TABLE 10 Stroke/TIA event rates 52

TABLE 11 Adverse event rates 53

TABLE 12 Costs used in the model 54

TABLE 13 Quality-of-life utility values used in the model 55

TABLE 14 Deterministic mean per patient costs and QALYs for the four strategies undertaken at age 45, 55 and 65 years at the index event 56

TABLE 15 Age 45 years deterministic results 56

TABLE 16 Age 55 years deterministic results 57

TABLE 17 Age 65 years deterministic results 57

TABLE 18 Probabilistic mean per patient costs and QALYs for the four strategies undertaken at age 45, 55 and 65 years at the index event 58

TABLE 19 Age 45 years probabilistic results 58

TABLE 20 Age 55 years probabilistic results 58

TABLE 21 Age 65 years probabilistic results 59

TABLE 22 Probabilistic sensitivity analysis assuming correlation between tests: age 45 years 60

TABLE 23 Probabilistic sensitivity analysis assuming correlation between tests: age 55 years 61

TABLE 24 Probabilistic sensitivity analysis assuming correlation between tests: age 65 years 61

TABLE 25 Model 1 results: age 45 years 62

TABLE 26 Model 1 results: age 55 years 62

TABLE 27 Model 1 results: age 65 years 62

TABLE 28 Cost-effectiveness of warfarin: age 45 years 62

TABLE 29 Cost-effectiveness of warfarin: age 55 years 63

TABLE 30 Cost-effectiveness of warfarin: age 65 years 63

TABLE 31 Per-person and population EVPI results by age 63

List of figures

FIGURE 1 The PRISMA flow chart of included and excluded studies 9

FIGURE 2 The PRISMA flow chart of included and excluded studies 16

FIGURE 3 Methodological quality summary: review authors' judgements about each methodological quality item presented as percentages across all included studies 22

FIGURE 4 Methodological quality summary: review authors' judgements about each methodological quality item for each included study 23

FIGURE 5 Sensitivity and specificity of TTEf to detect PFO vs. TOE 27

FIGURE 6 Summary receiver operating characteristic plot of pooled TTEf detection of PFO 28

FIGURE 7 Sensitivity and specificity of TTEh to detect PFO vs. TOE 29

FIGURE 8 Summary receiver operating characteristic plot of pooled TTEh detection of PFO 30

FIGURE 9 Sensitivity and specificity of TTEf to detect left atrial thrombi vs. TOE 31

FIGURE 10 Sensitivity and specificity of TTEh to detect left atrial thrombi vs. TOE 31

FIGURE 11 Sensitivity and specificity of TTEf to detect atrial septal defect vs. TOE 31

FIGURE 12 Sensitivity and specificity of TTEh to detect atrial septal defect vs. TOE 32

FIGURE 13 Sensitivity and specificity of TTEf to detect atrial septal aneurysm vs. TOE 32

FIGURE 14 Sensitivity and specificity of TTEf to detect left atrial appendage thrombi vs. TOE 32

FIGURE 15 Sensitivity and specificity of TTEf to detect SEC vs. TOE 33

FIGURE 16 Sensitivity and specificity of TTEf to detect left atrial SEC vs. TOE 33

FIGURE 17 Sensitivity and specificity of TTEf to detect left ventricular aneurysm vs. left ventriculography 34

FIGURE 18 Sensitivity and specificity of TTEh to detect cardiac vegetations vs. TOE 34

FIGURE 19 Model diagram. IC, intracranial 48

FIGURE 20 Cost-effectiveness acceptability curve for age 45 years 59

FIGURE 21 Cost-effectiveness acceptability curve for age 55 years 60

FIGURE 22 Cost-effectiveness acceptability curve for age 65 years 60

FIGURE 23 Per-person and population EVPI results by age 64

Glossary

Aortic valve stenosis A disease of the heart valves in which the opening of the aortic valve is narrowed.

Atrial myxoma A non-cancerous tumour in the upper left or right side of the heart. It grows on the wall (atrial septum) that separates the two sides of the heart.

Atrial septal aneurysm An abnormally enlarged, bulging and mobile atrial septum. The atrial septum is the membrane that separates the left and the right upper chambers of the heart (the atria).

Atrial septal defect A congenital heart defect in which the wall that separates the upper heart chambers (atria) does not close completely. 'Congenital' means that the defect is present at birth.

Cardiac vegetations An abnormal growth of tissue around a valve composed of fibrin, platelets and bacteria.

False negative A patient with a condition who is wrongly diagnosed as not having it.

False positive A patient without a condition who is wrongly diagnosed as having it.

Left ventricular aneurysm Left ventricular aneurysm is due to weakened tissue in the left ventricular wall, which swells into a bubble filled with blood. This in turn may block the passageways leading out of the heart, leading to severely constricted blood flow to the body.

Mitral valve prolapse A valvular heart disease characterised by the displacement of an abnormally thickened mitral valve leaflet into the left atrium during systole.

Mitral valve regurgitation A backflow of blood from the left ventricle to the left atrium of the heart due to mitral insufficiency from incomplete closure of the mitral valve.

Mitral valve stenosis A narrowing of the mitral valve in the heart. This restricts the flow of blood through the valve leading to back pressure that builds up behind the narrowed valve.

Patent foramen ovale A patent foramen ovale is a defect in the septum wall between the two upper (atrial) chambers of the heart. Specifically, the defect is an incomplete closure of the atrial septum that results in the creation of a flap or valve-like opening in the atrial septal wall. A patent foramen ovale is present in everyone before birth but seals shut in about 80% of people.

Sensitivity The effectiveness of a diagnostic test in correctly identifying those with a condition (true positives divided by all those with the condition).

Specificity The effectiveness of a diagnostic test in correctly diagnosing as negative those who do not have a condition (true negatives divided by all those without the condition).

Spontaneous echo contrast Spontaneous echo contrast is a swirling pattern of blood flow, distinct from white noise artefacts, caused by an increased ultrasonic backscatter from aggregation of the cellular components of blood in the conditions of blood stasis or low-velocity blood flow.

Transoesophageal echocardiogram A test using ultrasound waves via a probe passed into the patient's oesophagus to obtain images of the heart. Ultrasound waves are sent through the probe, which picks up echoes of the sound waves as they bounce off different parts of the heart. These echoes are turned into moving pictures of the heart.

Transthoracic echocardiogram A test using ultrasound waves via a probe passed over the outside of the chest wall to obtain images of the heart. Ultrasound waves are sent through the probe, which picks up echoes of the sound waves as they bounce off different parts of the heart. These echoes are turned into moving pictures of the heart.

True negative A patient without a condition who is correctly diagnosed as not having it.

True positive A patient with a condition who is correctly diagnosed as having it.

List of abbreviations

AF	atrial fibrillation
CEAC	cost-effectiveness acceptability curve
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CrI	credible interval
CT	computerised tomography
DARE	Database of Abstracts of Reviews of Effects
ECG	electrocardiogram
EVPI	expected value of perfect information
FN	false negative
FP	false positive
GOS	Glasgow Outcome Score
HRG	Healthcare Resource Group
HTA	Health Technology Assessment
IC	intracranial
ICER	incremental cost-effectiveness ratio
ICH	intracranial haemorrhage
IST	International Stroke Trial
LSR	Lothian Stroke Register
MCMC	Markov chain Monte Carlo
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PFO	patent foramen ovale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
PVS	persistent vegetative state
QALY	quality-adjusted life-year
QoL	quality of life
SE	standard error
SEC	spontaneous echo contrast
SIGN	Scottish Intercollegiate Guidelines Network
SMT	standard medical treatment
STARD	Standards for Reporting of Diagnostic Accuracy
TCD	transcranial Doppler
TIA	transient ischaemic attack
TMD	transmitral Doppler
TN	true negative
TOE	transoesophageal echocardiography
TP	true positive
TTE	transthoracic echocardiography
TTEf	transthoracic echocardiography in fundamental imaging mode
TTEh	transthoracic echocardiography in second harmonic imaging mode
TTEh +ve TOE	perform TOE on those patients testing positive on TTEh imaging
TTEh –ve TOE	perform TOE on those patients testing negative on TTEh imaging
WTP	willingness to pay

Scientific summary

Background

Stroke is a major cause of mortality in the UK. As a single cause of death, stroke is second only to coronary heart disease and it can cause a range of disabilities including speech problems, limb paralysis and dementia. Approximately half of all those affected by stroke are dependent on others for help with daily activities. A transient ischaemic attack (TIA) produces symptoms similar to those of a stroke but these symptoms resolve within 24 hours and usually within a few hours. One-fifth of patients who have experienced a TIA will later develop a stroke. Identification of the underlying cause of stroke and TIA is important so that preventative therapy can be used to reduce the risk of recurrence. The causes of stroke vary although it is thought that about 20% of ischaemic strokes are cardioembolic. Transthoracic echocardiography (TTE) is a diagnostic tool used to identify cardiac sources of stroke by using sound waves to produce images of the heart, facilitating the detection of blood clots, valvular disorders and structural defects associated with stroke. TTE can be performed in fundamental imaging mode (TTEf), which uses the reflected echoes from the same spectral band as that of the emitted pulse, or in second harmonic imaging mode (TTEh), which employs the second harmonic of the emitted frequency band to construct images. Transoesophageal echocardiography (TOE) uses similar sound wave technology to produce images of the heart; however, with TOE the ultrasound transducer, positioned on an endoscope, is guided down the patient's throat into the oesophagus. TOE is therefore more invasive than TTE but provides images without interference from the ribs or lungs.

Objectives

The overall aim was to use secondary research methods to determine the most appropriate echocardiography diagnostic management strategy for first-episode diagnosed stroke and TIA patients. More specifically, the objectives were to:

- undertake systematic reviews to determine (a) the prevalence of potential cardiac sources of stroke and TIA and (b) the diagnostic accuracy of echocardiography
- undertake a survey to describe current practice in the NHS in terms of guidelines and management strategies used by stroke centres
- evaluate the cost-effectiveness of the addition of TTE to the routine assessment of patients who have had a first-episode diagnosed stroke or TIA in the UK.

Methods

A systematic review was undertaken to identify the prevalence rates of cardiac sources of stroke and TIA in patients with first-episode ischaemic stroke or TIA. Major databases including EMBASE, MEDLINE and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched from inception to December 2010 and prevalence ranges were reported. In addition, diagnostic accuracy studies of sources of stroke that are not clinically apparent on routine examination were sought in MEDLINE, EMBASE, CINAHL, PsycINFO, Web of Science, The Cochrane Library (including the Cochrane Central Register of Controlled Trials and the Database of Abstracts of Reviews of Effects), the NHS Economic Evaluation Database and the Health Technology Assessment database (from inception to September 2011). Study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist. Included studies were meta-analysed using WinBUGS, using a bivariate normal model to calculate the logit sensitivities and specificities in each study to account for correlation within studies.

For the economic analysis a discrete event decision-analytic model was developed to estimate the costs and quality-adjusted life-years (QALYs) accrued by each potential echocardiography strategy in the management of stroke and TIA. The model took a lifetime horizon and the perspective of the NHS. Costs and health benefits were discounted at an annual rate of 3.5% as recommended by the National Institute for Health and Care Excellence. Utility values were identified by a literature review. Univariate and probabilistic sensitivity analyses were conducted. The only pathology for which evidence was found to enable modelling was left atrial thrombus. The cost-effectiveness of echocardiography is therefore based on all stroke patients being tested (apart from those contraindicated echocardiography) but only those with a left atrial thrombus receiving the benefits and harms of treatment. The benefits of early detection of left atrial thrombi were modelled using literature reviews to estimate the diagnostic accuracy of TTEh and TOE, the benefits and harms of treatment and the risks of stroke in treated and untreated patients with and without left atrial thrombi. Hospital and long-term care costs were estimated for each strategy and each stroke outcome. The analysis was conducted for patients aged 45, 55 and 65 years and the costs and QALYs accrued for each cohort were estimated for each diagnostic strategy.

To describe current NHS stroke management practice we provided a questionnaire survey to the lead clinician of all stroke units in the UK.

Results

The searches identified 17,278 citations for the systematic review of the prevalence of potential cardiac sources of stroke and TIA, of which 65 studies were included. From the studies retrieved, TOE (45 studies) was the most frequently reported diagnostic tool used to assess cardiac pathologies followed by TTE (38 studies of TTEh and TTEf). The prevalence rates of the identified pathologies in the selected study populations were wide-ranging. From the studies identified, patent foramen ovale (PFO) was the most frequently reported pathology (39 studies) with a prevalence ranging from 0.25% to 73%, followed by atrial septal aneurysm (28 studies) with a prevalence ranging from 0.4% to 28% and mitral valve prolapse (17 studies) with a prevalence ranging from 0% to 31.6%.

The searches identified 16,504 citations for the systematic review of the diagnostic accuracy of echocardiography, of which 51 studies were included. The pooled sensitivity to detect left atrial thrombus in three studies using TTEf was 0.34 [95% credible interval (CrI) 0.07 to 0.71] with a specificity of 1.00 (95% CrI 0.97 to 1.00) compared with TOE. The pooled sensitivity to detect left atrial thrombus in three studies using TTEh was 0.79 (95% CrI 0.47 to 0.94) with a specificity of 1.00 (95% CrI 0.99 to 1.00) compared with TOE. The pooled sensitivity to detect PFO in 13 studies using TTEf was 0.34 (95% CrI 0.21 to 0.47) with a specificity of 1.00 (95% CrI 0.99 to 1.00) compared with TOE. The pooled sensitivity to detect PFO in 11 studies using TTEh was 0.89 (95% CrI 0.80 to 0.95) with a specificity of 0.99 (95% CrI 0.97 to 1.00) compared with TOE. The pooled sensitivity to detect spontaneous echo contrast (SEC) in the left atrium in four studies using TTEf was 0.00 (95% CrI 0.00 to 0.02) with a specificity of 1.00 (95% CrI 0.99 to 1.00) compared with TOE. Superior diagnostic accuracy was found using TTEh to detect left atrial SEC, with a sensitivity of 0.88 (95% CrI 0.78 to 0.94) and a specificity of 1.00 (95% CrI 0.03 to 1.00) compared with TOE, although this was based on a single study. Differences in the diagnostic accuracy of TTE and TOE occurred mostly in their sensitivity to detect cardiac sources of stroke; in most studies the specificity of TTE and TOE was similar. No adverse events data were reported.

Our principal economic finding is that TTEh is a cost-effective use of NHS resources compared with TOE in those cases where clinicians deem it the most appropriate form of testing. Because of data limitations we have not evaluated the cost-effectiveness of TOE in those cases in which clinicians regard it the most appropriate test.

The survey of UK stroke units showed that the decision-making process in the management of stroke and TIA is very complex and varies considerably by site. It is clear that to accurately describe current management practice a very sophisticated questionnaire would be required, which may result in poor response rates and thus yield little useful information.

Discussion

There was considerable variation in the prevalence of cardiac causes of stroke, reflecting the heterogeneity of the included studies and the uncertainty surrounding the clinical importance of these cardiac pathologies in ischaemic stroke. Data were derived from risk factor findings on routine examination rather than established aetiology, and the relative importance of each of the cardiac pathologies in ischaemic stroke is uncertain.

Across a range of cardiac pathologies (PFO, atrial thrombus, atrial septal defect, atrial septal aneurysm, left atrial appendage thrombus, SEC) the diagnostic accuracy of TTEh was superior to that of TTEf, although the consequence of the improved sensitivity of TTEh was a decrease in specificity. The diagnostic accuracy of TOE was superior to that of TTEh across most cardiac pathologies, although TOE also demonstrated imperfect accuracy for the detection of PFO.

The deterministic and probabilistic economic analyses both show that in those cases in which clinicians consider TTEh to be the most appropriate test it is a cost-effective use of NHS resources. It should be noted that the evidence base for the analysis for some of the main parameters in the model was poor and thus the conclusions reached should be treated with a certain amount of caution.

This analysis has highlighted the need for further evaluation of current echocardiography technologies, the causal associations between potential risk factors and stroke and whether or not anticoagulation therapies prevent recurrent stroke. In the presence of multiple risk factors, establishing the cause of cardioembolic stroke is complex and unlikely to provide an unequivocal answer. Studies attempting to establish the prevalence of cardiac sources of stroke should perform a thorough clinical evaluation to identify all potential risk factors, rule out those that are not relevant and, when possible, grade the findings according to risk. Research is needed to reduce the uncertainty around the estimates of the sensitivity and specificity of TTEh and TOE, singly and in combination, in detecting treatable cardiac abnormalities compared with the 'gold standard' in each pathology. Answering these research questions would improve the accuracy of the results produced by the economic model.

Conclusion

The economic analysis indicates that, in those cases in which TTEh is deemed the most appropriate test for the management of stroke and TIA, it is a cost-effective use of NHS resources. Because of data limitations it was not possible to evaluate the cost-effectiveness of TTEh compared with TOE in subsets of cases in which TOE is considered most appropriate.

However, this analysis has highlighted the need for more research in several areas and until this is carried out the results of the economic evaluation should be treated with a certain amount of caution. The main research priorities are long-term UK-based studies measuring stroke recurrence rates, the efficacy of treatment and the diagnostic accuracy of TTEh and TOE in detecting cardiac abnormalities that respond to treatment.

Study registration

This study is registered as PROSPERO no. CRD42011001353.

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Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

Description of the health problem

Stroke

Stroke is a serious medical condition in which the blood supply to the brain is disrupted, potentially resulting in disability and mortality. The World Health Organization (WHO) defined stroke as rapidly developing clinical signs of focal (sometimes global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin.[1] Symptoms of stroke include weakness, numbness, visual loss, speech disturbance and unsteadiness. There are two major types of stroke: ischaemic stroke, which accounts for 85% of strokes, is caused by disrupted blood supply as a result of narrowing or blockage of the circulatory system; haemorrhagic stroke, which accounts for about 15% of strokes, is due to vascular rupture with bleeding into the brain. Brain imaging is required to differentiate between the two types.

Stroke is the second largest cause of death in the UK after heart disease[2] and results in > 60,000 deaths each year in the UK.[3] More than 56,000 deaths due to stroke were recorded in England and Wales in 1999, which represents 11% of all deaths recorded that year.[4] Annually in England about 110,000 people have a first or recurrent stroke[5] and a further 54,000 individuals have a transient ischaemic attack (TIA).[6]

More than 900,000 people in England are living with the effects of stroke, with half of these being dependent on other people for help with everyday activities.[7] Stroke causes a greater range of disabilities than any other condition[8] and also causes secondary medical problems including dementia, depression, epilepsy, falls and fractures that place a considerable burden on the economy in England, resulting in estimated annual direct costs to the NHS of £2.8B.[4]

Transient ischaemic attack

Transient ischaemic attack has been defined as 'a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischaemia, without acute infarction' (p. 2277).[9] In a TIA, symptoms typically subside within a few hours; however, people who have experienced a TIA have a higher risk of stroke, with approximately 20% of TIA patients developing a stroke,[10] and therefore patients require prompt medical attention to prevent complications. It has been reported that 10–15% of TIA patients experience a stroke within 3 months,[9] with the greatest risk being within the first 72 hours,[11] and the risk of a recurrent stroke is 30–43% within 5 years.[4]

Risk factors

There are a number of modifiable risk factors, including hypertension, cardiac disease [particularly atrial fibrillation (AF)], diabetes, cigarette smoking, alcohol consumption, hyperlipidaemia and carotid stenosis.[12] Epidemiological research has shown that raised blood pressure is the most important risk factor for ischaemic stroke.[13] The incidence of stroke increases with decreasing socioeconomic conditions.[14] Important non-modifiable risk factors for ischaemic stroke include age, gender, ethnicity and heredity.[12]

Age is an important risk factor for ischaemic stroke. The overall incidence by 75–84 years of age is approximately 25 times higher than that at age 45–54 years.[10,15] Ischaemic stroke in adults aged < 45 years is relatively rare, with surveys estimating that about 5% of all cerebral ischaemic infarctions occur in this age group,[16] although others studies have indicated this figure to be > 10%.[17]

Aetiology

Cerebral embolism may be arterial or cardiac in origin. Cardiac embolism results from thrombus formation in the heart, which then embolises to the intracranial circulation. Cardiac emboli can be of any size but those arising from the cardiac chambers are often large and more likely to cause severe stroke, disability and death.

Cardiac embolism

Estimates of the relative frequency of cardioembolic stroke vary, although cardioembolic stroke has been estimated to result in approximately 20% of ischaemic strokes.[18] There are several potential cardiac sources of embolism but it may be difficult to be certain whether an identified embolic source is the actual cause of stroke, particularly if there are alternative causes such as coexistent large artery disease.

Atrial fibrillation is found in about 15% of all stroke patients[19] and is detectable from either clinical examination or electrocardiogram (ECG) monitoring. In the case of patients with cardioembolic stroke, a higher percentage of about 45% are associated with AF.[20]

Other potential causes of stroke include left ventricular dysfunction (congestive heart failure), valve disease including prosthetic valves, intracardiac right-to-left shunts [patent foramen ovale (PFO), particularly in conjunction with atrial septum aneurysm] and atheroma of the ascending aorta and the aortic arch.[21] Other conditions that are also considered to be potential sources include sinoatrial disorder, recent acute myocardial infarction, marantic or infective endocarditis, and cardiac tumours.[22]

Mitral valve disease is associated with a significant proportion of cardioembolic stroke in young patients and is more common in some populations because of a high prevalence of rheumatic heart disease.[23] The risk of cardioembolic stroke associated with rheumatic heart disease (in the presence or absence of synthetic valve prosthesis) varies considerably (40–70%) among different geographical stroke registries; in Finland, with the virtual disappearance of rheumatic fever, the incidence of rheumatic heart disease is much lower.[24]

Diagnosis

Identification of the underlying mechanisms and aetiologies is important so that appropriate therapy can be initiated to decrease the risk of recurrent stroke, although in about one-third of stroke patients no identifiable aetiology is found,[25–27] even after complete clinical evaluation. No quantitatively valid clinical criteria exist for the diagnosis of cardioembolic stroke. The diagnosis is based on identifying a potential cardiac source of embolism, eliminating other potential sources of cerebral ischaemia and considering the clinical neurological features for suspected cardioembolic stroke.[18]

Abrupt onset of the neurological deficit is not helpful in determining the origin of the stroke as abrupt onset of a maximal neurological deficit occurs in the majority of patients with ischaemic stroke from other causes, such as stroke with a carotid origin. The location of the infarct does not always help to determine causation, even though cardiogenic emboli most commonly lodge in the middle cerebral artery or its branches, as emboli to the vertebrobasilar or anterior cerebral artery can also occur. However, multiple acute brain infarctions in both cerebral hemispheres usually suggest an embolic mechanism, particularly one of aortic or cardiac origin.[28] Other morbidities that can obscure diagnosis are emboli from proximal sources such as the carotid arteries, which may have a similar presentation as those of cardioembolic origin.

Current service provision

No recommendations relating to the use of echocardiography in the assessment of first-episode diagnosed stroke and TIA patients were made within the *National Clinical Guideline for Stroke* published by the Royal College of Physicians,[29] the National Institute for Health and Care Excellence (NICE) acute stroke and TIA guideline[30] or the Department of Health *National Stroke Strategy*.[31] The use of this technology in the management of stroke and TIA patients in the UK appears to be variable (see *Chapter 4*). The British Society of Echocardiography[32] stated that echocardiography was indicated (1) in adults with neurological disease that includes unexplained stroke or TIA without evidence of previous cerebrovascular disease or without significant risk factors for other cause [with the suggestion that saline contrast echocardiography by transthoracic echocardiography (TTE) or transoesophageal echocardiography (TOE) should be used], and (2) in patients for whom a therapeutic decision will depend on the outcome of echocardiography (e.g. anticoagulation). This guidance also stated that echocardiography was not indicated in patients in whom echocardiography would not affect the decision to begin anticoagulation (e.g. patients in AF with a cerebrovascular event and no suspicion of structural heart disease).

Description of technology under assessment

Transthoracic echocardiography is a non-invasive imaging technique that uses sound waves to create a moving picture of the heart. In the UK, a trained sonographer performs the test and interprets the results. An instrument called a transducer that releases high-frequency ultrasound waves is placed between the ribs and the upper abdomen directed towards the heart. The transducer picks up the echoes of ultrasound waves and transmits them as electrical impulses. The echocardiography machine converts these impulses into moving pictures of the heart. Pictures can be two-dimensional or three-dimensional, depending on the part of the heart being evaluated and the type of machine. This technique can provide information about cardiac structure and function, helping to establish the diagnosis and guide therapy. TTE can be performed in fundamental imaging mode (TTEf), which uses the reflected echoes from the same spectral band as that of the emitted pulse, or in second harmonic imaging mode (TTEh), which employs the second harmonic of the emitted frequency band to construct images. The transmission frequency determines the trade-off between penetration depth and spatial resolution.[33]

Echocardiography can be performed to identify cardiogenic sources of emboli and has been recommended as a routine test in stroke management.[34] However, the cost-effectiveness of echocardiography in the secondary prevention of stroke is unclear. Some investigators have recommended the use of TTE in all stroke patients[35] whereas other evidence suggests the need to perform TOE when no indications for anticoagulation are found with TTE.[36] TOE is used to check the structure and function of the heart. The test requires patients to swallow a probe that is attached to an ultrasound machine. This obtains images of the heart from within the oesophagus, which lies just behind the heart, and can give a clearer view of the heart than normal echocardiography. Procedural risks are low but include transient throat pain, laryngospasm, aspiration, hypotension, hypertension, tachycardia, mucosal bleeding, oesophageal rupture and a rare risk of death. Benzocaine topical spray can cause toxic methaemoglobinaemia.

Chapter 2 Definition of the decision problem

Decision problem

Population

Patients with cardiac pathologies (see *Appendix 1*) relevant to ischaemic stroke or TIA were included. However, cardiac pathologies that are clinically identifiable without the need for echocardiography, or which are present with symptoms that represent other indications for echocardiography[37] such as recent myocardial infarction, dilated cardiomyopathy and infective endocarditis, were excluded.

Echocardiography in newly diagnosed AF patients has been commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme as a separate project (reference no. 08/45/01 HTA Technology Assessment Report) and AF is therefore not included in this study.

Intervention (diagnostic index test)

Transthoracic echocardiography is an ultrasound imaging technique utilising beams of ultrasound transmitted at frequencies of 2.5–5 MHz. A transducer is placed on the chest wall, allowing the structures of the heart and velocity of blood flow to be visualised.[38] TTE may be used to determine cardiac sources of stroke or TIA and facilitate treatment and secondary prevention strategies.

The index tests assessed in this review are:

- TTEf
- TTEh.

Relevant comparators

The accepted reference standards for the detection of cardiac pathologies are not well defined, and none of the tests, apart from invasive surgical procedures, provides a definitive diagnosis. For the detection of PFO, TOE is often considered the 'gold standard' to measure other tests against,[21] and this was selected as the reference standard to measure the performance of TTE. Because of the uncertainty of relevant reference standards for other cardiac sources of stroke and TIA, no a priori comparators were stated and all studies were included that compared the diagnostic accuracy of TTE against other commonly available tests.

Outcomes

Patients are classified by the index test (TTE) as being either positive or negative for the cardiac pathology under investigation. The reference standard is also undertaken to identify patients' true health status. The reference standard is assumed to have 100% sensitivity and specificity; however, subgroup analyses are undertaken whenever possible to test the effect of using different reference standards. Patients fall into one of four groups. When the index test is positive, patients may be true positive (TP), in which case both tests agree that they have a cardiac pathology, or false positive (FP), in which case the index test indicates that they have the cardiac pathology but the reference standard does not. When the index test is negative, patients may be true negative (TN), in which case both tests agree that they are cardiac pathology free, or false negative (FN), in which case the index test incorrectly classifies them as being free of the pathology.

This can be represented in a 2 × 2 table (*Table 1*). In the clinical setting, FPs can result in patients receiving unnecessary treatment whereas FNs can result in people not receiving the treatment that they require. Sensitivity indicates the effectiveness of the index test in correctly identifying cardiac pathologies. Specificity indicates the effectiveness of the index test in correctly classifying people as cardiac pathology free. Sensitivity and specificity can be calculated as simple percentages. In practice, diagnostic tests often

TABLE 1 Calculation of sensitivity and specificity

Index test result	Reference standard positive	Reference standard negative
Index test positive	TP	FP
Index test negative	FN	TN
	Sensitivity = [TP/(TP + FN)] × 100	Specificity = [TN/(TN + FP)] × 100

have a high sensitivity at the expense of a low specificity and vice versa. Ideally, a test would have both high sensitivity and high specificity.

The majority of included studies used TOE as the reference standard to measure the accuracy of TTE. Other reference tests included ultrafast computerised tomography (CT) for the detection of right and left atrial thrombi and contrast-enhanced magnetic resonance imaging (MRI) and cardiac MRI for the detection of left ventricular thrombus. Additionally, non-imaging tests were used as reference tests, including surgical and cardiac catheterisation to confirm atrial septal defect, and autopsy, aneurysmectomy and indium-111 imaging to confirm left ventricular thrombus. The reference test used for PFO was TOE, but transmitral Doppler (TMD) and transcranial Doppler (TCD) studies were also included (as the reference standard) to measure the accuracy of TOE.

Studies were included only if they reported the numbers of TP, FN, TN and FP results for TTE in comparison to a reference standard test. These values can be used to calculate measures of diagnostic accuracy such as sensitivity and specificity.

Overall aims and objectives of the assessment

The overall aim was to use secondary research methods to determine the most appropriate echocardiographic diagnostic management strategy for first-episode diagnosed stroke and TIA patients in the UK. More specifically, the objectives were to:

- undertake systematic reviews to determine (1) the prevalence of potential cardiac sources of stroke and TIA and (2) the diagnostic accuracy of echocardiography
- undertake a survey to describe current practice in the NHS in terms of guidelines and management strategies used by stroke centres
- evaluate the cost-effectiveness of the addition of TTE to the routine assessment of patients who have had a first-episode diagnosed stroke or TIA in the UK.

Chapter 3 Assessment of prevalence of cardiac sources of stroke and transient ischaemic attack

Methods for reviewing prevalence

A systematic review was undertaken according to the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[39]

Identification of studies

Search strategy

The search strategy comprised the following elements:

- searching of electronic databases
- scrutiny of bibliographies of retrieved papers and previous reviews
- contact with experts in the field.

Databases

The following databases were searched:

- MEDLINE (1950 to December 2010)
- EMBASE (1980 to December 2010)
- PsycINFO (1806 to December 2010)
- Web of Science (1899 to December 2010)
- The Cochrane library (1995 to December 2010)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981 to December 2010).

Sensitive keyword strategies using free text and, when available, thesaurus terms using Boolean operators and database-specific syntax were developed to search the electronic databases. Synonyms relating to the condition were combined with search filters aimed at restricting results to prevalence studies and excluding animal studies (used in the searches of MEDLINE, CINAHL, EMBASE and PsycINFO, with an amended version used for Web of Science). Date limits or language restrictions were not used on any database. All resources were searched from inception to December 2010. An example of the MEDLINE search strategy is provided in *Appendix 2*.

All identified citations from the electronic searches and other resources were imported into and managed using the Reference Manager bibliographic software (version 12.0; Thomson Reuters, Philadelphia, PA, USA).

Titles and abstracts were screened for inclusion by two reviewers. Full-text relevant papers were screened against the inclusion criteria by two reviewers and any disagreements were resolved by consensus.

Inclusion and exclusion criteria

Inclusion criteria

Studies were included if they assessed the prevalence of cardiac sources of embolism in first-episode ischaemic stroke and TIA. Cardiac pathologies that are detectable without the need for echocardiography, for example myocardial infarction, were not included in this evaluation. Inclusion of relevant cardiac pathologies (see *Appendix 1*) was determined through consultation with clinical experts and with reference to previously published studies.[37,40]

Echocardiography in newly diagnosed AF patients has been commissioned by the NIHR HTA Programme as a separate project (reference no. 08/45/01 HTA Technology Assessment Report) and AF is therefore not included in this study.

Exclusion criteria

The following studies were excluded: non-English-language publications, narrative reviews and editorials.

Data extraction strategy

Data were extracted by two reviewers using a standardised data extraction form and cross-checked for accuracy. Discrepancies were resolved by discussion.

Critical appraisal strategy

The diagnosis of specific cardiac sources of stroke is usually unclear and relies on the identification of a potential cardiac source of embolism in the absence of significant cerebrovascular occlusive disease. Patients need to undergo thorough neurological and cardiovascular evaluation including the assessment of clinical findings to distinguish between other potential causes of stroke. Many confounding comorbidities such as AF can coexist in the presence of other cardiac sources of stroke. When several confounding factors are present, establishing the aetiology can be difficult, and often the cause of stroke remains unknown.

The quality of the studies included in the prevalence aspect of this review was not formally evaluated; a consensus decision was taken by the review team based on the data retrieved during the data extraction phase of the review. Many of the included studies were not designed to investigate cardiac sources of embolism to determine prevalence. The data reported were primary risk factor data and methodological detail was limited. Most studies reported cardiac pathologies through routine examination but did not attempt to establish a causal relationship. Hence, it was felt that formal quality appraisal would add little, if any, value to the prevalence review.

Methods of data synthesis

Because of the heterogeneity of the included studies relating to study design, population characteristics, detection methods used and absence of a causal relationship to identify cardiac sources of embolism, a meta-analysis was not undertaken. Instead, the data are tabulated and discussed narratively.

Results

Quantity of research available

The electronic search identified 17,276 citations. Two further studies were identified from hand searching the reference lists of the included studies (*Figure 1*). Once duplicates were removed, a further 12,658 studies were excluded at the title/abstract stage and 417 were obtained for examination of the full text. Of these, 352 were excluded because no usable data were reported (see *Appendix 3*). In total, 65 citations[23,26,27,41–102] relating to 65 studies were included in the review.

Study characteristics

The cardiac pathologies identified from the included studies, the age range of participants and the diagnostic tests used are reported in *Appendix 4*. Participants ranged in age from 1 to 94 years. Most studies assessed patients with stroke or TIA who were aged > 40 years.

Most studies reported using a battery of tests, some ancillary, to evaluate potential sources of cardiac emboli. Of these, TOE was the most frequently reported diagnostic tool used to assess cardiac pathologies (45 studies[23,26,27,41–82]); 38 studies[23,26,27,42–45,47,48,50–52,55–65,67–69,71–74,76,77,79,83–87] used TTE during the diagnostic work-up. Only six studies[88–93] did not report including a form of electrocardiography during the diagnostic work-up. In total, 27 studies[27,42,46,50–52,56–58,60–63,67,68,71,72,79,81–84,88,91,93–95] used MRI;

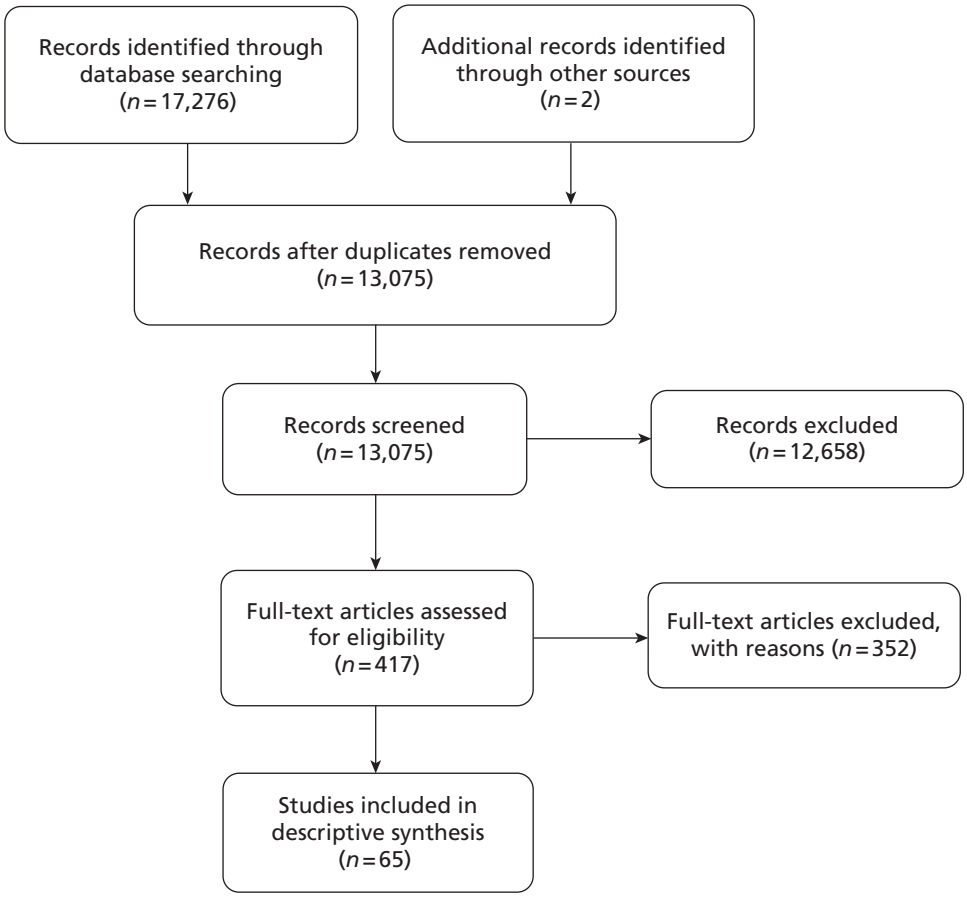

FIGURE 1 The PRISMA flow chart of included and excluded studies.

36 studies[23,27,42,46,50,51,55–63,65,67,68,71,72,74,75,81,82,86,88,89,91,93–100] used CT; four studies[27,41,43,51] used carotid ultrasonography; 33 studies[23,26,42,52,53,56,57,59–61,63,65,67–69,71–74,76,79,82,86,88,91,93–96,98–101] used electrocardiography; five studies[42,76,79,91,93] used magnetic resonance angiography (MRA); seven studies[23,52,53,65,79,95,96] used 24-hour Holter monitoring; nine studies[47,84,94,95,97,99–102] used electrocardiography but did not specify which type; one study[96] reported autopsy findings; three studies[61,77,88] used Doppler ultrasonography; two studies[89,98] used angiography; and 10 studies[51,62,67,68,72–74,76,83,93] used TCD ultrasonography. The cardiac pathologies identified, including the prevalence range and median values, are reported in *Table 2*.

Discussion

This systematic review summarises the results of 65 studies that have reported the prevalence of potential cardiac sources of stroke and TIA. The multiple sources of potential cardiac pathologies contributing to stroke and TIA reflect the heterogeneous nature of cardioembolic stroke.[37,103]

Previous reports have classified cardiac pathologies into major (e.g. left ventricular thrombus, mitral valve stenosis and atrial myxoma) and minor (mitral valve prolapse, mitral annular calcification, aortic stenosis, mitral valve strands, atrial septal aneurysm and PFO) risk factors for stroke.[40] The prevalence rates identified from the included studies for major risk factors ranged from 0% to 9%; for minor risk factors, for which further uncertainty exists around their role in stroke aetiology, the range was wider (0–73%).

Patent foramen ovale was the most frequently reported cardiac pathology, with 39 studies providing data. PFO also exhibited the largest degree of heterogeneity, with prevalence rates ranging from 0.25% to 73%. The study characteristics, however, did not indicate that the heterogeneity was due to differences in the age of patients, tests used or study sample sizes.

TABLE 2 Prevalence of cardiac pathologies

Cardiac pathology	No. of studies	Prevalence range (%)	Median prevalence (%)	Total population, *n*	Age (years)
Atrial septal aneurysm[26,41,42,46–49,51,53,54,56–58,63,65,66,68,70,71,74,77–81,85,88,97]	28	0.4–28	9.3	5560	14–93
PFO[23,26,27,43–58,62,63,67,68,70–75,77–85,92,94,102]	39	0.25–73	17	9002	2–93
PFO with atrial septal aneurysm[26,47,50,63,68,70,75]	6	4.1–24.1	10.75	1568	14–92
PFO with atrial septal defect[80,92]	2	3.4–29.6	16.5	262	18–65
Rheumatic valvular disease[23,43–45,55,96,97]	7	0.65–26.8	4.5	1378	15–80
Left ventricular thrombus[23,27,48,49,61,71,73,77,97]	9	0.2–4.3	0.83	1892	15–93
Atrial septal defect[48,53,57,61,68,79,82]	7	0.25–9	2.7	1011	16–90
Left ventricular hypertrophy[49,59,69,82,87,97,102]	7	3–42	7.7	1154	16–92
Left atrial thrombus[49,57,64,71,76,77]	5	0.9–9	1.4	1692	38–93
Mitral valve regurgitation including mitral valve insufficiency and mitral valve incompetence[49,61,63,76,82]	5	1.4–73.2	10.3	873	16–92
SEC left ventricle[49]	1	4	4	523	26–92
Unspecified SEC[77,80,81]	3	0–3.7	1.1	740	18–91
SEC LA[49]	1	15.5	15.5	523	26–92
Aorta SEC[49]	1	8.6	8.6	523	26–92
Mitral valve stenosis including mitral valve thickening[49,61,64,78,82,87,89,91]	8	0.7–9	4.15	856	16–87
Aortic valve stenosis[49,97]	2	0.6–0.65	0.625	678	16–92
Aortic valve calcification including aortic valve sclerosis and aortic valve thickening[49,80,82,99]	4	4.5–29.8	5.85	919	16–92
Cardiac tumour[26,68,73,77,82,95,98]	7	0–2.0	1	1389	14–81
Valvular vegetations[61,82,87]	3	1–9.7	1.67	178	16–81
Mitral valve prolapse[26,59,61,63,69,71,77,79,80,82,86,87,89,90,97,100,101]	17	0–31.6	3.3	1731	1–93
Atrial appendage thrombus[55]	1	1.1	1.1	239	Mean 66
Ventricular hypokinesia[55]	1	0.5	0.5	239	Mean 66
Mitral annular calcification[26,58,77,80,99,100]	6	0.5–9.7	1.95	1254	18–86
Rheumatic heart disease[86,90,91,95,98,101]	6	5.1–29.5	12.05	455	15–87
Aortic arch atheroma[63]	1	3.4	3.4	118	23–59
Ejection fraction < 35%[71]	1	5	5	121	38–93
Ejection fraction < 40%[93]	1	16.7	16.7	6	49–75
Left atrial dilatation[76]	1	6.8	6.8	74	16–87
Left ventricular dilatation[76]	1	5.4	5.4	74	16–87
Left ventricular aneurysm[77]	1	1.6	1.6	441	No details
Aortic aneurysm[77]	1	0.2	0.2	441	No details
Mitral valve strands[78]	1	16	16	318	28–87
Intracardiac thrombus[76,79,81,92]	4	0–2.7	1.9	538	16–91

LA, left atrium; SEC, spontaneous echo contrast.

Because of the heterogeneous nature of stroke, the diagnosis of cardioembolic stroke or TIA is often uncertain and is reliant on the detection of a potential cardiac source of embolus in the absence of other potential sources of cerebral ischaemia.[103] However, some studies reported the presence of two or more potential sources in one person, which generates further diagnostic uncertainty, although such findings would not necessarily alter the treatment regime.

The studies did not report or indicate that a thorough diagnostic evaluation was undertaken to establish a causal link with stroke; instead, cardiac findings were reported as associated risk factors, and these were often derived using different diagnostic techniques. The systematic review found wide variation in reported rates of cardiac sources of stroke, and this variability is most likely the result of the methodological limitations of the included studies and the heterogeneity of stroke.

Chapter 4 Assessment of diagnostic accuracy

Methods for reviewing diagnostic accuracy

A systematic review was undertaken according to the general principles recommended in the PRISMA statement.[39] Methods used for the analysis and the inclusion criteria were prespecified and documented in the protocol (PROSPERO no. CRD42011001353[104]).

Identification of studies

Search strategy

The search strategy comprised the following elements:

- searching of electronic databases
- scrutiny of bibliographies of retrieved papers and previous reviews
- contact with experts in the field.

Databases

The following databases were searched:

- MEDLINE (1950 to September 2011)
- EMBASE (1980 to September 2011)
- PsycINFO (1806 to September 2011)
- Web of Science (1899 to September 2011)
- The Cochrane Library [including Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and HTA database] (1995 to September 2011)
- CINAHL (1981 to September 2011).

Sensitive keyword strategies using free text and, when available, thesaurus terms using Boolean operators and database-specific syntax were developed to search the electronic databases. Synonyms relating to the condition (stroke) were combined with terms relating to the technology and a filter was applied aimed at restricting results to diagnostic studies (used in the searches of MEDLINE, CINAHL, EMBASE and PsycINFO, with an amended version used for Web of Science). Date limits or language restrictions were not used on any database. All resources were searched from inception to March 2011. A further update search was performed in September 2011; this included all types of cardiac pathology, irrespective of stroke occurrence. An example of the MEDLINE search strategy is provided in *Appendix 5*.

All identified citations from the electronic searches and other resources were imported into, and managed using, Reference Manager bibliographic software.

Titles and abstracts were screened for inclusion by two reviewers. Full-text relevant papers were screened against the inclusion criteria by two reviewers and any disagreements were resolved by consensus.

Inclusion and exclusion criteria

Inclusion criteria

Prospective or retrospective studies were included if they assessed the diagnostic accuracy of TTE in patients with cardiac conditions identified as potential sources of stroke or TIA (see *Appendix 1*). Studies were included only if they reported the numbers of TP, FN, TN and FP results for TTE in comparison to a reference standard test or reported the total number of participants, prevalence (%), sensitivity (%) and specificity (%). Comparators to TTE include other tests that are established reference standards, for example TOE for PFO. When no established reference standard exists for a cardiac condition, studies reporting diagnostic accuracy data between TTE and other tests (e.g. MRI, TMD, TCD, invasive procedures such as surgery) were included.

Exclusion criteria

Non-English-language studies were excluded. Case–control studies (in which the test is evaluated in a group of patients already known to have the outcome and a separate group of patients without the outcome) were excluded.

Data extraction

Data were extracted by two reviewers using a standardised data extraction form and cross-checked for accuracy. Discrepancies were resolved by discussion.

Critical appraisal strategy

Study quality was assessed by one reviewer and checked by a second using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist.[105]

Methods of data synthesis

Sensitivity and specificity are presented for each study. Meta-analysis was undertaken to calculate a mean sensitivity and specificity across studies. Sensitivity and specificity are linked so that changing the threshold at which a test is considered positive will tend to increase the sensitivity but decrease the specificity, or vice versa. Forest plots were generated in R statistical software (2011; see www.r-project.org) and summary receiver operating characteristic (SROC) plots were generated within Review Manager software (RevMan 5; see http://ims.cochrane.org/revman).

The diagnostic test data were meta-analysed as follows. A bivariate normal model was used for the logit sensitivities and logit specificities in each study to account for correlation within studies. We let:

$$TP_i \sim Binomial(\pi_{Ai}, (TP_i + FN_i)) \tag{1}$$

$$TN_i \sim Binomial(\pi_{Bi}, (FP_i + TN_i)) \tag{2}$$

$$\mu_{Ai} = logit(\pi_{Ai}) \tag{3}$$

$$\mu_{Bi} = logit(\pi_{Bi}) \tag{4}$$

$$\begin{pmatrix} \mu_{Ai} \\ \mu_{Bi} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_A \\ \mu_B \end{pmatrix}, \Sigma_{AB} \right) \tag{5}$$

$$\Sigma_{AB} = \begin{pmatrix} \sigma_A^2 & \sigma_{AB} \\ \sigma_{AB} & \sigma_B^2 \end{pmatrix} \tag{6}$$

The model was completed by giving the uncertain parameters the following prior distributions:

$$\mu_A \sim N(0,10) \tag{7}$$

$$\mu_B \sim N(0,10) \tag{8}$$

$$\Sigma_{AB} \sim IW\left(\begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}, R = 5\right) \tag{9}$$

These prior distributions are weakly informative but are slightly more informative than the conventional non-informative prior distribution that is generally used in the analysis of diagnostic test data when there is sufficient data to dominate the prior distributions. The conventional non-informative prior distributions are:

$$\mu_A \sim N(0,1000) \tag{10}$$

$$\mu_B \sim N(0,1000) \tag{11}$$

$$\Sigma_{AB} \sim IW\left(\begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}, R = 2\right) \tag{12}$$

This was done because, in many cases, the model failed to fit with a conventional weak prior distribution as a consequence of (1) some meta-analyses being based on very few studies, (2) several meta-analyses involving a large number of studies with zero counts, mainly for patients classified as being a FP (i.e. control patients) but also for patients classified as being a TP (i.e. patients with the condition) and (3) several meta-analyses including only a small number of patients who actually had the condition.

The consequence of the weakly informative prior distribution for the prior estimate of the between-study standard deviation relative to that based on conventional non-informative prior distributions was to reduce the uncertainty about the prior estimate from 1.5 [95% credible interval (CrI) 0.4 to 32.3] to 0.5 (95% CrI 0.3 to 1.4). This gives more weight to smaller values of the between-study standard deviation whilst acknowledging the possibility of moderate to large heterogeneity between studies a priori.

The consequence of the weakly informative prior distribution had relatively little impact on the prior estimates of the population sensitivities and specificities. The conventional prior distribution is interpreted such that we are uncertain exactly what the population values are but we believe them to be either 0 or 1. In the case of the weakly informative prior distribution we give slightly more weight to other values being plausible.

Data were analysed using freeware WinBUGS software (version 1.4.3; MRC Biostatistics Unit, Cambridge, UK). Convergence was assessed using the Gelman–Rubin convergence statistic.[106] In at least one meta-analysis, convergence occurred after 100,000 iterations and so we used a burn-in of 100,000 for all meta-analyses for consistency. In most meta-analyses there was strong evidence of autocorrelation between successive samples of the Markov chain Monte Carlo (MCMC) method, which indicates that the chains were not mixing well across the posterior distributions. To account for this, the posterior distributions were estimated by generating 20,000 samples after thinning the chains by retaining every 10th iteration of the MCMC chains.

Results of the review of diagnostic accuracy

Results of the search

A total of 9855 citations were identified from the initial database search and 18 from other sources such as reference lists; a further 6631 citations were identified using an expanded search phrase but with the year restricted to 1999–2011 (*Figure 2*). Of these citations, 13,748 were excluded at the title/abstract stage

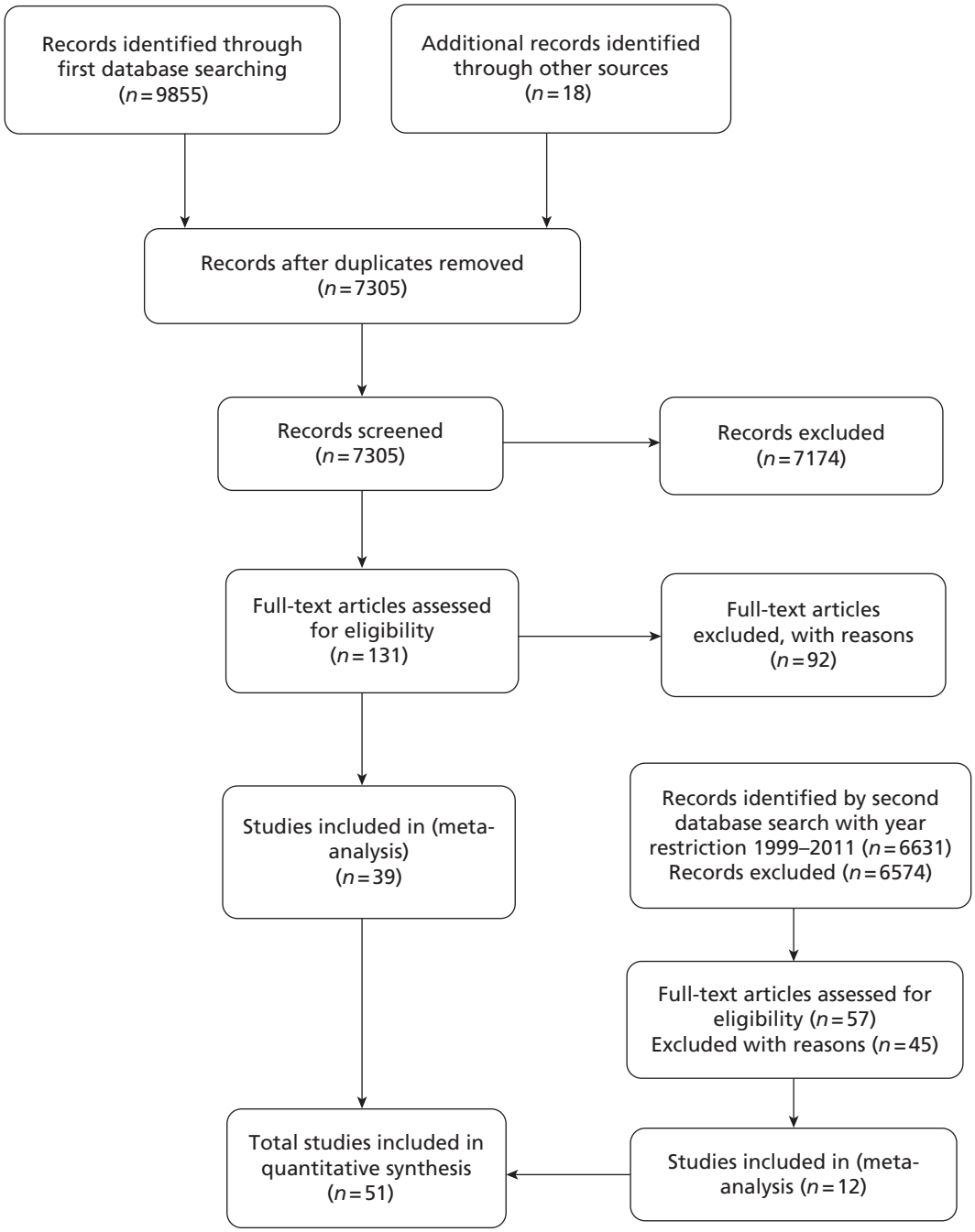

FIGURE 2 The PRISMA flow chart of included and excluded studies.

and 188 full-text reports were obtained for inspection. Of these, 137 were excluded and 51 studies[61,107–156] were included in the review.

Included studies

A summary of the 51 included studies is provided in *Table 3*. Full details of studies are provided in *Appendix 6*.

Settings

Eighteen studies[107–124] were conducted in the USA; nine[125–133] in Germany; one in Austria;[134] one in China;[135] two in South Korea;[136,137] one in Japan;[138] one in Taiwan;[139] one in Belgium;[140] two in Holland;[141,142] two in the UK;[143,144] one in Israel;[145] two in Spain;[146,147] one in Croatia;[148] four in Italy;[61,149–151] two in Canada;[152,153] and three in Australia.[154–156] Most studies were undertaken in a hospital/clinical

TABLE 3 Characteristics of the included studies

	Methods					Participants			Interventions			Outcomes	
Study, year	Prospective	Retrospective	Index test results blinded	Reference test results blinded	Representative spectrum of participants	Country	Age (years)	Sex	TTEf	TTEh	Reference standard	PFO	Other outcomes
Akosah 1998[107]		•	U/K	U/K	•	USA	40–85	M	•		TOE	•	ASD, AAT
Aschenberg 1986[125]	•		U/K	U/K	•	Germany	Mean 51	M and F	•		TOE		LAAT
Baur 1982[108]	•		U/K	U/K	•	USA	Mean 56	U/K	•		LV		LVA
Belkin 2011[109]	•		U/K	U/K	•	USA	19–73	M and F	•		TOE	•	
Black 1991[154]	•		U/K	U/K	•	Australia	18–90	M and F	•		TOE		SEC
Black 1991[155]	•		U/K	U/K	•	Australia	25–86	M and F	•		TOE		SEC
Blum 2004[145]		•	U/K	U/K	•	Israel	Mean 57	M and F	•		TOE	•	ASD, LAT
Chen 1992[139]	•		U/K	U/K	•	Taiwan	17–68	M and F	•		TOE	•	
Chirillo 2005[149]	•		Y	Y	•	Italy	Mean 46	M and F		•	TOE		Cardiac vegetations
Clarke 2004[143]	•		Y	Y	•	UK	Mean 58	M and F		•	TOE	•	
Cujec 1991[152]	•		U/K	U/K	•	Canada	18–87	M and F	•		TOE	•	ASA, LAAT, SEC
Daniels 2004[140]	•		Y	Y	•	Belgium	Mean 63	M and F		•	TOE	•	
de Bruijn 2006[141]	•		Y	Y	•	Holland	U/K	U/K		•	TOE		LAT
Di Tullio 1993[110]	•		Y	Y	•	USA	63	M and F	•		TOE	•	ASA
Fatkin 1996[156]	•		U/K	U/K	•	Australia	38–74	M and F	•		TOE		LAT, LAAT
Gonzalez-Alujas 2011[146]	•		U/K	U/K	•	Spain	17–75	M and F		•	TOE	•	ASA

continued

TABLE 3 Characteristics of the included studies (*continued*)

	Methods					Participants			Interventions			Outcomes	
Study, year	Prospective	Retrospective	Index test results blinded	Reference test results blinded	Representative spectrum of participants	Country	Age (years)	Sex	TTEf	TTEh	Reference standard	PFO	Other outcomes
Gutiérrez-Chico 2008[147]	•		Y	Y	•	Spain	15–92	M and F		•	TOE		MVP
Ha 2000[136]	•		U/K	U/K	•	South Korea	Mean 51	M and F	•	•	TOE		LAT, SEC
Ha 2001[137]	•		U/K	U/K	•	South Korea	24–89	U/K	•	•	TOE	•	
Hirata 2008[111]	•		Y	Y	•	USA	Mean 57	M and F		•	TOE		MVP
Hubail 2011[112]	•		U/K	U/K	•	USA	1.2 to 8.6	M and F	•	•	TOE	•	
Illien 2002[126]	•		U/K	U/K	•	Germany	57–67	M and F		•	TOE		LAT
Jassal 2007[5]	•		Y	Y	•	Canada	Mean 57, 18–63	M and F		•	TOE		Cardiac vegetations
Jax 2010[127]	•		U/K	U/K	•	Germany	U/K	U/K	U/K	U/K	TOE	•	
Kerr 2000[113]	•		Y	Y	•	USA	34–76	M and F	•	•	TOE	•	
Kitayama 1997[138]	•		U/K	U/K	•	Japan	Mean 68	M and F	•		CUCT		LAT
Kuhl 1999[128]	•		U/K	U/K	•	Germany	20–86	M and F	•	•	TOE		ASD
Lee 1991[114]	•		Y	Y	•	USA	20–82	M and F	•		TOE	•	SEC
Lembcke 2009[129]	•		U/K	U/K	•	Germany	Mean 68	M and F	U/K	U/K	CC		AVS
Li 2009[135]	•		U/K	U/K	•	China	43–73	M and F	U/K	U/K	LV		LVA
Lipke 2007[130]	•		Y	Y	•	Germany	Mean 63	M and F		•	MRI		LVT

	Methods					Participants			Interventions			Outcomes	
Study, year	Prospective	Retrospective	Index test results blinded	Reference test results blinded	Representative spectrum of participants	Country	Age (years)	Sex	TTEf	TTEh	Reference standard	PFO	Other outcomes
Madala 2004[115]	•		Y	Y	•	USA	21–88	M and F		•	TOE	•	
Maffè 2010[150]	•		Y	Y	•	Italy	36–62	M and F		•	TOE	•	
Mugge 1995[131]	•		U/K	U/K	•	Germany	18–85	M and F	•		TOE		ASA
Musolino 2003[61]	•		U/K	U/K	•	Italy	17–45	M and F	•		TOE	•	MVS, MVR, LAAT, ASD, ASA
Nemec 1991[116]	•		U/K	U/K	•	USA	22–78	M and F	•		TOE	•	
Neuman 2003[117]	•		Y	Y	•	USA	Mean 78	M and F	•		TOE		Mitral and aortic regurgitation
Omran 1999[132]	•		Y	Y	•	Germany	Mean 54	M and F	•		TOE		LAAT, SEC
Pearson 1991[118]	•		Y	Y	•	USA	17–84	M and F	•		TOE		SEC
Pop 1990[142]	•		U/K	U/K	•	Holland	Mean 60	M and F	•		TOE		LAAT, SEC
Roldan 2008[119]	•		U/K	U/K	•	USA	Mean 37	M and F		•	TOE		MVR
Sallach 2009[120]	•		Y	U/K	•	USA	Mean 67	M and F	•	•	TOE		LAAT
Shub 1983[121]	•		U/K	U/K	•	USA	Mean 31	M and F	•		CC		ASD
Siostrzonek 1991[134]	•		U/K	U/K	•	Austria	Mean 52	M and F	•		TOE	•	
Stendel 2000[133]	•		Y	Y	•	Germany	Mean 51	M and F	•		TOE	•	
Stratton 1982[122]	•		Y	Y	•	USA	Mean 58	M and F	•		Autopsy and UPIPI		LVT

continued

TABLE 3 Characteristics of the included studies (*continued*)

	Methods					Participants			Interventions			Outcomes	
Study, year	Prospective	Retrospective	Index test results blinded	Reference test results blinded	Representative spectrum of participants	Country	Age (years)	Sex	TTEf	TTEh	Reference standard	PFO	Other outcomes
Thanigaraj 2005[123]	•		U/K	U/K	•	USA	Mean 45	M and F		•	TOE	•	ASD
Trevelyan 2006[144]	•		Y	Y	•	UK	Mean 55	M and F		•	TOE	•	
Vincelj 2001[148]	•		U/K	U/K	•	Croatia	Mean 55	M and F	U/K	U/K	TOE		Atrial myxoma, LAT
Weinsaft 2011[124]	•	•	U/K	U/K	•	USA	Mean 60	M and F		•	MRI		LVT
Zito 2009[151]	•		Y	Y	•	Italy	Mean 49	M and F		•	TOE	•	

AAT, atrial appendage thrombus; ASA, atrial septal aneurysm; ASD, atrial septal defect; AVS, aortic valve stenosis; CC, cardiac catheterisation; CUCT, cardiac ultrafast computerised tomography; F, female; LAAT, left atrial appendage thrombus; LAT, left atrial thrombus; LV, left ventriculography; LVA, left ventricular aneurysm; LVT, left ventricular thrombus; M, male; MVP, mitral valve prolapse; MVR, mitral valve regurgitation; MVS, mitral valve stenosis; SEC, spontaneous echo contrast; U/K, unknown; UPIPI, unequivocally positive indium-111 platelet imaging; Y, yes.

setting, although six studies[120,124,131,136,137,151] did not clearly state where the tests were performed. Study size ranged from just 12 participants[148] to 400.[154] The mean age of the sample was 56 years.

Reference tests

Two studies[108,135] compared TTE with left ventriculography; one study[121] compared TTE with surgical and cardiac catheterisation; two studies[124,130] compared TTE with cardiac MRI; one study[129] compared TTE with cardiac catheterisation; one study[138] compared TTE with cardiac ultrafast CT; and one study[122]compared TTE for assessment of left ventricular thrombus with a combination of procedures: autopsy, aneurysmectomy and unequivocally positive indium-111 platelet imaging.

Eighteen studies[112,113,115,119,120,123,124,126,128,136,137,140,143,144,146,149,150,153] compared TTEh with TOE and 19 studies[61,107,109,110,114,116–118,125,131–134,139,142,152,154–156] compared TTEf with TOE.

Four studies[127,141,145,148] compared TTE with TOE but it was not possible to determine whether TTE was performed in fundamental or second harmonic imaging mode.

Outcome data reported

Patent foramen ovale was reported in 23 studies, 13 using TTEf[61,107,109,110,114–116,133,134,137,139,145,152] and 11 using TTEh.[112,113,115,123,137,140,143,144,146,150,151]

Four studies[61,107,128,145] reported data for atrial septal defect using TTEf and two[123,128] reported data for atrial septal defect using TTEh. One study[121] reported data for oscium secundum atrial septal defect and ostium primum atrial septal defect using TTEf.

Atrial septal aneurysm data were reported in four studies[61,110,131,152] using TTEf and one study[146] using TTEh. Two studies[61,117] reported data for mitral valve regurgitation using TTEf and one study[119] reported data for mitral valve regurgitation using TTEh; eight studies[61,107,120,125,132,142,152,156] reported data for left atrial appendage thrombi using fundamental imaging and one study[120] used harmonic imaging. Left atrial thrombi data were reported in three studies[145,148,156] using TTEf and three studies[126,136,141] using TTEh; one study[138] reported data for right atrial thrombi using TTEf; three studies[122,124,130] reported TTEh and TTEf data for left ventricular thrombi; three studies[114,132,142] reported TTEf data for spontaneous echo contrast (SEC); four studies[118,152,154,155] reported TTEf data for left atrial SEC and one study[136] reported TTEh data for left atrial SEC; one study[154] reported data for left ventricular SEC with TTEf; two studies reported TTEf and TTEh data for left ventricular aneurysm;[108,135] two studies reported TTEh data for cardiac vegetations[149,153] and one study[149] reported TTEf data; one study[129] reported TTEf data for aortic valve stenosis; one study[61] reported TTEf data for mitral valve stenosis; two studies[111,147] reported TTEh data for mitral valve prolapse; and one study[148] reported TTEf data for atrial myxoma.

Excluded studies

A total of 137 studies were excluded (see *Appendix 7*). Of these, 72 were excluded because no usable data were reported; six were excluded because concordance could not be established between the test procedures; 12 were excluded because studies did not report relevant cardiac pathologies; 27 were not diagnostic accuracy studies; 15 were not available in the English language; and five did not include a relevant reference standard.

Study quality

A summary of methodological quality across all studies is provided in *Figure 3*. The methodological quality for each included study is illustrated in *Figure 4*.

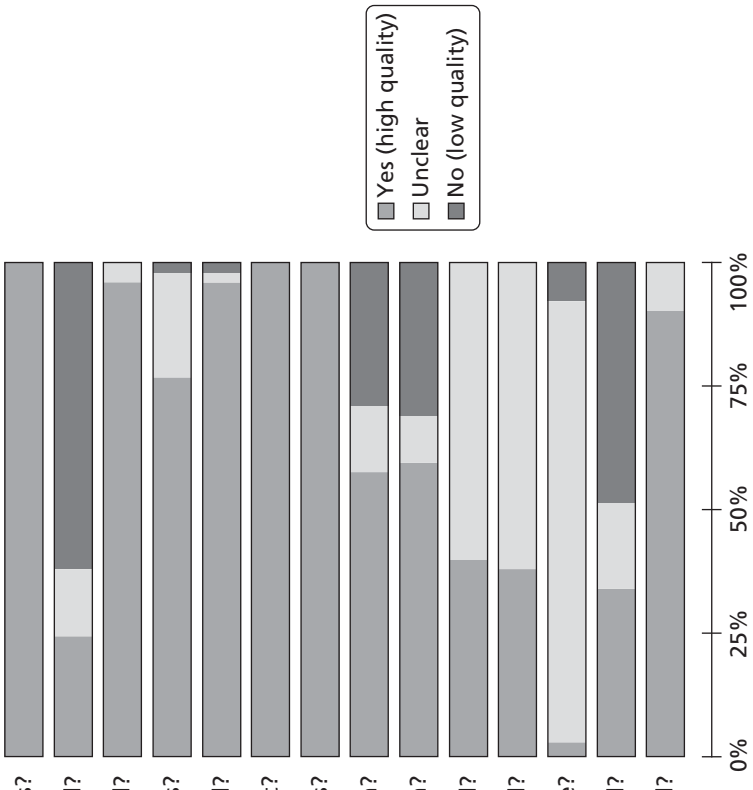

FIGURE 3 Methodological quality summary: review authors' judgements about each methodological quality item presented as percentages across all included studies.

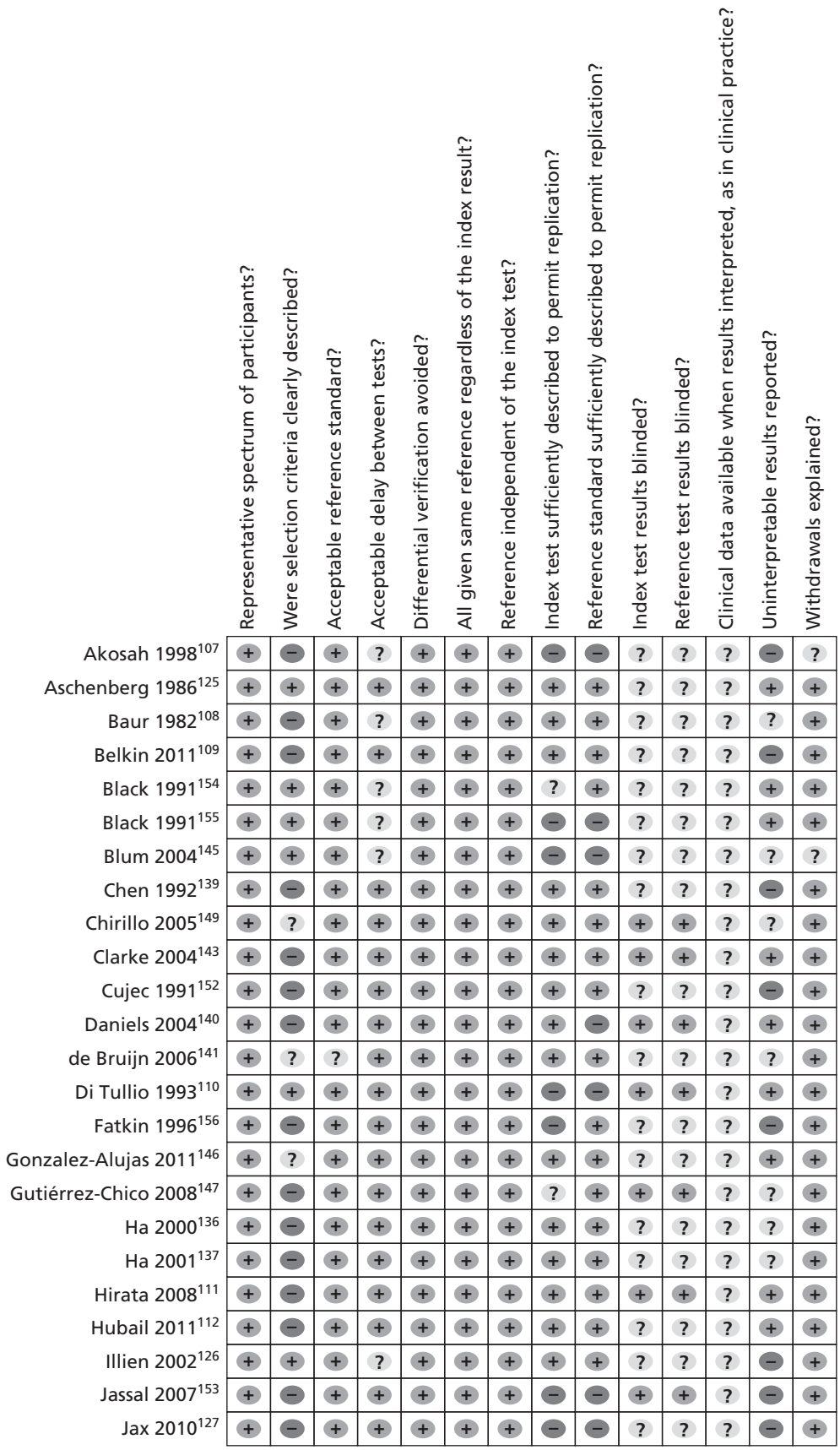

FIGURE 4 Methodological quality summary: review authors' judgements about each methodological quality item for each included study. (*continued*)

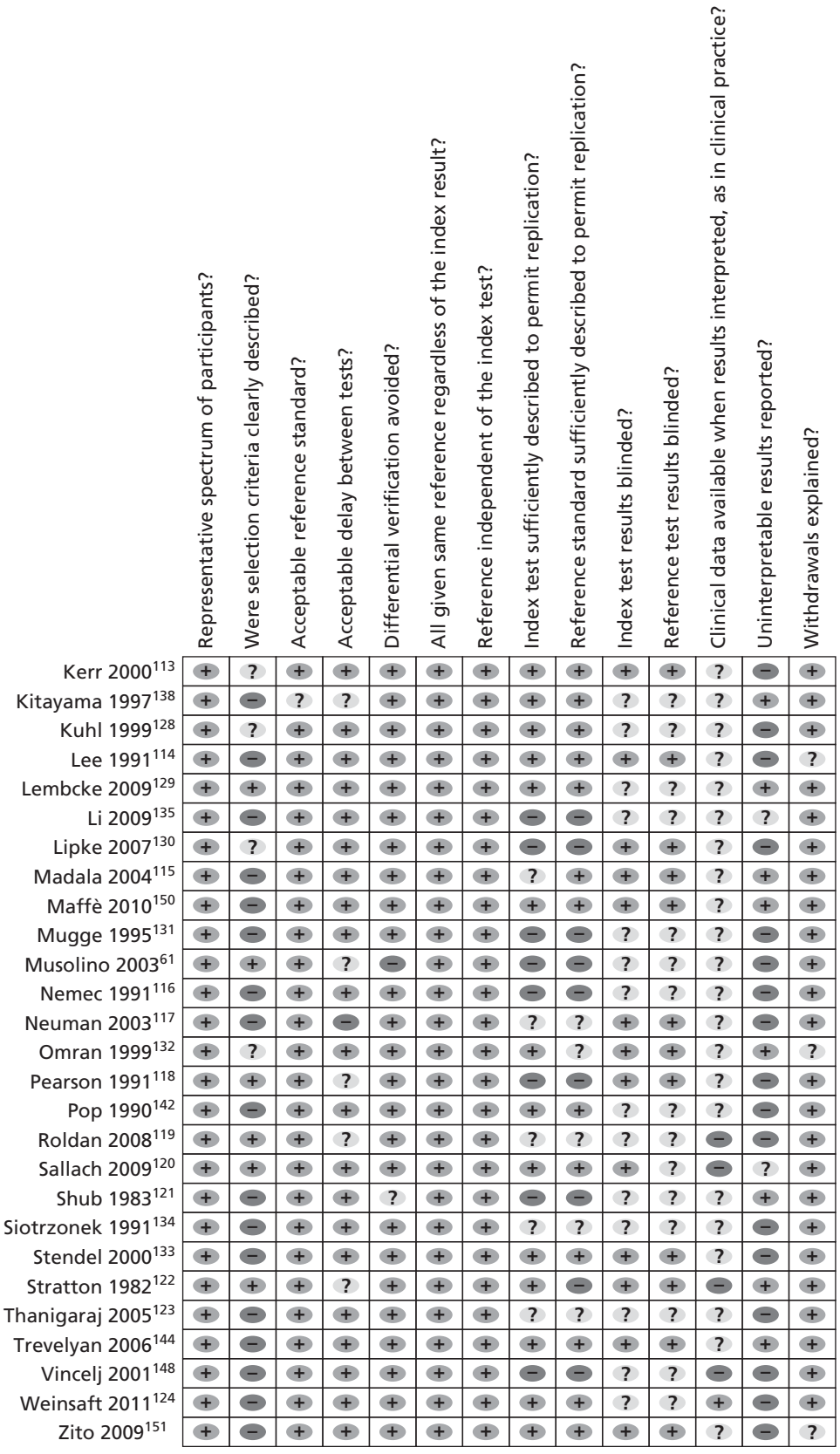

FIGURE 4 Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

Spectrum of participants
All 51 studies included patient samples that would be considered representative of the population using the test in practice.

Selection criteria
Most studies ($n = 32$[107–109,111,112,114–117,121,123,124,127,131,133–140,142–144,147,148,150–153,156]) did not report how participants were selected for inclusion into the study; 12 studies[61,110,118–120,122,125,126,129,145,154,155] provided details on patient selection and seven[113,128,130,132,141,146,149] reported only brief details.

Reference standard
Most studies[61,107–137,139,140,142–156] used a reference standard that was considered to classify the target condition correctly, and most studies used TOE as the reference standard, that is, the 'gold standard'. TOE is considered the gold standard for assessing PFO but the test is acknowledged to be imperfect, although it is assumed to be superior to the index test TTE. Other cardiac pathologies used TOE as the reference standard but the literature is less supportive of its status as the reference standard. Four studies compared TTE with invasive procedures including left ventriculography,[108,135] surgical procedures and cardiac catheterisation,[121] and aneurysmectomy, autopsy and positive indium-111 platelet imaging[122] to determine thrombus.

Time between tests
Most studies[109–116,120,121,123–125,127–137,139–144,146–153,156] reported the time taken between administering the reference test and the index test, and this was judged to be reasonably short enough to ensure that the target condition did not change. Some studies[61,107,108,117,118,119,122,126,138,145,154,155] did not report the time taken between tests for the assessment of PFO, but these studies were not downgraded on quality as PFO will not be affected during the study period.

Selection bias
The majority of studies[107–120,122–156] included the original sample for verification with the reference test. Some studies excluded patients who could not provide a clear image on testing or who did not complete the imaging procedure. Overall, the data suggest a low risk of bias.

Verification and incorporation bias
All studies used the same reference standard regardless of the index test result, and the reference standard was independent of the index test in all studies. The majority of studies[108–115,120,124–126,128,129,133,136–139,141–144,146,147,149–152,154,156] provided sufficient details to permit replication of the reference and index tests. However, many studies did not report the procedures used,[61,107,110,116,118,121,122,124,127,130,131,135,140,145,148,153,154] with some[115,117,119,123,132,134,147,154] reporting only brief details.

Review bias
In about 40% of the studies[66,110,111,113–115,117,120,122,130,132,133,140,143,144,147,149–151,153] the results of either the index test or the reference test were interpreted without knowing the findings of the comparator test. Most studies[107–109,112–115,117,118,120,122,125–127,130,132,133,136,137,139,141,144–146,150–152,155,156] did not report whether blinding between test results was used, and it is unclear whether the interpretation of the results of the index test may have been influenced by knowledge of the results of the reference standard, although the data do not indicate a greater or lesser diagnostic accuracy when blinding is not known.

Availability of clinical information
The majority of studies[61,107–123,125–156] did not state whether patients' clinical data were available to the investigative team and it is not known whether this influenced the diagnostic test results.

Uninterpretable data reporting

About 30% of included studies[110–112,115,121,122,125,129,132,138,140,143,144,146,150,154,155] reported uninterpretable, indeterminate or intermediate test results. Some studies[108,120,135–137,141,145,147,149] removed these data from the analysis but most studies[61,107,109,113,114,116–119,123,124,126–128,130,133,134,136,139,142,148,151–153,156] did not report how inadequate images were utilised for the diagnostic accuracy test or only briefly reported this information with no clear explanation of how these findings were interpreted.

Withdrawals

The majority of studies did not have any patient withdrawals;[61,108–113,115–131,133–144,146–150,152–156] when withdrawals did occur these were explained by the authors.

Analysis of diagnostic accuracy data: transthoracic echocardiography studies

The total number of patients per study is the sum of the TP, FP, FN and TN values. A summary of all outcomes is shown in *Appendix 8*.

Patent foramen ovale

From 13 studies[61,107,109,114–116,133,134,137,139,140,145,152] with 905 participants (*Figures 5* and *6*), the pooled sensitivity of TTE to detect PFO in fundamental imaging mode was 0.34 (95% CrI 0.21 to 0.47) with a pooled specificity of 1.00 (95% CrI 0.99 to 1.00) compared with TOE.

In second harmonic imaging mode (11 studies,[112,113,115,123,137,140,143,144,146,150,151] $n = 1115$) the pooled sensitivity of TTE to detect PFO was 0.89 (95% CrI 0.80 to 0.95) with a specificity of 0.99 (95% CrI 0.97 to 1.00) (*Figures 7* and *8*). In one study,[127] frequency mode not specified, the sensitivity of TTE to detect PFO was 0.48 (95% CrI 0.33 to 0.63). Specificity could not be calculated as all patients were positive for PFO.

Sensitivity analysis (transoesophageal echocardiography compared with other tests)

In a single study[146] ($n = 134$) comparing the diagnostic accuracy of TOE with that of TCD, the sensitivity of TOE to detect PFO was 0.97 (95% CrI 0.91 to 0.99) with a specificity of 0.98 (95% CrI 0.87 to 1.00). When TOE was compared with TMD[113] ($n = 44$) to detect PFO, the sensitivity of TOE was 0.94 (95% CrI 0.73 to 1.00) with a specificity of 1.00 (95% CrI 0.87 to 1.00).

Atrial thrombi

In Kitayama *et al.*[138] ($n = 70$) the sensitivity of TTEf to detect left atrial thrombi was 0.67 (95% CrI 0.22 to 0.96) with a specificity of 1.00 (95% CrI 0.94 to 1.00) compared with ultrafast CT scan.

In three studies[145,148,156] ($n = 142$) the pooled sensitivity of TTEf to detect left atrial thrombi was 0.34 (95% CrI 0.07 to 0.71) with a specificity of 1.00 (95% CrI 0.97 to 1.00) compared with TOE (*Figure 9*).

In second harmonic imaging mode the pooled sensitivity of TTE in three studies[126,136,141] ($n = 477$) to detect left atrial thrombi was 0.79 (95% CrI 0.47 to 0.94) with a specificity of 1.00 (95% CrI 0.99 to 1.00) compared with TOE (*Figure 10*).

Left ventricular thrombi

In Stratton *et al.*[122] ($n = 78$), when TTEf was compared with independent verification of left ventricular thrombi, TTEf had a sensitivity of 0.86 (95% CrI 0.65 to 0.97) with a specificity of 0.95 (95% CrI 0.85 to 0.99). Compared with MRI, the Lipke *et al.* study[130] ($n = 34$) found that TTEh has a sensitivity to detect left ventricular thrombi of 0.53 (95% CrI 0.27 to 0.79) and a specificity of 0.74 (95% CrI 0.49 to 0.91). In a single study[124] ($n = 243$) using TTE (frequency mode unclear), the sensitivity to detect left ventricular thrombi was 0.33 (95% CrI 0.16 to 0.55) with a specificity of 0.91 (95% CrI 0.86 to 0.94).

FIGURE 5 Sensitivity and specificity of TTEf to detect PFO vs. TOE.

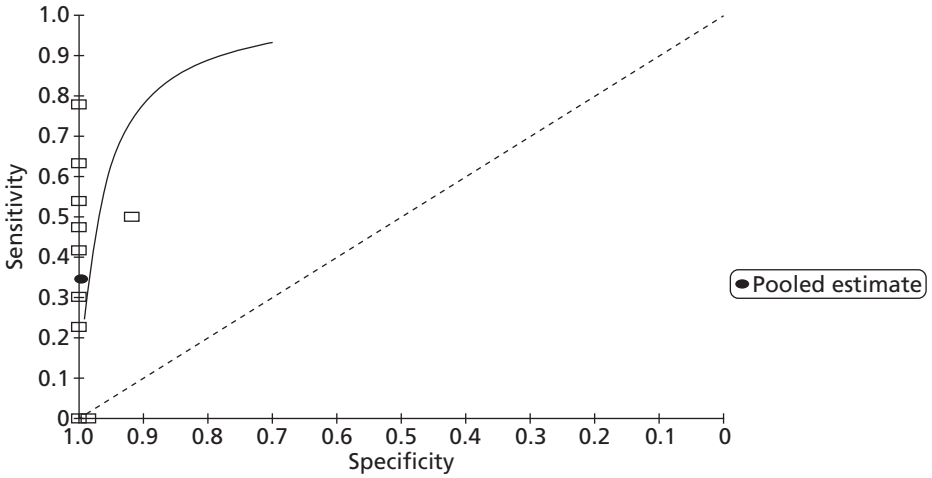

FIGURE 6 Summary receiver operating characteristic plot of pooled TTEf detection of PFO.

Atrial septal defect

In four studies[61,107,128,145] ($n = 363$) the pooled sensitivity of TTE in fundamental imaging mode to detect atrial septal defect was 0.36 (95% CrI 0.10 to 0.62) with a specificity of 1.00 (95% CrI 0.99 to 1.00) compared with TOE (*Figure 11*). In two studies[123,128] ($n = 205$) the pooled sensitivity of TTEh to detect atrial septal defect was 0.92 (95% CrI 0.75 to 0.98) with a specificity of 1.00 (95% CrI 0.98 to 1.00) compared with TOE (*Figure 12*). In Shub *et al.*[121] the sensitivity of TTEf compared with surgical and cardiac catheterisation for the detection of oscium secundum atrial septal defect was 0.89 ($n = 105$, 95% CrI 0.81 to 0.94) and for the detection of ostium primum atrial septal defect was 1.00 (95% CrI 0.89 to 1.00); specificity was not estimated as all were positive for atrial septal defect .

Atrial septal aneurysm

In three studies[61,110,152] ($n = 135$) the pooled sensitivity of TTEf to detect atrial septal aneurysm was 0.01 (95% CrI 0.00 to 0.15) with a pooled specificity of 1.00 (95% CrI 0.97 to 1.00) compared with TOE (*Figure 13*). In a single study[131] the sensitivity of TTEf to detect an atrial septal aneurysm was 53% compared with TOE; specificity was not calculable as all participants had atrial septal aneurysm. In the study by Gonzalez-Alujas *et al.*[146] ($n = 55$), TTEh had a sensitivity to detect an atrial septal aneurysm of 0.97 (95% CrI 0.85 to 1.00) with a specificity of 1.00 (95% CrI 0.85 to 1.00) compared with TOE.

Left atrial appendage thrombi

In eight studies[61,107,120,125,132,142,152,156] ($n = 544$) the pooled sensitivity of TTEf to detect left atrial appendage thrombi was 0.06 (95% CrI 0.00 to 0.26) with a specificity of 1.00 (95% CrI 0.99 to 1.00) compared with TOE (*Figure 14*). In a single study[120] using TTEh ($n = 118$) the sensitivity to detect left atrial appendage thrombi was 1.00 (95% CrI 0.16 to 1.00) with a specificity of 1.00 (95% CrI 0.97 to 1.00).

Spontaneous echo contrast

The pooled sensitivity of TTEf to detect SEC from three studies[114,132,142] ($n = 185$) was 0.05 (95% CrI 0.01 to 0.16) with a specificity of 1.00 (95% CrI 0.98 to 1.00) compared with TOE (*Figure 15*). The pooled sensitivity of TTEf to detect left atrial SEC (four studies,[118,152,154,155] $n = 605$) was 0.00 (95% CrI 0.00 to 0.02) with a specificity of 1.00 (95% CrI 0.99 to 1.00) compared with TOE (*Figure 16*). In the study by Ha *et al.*[136] comparing TTEh with TOE ($n = 73$), the sensitivity to detect left atrial SEC was 0.88 (95% CrI 0.7 to 0.94) with a specificity of 1.00 (95% CrI 0.03 to 1.00). In the study by Black *et al.*[154] ($n = 100$), the sensitivity of TTEf to detect left ventricular SEC was 0.00 (95% CrI 0.00 to 0.84) with a specificity of 1.00 (95% CrI 0.96 to 1.00) compared with TOE.

FIGURE 7 Sensitivity and specificity of TTEh to detect PFO vs. TOE.

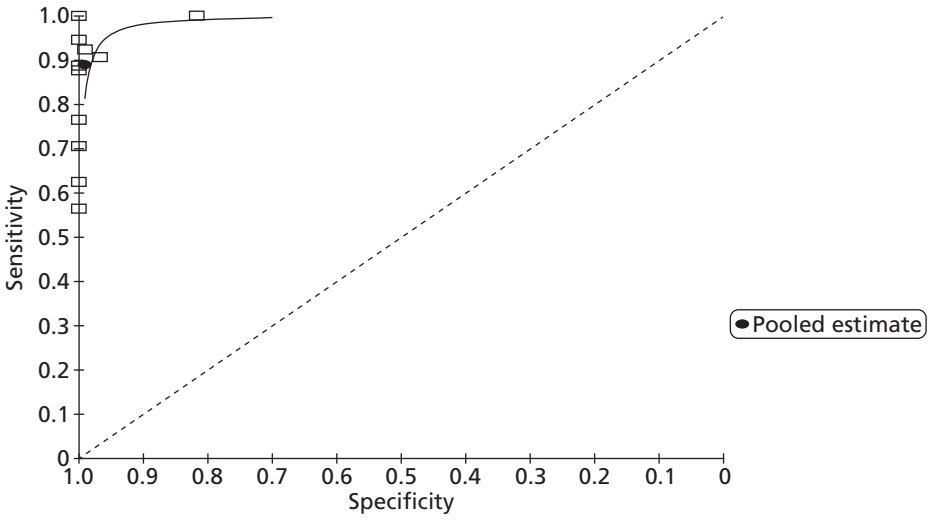

FIGURE 8 Summary receiver operating characteristic plot of pooled TTEh detection of PFO.

Left ventricular aneurysm

The pooled sensitivity of TTEf to detect left ventricular aneurysm in two studies[108,135] ($n = 64$) was 0.82 (95% CrI 0.58 to 0.94) with a specificity of 0.97 (95% CrI 0.83 to 1.00) compared with left ventriculography (*Figure 17*).

Cardiac vegetations

In two studies[149,153] ($n = 175$) the sensitivity of TTEh to detect cardiac vegetation was 0.83 (95% CrI 0.62 to 0.94) with a specificity of 0.96 (95% CrI 0.86 to 0.99) compared with TOE (*Figure 18*). In the study by Chirillo *et al.*[149] ($n = 139$), the sensitivity of TTEf to detect cardiac vegetations was 0.36 (95% CrI 0.19 to 0.56) with a specificity of 0.80 (95% CrI 0.72 to 0.87) compared with TOE.

Aortic valve stenosis

From a single study[129] ($n = 202$) the sensitivity of TTEh to detect aortic valve stenosis compared with cardiac catheterisation was 1.00 (95% CrI 0.98 to 1.00) with a specificity of 0.93 (95% CrI 0.81 to 0.99).

Mitral valve regurgitation

In two studies,[61,117] ($n = 114$) the pooled sensitivity of TTEf to detect mitral valve regurgitation was 0.96 (95% CrI 0.77 to 1.00) compared with TOE; specificity could not be calculated as all patients in one study[117] were positive for mitral valve regurgitation. The accuracy of TTEh in one study[119] ($n = 80$) for the detection of mitral valve regurgitation was lower than that of TOE, with a sensitivity of 0.57 (95% CrI 0.29 to 0.82) and a specificity of 0.94 (95% CrI 0.85 to 0.98).

Mitral valve stenosis

In the study by Musolino *et al.*[61] ($n = 60$), the sensitivity of TTEf to detect mitral valve stenosis was 1.00 (95% CrI 0.16 to 1.00) with a specificity of 1.00 (95% CrI 0.94 to 1.00) compared with TOE.

Mitral valve prolapse

In one study[111] ($n = 42$) the sensitivity of TTEh compared with TOE to detect mitral valve prolapse was 0.93 (95% CrI 0.81 to 0.99). Specificity was not calculable as all participants were positive for mitral valve prolapse. In two studies[111,147] using three-dimensional TTEh ($n = 83$) the pooled sensitivity to detect mitral valve prolapse was 0.97 (95% CrI 0.84 to 1.00) compared with TOE. Specificity could not be calculated, as all patients were positive for mitral valve prolapse.

Study	TP	FP	FN	TN	Sensitivity	Specificity
Fatkin 1996[156]	2	0	3	55	0.35 (0.09 to 0.71)	1.00 (0.98 to 1.00)
Blum 2004[145]	0	0	3	65	0.27 (0.04 to 0.66)	1.00 (0.98 to 1.00)
Vincelj 2001[148]	1	0	0	13	0.39 (0.07 to 0.86)	1.00 (0.97 to 1.00)
Pooled effect					0.34 (0.07 to 0.71)	1.00 (0.97 to 1.00)
Predictive effect					0.35 (0.05 to 0.81)	1.00 (0.96 to 1.00)

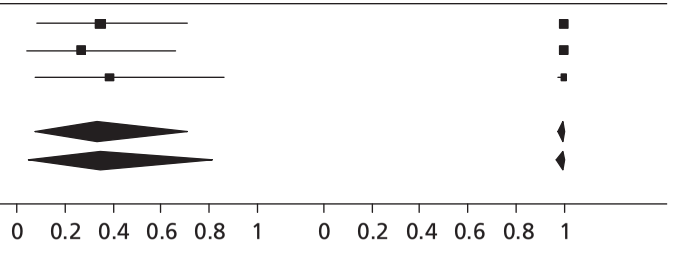

FIGURE 9 Sensitivity and specificity of TTEf to detect left atrial thrombi vs. TOE.

Study	TP	FP	FN	TN	Sensitivity	Specificity
Ha 2000[136]	9	0	3	62	0.78 (0.55 to 0.92)	1.00 (0.99 to 1.00)
Illien 2002[126]	11	0	1	160	0.84 (0.64 to 0.96)	1.00 (0.99 to 1.00)
de Bruijn 2006[141]	0	0	1	230	0.75 (0.26 to 0.94)	1.00 (0.99 to 1.00)
Pooled effect					0.79 (0.47 to 0.94)	1.00 (0.99 to 1.00)
Predictive effect					0.79 (0.33 to 0.97)	1.00 (0.99 to 1.00)

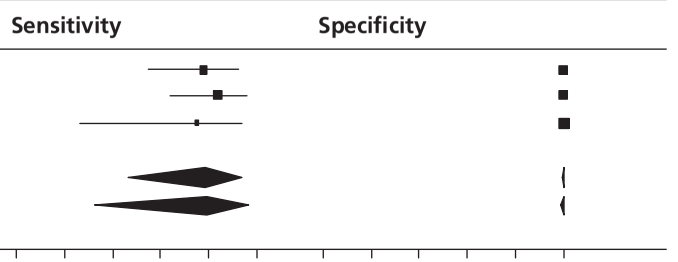

FIGURE 10 Sensitivity and specificity of TTEh to detect left atrial thrombi vs. TOE.

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kuhl 1999[128]	31	0	20	60	0.57 (0.43 to 0.70)	1.00 (0.99 to 1.00)
Akosah 1998[107]	0	0	5	119	0.24 (0.03 to 0.55)	1.00 (0.99 to 1.00)
Musolino 2003[61]	1	0	3	56	0.32 (0.07 to 0.64)	1.00 (0.99 to 1.00)
Blum 2004[145]	0	0	1	67	0.32 (0.04 to 0.69)	1.00 (0.99 to 1.00)
Pooled effect					0.36 (0.10 to 0.62)	1.00 (0.99 to 1.00)
Predictive effect					0.38 (0.04 to 0.79)	1.00 (0.98 to 1.00)

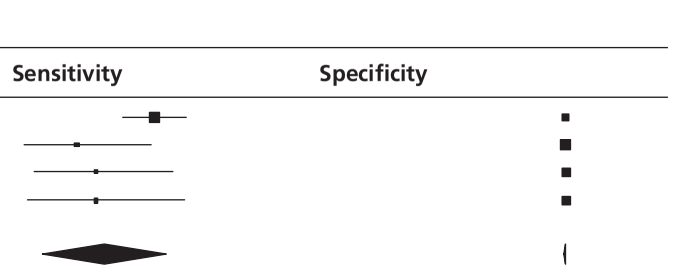

FIGURE 11 Sensitivity and specificity of TTEf to detect atrial septal defect vs. TOE.

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Kuhl 1999[128]	46	0	5	60	0.91 (0.82 to 0.97)	1.00 (0.98 to 1.00)		
Thanigaraj 2005[123]	7	0	0	87	0.93 (0.77 to 0.99)	1.00 (0.98 to 1.00)		
Pooled effect					0.92 (0.75 to 0.98)	1.00 (0.98 to 1.00)		
Predictive effect					0.92 (0.65 to 0.99)	1.00 (0.97 to 1.00)		

FIGURE 12 Sensitivity and specificity of TTEh to detect atrial septal defect vs. TOE.

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Cujec 1991[152]	0	0	2	24	0.01 (0.00 to 0.19)	1.00 (0.97 to 1.00)		
Di Tullio 1993[110]	0	0	2	47	0.01 (0.00 to 0.16)	1.00 (0.98 to 1.00)		
Musolino 2003[61]	0	0	11	49	0.01 (0.00 to 0.14)	1.00 (0.98 to 1.00)		
Pooled effect					0.01 (0.00 to 0.15)	1.00 (0.97 to 1.00)		
Predictive effect					0.01 (0.00 to 0.21)	1.00 (0.96 to 1.00)		

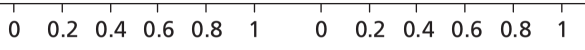

FIGURE 13 Sensitivity and specificity of TTEf to detect atrial septal aneurysm vs. TOE.

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Sallach 2009[120]	0	0	2	116	0.04 (0.00 to 0.40)	1.00 (0.99 to 1.00)		
Akosah 1998[107]	0	0	18	106	0.02 (0.00 to 0.13)	1.00 (0.99 to 1.00)		
Aschenberg 1986[125]	0	0	6	15	0.03 (0.00 to 0.25)	1.00 (0.99 to 1.00)		
Cujec 1991[152]	0	0	1	25	0.05 (0.00 to 0.58)	1.00 (0.99 to 1.00)		
Fatkin 1996[156]	0	0	4	56	0.03 (0.00 to 0.32)	1.00 (0.99 to 1.00)		
Musolino 2003[61]	0	0	1	59	0.05 (0.00 to 0.51)	1.00 (0.99 to 1.00)		
Omran 1999[132]	10	0	2	104	0.73 (0.42 to 0.93)	1.00 (0.99 to 1.00)		
Pop 1990[142]	0	0	2	17	0.04 (0.00 to 0.40)	1.00 (0.99 to 1.00)		
Pooled effect					0.06 (0.00 to 0.26)	1.00 (0.99 to 1.00)		
Predictive effect					0.07 (0.00 to 0.84)	1.00 (0.99 to 1.00)		

FIGURE 14 Sensitivity and specificity of TTEf to detect left atrial appendage thrombi vs. TOE.

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Lee 1991[114]	0	0	9	41	0.05 (0.01 to 0.16)	1.00 (0.97 to 1.00)		
Omran 1999[132]	4	0	51	61	0.06 (0.02 to 0.14)	1.00 (0.98 to 1.00)		
Pop 1990[142]	0	0	2	17	0.05 (0.01 to 0.21)	1.00 (0.97 to 1.00)		
Pooled effect					0.05 (0.01 to 0.16)	1.00 (0.98 to 1.00)		
Predictive effect					0.05 (0.01 to 0.27)	1.00 (0.96 to 1.00)		

FIGURE 15 Sensitivity and specificity of TTEf to detect SEC vs. TOE.

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Black 1991[154]	0	0	75	325	0.00 (0.00 to 0.02)	1.00 (0.99 to 1.00)		
Black 1991[155]	0	0	33	67	0.00 (0.00 to 0.03)	1.00 (0.99 to 1.00)		
Cujec 1991[152]	0	0	7	19	0.00 (0.00 to 0.03)	1.00 (0.99 to 1.00)		
Pearson 1991[118]	0	0	13	66	0.00 (0.00 to 0.03)	1.00 (0.99 to 1.00)		
Pooled effect					0.00 (0.00 to 0.02)	1.00 (0.99 to 1.00)		
Predictive effect					0.00 (0.00 to 0.03)	1.00 (0.99 to 1.00)		

FIGURE 16 Sensitivity and specificity of TTEf to detect left atrial SEC vs. TOE.

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Li 2009[135]	13	1	3	21	0.82 (0.63 to 0.93)	0.97 (0.86 to 1.00)		
Baur 1982[108]	14	0	3	9	0.83 (0.64 to 0.94)	0.97 (0.86 to 1.00)		
Pooled effect					0.82 (0.58 to 0.94)	0.97 (0.83 to 1.00)		
Predictive effect					0.82 (0.45 to 0.96)	0.97 (0.76 to 1.00)		

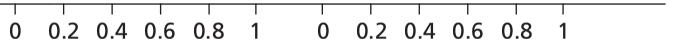

FIGURE 17 Sensitivity and specificity of TTEf to detect left ventricular aneurysm vs. left ventriculography.

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Chirillo 2005[149]	23	2	5	109	0.83 (0.68 to 0.93)	0.97 (0.93 to 0.99)		
Jassal 2007[153]	16	2	3	15	0.84 (0.68 to 0.94)	0.95 (0.83 to 0.99)		
Pooled effect					0.83 (0.62 to 0.94)	0.96 (0.86 to 0.99)		
Predictive effect					0.83 (0.49 to 0.96)	0.96 (0.77 to 0.99)		

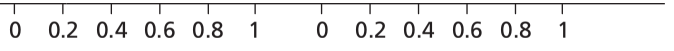

FIGURE 18 Sensitivity and specificity of TTEh to detect cardiac vegetations vs. TOE.

Atrial myxoma

In one study[148] ($n = 14$) the sensitivity of TTEf to detect atrial myxoma was lower than that of TOE, with a sensitivity of 0.80 (95% CrI 0.44 to 0.97) and a specificity of 1.00 (95% CrI 0.40 to 1.00).

Discussion of clinical effectiveness

Patent foramen ovale

For the diagnostic accuracy of TTEf for the detection of PFO using TOE as the reference standard, the pooled sensitivity was 34% with 100% specificity. The performance of TTEh was superior, with a sensitivity of 89%, but at the expense of specificity, which was 96%. TOE is considered the gold standard for the detection of PFO but its accuracy relies on an adequately performed Valsalva manoeuvre, which is not always possible in immobilised patients, and other studies have found that the sensitivity of TOE was marginally lower when compared with TCD[146] and TMD.[113] The poorer performance of TOE in these studies suggests that it is an imperfect gold standard, unless TCD and TMD both gave FP results.

Atrial thrombi

The pooled sensitivity of TTEf to detect left atrial thrombi was 34% based on three studies,[145,148,156] although in one study[148] sensitivity was 100% based on one participant out of 14 being positive for left atrial thrombi; however, this may be over-representing the sensitivity given the low prevalence within the sample. The sensitivity of TTEh to detect left atrial thrombus was 79%, again based on just three studies,[126,136,141] including one study[141] that included only one patient positive for left atrial thrombi, which was undetected. Its contribution to the meta-analysis is that it may cause the sensitivity of TTEh to be underestimated. Detection of left atrial thrombus (67%) by TTEf compared with ultrafast CT showed considerable variation in TP detection rates, possibly because of the inclusion of poorly confirmed positive results in the left atrial thrombus group, and these figures may cause the diagnostic accuracy of TTEf to be overestimated.[138]

Left ventricular thrombi

The diagnostic accuracy of TTEh to detect left ventricular thrombi was poor (53%) and showed considerable variation in two studies[124,130] that used contrast-enhanced cardiac MRI as the reference standard. In another study[122] using less advanced technology, TTEf had a sensitivity of 86% to detect left ventricular thrombus compared with positive identification of thrombi by independent verification (autopsy, aneurysmectomy and unequivocally positive indium-111 platelet imaging).

Atrial septal defect

In four studies[61,107,128,145] the pooled sensitivity of TTEf to detect atrial septal defect was 36% with 100% specificity. The sensitivities between studies were heterogeneous, which may be because different subtypes of atrial septal defect (ostium secundum, ostium primum, sinus venosus, coronary sinus) were included in the sample populations, although none of the studies stated what type of atrial septal defect was identified. TTEh showed greater sensitivity (92%) to detect atrial septal defect, with 100% specificity, but did not equal the performance of TOE. The single study using surgical and cardiac catheterisation as the gold standard[121] found that the sensitivity of TTEf to detect ostium secundum atrial septal defect was 89% and to detect ostium primum atrial septal defect was 100%.

Atrial septal aneurysm

The pooled diagnostic accuracy of TTEf to detect atrial septal aneurysm was 1%. In a single study[131] the sensitivity was much higher (53%); however, in this study all 103 participants were positive for atrial septal aneurysm and it is not known whether study personnel were blinded to reference tests results or knowledge of participants' cardiac condition. Knowing that all participants have atrial septal aneurysm could introduce performance bias, and such variability in sensitivity does not indicate that TTEf is a reliable test to detect atrial septal aneurysm. Only one study[146] was included reporting data for the newer TTEh technology and the sensitivity (97%) and specificity (100%) detected are superior to those of the older TTE

technology. Only one patient with atrial septal aneurysm was not detected by TTEh, suggesting that its performance is similar to that of TOE.

Left atrial appendage thrombi

The pooled sensitivity of the eight studies[61,107,120,125,132,142,152,156] reporting TTEf data for left atrial appendage thrombi was 0.06% with a specificity of 100%. Seven of the studies[61,107,120,125,142,152,156] failed to detect a single left atrial appendage thrombus, but one study[132] had a detection rate of 83%. It is unclear why there is such inconsistency in the results. When TTEh was used to detect left atrial appendage thrombi the sensitivity and specificity were 100%, although this single study[120] had only a small prevalence (2/116) and it is unclear whether this degree of accuracy would be replicated in a larger population.

Spontaneous echo contrast

The diagnostic accuracy of TTEf for detecting cardiac SEC (5%), left atrial SEC (0%) and left ventricular SEC (0%) was poor. TTEh detected more patients with left atrial SEC (sensitivity 88%) but was inferior to TOE, with nine out of 72 cases of left atrial SEC being undetected.

Left ventricular aneurysm

When TTEf was compared with left ventriculography for the detection of left ventricular aneurysm the sensitivity was lower (82%). No data were available to compare TTEf or TTEh against TOE or other routine diagnostic tests.

Aortic valve stenosis

Harmonic TTE had 100% diagnostic accuracy for the detection of aortic valve stenosis but did detect three FPs, resulting in a specificity of 93% compared with cardiac catheterisation. The results are based on only one study[129] ($n = 202$); however, this study included a high proportion of patients ($n = 160$) with aortic valve stenosis, which decreases the possibility that this is a chance finding.

Cardiac vegetations

The detection of cardiac vegetations with TTEh (83% sensitivity and 96% specificity) was superior to detection with TTEf (36% sensitivity and 80% specificity) compared with TOE, although the use of TTEh would result in an estimated 17% of positive cardiac vegetations cases being undetected.

Mitral valve disorders

Based on two studies[61,117] TTEf had an average sensitivity of 96% for the detection of mitral valve regurgitation and identified more patients with mitral valve regurgitation than TTEh (57% sensitivity) using TOE as the reference standard. This reversal in diagnostic accuracy, with the older technology being superior, is probably a reflection of the general heterogeneity in diagnostic accuracy studies and is likely to be a chance finding. For mitral valve stenosis, one study[61] found that TTEf was 100% sensitive and specific but only two out of a sample of 60 patients had mitral valve stenosis, which limits the generalisation of this finding. The accuracy of TTEh with three-dimensional imaging for detecting mitral valve prolapse, a minor cardiac risk factor for stroke, was similar to that of TOE (97%). These findings are limited by the small number of studies included.

Atrial myxoma

Only one study[148] reported data for atrial myxoma, indicating that TTEf has a lower (80%) sensitivity to detect this cardiac pathology than TOE. No studies using TTEh were identified.

Adverse effects and contraindications

None of the studies reported adverse events. TTE is considered a safe procedure being non-invasive. TOE is also considered a safe procedure although it is dependent on patient willingness and ability to undergo the procedure.

Discussion

The average sensitivity and specificity of TTE in both fundamental imaging mode and harmonic imaging mode were lower than those of the gold standard TOE. Generally, TTEh was superior to TTEf but the greater sensitivity did lead to a decreased specificity. TTEh demonstrated lower sensitivity than reference standards for the detection of cardiac pathologies requiring anticoagulation therapy such as left atrial thrombi and left ventricular thrombi. However, TOE is not suited to the detection of left ventricular apical thrombi, and TTE, although not as accurate as contrast-enhanced MRI, could serve as a screening tool for this pathology. TTEh had good sensitivity and specificity for the detection of left atrial appendage thrombi, albeit based on a small data set. Overall, these findings are limited by the small number of studies and the low prevalence rates within some studies.

Transoesophageal echocardiography demonstrated a greater diagnostic accuracy over a range of cardiac pathologies. However, TOE did not detect all PFO compared with TMD and TCD. Diagnosis of PFO relies on the correct execution of the Valsalva manoeuvre to provoke movement of micro-bubbles across the atrial septum, and this may have reduced the sensitivity of TOE. Most studies used TOE as the reference test to measure the accuracy of TTE and none reported any adverse event data. The differences in the diagnostic accuracy of TTE and TOE were found mainly in their sensitivity to detect cardiac sources of stroke, that is, the probability that the index test (TTE) will be positive in diseased cases; differences in specificity to correctly identify non-diseased cases were less remarkable with most studies reporting a specificity of 1.00.

Although both TTE and TOE are considered safe procedures, TOE is a semi-invasive procedure and requires a fasted patient and more personnel present. TTE is non-invasive, quicker to perform than TOE and needs only one sonographer. However, skeletal structure and tissue may impede test performance of TTE compared with TOE, and TOE is more appropriate for detecting some cardiac pathologies such as left atrial appendage thrombi. Therefore, TTE might be applied primarily to patients with stroke of undetermined aetiology (i.e. patients showing normal results on electrocardiography or carotid ultrasound) and who are candidates for oral anticoagulation, before escalation of further diagnostic tests. With improvements in TTE technology further diagnostic accuracy studies will be needed, and these should conform to the reporting standards of the Standards for Reporting of Diagnostic Accuracy (STARD) initiative[157] to ensure that valuable data are accessible.

Chapter 5 Survey of relevant comparators

A survey was conducted with the main aim of gaining knowledge of current UK stroke centre diagnostic protocols to inform the decision as to which diagnostic test should be used as a comparator to TTE. A secondary aim was to gain knowledge of which guidelines are used by stroke centres to investigate and manage stroke or TIA (see *Appendix 12* for the survey). The survey was sent by the Royal College of Physicians on our behalf to 170 NHS trusts in England and 15 health boards in Wales, and by NHS National Services of Scotland to 14 health boards in Scotland. The number of responses was 50, 9 and 12 from the English, Welsh and Scottish health authorities respectively. For 43 responders the country of origin is unknown. This represents a 57% response overall. Respondents were given the choice of either completing the survey online via Google Docs or completing the survey in Microsoft Word and returning the file by e-mail. The URL for the Google Docs survey and the Word file were provided in the e-mail sent to stroke units by the Royal College of Physicians and the NHS National Services of Scotland.

There are two questions in the questionnaire. The first asks which diagnostic tests are used in the following circumstances: never, only in young cases, only if all other tests are normal, only if there is strong clinical suggestion of cerebral embolism and in all cases. The second question asks which guidelines are used to investigate and manage stroke or TIA. The diagnostic tests included in the questionnaire were chosen on the advice of our clinical advisors and are 12-lead ECG, Holter monitoring, TOE, TTE, TTE with bubble contrast and 'other' tests. Twelve-lead ECG is a transthoracic interpretation of the electrical activity of the heart over a short period of time and is used to detect the underlying pathology of stroke. A Holter monitor is a portable ECG device used to monitor electrical activity of the cardiovascular system over longer periods of time than is possible with a 12-lead ECG.

The responses to the question 'How often are the following tests used to investigate ischaemic stroke or TIA?' are provided in *Table 4*. For 12-lead ECG the 0.88% of centres that use this tool only when there is a strong clinical suggestion of cardioembolism actually represents one centre out of the 114 responders; all other centres use this tool in all cases. Holter monitoring is used by 65% of centres only if there is a strong clinical suggestion of cardioembolism, by 16% of centres only if all other tests are normal and by 14% of centres in all cases. Only 1% of centres never use Holter monitoring. A total of 46% of centres use TOE only in young cases, 35% of centres use TOE only if there is a strong clinical suggestion of cardioembolism, 7% of centres never use TOE and no centres use TOE in all cases. In total, 67% of centres use TTE only if there is a strong clinical suggestion of cardioembolism, 15% of centres use TTE only if all other tests are normal, 9% of centres use TTE only in young cases, 8% of centres use TTE in all cases and 1% of centres never use TTE. A total of 62% of centres use TTE with bubble contrast only in young cases, 21% of centres use it only if there is a strong clinical suggestion of cardioembolism, 13% of centres use this method only if all other tests are normal, 5% of centres never use this method and no centres use this method in all cases.

In England and Wales the Royal College of Physicians guidelines and NICE guidelines are used to investigate stroke or TIA by 44% and 37% of stroke centres respectively. Amended guidelines, internal guidelines and no guidelines are used to investigate stroke or TIA by 10%, 5% and 4% of stroke centres respectively. No centres use 'other' guidelines for investigation (*Table 5*). NICE guidelines and the Royal college of Physicians guidelines are used to manage stroke or TIA by 42% and 40% of stroke centres respectively. Amended guidelines, internal guidelines and no guidelines are used to manage stroke by 10%, 7% and 1% of stroke centres respectively (see *Table 5*). Stroke centres were asked to provide copies of amended guidelines; unfortunately, however, none were provided and we therefore have no information regarding the amendments.

In Scotland, 75%, 17% and 8% of stroke centres use Scottish Intercollegiate Guidelines Network (SIGN) guidelines, amended guidelines for local use and no guidelines, respectively, to investigate stroke or TIA. No stroke centres use internal, NICE, Royal College of Physicians or other guidelines to investigate stroke or TIA (*Table 6*). Other guidelines, amended guidelines, internal guidelines, NICE guidelines and no

TABLE 4 Responses to the question 'How often are the following tests used to investigate ischaemic stroke or TIA?'

Survey response options	12-lead ECG, *n* (%)	Holter monitoring, *n* (%)	TOE, *n* (%)	TTE, *n* (%)	TTE with bubble contrast, *n* (%)
Never	0 (0)	1 (1)	8 (7)	1 (1)	6 (5)
Only young cases	0 (0)	4 (4)	52 (46)	10 (9)	69 (62)
Only if all other tests are normal	0 (0)	18 (16)	14 (12)	17 (15)	14 (13)
Only if strong clinical suggestion of cerebral embolism	1 (0.88)	74 (65)	39 (35)	76 (67)	23 (21)
All cases	113 (99.12)	16 (14)	0 (0)	9 (8)	0 (0)
No response to question	0 (0)	1 (1)	1 (1)	1 (1)	2 (2)
Total	114 (100)	113 (100)	113 (100)	113 (100)	112 (100)

TABLE 5 Responses to the question 'What guidelines do you use to investigate and manage ischaemic stroke or TIA?' (England and Wales)

Guidelines	Investigate, *n* (%)	Manage, *n* (%)
Internal	5 (5)	7 (7)
NICE	38 (37)	43 (42)
Royal College of Physicians	45 (44)	41 (40)
Other	0 (0)	1 (1)
Amended for local use	10 (10)	10 (10)
None	4 (4)	1 (1)
Total	102 (100)	103 (100)

TABLE 6 Responses to the question 'What guidelines do you use to investigate and manage ischaemic stroke or TIA?' (Scotland)

Guidelines	Investigate, *n* (%)	Manage, *n* (%)
Internal	0 (0)	1 (9)
SIGN	9 (75)	0 (0)
NICE	0 (0)	1 (9)
Royal College of Physicians	0 (0)	0 (0)
Other	0 (0)	5 (45)
Amended for local use	2 (17)	3 (27)
None	1 (8)	1 (9)
Total	12 (100)	11 (100)

guidelines are used by 45%, 27%, 9%, 9% and 9% of centres, respectively, to manage stroke or TIA. No stroke centres use Royal College of Physicians or SIGN guidelines to manage stroke or TIA (see *Table 6*). We are unable to explain why 75% of centres use SIGN guidelines to investigate stroke or TIA but none of these centres use these guidelines to manage these conditions.

Discussion of survey results

In the 'Please state other diagnostic test' response box, many clinicians took the opportunity to give more details about the decision-making processes that are used to decide which test should be used in which circumstance. A sample of clinicians' comments can be seen in *Appendix 13*. It is clear from these responses that protocols are much more complicated and varied than we expected and could not be captured accurately by our questionnaire. To accurately describe current management practice a very sophisticated questionnaire would be required, which may result in poor response rates and yield little useful information. Although the survey distributed had been approved by our clinical advisors, a preferable approach would have been to have convened experts to write guidelines; however, this was beyond the remit of this study. The results of question 1 of our survey should therefore be viewed as a simple overview of the types of protocols used.

Chapter 6 Assessment of cost-effectiveness

This chapter of the report focuses on the health economics of echocardiography diagnostic strategies for the management of ischaemic stroke and TIA. It includes a brief review of existing economic evaluations and a detailed explanation of the methodologies and results of a de novo economic model. The population in the assessment of cost-effectiveness is the same as that defined in *Chapter 2* (see *Decision problem*).

Systematic review of existing cost-effectiveness evidence

The primary objective of this review was to identify and evaluate studies exploring the cost-effectiveness of TTE in the assessment of first-episode diagnosed ischaemic stroke and TIA patients in secondary care. The secondary objective was to evaluate published modelling methodologies to inform our own modelling methodology.

Identification of studies

Electronic databases

Studies were identified by searching the following electronic databases during March 2011:

- MEDLINE In-Process & Other Non-Indexed Citations (via Ovid SP) (1950 to present)
- CINAHL (via EBSCO*host*) (1981 to present)
- EMBASE (via Ovid SP) (1980 to present)
- Web of Science (includes Science Citation Index and Conference Proceedings Citation Index) (via Web of Knowledge) (1899 to present)
- DARE (via The Cochrane Library) (approximately 1995 to present)
- NHS EED (via The Cochrane Library) (approximately 1995 to present)
- PsycINFO (via Ovid SP) (1806 to October 2011 week 4).

Sensitive keyword strategies using free-text and, when available, thesaurus terms using Boolean operators and database-specific syntax were developed to search the electronic databases. Synonyms relating to the condition were combined with a search filter aimed at restricting results to economic and cost-related studies (used in the searches of MEDLINE, CINAHL, EMBASE and PsycINFO, with an amended version used for Web of Science). Date limits or language restrictions were not used on any database. All resources were searched from inception to March 2011. An example of the MEDLINE search strategy is provided in *Appendix 9*.

All identified citations from the electronic searches and other resources were imported into, and managed using, Reference Manager bibliographic software.

Inclusion and exclusion criteria

Studies were selected for inclusion according to predetermined inclusion and exclusion criteria. Studies were included if they reported the cost-effectiveness of TTE in first-episode diagnosed stroke and TIA patients, and estimated the benefits in terms of life-years gained or quality-adjusted life-years (QALYs). Studies that did not report costs and outcome estimates or that did not report an estimate of cost-effectiveness (e.g. costing studies) were excluded. Studies not published in the English language were also excluded.

One reviewer (AR) independently screened all titles and abstracts. When there was uncertainty in the decision a second reviewer (MH) was used and a consensus was obtained through discussion. Full papers were obtained for any titles/abstracts that were considered relevant or when the title/abstract information was not sufficient to make a decision.

Quality assessment strategy

The quality of the economic evaluation studies that met the inclusion criteria was assessed using an adapted version[158] of the Drummond and Jefferson *British Medical Journal* criteria for economic evaluation[159] and the Consensus on Health Economic Criteria (CHEC)-list (see *Appendix 11*).[160] The use of these checklists ensures a consistent approach to assessing the quality of each economic evaluation.

Results of the cost-effectiveness review

The systematic searches identified 1746 potentially relevant citations. After screening titles and abstracts, two full-text papers[37,161] were retrieved and assessed in detail; both of these papers were considered to meet the inclusion criteria for the review. A flow chart describing the process of identifying relevant literature can be found in *Appendix 10*.

Meenan *et al.*[37]

Overview

Meenan *et al.*[37] developed a decision-analytic Markov model to evaluate the cost-effectiveness of imaging strategies that use TTE and TOE for identifying intracardiac thrombus in new stroke and TIA patients. A systematic review of the evidence was performed to (1) identify the pathologies for which there is evidence of a causal association for stroke or TIA and for which there is evidence that identification of the pathology on echocardiography will change patient management and (2) find data on the sensitivity and specificity of TTE and TOE in detecting intracardiac thrombus. Pathologies that do not represent conditions for which echocardiography is typically used as a screening tool were excluded, as were disorders that may be associated with stroke but which are clinically apparent without echocardiography. In consultation with an expert panel the authors decided that only the identification of left atrial and left ventricular thrombus on echocardiography would alter patient management; all other conditions were excluded.

The model follows for 30 years a cohort of first-episode diagnosed white male stroke patients with a mean starting age of 65 years. Patients diagnosed with either left atrial or left ventricular thrombus received standard medical treatment (SMT) plus warfarin; those without a thrombus received SMT. SMT was assumed to be aspirin alone. The authors did not include other antiplatelet therapies in the model because of a lack of clinical effectiveness evidence for them at the time. Nine testing strategies were evaluated:

1. treat all with SMT
2. treat all with anticoagulation plus SMT (AC; anticoagulation)
3. all receive TTE (all TTE)
4. all receive TOE (all TOE)
5. all with heart disease receive TTE; others receive SMT (cardiac TTE)
6. all with heart disease receive TOE; others receive SMT (cardiac TOE)
7. all receive TTE, negative TTE prompts TOE (TTE sequential)
8. all with heart disease receive TTE, negative TTE prompts TOE (cardiac sequential)
9. all with heart disease receive TTE, negative TTE prompts TOE; all with no heart disease receive TOE (combined sequential).

The only functional difference in the model between patients with heart disease and patients without heart disease was a higher prevalence of intracardiac thrombus in the former.

The states in the Markov model were:

- TIA
- minor stroke
- moderate stroke
- severe stroke
- short-term complications
- long-term complications
- dead.

A monthly cycle and a half-cycle correction were used. Transition probabilities varied over time. The only adverse event included for echocardiography was a small mortality risk and a transient quality-of-life (QoL) reduction from undergoing TOE. Adverse events from anticoagulation included gastrointestinal bleeding and intracranial haemorrhage (ICH). Life tables were used to establish baseline mortality rates.

All direct costs related to stroke management were included. Cost estimates were taken from the literature or from Medicare fee schedules. QoL utilities were taken from the Stroke Patient Outcomes Research Team.[162] The utility of a long-term ICH was assumed to be the same as that of a severe stroke and the utility of a short-term ICH was assumed to be equal to that of a minor stroke. Costs and utilities were discounted at an annual rate of 3%.

Both univariate sensitivity analysis and probabilistic sensitivity analysis (PSA) were undertaken. Cost-effectiveness acceptability curves (CEACs) were used to report the PSA results.

In the deterministic analysis the incremental cost-effectiveness ratios (ICERs) for both cardiac TTE and cardiac TOE compared with SMT are in excess of $83,000; all other strategies are dominated by SMT. In the univariate sensitivity analysis, for both cardiac TTE and cardiac TOE compared with SMT, the ICERs were > $59,000, with one exception. When the prevalence of thrombus with heart disease was increased to 0.3 (compared with the baseline value of 0.05), the ICER for cardiac TOE was $33,000. Mean values from the PSA are not reported. The CEAC indicates that SMT is likely to be cost-effective compared with all other strategies at willingness-to-pay (WTP) thresholds of < $58,000. Above this threshold the cardiac TOE strategy was likely to be cost-effective compared with all other strategies. Expected value of perfect information (EVPI) analysis estimated that the EVPI for an individual person is around $100 (threshold stated by the author to be low but the actual threshold is not stated), which equates to $20M on a population basis based on stroke incidence in the USA.

Comments

This appears to be a well-constructed model parameterised by relevant data at the time. This study scored highly on the assessment criteria.

McNamara *et al.*[161]

Overview

This study used Markov decision-analysis techniques to evaluate the cost-effectiveness of nine diagnostic strategies in a cohort of 65-year-old patients with first-episode diagnosed stroke. The model cycle was monthly for events including recurrent cerebrovascular accident, ICH, gastrointestinal bleeding and death. The strategies evaluated are:

1. no imaging, treat all
2. no imaging, treat none
3. cardiac history, TTE
4. cardiac history, TTE then TOE if TTE negative
5. no cardiac history, TOE

6. cardiac history, TOE
7. all TTE
8. all TTE then TOE if TTE negative
9. all TOE.

The pathological conditions evaluated in the model are left atrial thrombus, other potential cardiac sources of thrombus, aortic plaque only and no identifiable cardiovascular source of thrombus. SMT appears to be aspirin. Patients with AF were excluded from the model.

All data used in the model were determined using the best available estimates identified from a systematic review of the literature.

Costs in the model included direct medical costs, staff and technical costs and costs due to lost productivity. The model thus takes a societal perspective. Utilities in the model were taken from a study by Solomon *et al.*[163] Costs and utilities were discounted at an annual rate of 3%.

A univariate sensitivity analysis was undertaken but PSA was not undertaken.

In the base-case results, both the 'selective TOE' and the 'all TOE' strategies had ICERs that were < $20,000. Strategies that used TTE alone or in sequence with TOE were not found to be cost-effective. In the sensitivity analysis the results were most sensitive to the efficacy of anticoagulation and the rate of ICH with anticoagulation. Of interest is that the results were not sensitive to the sensitivity of TOE.

Comments

This is a moderately well-constructed model with the main criticism being the lack of a PSA analysis. TOE was found to be cost-effective in this model whereas in the model of Meenan *et al.*[37] it was not. The likely reasons for this discrepancy were outlined in the Meenan *et al.*[37] study. First, thrombus prevalence was assumed to be 8% in the study by McNamara *et al.*[160] compared with 2% in the study of Meenan *et al.*,[37] which could be because the McNamara *et al.*[161] study used prevalence data that included AF patients. Second, in the base case TOE was assumed to have 100% accuracy in the McNamara *et al.*[161] study; however, this is unlikely. Third, the stroke recurrence rate was assumed to be 40% in the McNamara *et al.*[161] study, which is substantially higher than the rate used by Meenan *et al.*[37] Fourth, all thrombi were assumed to be left atrial and, fifth, the duration of anticoagulation was unspecified in the McNamara *et al.*[161] study. Finally, the cost of TOE was substantially lower in the McNamara *et al.*[161] model than in the Meenan *et al.*[37] model. These assumptions would all favour TOE.

Independent economic assessment

This section details the methods and results of our health economic model, constructed to evaluate the cost-effectiveness of the addition of TTEh to the routine assessment of patients who have had a first-episode diagnosed stroke or TIA in the UK. The project's clinical advisors provided information that TTEh has superseded TTEf in most hospitals in the UK. For this reason, and also because of the improved diagnostic accuracy of TTEh compared with TTEf, we have considered TTEh as the baseline in this analysis. The strategies evaluated were no test and no treatment; TOE only; TTEh only; TTEh then TOE in patients testing positive on TTEh (TTEh +ve TOE, attempting to identify FPs); and TTEh then TOE in patients testing negative on TTEh (TTEh –ve TOE, attempting to identify FNs). We were unable to include strategies in subgroups of patients in which, for example, TTEh is used first and then TOE is used. Possible subgroups would include young patients with cryptogenic stroke or patients with PFO or atrial septal defect in which greater anatomical/physiological accuracy is needed. This is because of the lack of evidence regarding the rate of recurrent stroke in these subpopulations. The analysis was undertaken to address the lack of any published cost-effectiveness evidence from the perspective of the NHS in the UK. The key aim was to determine the optimal echocardiography management strategy in terms of cost-effectiveness.

Methods

Included and excluded pathologies

The systematic review evaluated the published evidence on the diagnostic accuracy of echocardiography in patients with cardiac pathologies identified to be risk factors for stroke or TIA. The pathologies for which published evidence of diagnostic accuracy was available are:

- PFO
- atrial septal defect
- atrial septal aneurysm
- mitral valve regurgitation
- left atrial thrombi
- left atrial appendage thrombi
- SEC
- left atrial SEC
- mitral valve stenosis
- left ventricular SEC.

However, for the economic modelling it is important to include only those pathologies for which knowledge of them on echocardiography would alter patient management and for which there is published evidence that treatment of the pathology is effective in preventing further strokes. On the advice of our clinical advisors the only pathologies for which this criterion applies are left atrial and left ventricular thrombi. However, no studies were identified in the systematic review that evaluated the diagnostic accuracy of echocardiography for left ventricular thrombi and therefore only the finding of left atrial thrombi is included in the analysis. The model incorporates an estimate of the prevalence of left atrial thrombus and only these patients receive the benefits, harms and costs of treatment. It should be noted that there is little evidence showing an association between left atrial thrombus (without AF) and stroke; however, we agree with the opinions expressed in the Meenan *et al.*[37] study that biomedical knowledge suggests that left atrial thrombus is a likely cause of cardioembolic stroke and that there is a general consensus that treatment of intracardiac thrombus with anticoagulants is appropriate and probably reduces the risk of recurrent stroke. The sensitivity of TTEh to detect left atrial thrombus was 79%; this was based on just three studies[126,136,141] including one study[141] that included only one patient positive for left atrial thrombus, which was undetected. Its contribution to the meta-analysis is that it may cause the sensitivity of TTEh to be underestimated.

The costs and benefits of echocardiography in the management of patients with a first-episode diagnosed stroke or transient ischaemic attack

The main benefits of echocardiography relate to the rapid identification and treatment of patients with left atrial thrombi. The main disadvantage is the risk of bleeding associated with anticoagulation. The direct costs are those of echocardiography, anticoagulation treatment including adverse events (intracranial and gastrointestinal bleeds) and initial stroke or TIA treatment including the CT scan and costs associated with the long-term care of mild, moderate and severe disability due to a stroke. We constructed a model to allow us to analyse the effects of different echocardiography management strategies on these costs and benefits.

The decision-analysis model structure

The modelling was conducted in two stages.

Model 1

This model is an individual patient micro-simulation developed using Simul8 software (version 17; Simul8 Corporation, Boston, MA, USA) to explore the costs and health outcomes associated with echocardiography in the management of TIA/stroke. The analysis was conducted for 100,000 patients aged 45, 55 and 65 years of age when presenting to the emergency department. The model takes a lifetime horizon with mean life expectancy based on UK interim life tables.[164] The analysis did not consider men and women separately. The economic perspective of the model is the NHS in the UK. Costs and health benefits were discounted at an annual rate of 3.5% as recommended by the NICE guide to the methods of technology appraisal.[165] *Figure 19* shows the treatment pathways in the model.

The outcomes of this model are the costs and QALYs associated with the following: (1) patients with an intracardiac thrombus and treated (TPs), (2) patients with an intracardiac thrombus and untreated (FNs), (3) patients without an intracardiac thrombus and treated (FPs), (4) patients without an intracardiac thrombus and untreated (TNs).

Patients enter the model with a TIA, a stroke leading to an independent outcome or a stroke leading to a dependent outcome. Patients in the TIA state can have an independent stroke, a dependent stroke or a fatal stroke, or can die from other causes. Patients in the independent stroke state can have a recurrent independent stroke, a dependent stroke or a fatal stroke, or can die of other causes. Patients in the dependent stroke state can have a recurrent dependent stroke, an independent stroke or a fatal stroke or can die of other causes. Patients in the dependent stroke state experiencing an independent stroke incur the cost of initial treatment and remain in the dependent stroke state. We assume that patients in the dependent stroke state already have a poor QoL and this is unaffected by a further independent stroke. Patients receiving anticoagulation treatment can experience a gastrointestinal or an intracranial (IC) bleed. For patients experiencing a bleed event it is assumed that treatment is immediately stopped. Patients with

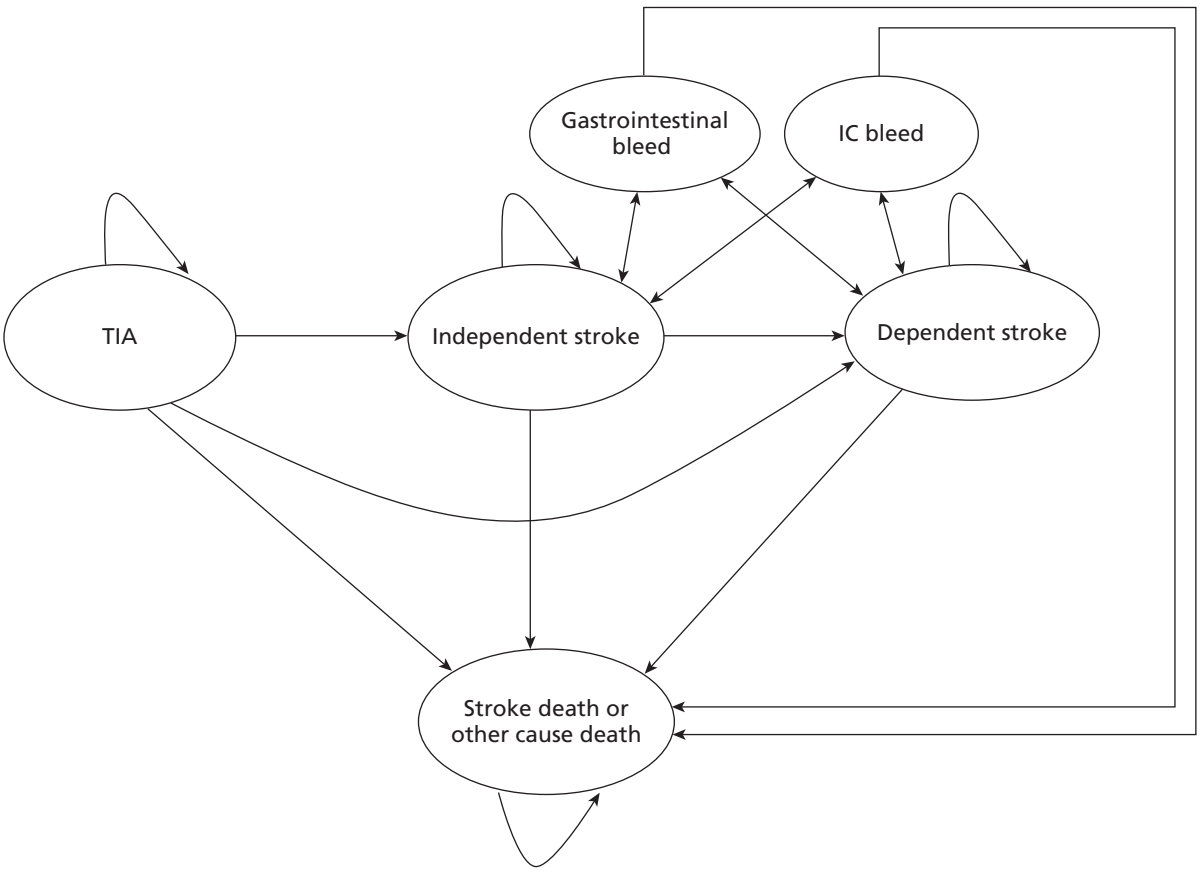

FIGURE 19 Model diagram. IC, intracranial.

a gastrointestinal bleed incur a cost of treating the bleed and a temporary QALY decrement. Patients with an IC bleed will have an outcome represented by a Glasgow Outcome Score (GOS) ranging from 1 to 5, where GOS 1 = death, GOS 2 = persistent vegetative state (PVS), GOS 3 = severe disability, GOS 4 = moderately disabled and GOS 5 = good recovery. Patients incur appropriate costs and QALYs associated with these outcomes (see *Tables 10* and *11*).

In the model, the time to the next event determines the pathway that a patient will take. For each of the events described above, the time to the event is sampled and the patient will experience the event that occurs first (see *Tables 10* and *11*).

All patients are assumed to have an ECG. To model otherwise would require estimates of the diagnostic accuracy of whatever test or clinical decision-making strategy was used and this information is not available.

Model 2

This model was constructed in Microsoft Excel (version 12; Microsoft Corporation, Redmond, WA, USA) to enable the results of the first model (costs and QALYs of TPs, FNs, TPs and TNs) to be combined with the prevalence of left atrial thrombi and the costs and diagnostic accuracy of the different tests to obtain estimates of the costs and QALYs of the five strategies being investigated.

Most studies identified in the assessment of diagnostic accuracy section used TOE as a reference standard to measure the diagnostic accuracy of TTEh, under the assumption that TOE is 100% accurate. In the modelling we have not assumed that TOE is 100% accurate; instead, we have based the diagnostic accuracy of TOE on a study by Meenan *et al.*[166] As the diagnostic accuracy of TTEh is based on a comparison with TOE, the accuracy of TTEh has been adjusted by multiplying the sensitivity and specificity of TTEh by the sensitivity and specificity of TOE as reported by Meenan *et al.*[166] This would underestimate the accuracy of TTEh in the case in which the results were discordant between TTEh and TOE and the TTEh diagnosis was actually correct. However, this is expected to introduce little bias.

To model the strategies in which two tests were performed, an estimate of the combined diagnostic accuracy is needed. For example, for the TTEh –ve TOE strategy, using a hypothetical cohort of 1000 patients, the numbers of patients who would be identified as FN, FP, TN and TP were calculated using the prevalence of thrombi and the sensitivity and specificity of each test. Patients who were positive on TTEh were not evaluated further and thus there was a combination of TPs and FPs associated with the test characteristics of TTEh.

Those patients who were diagnosed as negative represented a cohort of TNs and FNs, based on the test characteristics of TTEh. These patients were then assessed with TOE with some patients being reclassified as positives. The final categorisation of patients was used to form an initial estimate of the sensitivity and specificity of the combination of tests. This methodology was repeated for the TTEh +ve TOE strategy. See worked examples below.

TTE –ve transoesophageal echocardiography strategy methodology

Table 7 shows the results of the initial TTEh test. The methodology is shown below:

- number of patients testing as TP = 1000 × sensitivity (0.7282) × thrombi prevalence (0.0545) = 39.7
- number of patients testing as TN = 1000 × specificity (0.9685) × 1 – thrombi prevalence (0.9455) = 915.7
- number of patients testing as FN = 1000 × 1 – sensitivity (0.2718) × thrombi prevalence (0.0545) = 14.8
- number of patients testing as FP = 1000 × 1 – specificity (0.0315) × 1 – thrombi prevalence (0.9455) = 29.8

TABLE 7 Classification of patients after testing with TTEh

	Test	
Actual	+	–
+	39.7	14.8
–	29.8	915.7

Therefore, 14.8 + 915.7 patients are retested and, of these, 14.8 × the sensitivity of TOE (0.93) move to TPs (13.8), leaving 1.0 FN, and 915.7 × (1 – the specificity of TOE) (0.03) move to FPs (27.5), leaving 888.2 TNs.

When considering those who initially tested negative on TTEh, the overall accuracy is as given in *Table 8*.

The sensitivity of the combined tests (TTEh –ve TOE) is 53.5/(53.5 + 1) = 0.982 and the specificity of the combined tests is 888.2/(888.2 + 57.3) = 0.939.

These estimates, however, indicated that, for the TTEh –ve TOE strategy, the sensitivity of the combined tests would be greater than that of TOE alone. Clinically, however, it is believed that TOE is the more sensitive diagnostic test, with TTEh identifying only a subset of those TP patients diagnosed by TOE. As such, it was not deemed plausible that the combined tests would have a greater sensitivity than TOE alone and therefore the sensitivity of the combined tests was set to the value for TOE alone.

TTE +ve transoesophageal echocardiography strategy methodology

The results of the TTEh +ve TOE strategy in 1000 hypothetical patients are shown in *Table 9*.

Referring back to *Table 7*, 39.7 + 29.8 patients are retested and, of these, 39.7 × (1 – sensitivity of TOE) (0.07) move to FN, with the remainder staying as TP, and 29.8 × specificity of TOE (0.97) move to TN, with the remainder staying as FP.

TABLE 8 The TTEh –ve TOE strategy results

	Test	
Actual	+	–
+	53.5	1.0
–	57.3	888.2

TABLE 9 The TTEh +ve TOE strategy results

	Test	
Actual	+	–
+	36.9	17.6
–	0.9	944.6

When considering those who initially tested positive on TTEh the overall accuracy is as given in *Table 9*.

The sensitivity of the combined tests (TTEh +ve TOE) is 36.9/(36.9 + 17.6) = 0.677 and the specificity of the combined tests is 944.6/(944.6 + 0.9) = 0.999.

The effectiveness of TOE and TTEh is based on the meta-analysis of the sensitivity and specificity of these tests described in the clinical systematic review (see *Chapter 4*, *Data analyses of diagnostic accuracy*). A weighted average of the costs and QALYs of the four scenarios described above (TP, FP, FN and TN) is estimated based on the prevalence of left atrial thrombus in stroke patients and the sensitivity and specificity of TOE and TTEh.

The methodology above assumes that the tests are not correlated, which we believe to be unlikely. We therefore re-estimated the sensitivity and specificity of the combined tests under the assumption that there was correlation between them. We are unaware of any evidence regarding the degree of correlation and therefore estimated values regarded as sensible. Under these assumptions the sensitivity and specificity of the combined test strategies were estimated at 0.92 and 0.97 respectively. The cost-effectiveness implications of these estimates was evaluated in a sensitivity analysis (see *Probabilistic sensitivity analysis results*).

Initial and subsequent stroke or transient ischaemic events

The numbers of initial and subsequent TIA or stroke events were taken from a study undertaken for NICE.[167] The proportions of initial strokes that were independent or dependent were taken from a national stroke audit undertaken by the Royal College of Physicians[168] and a study by Clark *et al.*[169] that measured the long-term risks of stroke in patients with a TIA. The proportions of subsequent strokes that were independent, dependent or fatal were also taken from the above studies.[168,169]

Stroke recurrence

A literature review was conducted to identify studies that measured the rate of stroke recurrence in patients with a thrombus who were treated and who were untreated. A similar literature review was also conducted by Meenan *et al.*[37] as part of their cost-effectiveness analysis. Our review failed to identify any further studies than those already identified by Meenan *et al.*[37] We also reviewed publications by the South London Stroke Register but were unable to find the specific recurrence rates needed for the modelling. The rates of stroke recurrence used for treated and untreated patients are therefore the same as those used by Meenan *et al.*[37]

Anticoagulation complications

The annual rates of fatal and non-fatal gastrointestinal and ICH are taken from Simpson *et al.*[170] Rates are higher in the first 3 months, which may be due to overprescribing whilst the optimal dose is determined.[170] The GOS outcomes of those surviving are taken from a study by Holmes *et al.*[171] This study estimated GOS outcomes for patients with an IC bleed requiring surgery that is delayed because the patient is not in hospital when the haemorrhage occurs. It is assumed that this would be the case in our model and it is therefore appropriate to assume delayed treatment. It is assumed that all patients with an ICH require neurosurgery. A gastrointestinal haemorrhage was assumed to be equal to hospitalisation for 2 weeks.[172] During this time patients were assumed to accrue no QALYs but afterwards were assumed to have a normal health-related QoL. The Multi-Society Task Force on Persistent Vegetative State reported the mean length of survival for adults in a PVS (GOS 2) as 3.6 years, which was used in the model.[173]

All event rates are shown in *Tables 10* and *11*.

TABLE 10 Stroke/TIA event rates

Description	Mean value	Distribution	Statistical parameters	Source
Initial TIA	0.208	Dirichlet	a = 208, b = 792	NICE[167]
Initial stroke	0.792	Dirichlet		
Independent stroke	0.42	Dirichlet	a = 420, b = 580	ISWP,[168] Clark *et al.*[169]
Dependent stroke	0.58	Dirichlet		
Rate of stroke recurrence or initial stroke following a TIA				
In patients with an untreated thrombus in year 1	0.22	Beta	a = 1.32, b = 4.68	Meenan *et al.*[37]
In all patients with a thrombus (untreated or treated) after year 1	0.03	Beta	a = 1.17, b = 37.8	
In untreated patients without a thrombus in year 1	0.12	Beta	a = 42.6, b = 311	
In untreated patients without a thrombus after year 1	0.03	Normal	Mean 0.0287, SD 0.0027	Assumption
Effect of treatment on rate of stroke recurrence (relative risk)				
For patients with a thrombus in year 1	0.57	Beta	a = 2.28, b = 1.72	Meenan *et al.*[37]
For patients without a thrombus in year 1	0.76	Normal	Mean 0.7666, SD 0.0587	Sandercock *et al.*[174]
Patient outcome of recurrent stroke				
Independent outcome	0.2333	Dirichlet	a = 233.33, b = 322.22, c = 444.45	ISWP,[168] Clark[169]
Dependent outcome	0.3222	Dirichlet		
Fatal outcome	0.4445	Dirichlet		

ISWP, Intercollegiate Stroke Working Party; SD, standard deviation.

Costs

Costs included in the model are:

- initial treatment costs for TIA and independent and dependent stroke patients, including emergency room treatment, CT scan and short-term hospitalisation when appropriate
- long-term cost for patients in the independent stroke state
- long-term cost for patients in the dependant stroke state
- costs of warfarin treatment
- treatment costs for gastrointestinal haemorrhage
- initial treatment costs for patients with an ICH including emergency room treatment, CT scan and surgery
- long-term costs of care for patients with moderate disability, with severe disability or who are in a PVS following an ICH.

Initial treatment costs are taken from the Department of Health *NHS Reference Costs*,[175] annual care costs for independent and dependent stroke are taken from the Department of Health *Impact Assessment of National Stroke Strategy* publication[176] and the cost of being in GOS states 2–4 are taken from Holmes *et al.*[171]

The cost of warfarin treatment is taken from Simpson *et al.*[170] All costs have been inflated to 2009–10 prices using the Hospital and Community Health Services Pay and Prices Index.[177] Costs used in the model

TABLE 11 Adverse event rates

Description	Mean value	Distribution	Statistical parameters	Source
Probability of anticoagulation-induced haemorrhage				
In the initial 3 months of treatment	0.0219	Normal	Mean 0.0219, SE 0.0015	Simpson *et al.*[170]
Subsequently in patients aged 40–49 years	0.0060	Normal	Mean 0.0060, SE 0.0004	
Subsequently in patients aged 50–59 years	0.0100	Normal	Mean 0.0100, SE 0.0007	
Subsequently in patients aged 60–69 years	0.0220	Normal	Mean 0.0220, SE 0.0015	
Subsequently in patients aged ≥ 70 years	0.0320	Normal	Mean 0.0320, SE 0.0021	
Haemorrhages in the first 3 months				
Non-fatal and non-IC	0.801	Dirichlet	a = 10.4, b = 39.4, c = 200.2	Simpson *et al.*[170]
Non-fatal and IC	0.041	Dirichlet		
Fatal	0.158	Dirichlet		
Haemorrhages after 3 months				
Non-fatal and gastrointestinal	0.795	Dirichlet	a = 22.7, b = 28.4, c = 198.9	Simpson *et al.*[170]
Non-fatal and IC	0.091	Dirichlet		
Fatal	0.114	Dirichlet		
ICH outcomes				
GOS 2	0.116	Dirichlet	a = 115.5, b = 140.0, c = 79.3, d = 665.1	Holmes *et al.*[171]
GOS 3	0.140	Dirichlet		
GOS 4	0.079	Dirichlet		
GOS 5	0.665	Dirichlet		
Average patient life expectancy for patients in GOS 2 (years)	3.59	Normal	Mean 3.59, SD 0.18	Holmes *et al.*[171]

SD, standard deviation; SE, standard error.

with a description of the distributions and statistical parameters used in the PSA, and with Healthcare Resource Group (HRG) codes where applicable, are shown in *Table 12*.

Quality-of-life utility values

Quality-of-life utility values are taken from a study by Dorman *et al.*[178] This study reports QoL utility values from the Lothian Stroke Register (LSR) and the International Stroke Trial (IST). The LSR and the IST both used the European Quality of Life-5 Dimensions (EQ-5D) questionnaire to measure QoL in a cohort of stroke patients with outcomes of dependent, independent and recovered. The results are broadly similar; however, as the IST cohort ($n = 867$) is larger than the LSR cohort ($n = 147$) we have used the IST QoL utility values in the model.

The mean age in the IST cohort was 69 years. Data from Kind *et al.*[179] indicate that QoL utility values decrease with age. We would therefore expect the utility values estimated by Dorman *et al.*[178] to be slightly higher for younger patients. To adjust the Dorman *et al.* utilities for age, we first divided them by the population norm utility value at age 69 years (0.806) taken from the Kind *et al.* study[179] to obtain an

TABLE 12 Costs used in the model

Description	Mean cost (£)	Distribution	Statistical parameters (£)	Source (HRG or currency/service code)
TIA initial cost	417	Normal	SE 11	Department of Health[175] (AA29Z)
Independent stroke initial cost	542	Normal	SE 15	Department of Health[175] (AA22Z)
Independent stroke annual care cost	3195	Normal	SD 165	Department of Health[176]
Dependent stroke initial cost	2830	Normal	SE 62	Department of Health[175] (AA22Z)
Dependent stroke annual care cost	6386	Normal	SD 325	Department of Health[176]
Gastrointestinal haemorrhage initial cost	1261	Normal	SE 25	Department of Health[175] (FZ38E)
IC procedures except trauma with haemorrhagic cerebrovascular disorders	8829	Normal		Department of Health[175] (AA17Z)
GOS 2 intensive care cost	15,469	Gamma	a = 165, b = 94	Holmes *et al.*[171]
GOS 2 rehabilitation cost	27,960	Gamma	a = 250, b = 120	
GOS 2 weekly nursing home cost	893	Gamma	a = 159, b = 6	
GOS 3 intensive care cost	8829	Normal	SE 633	Department of Health[175] (AA17Z)
GOS 3 annual care cost	33,900	Gamma	a = 326, b = 104	Holmes *et al.*[171]
GOS 4 intensive care cost	8829	Normal	SE 633	Department of Health[176]
GOS 4 rehabilitation cost	17,160	Gamma	a = 385, b = 45	Holmes *et al.*[171]
Anticoagulation initiation cost	208	Fixed		Department of Health[175] (324)
Anticoagulation annual maintenance cost	439	Fixed		Simpson *et al.*[170]
TTE	79.14	Normal	SE 1.97	Department of Health[175] (RA69Z)
TOE	213	Normal	SE 1.97	Department of Health[175] (EA45Z)
CT scan	91	Normal	SE 3.94	Department of Health[175] (RA08Z)

SD, standard deviation; SE, standard error.

estimate of an age-related multiplier for dependent stroke, independent stroke and TIA (0.38, 0.88, 1.09 respectively). We then multiply the Kind *et al.* utilities at each age by these multipliers to provide age-related utility values for dependent stroke, independent stroke and TIA. The estimated multiplier for TIA is > 1 and is intuitively wrong as it would result in patients with a TIA having a higher QoL than that of the general population. We have therefore set the multiplier for TIA at 1 under the assumption that a TIA has no impact on QoL. The QoL utility value for patients with a TIA are thus the same as the population norms for a patient's age and are taken from Kind *et al.*[179] The QoL utility values used in the model are shown in *Table 13*.

TABLE 13 Quality-of-life utility values used in the model

Description	Mean value	Distribution	Statistical parameters	Source
Gastrointestinal haemorrhage	0.997	Uniform	Min. = 0.996, max. = 0.998	Simpson *et al.*[170]
GOS 3	0.15	Beta	a = 5.8, b = 32.7	Holmes *et al.*[171]
GOS 4	0.51	Beta	a = 22.6, b = 21.7	
GOS 5	0.88	Beta	a = 49.8, b = 6.8	

Max., maximum; min., minimum.
For the assumed effect of TIA, independent stroke and dependent stroke see text.

Model stability

The number of patients in each model run determines the stability of the results for estimating the optimal management strategy. This instability is a result of some events having a rare occurrence and stability can be achieved only by having sufficient numbers of patients to account for these rare events. With 100,000 or more patients the model results became stable and the model was therefore run with this number of patients.

Major assumptions

The following assumptions were made:

1. following their first TIA patients may experience subsequent attacks; however, no data were identified on the rate of TIA recurrence in patients with and without a thrombus, and thus recurrent TIA is not included in the model
2. the rate of stroke recurrence is not dependent on the previous number of strokes sustained
3. patients with an intracardiac thrombus are at a higher risk of experiencing a recurrent stroke in the first year following a stroke than in subsequent years
4. patients may experience any number of recurrent ischaemic strokes resulting in an independent or dependent patient outcome
5. anticoagulant treatment continues for 1 year at which point the patient is re-evaluated and from this point on is considered a new patient
6. anticoagulation treatment is discontinued for those patients experiencing a bleed event
7. the relative risk reduction of recurrent stroke as a result of anticoagulant treatment is constant for as long as the patient receives treatment
8. patients were not receiving anticoagulants or antiplatelet agents at the time of stroke.

Definition of cost-effectiveness terms

A deterministic analysis uses the mean or median value of each parameter in the model and does not take into account the effect of any non-linearities in the model that could affect the ICERs. In PSA each parameter in the model is assigned a distribution that encapsulates the uncertainty within the parameter. For each of the 1000 simulations (of 100,000 patients) each model parameter is randomly sampled from the distribution assigned to it. PSA, unlike deterministic analyses, take non-linearities within the model into consideration and thus the answers are more appropriate.[180]

The results are presented as mean and incremental costs and QALYs, ICERs and CEACs. The ICER measures the relative value of two strategies and is calculated as the mean incremental costs divided by the mean incremental benefits. A strategy is dominated when another strategy accrues more QALYs for less cost. Extended dominance occurs when a combination of two alternative strategies can produce the same QALYs as a chosen strategy but at a lower cost. Strategies that are neither dominated nor

extendedly dominated constitute the cost-effectiveness frontier and the ICER is reported for these strategies compared with the next least effective strategy.

A CEAC indicates the proportion of times within the PSA that each intervention is the most cost-effective of all scenarios at different WTP levels.[181] Net benefit (NB) is defined as WTP × QALYs – costs.

The WTP threshold is the amount of money that the decision-maker is willing to pay to gain 1 additional QALY. Typical thresholds for decision-making within the UK are considered to be around £20,000–30,000 per QALY.[165]

Results

Deterministic results

Table 14 shows the deterministic mean per patient costs and QALYs for the four strategies undertaken at age 45, 55 and 65 years at the index event (stroke or TIA). The costs and QALYs decrease as age increases because of shorter survival times.

Tables 15–17 show, for each age at the index event, the strategies ordered by ascending effectiveness (QALYs gained). For all ages, at a WTP threshold of £23,000, the optimal strategy is to perform TTEh only.

TABLE 14 Deterministic mean per patient costs and QALYs for the four strategies undertaken at age 45, 55 and 65 years at the index event

	Age 45 years		Age 55 years		Age 65 years	
Testing strategy	Mean cost (£)	Mean QALYs	Mean cost (£)	Mean QALYs	Mean cost (£)	Mean QALYs
No test	70,770	7.857	61,182	6.635	48,793	5.306
TTEh +ve TOE	70,999	7.868	61,392	6.644	48,974	5.313
TTEh only	71,037	7.872	61,419	6.647	48,993	5.315
TOE only	71,209	7.875	61,587	6.650	49,151	5.317
TTEh –ve TOE	71,317	7.878	61,685	6.652	49,243	5.318

TABLE 15 Age 45 years deterministic results

Testing strategy	Mean cost (£)	Mean QALYs	Incremental cost (£)	Incremental QALYs	ICER (£)
No test	70,770	7.857			
TTEh +ve TOE	70,999	7.868			Extendedly dominated
TTEh only	71,037	7.872	267	0.015	17,541
TOE only	71,209	7.875			Extendedly dominated
TTEh –ve TOE	71,317	7.878	280	0.006	44,492

TABLE 16 Age 55 years deterministic results

Testing strategy	Mean cost (£)	Mean QALYs	Incremental cost (£)	Incremental QALYs	ICER (£)
No test	61,182	6.635			
TTEh +ve TOE	61,392	6.644			Extendedly dominated
TTEh only	61,419	6.647	237	0.012	19,904
TOE only	61,587	6.650			Extendedly dominated
TTEh –ve TOE	61,685	6.652	265	0.005	56,587

TABLE 17 Age 65 years deterministic results

Testing strategy	Mean cost (£)	Mean QALYs	Incremental cost (£)	Incremental QALYs	ICER (£)
No test	48,793	5.306			
TTEh +ve TOE	48,974	5.313			Extendedly dominated
TTEh only	48,993	5.315	200	0.009	22,361
TOE only	49,151	5.317			Extendedly dominated
TTEh –ve TOE	49,243	5.318	251	0.003	73,735

Univariate sensitivity results

A univariate sensitivity analysis was carried out on the following parameters:

- rate of stroke recurrence or initial stroke following TIA in patients:
  - with an intracardiac thrombus in year 1
  - with an intracardiac thrombus subsequently
  - without an intracardiac thrombus in year 1
  - without an intracardiac thrombus subsequently
- efficacy of warfarin therapy:
  - relative risk in patients with an intracardiac thrombus
  - relative risk in patients without an intracardiac thrombus
- rate of anticoagulant-induced haemorrhage:
  - in the first 3 months of treatment
  - subsequently in patients aged 40–49 years
  - subsequently in patients aged 50–59 years
  - subsequently in patients aged 60–69 years
  - subsequently in patients aged $\geq$ 70 years
- the prevalence of left atrial thrombi.

For all of these parameters, altering the parameter to its highest and then lowest value had no effect on the optimal strategy reported in the deterministic results.

Probabilistic sensitivity analysis results

Table 18 shows the mean per patient costs and QALYs from the PSA for the four strategies undertaken at age 45, 55 and 65 years at the index event. As with the deterministic results, the costs and QALYs decrease as age increases because of shorter survival times.

Tables 19–21 show, for each age at the index event, the strategies ordered by ascending effectiveness (QALYs gained) and report whether they are subject to dominance. When a strategy is not dominated an ICER for each strategy compared with the next least effective treatment on the cost-effectiveness frontier is reported. For all ages, at a WTP threshold of £25,000, the optimal strategy is to perform TTEh only.

TABLE 18 Probabilistic mean per patient costs and QALYs for the four strategies undertaken at age 45, 55 and 65 years at the index event

	Age 45 years		Age 55 years		Age 65 years	
Testing strategy	Mean cost (£)	Mean QALYs	Mean cost (£)	Mean QALYs	Mean cost (£)	Mean QALYs
No test	71,075	7.920	61,399	6.679	48,928	5.336
TTEh +ve TOE	71,295	7.929	61,599	6.686	49,106	5.342
TTEh only	71,379	7.936	61,669	6.692	49,160	5.346
TTEh –ve TOE	71,574	7.937	61,861	6.693	49,350	5.346
TOE only	71,545	7.939	61,830	6.695	49,315	5.347

TABLE 19 Age 45 years probabilistic results

Testing strategy	Mean cost (£)	Mean QALYs	Incremental cost (£)	Incremental QALYs	ICER compared with next least effective treatment on the cost-effectiveness frontier (£)
No test	71,075	7.920			
TTEh +ve TOE	71,295	7.929			Extendedly dominated
TTEh only	71,379	7.936	304	0.016	18,526
TTEh –ve TOE	71,574	7.937			Dominated
TOE only	71,545	7.939	166	0.003	65,490

TABLE 20 Age 55 years probabilistic results

Testing strategy	Mean cost (£)	Mean QALYs	Incremental cost (£)	Incremental QALYs	ICER compared with next least effective treatment on the cost-effectiveness frontier (£)
No test	61,399	6.679			
TTEh +ve TOE	61,599	6.686			Extendedly dominated
TTEh only	61,669	6.692	270	0.0132	20,408
TTEh –ve TOE	61,861	6.693			Dominated
TOE only	61,830	6.695	161	0.0021	78,109

TABLE 21 Age 65 years probabilistic results

Testing strategy	Mean cost (£)	Mean QALYs	Incremental cost (£)	Incremental QALYs	ICER compared with next least effective treatment on the cost-effectiveness frontier (£)
No test	48,928	5.336			
TTEh +ve TOE	49,106	5.342			Extendedly dominated
TTEh only	49,160	5.346	232	0.009	24,648
TTEh –ve TOE	49,350	5.346			Dominated
TOE only	49,315	5.347	154	0.002	102,046

Figures 20–22 show the CEACs for ages 45, 55 and 65 years. For all ages the TTEh strategy is optimal at a WTP well above the £30,000 mark. The CEACs indicate that there is uncertainty in the results, although that it is only the no test and TTEh strategies that have non-trivial probabilities of being cost-effective in the range of £20,000–30,000 per QALY. As stated above, assuming a cost per QALY threshold of £25,000, TTEh would be the recommended diagnostic strategy.

Probabilistic sensitivity analysis assuming correlation between tests when carried out in sequence

The base case assumes that the tests are independent. A sensitivity analysis was carried out under the assumption that the tests are correlated (see *The decision-analysis model structure* for the methodology). Both the deterministic and probabilistic results were similar to the base-case results and the optimum strategy remained unchanged at a cost per QALY gained threshold of £25,000. The results of the probabilistic analysis are shown in *Tables 22–24*.

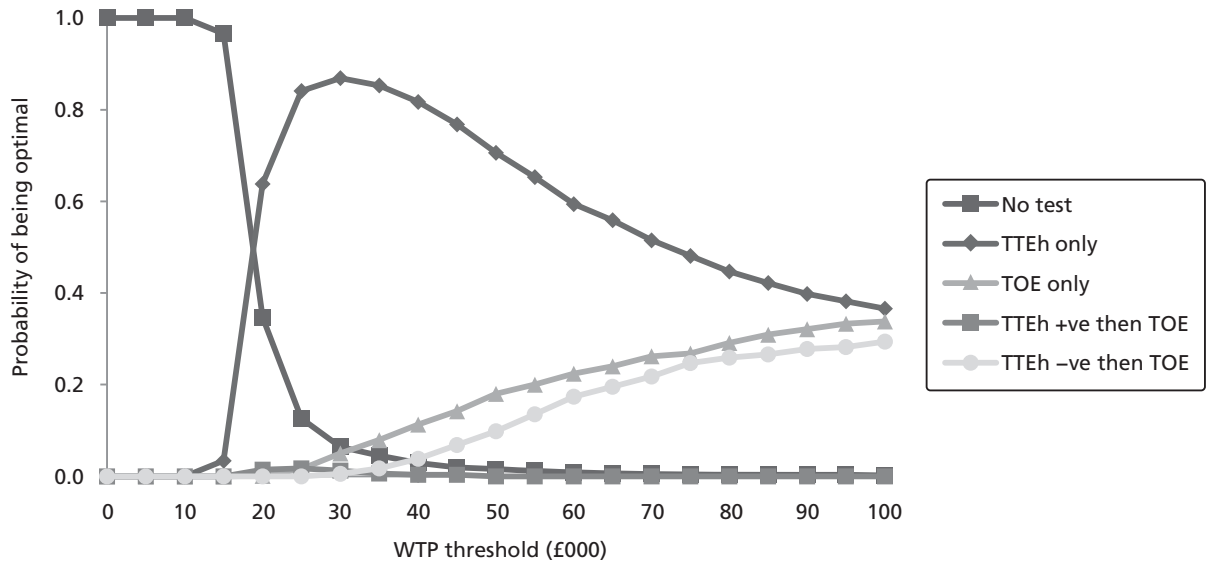

FIGURE 20 Cost-effectiveness acceptability curve for age 45 years.

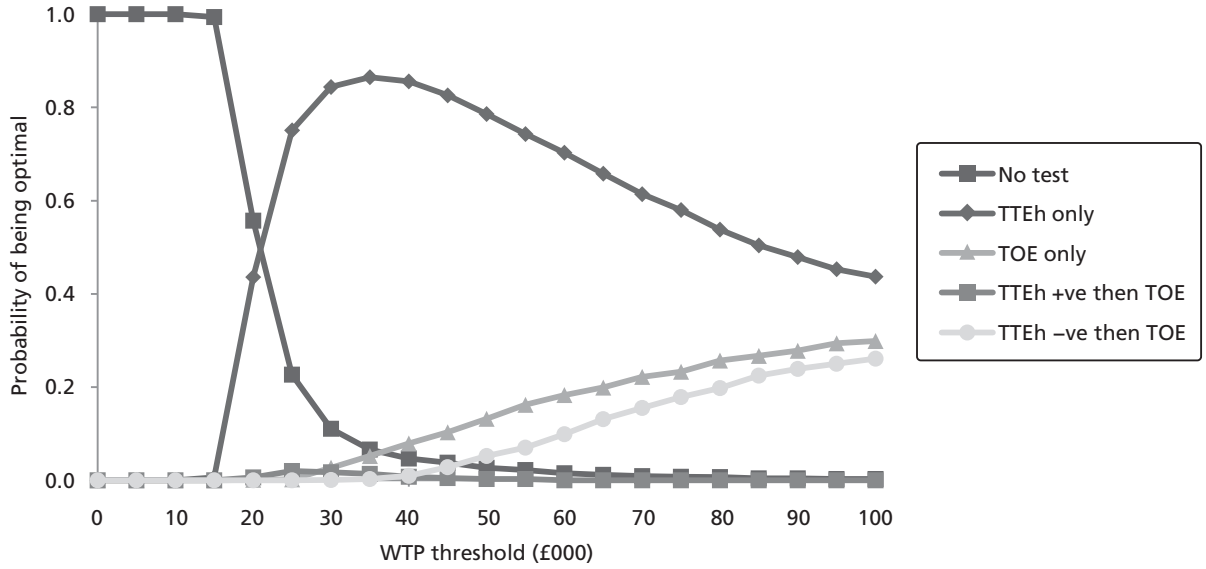

FIGURE 21 Cost-effectiveness acceptability curve for age 55 years.

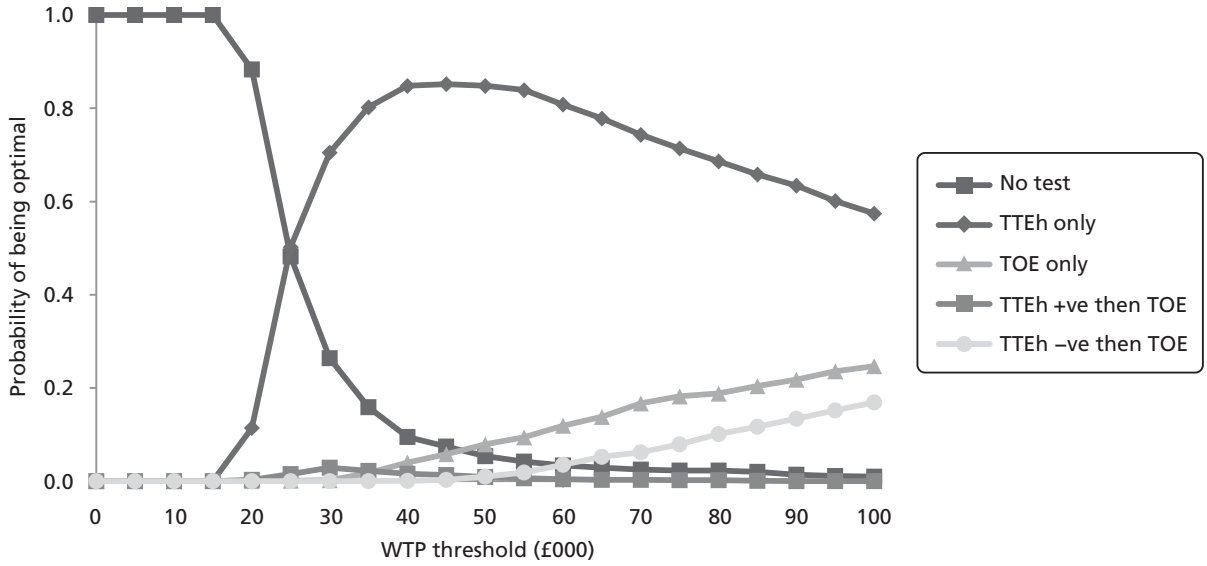

FIGURE 22 Cost-effectiveness acceptability curve for age 65 years.

TABLE 22 Probabilistic sensitivity analysis assuming correlation between tests: age 45 years

Testing strategy	Mean cost (£)	Mean QALYs	Incremental cost (£)	Incremental QALYs	ICER compared with next least effective treatment on the cost-effectiveness frontier (£)
No test	71,075	7.920			
TTEh +ve TOE	71,307	7.930			Extendedly dominated
TTEh –ve TOE	71,548	7.936			Dominated
TTEh only	71,379	7.937	304	0.0164	18,525
TOE only	71,545	7.939	166	0.0025	65,489

TABLE 23 Probabilistic sensitivity analysis assuming correlation between tests: age 55 years

Testing strategy	Mean cost (£)	Mean QALYs	Incremental cost (£)	Incremental QALYs	ICER compared with next least effective treatment on the cost-effectiveness frontier (£)
No test	61,399	6.680			
TTEh +ve TOE	61,609	6.688			Extendedly dominated
TTEh –ve TOE	61,838	6.692			Dominated
TTEh only	61,669	6.693	270	0.013	20,365
TOE only	61,830	6.695	161	0.002	77,947

TABLE 24 Probabilistic sensitivity analysis assuming correlation between tests: age 65 years

Testing strategy	Mean cost (£)	Mean QALYs	Incremental cost (£)	Incremental QALYs	ICER compared with next least effective treatment on the cost-effectiveness frontier (£)
No test	48,928	5.337			
TTEh +ve TOE	49,114	5.343			Extendedly dominated
TTEh –ve TOE	49,330	5.346			Dominated
TTEh only	49,160	5.346	232	0.009	24,648
TOE only	49,315	5.348	154	0.002	102,046

Results of the individual patient-level model (model 1)

As described in *The decision-analysis model structure*, the outcomes of model 1 are the costs and QALYs associated with the following:

1. patients with an intracardiac thrombus and treated (TP)
2. patients with an intracardiac thrombus and untreated (FN)
3. patients without an intracardiac thrombus and treated (FP)
4. patients without an intracardiac thrombus and untreated (TN).

The results of this analysis are presented in *Tables 25–27*. The results of the economic analysis are dependent on the results of model 1 and it is therefore important that the model 1 results are intuitively correct. We believe that the following comparisons represent intuitive results:

- Comparing those patients who have a thrombus (TP vs. FN), patients who are treated cost more and have more QALYs. This is intuitively correct as they get both the cost and benefits of treatment.
- Comparing those patients who do not have a thrombus (FP vs. TN), patients who receive treatment have additional costs and the treatment appears to have a preventative effect as these patients, on average, live a few months longer.
- Comparing those patients who receive treatment (TP vs. FP), patients without a thrombus live longer and thus gain additional costs.
- Comparing those patients who do not receive treatment (FN vs. TN), patients without a thrombus live longer and accrue more costs.

TABLE 25 Model 1 results: age 45 years

Description	Mean cost (£)	Mean QALYs
TP, correctly receive treatment	65,332	6.70
FN, incorrectly do not receive treatment	62,296	6.47
FP, incorrectly receive treatment	72,905	8.09
TN, correctly do not receive treatment	71,587	8.00

TABLE 26 Model 1 results: age 55 years

Description	Mean cost (£)	Mean QALYs
TP, correctly receive treatment	57,534	5.76
FN, incorrectly do not receive treatment	55,018	5.57
FP, incorrectly receive treatment	62,921	6.82
TN, correctly do not receive treatment	61,771	6.74

TABLE 27 Model 1 results: age 65 years

Description	Mean cost (£)	Mean QALYs
TP, correctly receive treatment	46,838	4.70
FN, incorrectly do not receive treatment	44,894	4.56
FP, incorrectly receive treatment	50,120	5.43
TN, correctly do not receive treatment	49,163	5.38

Cost-effectiveness of warfarin

This economic analysis allows us to estimate the cost-effectiveness of warfarin compared with no treatment in those patients who have a thrombus. Patients tested as TP have a thrombus and receive treatment whereas patients tested as FN have a thrombus and are not treated. *Tables 28–30* show the results of this analysis (based on PSA results). For all ages the ICER is well below accepted thresholds.

It can also be calculated that the use of warfarin in patients without a left atrial thrombus appears cost-effective, with ICERs ranging from £15,000 to £20,000. However, as the QALY gains are lower than those in patients with a thrombus (because of a reduced stroke risk but a constant bleed risk), the clinical community may see this as a less appealing option.

TABLE 28 Cost-effectiveness of warfarin: age 45 years

Description	Mean cost (£)	Mean QALYs	Incremental cost (£)	Incremental QALYs	ICER (£)
TP, correctly receive treatment	65,332	6.70			
FN, incorrectly do not receive treatment	62,296	6.47	3035	0.24	12,872

TABLE 29 Cost-effectiveness of warfarin: age 55 years

Description	Mean cost (£)	Mean QALYs	Incremental cost (£)	Incremental QALYs	ICER (£)
TP, correctly receive treatment	57,534	5.76			
FN, incorrectly do not receive treatment	55,018	5.57	2515	0.19	13,171

TABLE 30 Cost-effectiveness of warfarin: age 65 years

Description	Mean cost (£)	Mean QALYs	Incremental cost (£)	Incremental QALYs	ICER (£)
TP, correctly receive treatment	46,838	4.70			
FN, incorrectly do not receive treatment	44,894	4.56	1944	0.14	13,900

Expected value of perfect information analysis

The EVPI quantifies the economic value of removing uncertainty in a decision model.[182] An estimated 163,000 patients per year suffer a TIA or a stroke. Assuming a 10-year time horizon for the value of further research, the maximum amount of research funding to achieve perfect information is calculated as the EVPI per person × 163,000 × 10.

Table 31 and *Figure 23* show the per-person and population EVPI results at WTP thresholds of £20,000 and £30,000.

It is seen that, at all ages, the EVPI is large. Further research to reduce the uncertainty may well be a cost-effective use of resources.

Discussion of the economic analysis

We have explicitly evaluated the cost-effectiveness of TTEh compared with different diagnostic strategies. A limitation was that, because of the heterogeneous use of diagnostic strategies within the UK, explicit rules on the use of TTEh could not be formulated. We therefore assumed that all patients received TTEh; this would not be the case in practice and is likely to be unfavourable to the cost-effectiveness of TTEh. Furthermore, any incidental benefit that may arise from TTEh scanning, such as identifying thrombi in other locations or identifying those pathologies in which benefit is gained from preventative treatment, would also improve the ICER in the analyses undertaken. Despite these unfavourable biases, TTEh was shown to be cost-effective compared with no testing for all patients, indicating that the conclusion is robust and TTEh should be performed when a clinician deems it appropriate.

TABLE 31 Per-person and population EVPI results by age

WTP threshold	45 years (£)	55 years (£)	65 years (£)
£20,000			
Per patient	15	18	2
Population	23,873,671	28,779,564	3,998,567
£30,000			
Per patient	7	6	12
Population	10,878,722	10,462,040	19,270,629

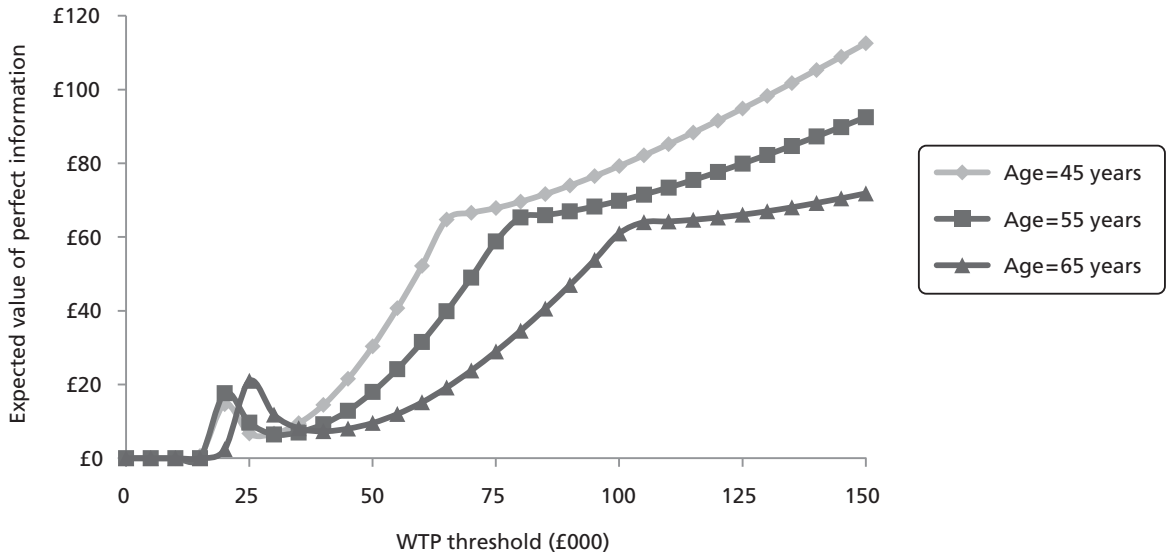

FIGURE 23 Per-person and population EVPI results by age.

However, there will be patients who, in their clinician's opinion, will require TOE, for example those in whom cardiac interventions are likely, when there is a high suspicion of endocarditis or patients aged < 50 years of age with unexplained cases of stroke. Because of data limitations it was not possible to evaluate the cost-effectiveness of TOE in subsets of such cases. Therefore, no statements could be made regarding the cost-effectiveness of the selective use of TOE when clinicians deem it appropriate.

The results of model 1 appear to suggest that preventative treatment in those patients who do not have a thrombus is beneficial and appears to be cost-effective; however, it may not be clinically appropriate in all circumstances.

Our analysis assumed that the benefits of treatment apply only to patients with a left atrial thrombus and it is reasonable to assume that thrombi in other locations may be identified and treated resulting in further health benefits. It is also reasonable to assume that other pathologies that are believed to be risk factors for thromboembolic events, such as cardiomyopathy, could be identified. For some pathologies that are believed to predispose to thrombi, preventative treatment with anticoagulants is recommended and this may improve the cost-effectiveness of TTEh.

Because of the limitations discussed below, however, the results of the economic analysis should be treated with some caution.

Summary of key results

Cost-effectiveness studies

Two cost-effectiveness studies from the USA were identified.[37,161] TOE was found to be cost-effective in one study[161] but not in the other.[37] Both studies found that TTE alone or in combination strategies was not cost-effective. The authors of both studies do not state whether they used TTEf or TTEh imaging techniques.

Strengths and limitations of the analysis

The economic analysis used current best practice to develop the model and followed recommendations produced by NICE.[165] However, economic models are inevitably constrained by the need to make assumptions in developing them and by the limitations of the primary data.

The rate of stroke recurrence is an important parameter in the model. However, we were able to identify only one small study[183] in which patients who were identified as having a left atrial thrombus on echocardiography were followed up long term to measure the rate of stroke recurrence.

We were unable to include pathologies other than left atrial thrombus because of a lack of evidence of treatment effect on stroke recurrence in other pathologies.

In this analysis we assumed that all patients received an echocardiogram. This is unlikely to be the case in the clinical setting; however, to model otherwise would require estimates of the diagnostic accuracy of whatever test or clinical decision-making protocol was used in each clinical setting and this information was not available.

Because of these limitations the results of the economic analysis should be treated with some caution.

Chapter 7 Assessment of factors relevant to the NHS and other parties

If a policy of performing TTEh were adopted it has the potential to save the NHS money as the more costly and invasive TOE procedure would be used less often. The potential reduction in the usage of TOE and the consequent impact on the NHS budget are difficult to quantify.

Chapter 8 Discussion

Statement of principal findings

Prevalence

The studies included in the prevalence systematic review report multiple sources of potential cardiac pathologies, reflecting the heterogeneous nature of cardioembolic stroke.[37,103] Because of the heterogeneous nature of stroke, the diagnosis of cardioembolic source of stroke or TIA is often uncertain and reliant on the detection of a potential cardiac source of embolus in the absence of other potential sources of cerebral ischaemia.[103] It is apparent that potential sources of cardioembolic stroke may be absent in patients with stroke or TIA and present in patients without stroke or TIA. Moreover, some studies report the presence of two or more potential sources in one person, which generates further diagnostic uncertainty, but would not necessarily alter the treatment regime. Generally, the studies did not report performing thorough diagnostic evaluations; instead, findings were reported as associated risk factors. Clearly, the value of the reported prevalence data might be regarded as limited when currently it does not appear possible to establish a causal link with any degree of certainty.

The divergent samples used in the included studies produced, in most cases, a prevalence rate with a wide range, making any finding difficult to generalise to larger populations. The prevalence rates identified from the included studies ranged from 0% to 9% for major risk factors and from 0% to 73% for minor risk factors, for which further uncertainty exists. This might be reflective of the heterogeneity relating to the participant populations included in the studies as well as the varying diagnostic methods employed to detect the various sources.

Diagnostic accuracy studies

The average sensitivity and specificity of TTE were lower than those of TOE in both fundamental and harmonic imaging mode. Generally, TTEh was superior to TTEf but the greater sensitivity did lead to a decreased specificity, which increased the number of FNs. TTEh demonstrated lower sensitivity than reference standards for the detection of cardiac pathologies requiring anticoagulation therapy such as left atrial thrombus and left ventricular thrombus. However, TOE is not suited to the detection of left ventricular apical thrombus and TTE, although not as accurate as contrast-enhanced MRI, could serve as a screening tool for this pathology. TTEh indicated good sensitivity and specificity for the detection of left atrial appendage thrombi, although based on a small data set. However, these finding are limited by the small number of studies and the low prevalence rates within some studies.

Transoesophageal echocardiography demonstrated a greater diagnostic accuracy over a range of cardiac pathologies. The difference in the diagnostic accuracy of TTE and TOE was found mainly in their sensitivity to detect cardiac sources of stroke, that is, the probability that the index test (TTE) will be positive in diseased cases; differences in the specificity to correctly identify non-diseased cases was less remarkable, with most studies reporting specificities of 1.00.

Although both TTE and TOE are considered safe procedures, TOE is a semi-invasive procedure and requires a fasted patient and more clinical resources. TTE is non-invasive, quicker to perform than TOE and needs only one sonographer. However, skeletal structure and tissue may impede test performance compared with TOE and TOE is more appropriate for detecting some cardiac pathologies such as left atrial appendage thrombi. Therefore, TTE might be applied primarily to patients with stroke of undetermined aetiology (i.e. patients showing normal results on electrocardiography or carotid ultrasound) and who are candidates for oral anticoagulation, prior to escalation of further diagnostic tests. With improvements in TTE technology further diagnostic accuracy studies will be needed.

Survey of relevant comparators

It is clear from the results of the survey that stroke management is a very complex procedure with protocols appearing to be different in every centre that responded. A more sophisticated questionnaire would be needed to capture the complexity of stroke and TIA management protocols. However, given the variation in protocols used across stroke centres, it is uncertain how informative this would be. To be of real value, the effectiveness of different protocols would need to be assessed in terms of stroke and TIA outcomes. In England and Wales, NICE or Royal College of Physicians guidelines were used by most centres in both the investigation and the management of stroke and TIA. Amended guidelines were used by 10% of centres but no information was provided as to what the amendments were. In Scotland the guidelines issued by the SIGN were used by most centres to investigate stroke and TIA with most centres using 'other' guidelines to manage stroke and TIA.

Economic evaluation

Two economic evaluations from the perspective of the US health-care system found that TTE, either alone or in strategies with TOE, was not cost-effective.[37,161] However, neither study reported whether TTEf or TTEH was evaluated. One study found TOE to be cost-effective[161] whereas the other did not.[37]

Our principal economic finding is that TTEh is a cost-effective use of NHS resources compared with TOE in those cases where clinicians deem it the most appropriate form of testing. We have not evaluated the cost-effectiveness of TOE in those cases where clinicians regard it the most appropriate test.

Our analysis appears to show that warfarin has benefit in a preventative role and that this is cost-effective; however, this may not be clinically relevant for all cases.

Because of the limitations discussed in the following section, the results of the economic analysis should be treated with a certain amount of caution.

Strengths and limitations of the assessment

Clinical evaluation

The prevalence review highlights the difficulty that clinicians face when identifying the cause of cardioembolic stroke with regard to the limitations of the tests, the confounding comorbidities and the inherent mobility of blood clots. The uncertainty surrounding the risk that each cardiac pathology confers on patients is a limiting factor that affects the clinical decision to give anticoagulants when there is risk of haemorrhage.

The diagnostic accuracy review identified > 50 studies and covered a wide range of cardiac pathologies, which enabled comparisons between the older imaging technique of TTEf and the newer technique of TTEh. Good evidence was reported for the diagnostic accuracy of both TTEf and TTEh for the detection of PFO. The value of some outcomes was limited by the small numbers of studies reporting data or because studies included too few participants with a cardiac pathology, leaving a large degree of uncertainty about the underlying diagnostic accuracy.

Survey of relevant comparators

It seems apparent from some of the responses to the questionnaire that the questions asked were not sophisticated enough to capture the complexity of stroke and TIA investigation and management. However, it is also not clear how useful a sufficiently sophisticated questionnaire would be. The results of the survey suggest that an adequately sophisticated survey would produce results that are too heterogeneous to be of value.

Economic evaluation

The economic analysis used current best practice to develop the model and followed recommendations produced by NICE.[165]

The model has limitations because of the limited data available for important parameters such as the efficacy of treatment in reducing stroke recurrence. We were unable to include pathologies other than left atrial thrombus because of the lack of evidence of treatment effect on stroke recurrence in other pathologies. It should be noted that the evidence base for the analysis for some of the main parameters in the model was poor and thus the conclusions reached should be treated with a certain amount of caution.

Economic models are inevitably limited by the need to make assumptions, such as the assumption of unlimited stroke recurrence in a single patient and the assumption that all patients receive an echocardiogram. In the case of stroke recurrence it is unlikely that data regarding the relationship between number of strokes and mortality will become available. It is also unlikely, in the clinical setting, that all patients would receive an echocardiogram; however, to model otherwise would require estimates of the diagnostic accuracy of whatever test or clinical decision-making protocol was used and this information was unavailable.

Uncertainties

A number of uncertainties were identified in this report:

- What are the age-related stroke and TIA recurrence rates in patients with and without those cardiac abnormalities that can be treated?
- What is the age-related relationship between the number of strokes and patient mortality?
- What are the age-related rates and outcomes of anticoagulation-induced haemorrhage?
- What are the long-term costs associated with disability outcomes resulting from stroke and adverse effects of treatment?
- What are patient outcomes measured by the Barthel Index,[184] which can be used to categorise patients into independent, mild, moderate, severe and very severe states?

Research is needed to reduce the uncertainty around the estimates of sensitivity and specificity of TTEh and TOE, singly and in combination, in detecting treatable cardiac abnormalities compared with the gold standard in each pathology.

Uncertainly remains as to the true prevalence rates for cardiac sources of stroke and TIA because of the methodological difficulty of establishing the aetiology of cardiac strokes. Prevalence data were derived mainly from risk factor findings and often patients had several coexisting pathologies, which further increased the uncertainty in these findings.

The above studies would be expensive; however, the results from the EVPI analysis suggest that a maximum of £20M could be spent in removing all uncertainty from the problem.

Chapter 9 Conclusions

Implications for service provision

The implementation of our research findings by the NHS may be money saving but this is difficult to quantify.

Suggested research priorities

The main research priorities suggested by this report are:

- Long-term UK-based studies measuring the efficacy of treatment for stroke recurrence rates, associated risk factors and patient outcomes. These studies should use the same outcome measure, such as the Barthel Index, to allow data to be combined.
- Studies measuring the diagnostic accuracy of TTEh and TOE in detecting cardiac abnormalities that respond to treatment. These studies should also include any newer technologies such as crystal and three-dimensional probe designs.
- To maximise the clinical utility of research findings, diagnostic accuracy studies need to ensure that test procedures and results are fully reported. Investigators conducting diagnostic accuracy studies should ensure that the dissemination of findings conforms to the STARD criteria, and journal editors should include the STARD criteria as a prerequisite for article publication.
- In the presence of multiple risk factors, establishing the cause of cardioembolic stroke is complex and unlikely to provide an unequivocal answer. Studies attempting to establish the prevalence of cardiac sources of stroke should perform a thorough clinical evaluation to identify all potential risk factors, rule out those that are not relevant and, when possible, grade the findings according to risk.

These research priorities mostly require a large patient cohort and thus substantial funding. When possible, attempts should be made to address multiple objectives in the same study, for example diagnostic test results, stroke recurrence rates, efficacy of treatment, incidence of haemorrhage and patient outcomes.

Any future research to further develop or refine diagnostic strategies may benefit from EVPI analysis using our model to determine whether the benefits of further research justify the costs.

Economic analysis

The economic analysis indicates that, in those cases in which clinicians deem it the most appropriate test, TTEh is a cost-effective use of NHS resources. This analysis has highlighted the need for more research in several areas and until this is carried out the results of the economic evaluation should be treated with a certain amount of caution.

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Contributions of authors

Mike Holmes (Operational Research Analyst) co-ordinated the review and was responsible for the acquisition of data, analysis and interpretation of data and model construction (for the health economic evaluation and survey of stroke centres) and drafting and revision of the final report.

John Rathbone (Systematic Reviewer) was responsible for the acquisition of data, analysis and interpretation of data (for the systematic reviews and survey of stroke centres), and drafting and revision of the final report.

Chris Littlewood (Systematic Reviewer) was responsible for the acquisition of data, analysis and interpretation of data (for the systematic reviews) and drafting and revision of the final report.

Andrew Rawdin (Cost-Effectiveness Modeller) was responsible for the acquisition of data, analysis and interpretation of data and model construction (for the health economic evaluation) and drafting and revision of the final report.

Matt Stevenson (Reader in Health Economics and Decision Science) oversaw the modelling and reviewed the final report.

John Stevens (Lecturer in Bayesian Statistics) and **Jenny Wang** (Research Assistant Statistician) provided statistical support and undertook the meta-analyses.

Rachel Archer (Systematic Reviewer) was responsible for the conception and design of the study and sifting the prevalence search results at the title and abstract stage.

Pippa Evans (Information Specialist) was responsible for developing and undertaking the electronic literature searches.

About the School of Health and Related Research

The School of Health and Related Research (ScHARR) is one of the four Schools that comprise the Faculty of Medicine at the University of Sheffield. ScHARR brings together a wide range of medical and health-related disciplines including public health, general practice, mental health, epidemiology, health economics, management sciences, medical statistics, operational research and information science. It includes the Sheffield unit of the Trent Institute for Health Services Research, which is funded by NHS R&D to facilitate high-quality health services research and capacity development.

The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the clinical effectiveness and cost-effectiveness of health-care interventions for the NIHR HTA programme on behalf of a range of policy makers, including NICE. ScHARR-TAG is part of a wider collaboration of a number of units from other regions including Southampton Health Technology Assessment Centre (SHTAC), University of Southampton; Aberdeen Health Technology Assessment Group (Aberdeen HTA Group), University of Aberdeen; Liverpool Reviews & Implementation Group (LRiG), University of Liverpool; Peninsula Technology Assessment Group (PenTAG), University of Exeter; the NHS Centre for Reviews and Dissemination, University of York; Warwick Evidence, University of Warwick; the BMJ Group; and Kleijnen Systematic Reviews.

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Appendix 1 Cardiac sources of stroke and transient ischaemic attack

Pathology	Potential cardiac source
Chamber defects	Atrial septal defect
	PFO
	Atrial shunt
	Atrial/interatrial/intra-atrial septal aneurysm
	Hypermobility of atrial septum
	Left atrial functional abnormality
	Left ventricular aneurysm
	Systolic left ventricular dysfunction of ischaemic and non-ischaemic aetiology
	Left ventricular ejection fraction < 40%
	Cor triatriatum
Valvular defects	Mitral valve stenosis
	Rheumatic mitral valve disease
	Mitral valve regurgitation
	Mitral valve prolapse
	Aortic valve stenosis
	Sclerosis/calcification of the aortic valve
	Rheumatic aortic valve disease
	Aortic valve regurgitation
	Mitral or aortic valve strands
	Artificial/prosthetic heart valve complication
Thrombosis	Ventricular or atrial thrombosis
	Left ventricular/left atrial thrombus
	Apical thrombosis
	Atrial appendage thrombus
Cardiac masses, endocarditis and vegetation	Cardiac tumour/mass
	Atrial myxoma
	Papillary fibroelastoma
	Libman–Sacks endocarditis
	Marantic endocarditis
	Non-bacterial thrombotic endocarditis
	Valvular vegetation

Pathology	Potential cardiac source
Cardiac enlargement	Dilated left atrium
	Left atrial enlargement
	Dilated left ventricle
	Left ventricle hypertrophy
	Left ventricular hypertrophic hypertensive disease
Pathologies of the aorta	Aortic aneurysm
	Dilated proximal aorta
	Calcification of the aorta
	Aortic dissection
SEC	SEC/'smoke'
	Left atrial appendage spontaneous contract
	Isolated left atrial 'smoke' on echocardiography (no mitral stenosis or AF)
Cardiomyopathy	Cardiomyopathy
	Dilated cardiomyopathy
	Left ventricular non-compaction
Rhythm dysfunction conditions	Atrial flutter
	Sick sinus syndrome
Others	Regional myocardial dyskinesia

Appendix 2 MEDLINE search strategy for the systematic review of prevalence studies

1. Stroke/ (38,966)
2. stroke$.mp. (139,568)
3. stroke volume/ (25,577)
4. stroke volume$.mp. (33,208)
5. Cerebrovascular accident.mp. (2654)
6. cerebrovascular event.mp. (478)
7. Cerebrovascular disease.mp. (9488)
8. transient ischaemic event.mp. (4)
9. transient ischaemic attack.mp. (867)
10. vascular accident.mp. (676)
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (148,787)
12. akinetic left ventricular segment.mp. (3)
13. artificial heart valve complication.mp. (0)
14. atherosclerotic aortic plaques.mp. (13)
15. calcification of the aorta.mp. (140)
16. canal defect$.mp. (264)
17. cardioemboli$.mp. (1386)
18. ((atrial or ventricular or cardiac) adj (thromb$ or clot$ or defect$ or patholog$)).mp. (6611)
19. ((infective or libman-sacks or marantic or non-bacterial thrombotic) adj endocarditis).mp. (6074)
20. ((mitrial valve or aortic valve or valve) adj (sclerosis or stenosis or calcification or disease or regurgitation or prolapse or strands)).mp. (41,648)
21. ((ventricular or atrial or apical) adj thromb$).mp. (2384)
22. (aortic adj (aneurysm or arch debris or atheroma or dissection or thrombus)).mp. (36,021)
23. (atrial adj (fibrilation or flutter or myxoma or sept$ or shunt)).mp. (16,689)
24. (cardiac adj (tumour or mass or embol$ or enlargement or mass$ origin$ or source$ or vegetation$)).mp. (2380)
25. cardiogenic.mp. (10,581)
26. Cardiomyopathies/ (18,868)
27. chamber defects.mp. (9)
28. chiari network.mp. (61)
29. congestive heart failure.mp. (28,205)
30. cor triatriatum.mp. (663)
31. coronary artery bypass graft surgery.mp. (3201)
32. dilated left atrium.mp. (82)
33. dilated proximal aorta.mp. (1)
34. Endocarditis/ (4784)
35. false tendon.mp. (70)
36. hypermobility of atrial septum.mp. (0)
37. Hypertrophy, Right Ventricular/ or Hypertrophy, Left Ventricular/ (10,219)
38. lambl's excrescences.mp. (30)
39. (left atrial adj (appendage functional abnormality or appendage spontaneous contract or band or enlargement or abnormality or septum abnormality)).mp. (562)
40. lipomatous hypertrophy.mp. (152)
41. Myocardial Infarction/co [Complications] (22,786)
42. papillary fibroelastoma.mp. (422)
43. Foramen Ovale, Patent/ (742)
44. pericardial mesothelioma.mp. (165)
45. persistent left superior vena cava.mp. (716)

46. polyarteritis nodosa.mp. (5648)
47. primary systemic amyloidosis.mp. (384)
48. prosthetic heart valve complication.mp. (0)
49. regional myocardial dyskinesia.mp. (2)
50. regional wall motion abnormalit$.mp. (882)
51. sick sinus syndrome.mp. (2807)
52. spontaneous echo contrast.mp. (410)
53. tetralogy of fallot.mp. (8529)
54. Thrombosis/ (49,029)
55. valvular defect$.mp. (219)
56. valvular vegetation.mp. (50)
57. eustachian valve.mp. (164)
58. ((atrial or interatrial or interaatrial) adj septal aneurysm).mp. (539)
59. akine$ segments.mp. (143)
60. congenital heart defect$.mp. (4718)
61. dilated left ventricle.mp. (214)
62. dyskine$ segments.mp. (120)
63. (left ventricle$ adj (hypertrophy or hypertension or anuerysm or dysfunction or ejection fraction or noncompaction)).mp. (551)
64. or/12-63 (261,412)
65. exp epidemiologic studies/ (1,296,793)
66. exp epidemiology/ (18,044)
67. epidemiology.tw. (78,229)
68. exp prevalence/ (144,996)
69. prevalence.ti. (65,013)
70. exp incidence/ (142,499)
71. incidence.ti. (61,659)
72. ep.fs. (966,875)
73. or/65-72 (2,048,519)
74. human/ (11,642,629)
75. animal/ (4,756,082)
76. 74 not (74 and 75) (10,408,432)
77. 11 and 64 and 73 and 76 (6298)

Appendix 3 List of excluded studies (studies all excluded as no relevant data were identified)

1. Stroke prevention in atrial fibrillation and other cardiac sources of embolism. *Cerebrovasc Dis* 1999;**9**(Suppl. 4):53–61.

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Appendix 4 Prevalence of cardiac sources of stroke by study

Study	Age (years)	Cardiac pathologies detected	Tests used
Agmon 1999[41]	> 45	ASA 28/355 (7.9%)	TOE, CU
Arboix 1997[88]	Mean 75, range 34–94	ASA with interatrial shunting 1/231 (0.4%)	DU, MRI, ECG, CT
Arnold 2008[42]	Mean 35.8	ASA 5/100 (5%)	TTE, TOE, CT, ECG, MRI, MRA
Awada 1999[43]	Range 10–80	RVD 34/756 (4.5%); PFO 3/756 (0.4%)	TTE, TOE, CU
Barinagarrementeria[43]	Mean 28, range 11–40	RVD 29/130 (22.3%); PFO 8/130 (6.2%)	TTE, TOE
Barinagarrementeria[44]	Mean 30	RVD 3/37 (8%); PFO 5/37 (13.5%)	TTE, TOE
Belvis 2007[46]	Mean 44.7, range 23–55	PFO 17/39 (43.5%); ASA 3/39 (7.7%)	TOE, CT, MRI
Benedik 2007[83]	Median 11.5, range 2–17	PFO 9/18 (50%)	MRI, TCD, ECG, TTE
Bevan 1990[96]	No details	RVD 2/48 (4.2%)	CT, autopsy, ECG, 24-hour HM, EC
Bogousslavsky[17]	< 60	PFO 140/340 (41.2%)	ECG, CT, MRI, EC
Cabanes 1993[47]	Mean 40	ASA 28/100 (28%); PFO 43/100 (43%); ASA and PFO 22/100 (22%)	TTE, TOE, EC
Fieschi 1996[48]	Median 39, range 18–47	LVT 1/160 (0.6%); PFO 22/160 (13.8%); ASA with or without PFO 14/160 (8.8%); ASD 1/160 (0.6%)	TTE TOE
Fukujima 2005[49]	Mean 63, range 26–92	LVH 208/523 (39.8%); SEC in left atrium 81/523 (15.5%); SEC in left ventricle 21/523 (4%); SEC in aorta 45/523 (8.6%); LAT 5/523 (0.9%); LVT 3/523 (0.6%); PFO 126/523 (24.1%); MVR 383/523 (73.2%); MVS 4/523 (0.7%); AVC 156/523 (29.8%); interatrial septum aneurysm 38/523 (7.3%); AVS 3/523 (0.6%)	TOE
Ghandehari 2006[23]	Range 15–45	RVD 18/67 (26.8%); PFO 2/67 (2.9%); LVT 1/67 (1.5%)	CT, ECG, 24-hour HM, TTE, TOE
Handke 2007[50]	Mean ~ 62, range 20–84	PFO 77/227 (33.9%); PFO with ASA 33/227 (14.5%)	TTE, TOE, CT, MRI
Hoffmann 2004[84]	18–49	PFO 6/133 (4.5%)	MRI, EC, TTE
Homma 1994[51]	No details	PFO 23/74 (31%); ASA 9/74 (12%)	TTE, TOE, CU, CT, MRI, TCD
Kang 2008[52]	Mean 65, range 29–88	PFO 1/100 (1%)	ECG, TTE, TOE, 24-hour HM, MRI
Kasner 2007[102]	Mean 63	PFO 18/264 (7%); LVH 110/264 (42%)	EC
Knebel 2009[53]	Range 18–90	PFO $n = 152$ (21.7%); ASD $n = 17$ (2.4%); ASA $n = 51$ (7.3%)	ECG, 24-hour HM, TOE
Kristensen 1997[85]	Range 18–44	PFO 32/97 (33%); ASA 9/100 (9%)	TTE
Lamy 2002[54]	Reported according to absence or presence of PFO: mean 44.5 vs. 40.1 respectively	PFO 267/581 (45.9%); ASA 61/581 (10.5%)	TOE

Study	Age (years)	Cardiac pathologies detected	Tests used
Lanzino 1991[97]	Range 16–45	LVH 12/155 (7.7%); MVP 5/155 (3.2%); hypertrophic cardiomyopathy with LVT 1/155 (0.65%); ASA 1/155 (0.65%); AVS 1/155 (0.65%); RMVD 1/155 (0.65%)	CT, two-dimensional EC
Lavados 2007[55]	Mean 66.4	RVD 3/185 (1.6%); AAT 2/185 (1.1%); PFO 2/185 (1.1%); ventricular hypokinesia 1/185 (0.5%)	CT, TTE, TOE
Lindgren 1994[56]	Mean 73.3	Severe mitral annulus calcification 49/166 (29.5%); PFO 20/166 (12%); ASA 24/166 (14.5%); calcific aortic stenosis 5/166 (3%)	CT, MRI, ECG, TTE, TOE
Luijckx 1993[98]	Median 39, range 17–50 in the Thai series; median 42, range 15–50 in the Dutch series	Thai series: RHD 13/56 (23%); myxoma cordis 1/56 (1.8%) Dutch series: RHD 1/55 (2%); MVP 3/55 (5.5%)	CT, ECG, EC, angiography
Malm 1999[57]	Mean 36.9	LAT 1/24 (4.2%); ASA 1/24 (4.2%); ASD 1/24 (4.2%); PFO 3/24 (12.5%)	CT, MRI, ECG, TTE, TOE
Mattioli 2001[58]	Mean 65.7, range 35–86	ASA 68/245 (27.7%); PFO 56/245 (22.8%); MAC 24/245 (9.7%); vegetations 3/245 (1.2%)	CT, MRI, TTE, TOE
Mehndiratta 2004[95]	Mean 31.5	RHD 16/109 (14.7%); atrial myxoma 1/109 (0.9%)	CT, MRI, 24-hour HM, ECG, EC
Mochan 2003[59]	Mean 32.1, range 20–61	LVH 1/33 (3%); MVP 1/33 (3%)	CT, ECG, TTE, TOE
Mok 2003[60]	Not adequately reported	Nil	CT, MRI, ECG, TTE, TOE
Musolino 2003[61]	Mean 36.4, range 17–45	Detected by TTE: MVR 6/60 (10%); mitral prosthesis 1/60 (1.67%); MVP 3/60 (5%); aortic valve vegetation 1/60 (1.67%); MVS 2/60 (3.3%); ASD 1/60 (1.67%); LVT 1/60 (1.67%) Detected by TOE (13/60 refused TEE, total = 47): MVR 5/47 (10.6%); mitral prosthesis 1/47 (2.1%); MVP 3/47 (6.4%); aortic valve vegetation 0/47 (0%); mitral stenosis 2/47 (4.3%); ASD 4/47 (8.5%); LVT 2/47 (4.3%); LAT 1/47 (2.1%); ASA 11/47 (23.4%); PFO 10/47 (21.3%); mitral prosthesis thrombus 2/47 (4.3%)	CT, MRI, ECG, DU, TTE, TOE
Negrão 2007[62]	Mean 33.9	PFO 47/168 (28%)	CT, MRI, TTE, TOE, TCD
Nighoghossian 1996[63]	Mean 47	ASA 11/118 (9.3%); PFO 8/118 (6.8%); ASA-PFO 18/118 (15.3%); MVP 9/118 (7.6%); ASA-PFO-MVP 4/118 (3.4%); MV incompetence 4/118 (3.4%); aortic arch atheroma 4/118 (3.4%)	CT, MRI, ECG, TTE, TOE
Omran 1999[132]	Average 48.6	LAT 6/583 (1%); mitral stenosis 3/583 (0.5%); MVS 7/583 (1%)	TTE, TOE
Ossemann 1995[65]	Mean 63	ASA 22/146 (15.1%)	CT, ECG, 24-hour ECG, TTE, TOE
Pearson 1991[118]	Mean 53	ASA 20/133 (15%)	TOE
Pessin 1987[89]	Average 58	Mitral stenosis 1/35 (2.9%); MVP 2/35 (5.7%)	CT, angiography

Study	Age (years)	Cardiac pathologies detected	Tests used
Pezzini 2003[67]	Mean 34.7	PFO 36/125 (28.8%)	CT, MRI, TCD, 12-lead ECG, TTE, TOE
Pun 1984[101]	Mean 54.4, range 20–87	RHD 38/129 (29.5%); MVP 1/129 (0.8%)	ECG, EC
Putaala 2009[26]	Mean 41.3	Atrial myxoma 2/198 (1%); PFO 74/198 (37%); PFO-ASA 13/198 (7%); ASA 4/198 (2%); MVP 1/198 (0.5%); MAC 1/198 (0.5%)	ECG, TTE, TOE
Rasura 2006[68]	Mean 36.4, range 14–47	ASD 1/394 (0.25%); atrial myxoma 2/394 (0.5%); PFO 60/394 (15.2%); ASA 22/394 (5.6%); PFO-ASA 16/394 (4.1%); aortic atheroma 5/394 (1.3%); aortic atheroma + PFO 2/394 (0.5%)	CT, MRI, ECG, TCD, TTE, TOE
Rauh 1996[69]	Median 62, 28–83	Findings detected by TTE: LVH 11/30 (36.6%); MVP 1/30 (3.3%) Additional findings detected by TOE: PFO 7/30 (23.3%); LAT 3/30 (10%); ASA 2/30 (6.7%)	ECG, TTE, TOE
Noce 2004[90]	Mean 5.7, range 2 months–15 years	RHD 2/39 (5.1%); MVP 1/39 (2.6%)	Not reported
Rodriguez 2003[70]	Mean 59	PFO 34%; ASA 11%; PFO-ASA 7%	TOE
Roijer 1997[71]	Mean 70.1, range 38–93	LAT 11/121 (9%); LVT 1/121 (1%); ejection fraction < 35% 6/121 (5%); LA myxoma 1/121 (1%); ASA 21/121 (17%); PFO 20/121 (17%); MVP 1/121 (1%); annular calcification 26/121 (21%)	CT, MRI, 12-lead ECG, TTE, TOE
Roquer 2003[72]	Mean 71.6	PFO 4/1581 (0.25%)	CT, MRI, ECG, TCD, TTE, TOE
Sandercock 1989[99]	Not reported	MVS 2/244 (0.8%); aortic sclerosis 11/244 (4.5%); MAC 5/244 (2%); mitral leaflet prolapsed 3/244 (1.2%); aortic stenosis 2/244 (0.8%)	CT, ECG, EC
Seifert 2005[73]	Mean 65.7, range 28–89	PFO 7/93 (7.5%); LVT 1/93 (1.1%); MV prosthesis 1/93 (1.1%); aortic valve myxoma 1/93 (1.1%)	ECG, TCD, TTE, TOE
Serena 1998[74]	Mean 64.8	PFO 22/44 (50%); ASA 5/44 (11.4%)	CT, 12-lead ECG, TCD, TTE, TOE
Silva 2005[75]	< 55	PFO 5/29 (17.2%); PFO-ASA 7/29 (24.1%)	CT, TOE
Siqueira 1996[86]	Range 15–40	MVP 6/106 (5.7%); RHD 10/106 (9.4%)	CT, ECG, Doppler ECG, TTE
Skidmore 2001[91]	Not adequately reported	RHD with severe MVS 1/16 (6.2%)	CT, ECG, MRI, MRA
Sloan 1998[87]	Mean 36, range 17–44	MV thickening 1/20 (5%); MVP 3/31 (9.7%); mitral vegetation 3/31 (9.7%); MVP with possible vegetation 1/31 (3.2%); mitral and aortic valve prolapse without vegetation 1/31 (3.2%); aortic and mitral vegetation and aortic regurgitation 1/31 (3.2%); MV nodular thickening 1/31 (3.2%); LVH 2/51 (3.9%)	TTE
Steinke 1997[76]	Mean 65, range 16–87	LA dilatation 5/74 (6.8%); LV dilatation 4/74 (5.4%); MV insufficiency 1/74 (1.4%); apical/atrial thrombus 2/74 (2.7%)	TCD, MRA, ECG, TTE, TOE

Study	Age (years)	Cardiac pathologies detected	Tests used
Strandberg 2008[77]	Not reported	LAT 6/441 (1.4%); LVT 1/441 (0.2%); atrial myxoma 0/441; MVS 1/441 (0.2%); MVP 16/441 (3.6%); MAC 7/441 (1.6%); calcified aortic stenosis 5/441 (1.1%); PFO 61/441 (13.8%); SEC 5/441 (1.1%); ASA 18/441 (4.1%); LV aneurysm 7/441 (1.6%); aortic aneurysm 1/441 (0.2%); false tendon 6/441 (1.4%)	TOE, TTE, DU
Tei 1993[100]	Mean 62.8	MVP 5/72 (6.9%); MAC 2/72 (2.8%)	CT, 12-lead ECG, two-dimensional EC
Tice 1996[78]	Mean 50, range 28–87	ASA 5/44 (11.4%); PFO 2/44 (5%); MV thickening 4/44 (9%); MV strands 7/44 (16%)	TOE
Ueno 2007[79]	Mean 67	PFO 8/11 (73%); ASD 1/11 (9%); large RLS 2/11 (18%); small RLS 7/11 (64%); ASA 2/11 (18%); intracardiac thrombus 0/11, MVP 0/11	MRI, MRA, 24-hour ECG, TTE, TOE
Varona 2007[27]	Mean 36	PFO 5/272 (1.8%); LVT 1/272 (0.4%)	CT, MRI, TTE, TOE, extracranial cerebrovascular studies
Walpot 2006[80]	Mean 52.2, range 18–65	PFO-ASD 16/54 (29.6%); ASA 7/54 (13%); SEC 0/54, AVC 3/54 (5.6%); MAC 1/54 (1.9%); MVP 0/54, aortic sclerosis 3/54 (5.6%)	TOE
Ward 2006[81]	Mean 60.3, range 25–91	SEC 3.7%; PFO 18.8%; ASA 3.3%; LAT/LVT 2.4%; vegetation/mass/tumour 7.8%	CT, MRI, TOE
Williams 1997[92]	Mean 23.2	PFO/ASD 7/208 (3.4%); LAT or LVT 3/208 (1.4%)	Not adequately reported
Wong 2001[93]	Range 49–75	Low ejection fraction (< 40%) 1/6 (16.7%)	CT, MRI, MRA, ECG, TCD
Zibaeenezhad 2006[82]	Mean 50.8, range 16–81	PFO 9/98 (9.1%); ASD 3/98 (3%); ventricular septal defect 2/98 (2%); interatrial septal aneurysm 2/98 (2%); mitral regurgitation 51/98 (52%); MVP 31/98 (31.6%); MVS 8/98 (8.1%); thick aortic valve 6/98 (6.1%); aortic stenosis 5/98 (5.1%); mass on aortic valve 2/98 (2%); MV vegetation (prosthetic valve) 1/98 (1%); LVH 3/98 (3%)	CT, MRI, ECG, TOE

AAT, atrial appendage thrombus; ASA, atrial septal aneurysm; ASD, atrial septal defect; AVC, aortic valve calcification; AVS, aortic valve stenosis; CU, carotid ultrasound; DU, Doppler ultrasound; EC, echocardiography; HM, Holter monitoring; LA, left atrial; LAT, left atrial thrombus; LV, left ventricular; LVH, left ventricular hypertrophy; LVT, left ventricular thrombus; MAC, mitral annual calcification; MRA, magnetic resonance angiography; MV, mitral valve; MVP, mitral valve prolapse; MVR, mitral valve regurgitation; MVS, mitral valve stenosis; PFO-ASA, patent foramen ovale with atrial septal aneurysm; PFO-ASD, patent foramen ovale with atrial septal defect; RHD, rheumatic heart disease; RLS, right-to-left shunt; RMVD, rheumatic mitral valve disease; RVD, rheumatic valvular disease.

Appendix 5 MEDLINE search strategy for the systematic review of diagnostic accuracy studies

1. Stroke/ (39,233)
2. stroke$.mp. (138,756)
3. stroke volume/ (25,237)
4. stroke volume$.mp. (32,752)
5. Cerebrovascular accident.mp. (2591)
6. cerebrovascular event.mp. (471)
7. Cerebrovascular disease.mp. (9405)
8. Ischemic Attack, Transient/ or transient ischemic event.mp. (16,035)
9. transient ischemic attack.mp. (3409)
10. vascular accident.mp. (674)
11. brain emboli$.mp. or Intracranial Embolism/ (2398)
12. cerebral emboli$.mp. (1923)
13. brain infarction.mp. or Brain Infarction/ (3554)
14. cerebral infarction.mp. or Cerebral Infarction/ (21,326)
15. or/1-14 (175,197)
16. Echocardiography.mp. or Echocardiography/ (105,417)
17. transthoracic echocardiography.mp. (4128)
18. Transoesophageal echocardiography.mp. (1369)
19. transesophageal echocardiography.mp. (8092)
20. (echocardiog$ adj (transthorac$ or trans-thorac$ or (trans$ and thorac$))).mp. (427)
21. (echocardiog$ adj (transoesophag$ or trans-oesophag$ or (trans and oesophag$))).mp. (46)
22. (echocardiog$ adj (transesophag$ or trans-esophag$ or (trans and esophag$))).mp. (12,231)
23. 24 hour holter.mp. (1157)
24. twenty four hour holter.mp. (111)
25. telemetr$.mp. (9058)
26. secondary prevention.mp. (9681)
27. cardiac imag$.mp. (1883)
28. cardiac magnetic resonance imaging.mp. (1315)
29. cardiac MR.mp. (349)
30. cardiac MRI.mp. (882)
31. carotid ultrasound.mp. (499)
32. carotid doppler.mp. (210)
33. transcranial doppler.mp. (5296)
34. transcranial doppler.mp. (5296)
35. R? Test Evolution.mp. (2)
36. R? Test.mp. (981)
37. reveal device.mp. (1)
38. implantable loop recorder.mp. (154)
39. diagnostic imag$.mp. (29,793)
40. Ultrasonography/ or diagnostic ultrasound.mp. (59,099)
41. ultrasonic diagnosis.mp. (1607)
42. magnetic resonance imaging.mp. or Magnetic Resonance Imaging/ (253,683)
43. or/16-42 (458,448)
44. exp "Sensitivity and Specificity"/ (324,293)

45. sensitivity.tw. (420,807)
46. ((pre-test or pretest) adj probability).tw. (940)
47. post-test probability.tw. (261)
48. predictive value$.tw. (51,868)
49. likelihood ratio$.tw. (6225)
50. or/44-49 (671,637)
51. 15 and 43 and 50 (3735)

Appendix 6 Description of included studies

Study	Setting	Age (years)	TTEf/TTEh	TTE details	Reference standard	Reference standard details
Akosah 1998[107]	Hunter Holmes McGuire Veterans Affairs Medical Centre, USA	Mean 67, range 40–85	TTE	TTE was performed using a single and multiplane probe; no further details	TOE	Studies were initially performed using a single-plane probe and later evaluation was performed using a multiplane probe
Aschenberg 1986[125]	Hospital, Germany	Mean 51	TTEf	A 2.25-MHz transducer connected to a Diasonics 3400 R phased-array sector scanner was used for the TTE study. The size of the left atrium and ventricle and the morphology and mobility of the mitral valve leaflets were assessed from the standard parasternal and apical views	TOE	TOE was performed with a 3.5-MHz phased-array transducer attached to the tip of a commercial 9-mm gastroscope connected to the same Diasonics sector scanner. With the patient lightly sedated (5–10-mg diazepam), lying supine or slightly upright and monitored by means of a three-lead ECG, the gastroscope was introduced into the oesophagus with the transducer facing anteriorly. After the orientational landmark of the aortic valve had been passed at a distance of 35–40 cm from the patient's teeth, the left ventricular inflow tract was imaged by means of a 20° left lateral rotation of the gastroscope and further advancement by about 20 mm
Baur 1982[108]	Hospital, USA	Mean 56	TTEf	Two-dimensional TTE was performed with a commercially available 80° phased-array sector scanner (Varian 3000). Examination was performed in supine and left lateral decubitus positions with a standard 2.25-MHz transducer. Each patient was examined in the parasternal apical and subxiphoid positions and standard long- and short-axis views as well as four-chamber and two-chamber views	Left ventriculography and coronary angiography	Left ventriculography and coronary angiography were accomplished with the Judkins technique in each case. Additionally, each patient had a complete physical examination and a 12-lead ECG

Study	Setting	Age (years)	TTEf/TTEh	TTE details	Reference standard	Reference standard details
Belkin 2011[109]	Hospital, USA	Range 19–73	TTEf	TTE was performed with the Hewlett-Packard Sonos 500 or 1500 system using a 2.5-MHz transducer in all accessible standard views; directed colour Doppler flow imaging of the interatrial septum was performed in all views in which the structure was visualised	TOE	TOE was performed with a 5-MHz single-plane probe. All patients received topical anaesthesia. The echoscope was inserted into the oesophagus with a patient lying in the left lateral decubitus position. Colour flow imaging of the interatrial septum was performed at multiple depths; microcavitation contrast was performed via an injection of 8–10 ml of agitation saline into a intravenous catheter inserted into the arm. Patients were instructed to perform the Valsalva manoeuvre during all contrast injections
Black 1991[154]	Hospital, Australia	Mean 59, range 18–90	TTEf	Patients underwent two-dimensional and Doppler (including colour flow mapping) TTE immediately before TOE with the use of a 2.5-MHz transducer (Hewlett-Packard 77020AC). The left atrial dimension was determined by standard M-mode criteria	TOE	TOE was performed with a 5-MHz single-plane phased-array transducer (Hewlett-Packard 21236A). Intravenous sedation was given to 289 patients (72%) using midazolam and fentanyl. Sixty patients (15%) received antibiotic prophylaxis. The hypopharynx was sprayed with 10% topical lidocaine and the probe introduced using standard techniques
Black 1991[155]	Hospital, Australia	Mean 60, range 25–86	TTEf	All patients had initial conventional cross-sectional and Doppler TTE, including colour flow mapping, with 1- to 9-MHz, 2- to 5-MHz and 3- to 5-MHz transducers (Hewlett-Packard 77020A)	TOE	TOE was performed with a standard 5-MHz single-plane phased-array transducer (Hewlett-Packard 21236A). Intravenous sedation (midazolam with fentanyl) was given in 74% of studies
Blum 2004[145]	Poria Medical Centre, Israel	Mean 57	TTEf	No details	TOE	No details

Study	Setting	Age (years)	TTEf/TTEh	TTE details	Reference standard	Reference standard details
Chen 1992[139]	Hospital, Taiwan	Mean 39, range 17–68	TTEf	All echocardiographic examinations were performed using an imaging system (Toshiba SSH-65A). A 2.5- or 3.0-MHz phased-array transducer was used for transthoracic examinations, whereas transoesophageal studies were carried out with a 3.75-MHz phased-array transducer fitted to the conventional 10.5-mm endoscope. Routine M-mode and two-dimensional images were assessed by the standard parasternal and apical views. Special attention was paid to the atrial septum using the apical and/or subcostal four-chamber views. Contrast echocardiography was then performed by injecting agitated 5% glucose solution through a 21-gauge winged infusion set into a peripheral vein. At least three injections were given to each patient to obtain optimal contrast effect in the resting state and during the release phase of a Valsalva manoeuvre (phase 3)	TOE	TOE was carried out subsequently to obtain the four-chamber view. After the fossa ovalis of the atrial myocardium septum was visualised, echo contrast was injected both during normal breathing and just before the release of a Valsalva manoeuvre. Shrinkage of the heart observed during the Valsalva manoeuvre indicates the efficiency of this manoeuvre. All studies were interpreted by at least two physicians with full experience of contrast echocardiography who had no previous information about the patient's status. Colour Doppler imaging was not performed in the present series
Chirillo 2005[149]	Hospital, Italy	Mean 46	TTEf and TTEh	All studies were performed with a Sequoia 256 system with a 3-V transducer. Each cardiac valve was examined in detail by M-mode, two-dimensional and Doppler colour flow mapping at minimum depth setting. TTE images were acquired in the fundamental imaging mode at the highest possible transducer frequency that still allowed clear delineation of valve structures. Gain settings were adjusted individually for each patient to visualise valve structures optimally. After all cardiac valves had been examined the transducer was switched into the harmonic mode with a transmitting frequency of 1.75 MHz. The receiver gain was again adjusted individually for each patient to obtain the best visualisation of the cardiac valves	TOE	TOE studies were performed after precordial examination by the same operator. Patients were positioned in the left lateral decubitus position after topical anaesthesia of the pharynx with lidocaine. An omniplane transducer with 5- to 7-MHz transmitting frequency was used. Valves were imaged in all available imaging planes at the highest possible frequency. Each valve was examined by M-mode echocardiography with a 100 cm/s sweep, two-dimensional cross-sectional echocardiography and colour Doppler. As with TTE, four 3-second clips with the best achieved image resolution were acquired for each valve and were stored digitally

Study	Setting	Age (years)	TTEf/TTEh	TTE details	Reference standard	Reference standard details
Clarke 2004[143]	Hospital, UK	Mean 58	TTEh	TTE was performed immediately before TOE. All studies were performed using a Hewlett-Packard Sonos 5500, using a broadband transthoracic transducer capable of second harmonic imaging (Hewlett-Packard S4 with 1.8/3.6 MHz). With harmonic imaging, ultrasound is transmitted at a fundamental frequency (1.8 MHz) and then echoes at the second harmonic frequency are selectively detected (3.6 MHz). Routine images were obtained: parasternal long- and short-axis, apical four-chamber, apical two-chamber and subcostal views using harmonic imaging. Continuous recording was obtained during bubble contrast injections with an apical four-chamber view. Following recordings during normal respiration, this was repeated during a Valsalva manoeuvre	TOE	TOE was performed using 10% topical lignocaine spray for the oropharynx and intravenous sedation (midazolam 3–10 mg). A Hewlett-Packard Sonos 5500 ultrasound machine with an omniplane 5-MHz transoesophageal probe was used in all cases. Patients underwent a complete TOE study including colour flow Doppler of the interatrial septum. The TOE was performed in the left lateral decubitus position
Cujec 1991[152]	Hospital, Canada	Mean 63, range 18–87	TTEf	Transthoracic colour Doppler echocardiography was performed on the same day as TOE. Standard parasternal and apical views were obtained using an Aloka 870 imaging system interfaced with a 2.5- or 3.5-MHz transducer. Intravenous saline contrast was not given during TTE	TOE	Transesophageal colour Doppler echocardiography was performed after the patient gave informed consent. A biplane transoesophageal 5-MHz transducer interfaced with the Aloka 870 imaging system was used. A complete biplane transoesophageal examination was performed in all patients. Thirty patients who had an intravenous line inserted for sedation also had saline contrast injected during TOE to exclude an intracardiac shunt

Study	Setting	Age (years)	TTEf/TTEh	TTE details	Reference standard	Reference standard details
Daniels 2004[140]	Four clinical centres, Belgium	Mean 63	TTEh	TOE and TTEh with the consecutive administration of three intravenous contrast injections of agitated saline injections before the release phase of the Valsalva manoeuvre were performed. Semiquantification and timing of contrast passage were assessed during both imaging modalities. A shunt was present if at least one imaging modality showed micro-bubbles appearing in the left atrium. PFO was defined when these bubbles appeared early and arteriovenous pulmonary malformations were suspected if bubbles appeared late after the opacification of the right atrium. Shunts were considered important when bubbles were present in one frame in the left atrium or left ventricle	TOE	See *TTE details*
de Bruijn 2006[141]	Hospital, Holland	No details	TTE	TTE was performed in the left lateral decubitus position using a commercially available system (Vingmed system FiVe/ Seven, General Electric-Vingmed). Images were obtained using a 3.5-MHz transducer at a depth of 16 cm in the parasternal (standard long- and short-axis images) and apical (standard long-axis and two- and four-chamber images) views. Standard two-dimensional and colour Doppler data, triggered to the QRS complex, were saved in cine loop format. Pulsed- and continuous-wave Doppler data were also stored digitally. Data were analysed using commercial software (Echopac 6.1, General Electric-Vingmed)	TOE	TOE was performed without sedation using a 5.0-MHz multiplane transducer; lidocaine spray was used for local pharyngeal anaesthesia. TOE was performed according to a standardised protocol including adequate visualisation of all cardiac structures with emphasis on both atria, left atrial appendage, interatrial septum, mitral valve apparatus and thoracic aorta; administration of intravenous sterile isotonic saline was used to assess atrial septal defects. Echo contrast with air (ratio 9 : 1) and a subsequent Valsalva manoeuvre was used to evaluate the presence of a PFO. All patients were instructed to perform a Valsalva manoeuvre just before the injection of the contrast and to release on command after arrival of contrast in the right atrium. The Valsalva manoeuvre was considered

Study	Setting	Age (years)	TTEf/TTEh	TTE details	Reference standard	Reference standard details
						successful if the interatrial septum in the fossa ovalis region showed a leftward deviation. A moderate to severe shunt secondary to PFO was defined as passage of a cloud of bubbles or intense opacification of the left atrium. All patients underwent TTE directly followed by TOE, which were performed by experienced sonographers according to a predefined protocol
Di Tullio 1993[110]	Hospital, USA	Mean 63.6	TTEf	Echocardiography was performed using Hewlett-Packard Sonos 1000 equipment with a 2.5-MHz transducer for transthoracic imaging and a 5.0-MHz biplane transducer for transoesophageal imaging	TOE	See *TTE details*
Fatkin 1996[156]	Hospital, Australia	Mean 60, range 38–74	TTEf	TTE was performed with a Hewlett-Packard Sonos 1000 or Acuson XPlO ultrasonograph using a 2.5- MHz transducer	TOE	TOE was performed using a biplane probe (Hewlett-Packard P21363A or Acuson V510B) in 57 patients and a multiplane probe (Hewlett-Packard 21364A) in three patients. After informed written consent was obtained, fasted patients received topical anaesthesia of the hypopharynx with 10% lidocaine spray and were sedated with midazolam hydrochloride 1–4 mg intravenously (plus fentanyl citrate 50–100 pg and glycopyrrolate 0.2 mg in one centre). In six patients TOE was performed intraoperatively after general anaesthesia but before cardiopulmonary bypass

Study	Setting	Age (years)	TTEf/TTEh	TTE details	Reference standard	Reference standard details
Gonzalez-Alujas 2011[146]	Hospital, Spain	Mean 46.4, range 17–75	TTEh	TTE was performed using the Vivid 7 system (General Electric) fitted with a 4.3-MHz multifrequency probe with harmonic imaging. The apical four-chamber view was used to optimise visualisation of the atria, ventricles and interatrial septum. Three patients had a suboptimal acoustic window but were not excluded from the study. Atrial septal aneurysm was diagnosed when there was a 10-mm midline shift in anatomical M-mode or when the total bidirectional shift was > 15 mm	TOE	TOE with colour Doppler was performed using the same system fitted with a 2.9- to 8-MHz multifrequency probe. Patients were sedated with intravenously administered midazolam at a starting dose of 2 mg followed by 2-mg increments until tolerance was reached. Baseline values were recorded during TTE and once every minute during TOE. An N-550 pulse oximeter (Nellcor) and an automatic M4-I Intellisense blood pressure gauge (Omron) were used
Gutiérrez-Chico 2008[147]	Hospital, Spain	Mean 59, range 15–92	TTEh	A complete three-dimensional echocardiographic study was performed including parasternal and apical real-time views of the mitral valve, apical full-volume acquisition plus systematic cropping, and three-dimensional colour views	TOE	TOE was performed with a Philips Sonos 5500 system and Philips T6H probe. Three-dimensional echo was performed with a Philips Sonos 7500 system and X4 matrix probe. Investigators performing TOE were blinded to the three-dimensional results. TOE was performed according to a standard protocol, using the guidelines of the American Society of Echocardiography. A scallop was considered prolapsing according to the criteria defined in this protocol
Ha 2000[136]	Setting unclear, South Korea	Mean 51	TTEh and TTEf	Parasternal long-axis and apical four-chamber views were obtained with the use of functional imaging and harmonic imaging sequentially. Harmonic mode denotes that the imaging system is programmed to transmit at one frequency and receive at twice that frequency – its second harmonic. Fundamental mode refers to the standard acquisition and signal processing of b-mode images. Fundamental imaging was performed with the broadband 2- to 4-MHz Sonos 5500 Hewlett-Packard transducer with a fusion setting of 1, 3, or 4 depending on which resulted in the best image quality	TOE	TOE was performed with a 5-MHz phased-array transducer attached to the tip of a commercially available gastroscope (Hewlett-Packard Sonos 5500). The patients who had fasted for at least 4 hours before the examination received mild local pharyngeal anaesthesia immediately before the gastroscope was inserted. TOE was performed in the supine and lateral positions

Study	Setting	Age (years)	TTEf/TTEh	TTE details	Reference standard	Reference standard details
Ha 2001[137]	Setting unclear, South Korea	Mean 59, range 24–89	TTEh	TTE was performed with a Hewlett-Packard Sonos 5500 and broadband (2- to 4-MHz) transducer. After obtaining an optimal apical four-chamber view with good delineation of both atria, the interatrial septum and both ventricles, 10 ml of agitated saline was rapidly injected into a right antecubital vein through an 18-gauge venous cannula. In each patient, TTE with functional imaging and harmonic imaging and agitated saline contrast injection were performed during normal respiration and during the Valsalva manoeuvre. If contrast bubbles reached the right atrium the patient was asked to perform the Valsalva manoeuvre. After the contrast bubbles had completely cleared from the right-sided cardiac chambers the transducer was switched into the harmonic mode, holding the probe in the same position as in the functional imaging mode. Thereafter, contrast injections were repeated. Functional imaging was performed using the broadband (2- to 4-MHz) transducer with a fusion setting of either 1, 3 or 5, depending on which setting resulted in the best image quality. Harmonic imaging was acquired with the same transducer using transmit and receiving frequency settings of 2.1 and 4.2 MHz	TOE	All patients underwent TOE using a 4- to 7-MHz multiplane probe. Patients received local pharyngeal anaesthesia with 10% topical lidocaine and performed the Valsalva manoeuvre before the procedure; its effectiveness was verified by a reduction in ventricular and atrial size and by bulging of the interatrial septum into the left atrium

Study	Setting	Age (years)	TTEf/TTEh	TTE details	Reference standard	Reference standard details
Hirata 2008[111]	Hospital, USA	Mean 57	TTEh	TTE diagnosis of mitral valve prolapse was made by measurement of maximal mitral leaflet superior systolic displacement relative to the line connecting the annular hinge points (displacement > 2 mm). Displacement of the anterior and posterior mitral leaflets was measured in the parasternal and apical long-axis views, which were scanned by tilting the transducer to visualise the medial, middle and lateral scallops of the posterior leaflets. All of the displacements were always confirmed in the other views. Real-time three-dimensional imaging was performed on all mitral valve prolapse patients using a 2.5-MHz (X4) matrix array transducer on the Philips Sonos 7500 ultrasound machine, version 5.1. The X4 transducer provides live RT3D images as well as full-volume acquisition. In live RT3D image mode, the image was displayed as a quadrangular pyramidal image in real time. In the full-volume acquisition mode, four wedges were collected over eight consecutive cardiac cycles during a breath hold with ECG gating. The three-dimensional image volume was obtained in parasternal and apical views using these modes	TOE	All TOE studies were performed using a 5.0-MHz multiplane transducer interfaced with the Sonos 5500 or 7500 ultrasound machine (Philips). Sedation was achieved with the intravenous administration of midazolam and meperidine. The mitral valve was examined using mid-oesophageal four-chamber, commissural, two-chamber, long-axis and transgastric views according to the American Society of Echocardiography criteria. The presence of prolapse was defined as 'any portion of the mitral valve that moved above the mitral annulus during systole'. The mitral valve was divided into six segments: three anterior leaflet scallops defined as lateral (A1), middle (A2) and medial (A3) and three posterior leaflet scallops defined as lateral (P1), middle (P2) and medial (P3)

Study	Setting	Age (years)	TTEf/TTEh	TTE details	Reference standard	Reference standard details
Hubail 2011[112]	Hospital, USA	Mean 9.5, range 1.2–8.6	TTEf and TTEh	Transducer type was chosen to obtain the optimal balance between spatial resolution (higher frequency) and penetration (lower frequency) using anywhere from 3- to 8-MHz transthoracic probes. Harmonics were used if the quality of the images was improved by this modality. Two-dimensional and colour Doppler images were obtained from subcostal, apical and parasternal views on TTE. If no interatrial communication was detected, a contrast study was performed with a 5-ml agitated saline injection in patients < 20 kg and 10 ml in larger patients. If no shunt was detected, the agitated saline injection was repeated with a Valsalva manoeuvre in co-operative patients	TOE	TOE was subsequently performed obtaining two-dimensional colour Doppler images using the TE-V7M probe in patients < 20 kg and the TE-V5Ms probe in larger patients. If required, agitated saline injections with and without the Valsalva manoeuvre
Illien 2002[126]	Hospital, Germany	Age range 57–67	TTEh	For TTE a 3.4-MHz transducer was used with a harmonic frequency at 1.7 MHz. All patients were examined in the left lateral, decubitus position. A one-lead ECG was recorded continuously. The M-mode left atrial dimension was measured at end-systole in the parasternal long-axis view and the left ventricular ejection fraction was determined according to the recommendations of the North American Society of Echocardiography	TOE	TOE was performed with a 6.7-MHz multiplane transducer. The oropharynx was anaesthetised with lidocaine spray and a viscous lidocaine solution was used to cover the tip of the transoesophageal probe. When needed, 2.5–5 mg of midazolam was injected for sedation. The probe was placed in the mid-oesophagus behind the left atrium and a transoesophageal four-chamber view was then employed
Jassal 2007[153]	Hospital, Canada	Mean 57	TTEh	All studies were performed with a Vivid 7 system (GE Medical Systems). TTEh was performed first using a 1.5- to 1.7-MHz transducer	TOE	All studies were performed with a Vivid 7 system. TOE was performed within 24 hours of TTEh using a 4.5- to 6.2-MHz multiplane transducer in all patients
Jax 2010[127]	Germany, Hospital	No details	TTE	No details	TOE	No details

Study	Setting	Age (years)	TTEf/TTEh	TTE details	Reference standard	Reference standard details
Kerr 2000[115]	Hospital, USA	Mean 59, range 34–76	TTEf and TTEh	TTE patients were supine in the partial left lateral position using one echocardiographic machine (Agilent Technology Sonos 5500, S4 transducer). For all saline contrast studies 10 ml of saline was agitated with 0.2 ml of air between two 10-ml syringes mounted on a three-way stopcock and injected rapidly through a 20G cannula in the right antecubital vein. Patients were tutored in the performance of the Valsalva manoeuvre and had several trial performances to maximise manoeuvre intensity and timing. The manoeuvre was continued for 5 seconds and release was co-ordinated with opacification of the right atrium	TOE	TOE patients had fasted for 6 hours and received topical pharyngeal anaesthetic (midazolam 1–7 mg and demerol 0–50 mg) for sedation. The TOE examination was performed with an Agilent Technology Sonos 5500 echocardiographic machine at 5.0 MHz with a multiplane transducer. The interatrial septum was carefully studied in multiple planes for evidence of separation of the septum primum from the septum secundum consistent with the diagnosis of a PFO. The same interrogation was performed using colour Doppler with the colour scale reduced to maximise detection of low-velocity flow across the interatrial septum. When a PFO was seen, the plane in which the separation of septum primum and septum secundum was best seen was imaged for at least 10 cardiac cycles and the maximum separation of the limiting orifice was measured. Two saline contrast studies were performed: the first at rest and the second with release of 5 seconds of abdominal compression on complete right atrial opacification
Kitayama 1997[138]	Hospital, Japan	Mean 68	TTEf	TTE studies, including M-mode echocardiography, two-dimensional imaging and pulsed and colour Doppler echocardiography, were performed in all 70 patients with use of a Toshiba Sonolayer SSH-140A system with a 2.5- or 3.75-MHz transducer. To detect intracardiac thrombi, two-dimensional echocardiograms were obtained with the transducer in the parasternal, apical and subcostal positions. Thrombus was defined as a mass of echoes in at least two views of the cardiac cavity, seen throughout the cardiac cycle, contiguous with the cardiac wall. The left atrial dimension was measured in the parasternal long-axis view	Cardiac ultrafast CT	Cardiac ultrafast CT was performed using an Imatoron C-100XL system with a matrix size of 512 × 512 cm and a field of view of 30 cm, which resulted in a pixel size of 0.36 mm^2. Patients were placed in the supine position on the scanner couch. An intravenous catheter (20 gauge) was inserted into the right antecubital vein for contrast medium injection (Iomeron 350). Contrast medium was administered at a rate of 2.5 ml/second (total dose 80–100 ml) to facilitate endocardial border identification

Study	Setting	Age (years)	TTEf/TTEh	TTE details	Reference standard	Reference standard details
Kuhl 1999[128]	Hospital, Germany	Mean 56, range 20–86	TTEf and TTEh	TTE studies were performed following the TOE study at least 3 minutes after contrast bubbles had disappeared from right heart chambers. There was no change in the patient position between the TOE and TTE studies. For the transthoracic cerebrovascular event study an apical four-chamber view with optimal delineation of both atria, the interatrial septum and both ventricles was selected. TTE images were acquired in the fundamental imaging mode using the highest possible transducer frequency that still allowed clear delineation of the cardiac morphology. After contrast bubbles had completely cleared from the right heart chambers the transducer was switched into the harmonic mode, holding the probe in the same position as in the fundamental imaging mode. Thereafter, contrast injections were repeated. All echocardiographic studies were recorded on S-VHS videotape for offline analysis	TOE	TOE was performed using colour Doppler using a multiplane probe (Omni II, Hewlett-Packard). The patient was positioned in the left lateral decubitus position after topical anaesthesia of the pharynx with lidocaine. All patients were mildly sedated with intravenous administration of 2–3 mg of midazolam; contrast injections were performed in the transoesophageal four-chamber view in the 0° image plane of the transducer. Care was taken to visualise optimally the left atrium, the left ventricle and the interatrial septum. Additional contrast injections were performed in 40–60° image planes and/or 110–130° image planes as needed to demonstrate clearly the site of contrast passage through the interatrial septum
Lee 1991[114]	Hospital, USA	Mean 63, range 20–82	TTEf	M-mode and two-dimensional TTE were performed with the patient in the left lateral decubitus position using a 77020A imaging system (Hewlett-Packard) including a 2.5- or 3.5-MHz transducer. Parasternal long- and short-axis views, apical views and subxiphoid views were obtained	TOE	TOE was performed with the patient in the left lateral decubitus position using the Hewlett-Packard 77020A ultrasound imaging system, including the Hewlett-Packard 21362A 5-MHz single-plane transoesophageal transducer. Basal short-axis views, four-chamber views and transgastric short-axis views were obtained. Limb leads were placed on each patient to obtain a simultaneous ECG rhythm strip

Study	Setting	Age (years)	TTEf/TTEh	TTE details	Reference standard	Reference standard details
Lembcke 2009[129]	Hospital, Germany	Mean 68.4 (SD 10.4)	TTEh	TTE was performed by a trained cardiologist or cardiac surgeon according to the recommendations of the American Society of Echocardiography. An ultrasound unit with a 2.5-MHz, 128-element, phased-array transducer was used (Vivid 7, General Electric Healthcare) and images were acquired by using standard imaging windows with short breath holds if needed	Cardiac catheterisation	Cardiac catheterisation was performed in a standardised fashion by an expert cardiologist. Using the percutaneous femoral approach, peak-to-mean and mean transvalvular gradients were routinely determined during a pull-back manoeuvre after retrograde crossing of the valve or alternatively by simultaneous measurements with two catheters, one placed trans-septally into the left ventricle and a second placed in the ascending aorta
Li 2009[135]	Hospital, China	Mean 51, range 43–73	TTE – no further details	The transthoracic 2-DE examination was carried out using a Sonos 7500 ultrasonographic system (Philips). On two-dimensional echocardiography examination, multiple views, including apical four- and two-chamber views, apical long-axis views and parasternal long-axis and short-axis views, were used to display the left ventricular wall motion. Left ventricular aneurysm was diagnosed if the localised portion of the left ventricular cavity was found to have (1) akinesis or dyskinesis; (2) protrusion outside during the systolic phase; and (3) a wide orifice and continuity in the ventricular wall	Left ventriculography	Left ventriculography is considered the gold standard in the determination of left ventricular aneurysm. An XR Advantx LCV+ Angiographic System (GE Healthcare) was used to perform left ventriculography. According to the methods used by al-Saadon[185] and Lee *et al.*,[114] a left ventricular aneurysm is a motion disturbance of the myocardium in which a part of the left ventricular wall shows localised akinesia or dyskinesia during the systolic phase of a cineangiogram
Lipke 2007[130]	Hospital, Germany	Mean 63 (SD 11)	TTEh	All echocardiographic studies were performed by sonographers with > 7 years' experience in scanning. All studies were performed on a Vivid 7 (General Electric) echo machine. A standard transducer (M3S) with harmonic capabilities was used. For all studies the Octave mode was applied using frequencies ranging from 1.7 to 2.0 MHz (emit) and from 3.4 to 4.3 MHz (receive)	MRI	Contrast-enhanced MRI was carried out with a 1.5-T scanner (Intera, Philips) using a five-element phased-array cardiac coil and electrocardiographic triggering

Study	Setting	Age (years)	TTEf/TTEh	TTE details	Reference standard	Reference standard details
Madala 2004[115]	Hospital, USA	Range 21–88	TTEh	Agitated saline contrast injection was given intravenously as a 5- to 10-ml bolus injection during TOE, TTEf and TTEh	TOE	During TOE, contrast imaging was carried out in the bicaval view at approximately 90° probe rotation, visualising both the superior and the inferior vena cavae along with the fossa ovalis. All studies were performed with the Agilent Sonos 5500 or Acuson ultrasound system
Maffè 2010[150]	Hospital, Italy	Mean 49, range 36–62	TTEh	The TTE studies were performed with a Philips iE33 platform, with a S5–1 transducer (from 5 to 1 MHz) for two-dimensional examination and a X3–1 transducer (from 3 to 1 MHz) for three-dimensional examination. An apical four-chamber view with optimal delineation of both atria, the interatrial septum and both ventricles was selected. Continuous recording was obtained during bubble contrast injections, in basal conditions, and during a Valsalva manoeuvre	TOE	TOE studies were performed with the omniplane MPT7–4 transoesophageal probe of the ATL HD 5000 ultrasound machine. During TOE, the patient was positioned in the left lateral decubitus, using 10% topical lignocaine spray for the oropharynx and eventually intravenous sedation (midazolam 3 mg)
Mugge 1995[131]	Setting unclear, Germany	Mean 54, range 18–85	TTEf	No details	TOE	No details
Musolino 2003[61]	Hospital, Italy	Mean 36, range 17–45	TTEf	TTE studies were carried out using a Vingmed 700 CFM system and since 1993 a Vingmed 800 CFM system	TOE	TOE studies were carried out using a monoplane and since 1995 a multiplane mechanical transducer (Vingmed)
Nemec 1991[116]	Hospital, USA	Mean 50, range 22–78	TTEf	Standard TTE and TOE examinations using commercially available machines were performed using two-dimensional, Doppler and colour Doppler evaluations; imaging after contrast injection was performed during normal respiration and during a Valsalva manoeuvre	TOE	See *TTE details*
Neuman 2003[117]	Medical centre/ hospital, USA	Mean 78	TTEf	Mitral regurgitation was assessed by colour flow Doppler mapping using the methods of Helmcke *et al.*[186]	TOE	See *TTE details*

Study	Setting	Age (years)	TTEf/TTEh	TTE details	Reference standard	Reference standard details
Omran 1999[132]	Hospital, Germany	Mean 54	TTEf	TTE was performed with a phased-array 3.3-MHz transducer with 128 elements used. All patients were examined in the left lateral decubitus position. A single-lead ECG was simultaneously recorded. The left atrium was imaged in the standard, parasternal short- and long-axis and apical transducer positions. The left atrial appendage was imaged as described by Herzog *et al.*[187] Digital image processing and storage were used	TOE	TOE was performed with a 5-MHz multiplane transducer. We used topical lignocaine spray and viscous lignocaine solution to anaesthetise the oropharynx before the transoesophageal study
Pearson 1991[118]	Hospital, USA	Mean 59, range 17–84	TTEf	All patients underwent TTE and TOE with contrast administration and Doppler colour flow imaging. TTE was performed within 3 days (usually 24 hours after TOE) using several commercially available ultrasound systems	TOE	See *TTE details*
Pop 1990[142]	Hospital, Netherlands	Mean 60, range 24–73	TTEf	TTE was performed with a Toshiba SSH-65A imaging system using 2.5- and 3.75-mHz probes	TOE	TOE was performed systemically and lasted generally for approximately 15 minutes. After introduction, the probe was manipulated until it was located in the stomach and then a series of cross-sectional short axis of the left ventricle views were recorded. The probe was pulled back within the oesophagus until a proper four-chamber view was obtained. In this section attention was focused on the mitral valve and its chordae and the aortic valve and the aortic root were visualised, orienting the probe superiorly

Study	Setting	Age (years)	TTEf/TTEh	TTE details	Reference standard	Reference standard details
Roldan 2008[119]	Hospital, USA	Mean ~37	TTEh	TTE and TOE were separately videotaped or digitally acquired for offline interpretation. Standard two-dimensional views were obtained at a depth of 8–12 cm for TTE and 4–6 cm for TOE with a narrow sector scan to improve image resolution of the heart valves	TOE	See *TTE details*
Sallach 2009[120]	Setting unclear, USA	Mean 67	TTEf and TTEh	TTE studies were performed using an ATL-Philips 5000 echocardiographic system. The left atrial appendage was first examined using fundamental imaging to assess the left atrial appendage area and the presence of thrombus. Harmonic imaging was then used to evaluate the left atrial appendage area and the presence of thrombus. Harmonic imaging was repeated with a lower mechanical index range of 0.4–0.6 following a single intravenous bolus of Optison	TOE	TOE studies were performed using an ATL-Philips 5000 echocardiographic system
Shub 1983[121]	Hospital, USA	Mean ~31, range ~2 months–74 years	TTEf	Two-dimensional echocardiographic equipment used in the study included commercially available 80° phased-array scanning systems with 2.25- and 3.5-MHz transducers and a mechanical sector scanner with 3- and 5-MHz transducers	Surgical and cardiac catheterisation	No details

Study	Setting	Age (years)	TTEf/TTEh	TTE details	Reference standard	Reference standard details
Siostrzonek 1991[134]	Hospital, Austria	Mean 52	TTEf	TTE and TOE were performed with a Vingmed CFM700 system using a 3.5-MHz and 5-MHz transducer for TTE and TOE respectively. After obtaining optimal visualisation of the atrial septum a bolus of 2–5 ml of a hand-agitated 5.5% solution of oxypolygelatine was injected into a large cubital vein over an in-dwelling 18-gauge cannula; subsequently the appearance of contrast agent in the right atrium was monitored and recorded on videotape. Contrast studies were performed during normal breathing and during Valsalva manoeuvre	TOE	See *TTE details*
Stendel 2000[133]	Hospital, Germany	Mean 51, range 25–72	TTEf	Contrast-enhanced TTE was performed using a 2.5-MHz monoplane electrical transducer and the Ultramark 9 system with the awake patient lying on his or her left side and the upper part of the body elevated by 30°. No sedation was used. The heart was imaged in a four-chamber view. A 10-ml bolus dose of echo-contrast medium was injected into the right cubital vein. The Valsalva manoeuvre was performed 5 seconds after the injection of the echo-contrast medium	TOE	Contrast-enhanced TOE was performed using a 5-MHz monoplane electrical transducer and the Ultramark 9 system with the awake patient lying on his or her left side and the upper part of the body elevated by 30°. Local anaesthesia of the pharynx was performed using lidocaine spray. The ultrasound probe was also prepared with 2% lidocaine gel
Stratton 1982[122]	Hospital, USA	Mean ~58	TTEf	Two-dimensional echocardiography was performed using either a wide-angle, phased-array sector scanner (Toshiba, 45 patients) or a wide-angle, mechanical sector scanner (ATL Laboratories, 33 patients). Parasternal long- and short-axis and apical two- and four-chamber views were obtained using standard transducer positions. In most studies, non-standard views were also obtained using apical and low parasternal echocardiographic windows to examine the apex more thoroughly	Autopsy, aneurysmectomy and unequivocally positive indium-111 platelet imaging	No details

Study	Setting	Age (years)	TTEf/TTEh	TTE details	Reference standard	Reference standard details
Thanigaraj 2005[123]	Hospital, USA	Mean 45, range 18–84	TTEh	TTE was performed using second-harmonic imaging (transmitting frequency 1.8–2 MHz, receiving frequency 3.6–4 MHz). Studies were carried out with the Sonos 5500 (Phillips), Sequoia C256 (Siemens) or Vivid 7 (General Electric) imaging systems	TOE	All TOE studies were performed using a Sequoia multiplanar transducer (Siemens) with fundamental imaging modality (transmitting frequency 3.5–7 MHz). Saline contrast injections and colour Doppler evaluations were performed in the 90° (bicaval) view to document right-to-left atrial shunting
Trevelyan 2006[144]	Hospital, UK	55, range 22–80	TTEh	TTE for the detection of a PFO was carried out using a Hewlett-Packard Sonos 5500 imaging system with second harmonic imaging. Imaging was performed in the apical four-chamber view with injection of 10 ml of agitated saline (9 ml saline, 0.5 ml blood, 0.5 ml air repeatedly agitated through a three-way tap), which achieved opacification of the right heart in all cases	TOE	TOE was performed under local anaesthesia and sedation with midazolam and the procedure repeated as for TTE with the interatrial septum imaged in the 110–130° plane
Vincelj 2001[148]	Hospital, Croatia	Mean 55.3	TTE	TTE was performed with a Toshiba SSH 160A imaging system	TOE	TOE was performed either with a Hitachi Ultrasound scanner EUB-555 with a 3.5-MHz biplane transducer, with an ATL 3000 scanner (Universal Diagnostic Solutions) or with a 5000 HDI ultrasound scanner (Philips). Patients were studied in the fasting state after application of topical anaesthesia of the hypopharynx with 10% lidocaine spray and intravenous sedation with diazepam. The oesophageal probe was inserted with patients in the left lateral decubitus position

Study	Setting	Age (years)	TTEf/TTEh	TTE details	Reference standard	Reference standard details
Weinsaft 2011[124]	Setting unclear, USA	Mean 60	TTEh	Two-dimensional TTE ECGs were obtained by experienced sonographers on commercially available equipment (Sonos 5500 or 7500, Philips) with phased- and sector-array transducers. Echoes were acquired in standard parasternal short- and long-axis as well as apical two-, three- and four-chamber imaging planes in accordance with American Society of Echocardiography consensus guidelines	Delayed enhancement cardiac MRI	MRI was undertaken with delayed enhancement using 1.5-T scanners (Siemens Sonata or Avanto)
Zito 2009[151]	Setting unclear, Italy	Mean 49	TTEh	A baseline TTE examination was performed with an Aloka ProSound Alpha 10 imaging system using a 3-MHz probe according to standard practice guidelines with the patient in the left lateral position. An apical four-chamber view with optimal visualisation of both the atria, ventricles, and atrial septum was selected and the gain setting was adjusted to analyse the fossa ovalis area	TOE	A TOE study was performed using a Vivid 7 machine (General Electric) with a 5.0-MHz multiplane probe according to a standard protocol including colour flow Doppler data. The atrial septum was analysed from the transverse mid-oesophageal four-chamber view to the longitudinal biatrial–bicaval view. Fourteen patients had a BMI > 30 kg/m^2

SD, standard deviation.

Appendix 7 Diagnostic accuracy excluded studies

Reason for exclusion	Study
No usable data	1–72
No concordance between groups	73–78
No relevant cardiac pathologies	79–90
Not diagnostic accuracy study	91–117
Not English language	118–132
No relevant comparator	133–137

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Appendix 8 Summary of results

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
TTE vs. ultrafast CT (left atrial thrombi)						
Kitayama 1997[138]	4	0	2	64	0.67 (0.22 to 0.96)	1.00 (0.94 to 1.00)
TTE vs. TOE (left atrial thrombi)						
Blum 2004[145]	0	0	3	65	0.00 (0.00 to 0.71)	1.00 (0.94 to 1.00)
Fatkin 1996[156]	2	0	3	55	0.40 (0.05 to 0.85)	1.00 (0.94 to 1.00)
Vincelj 2001[148]	1	0	0	13	1.00 (0.03 to 1.00)	1.00 (0.75 to 1.00)
TTEh vs. TOE (left atrial thrombi)						
de Bruijn 2006[141]	0	0	1	230	0.00 (0.00 to 0.97)	1.00 (0.98 to 1.00)
Ha 2000[136]	9	0	3	62	0.75 (0.43 to 0.95)	1.00 (0.94 to 1.00)
Illien 2002[126]	11	0	1	160	0.92 (0.62 to 1.00)	1.00 (0.98 to 1.00)
TTE vs. independent verification (left ventricular thrombus)						
Stratton 1982[122]	19	3	3	53	0.86 (0.65 to 0.97)	0.95 (0.85 to 0.99)
TTEh vs. contrast-enhanced MRI (left ventricular thrombus)						
Lipke 2007[130]	8	5	7	14	0.53 (0.27 to 0.79)	0.74 (0.49 to 0.91)
TTEh vs. cardiac MRI (left ventricular thrombus)						
Weinsaft 2011[124]	8	20	16	199	0.33 (0.16 to 0.55)	0.91 (0.86 to 0.94)
TTE vs. TOE (PFO)						
Akosah 1998[107]	0	0	2	122	0.00 (0.00 to 0.84)	1.00 (0.97 to 1.00)
Belkin 2011[109]	7	2	7	22	0.50 (0.23 to 0.77)	0.92 (0.73 to 0.99)
Blum 2004[145]	0	1	5	62	0.00 (0.00 to 0.52)	0.98 (0.91 to 1.00)
Chen 1992[139]	12	0	7	13	0.63 (0.38 to 0.84)	1.00 (0.75 to 1.00)
Cujec 1991[152]	0	0	2	24	0.00 (0.00 to 0.84)	1.00 (0.86 to 1.00)
Di Tullio 1993[110]	9	0	10	30	0.47 (0.24 to 0.71)	1.00 (0.88 to 1.00)
Ha 2001[137]	9	0	31	80	0.23 (0.11 to 0.38)	1.00 (0.95 to 1.00)
Lee 1991[114]	0	0	4	46	0.00 (0.00 to 0.60)	1.00 (0.92 to 1.00)
Madala 2004[115]	7	0	2	55	0.78 (0.40 to 0.97)	1.00 (0.94 to 1.00)
Musolino 2003[61]	0	0	10	50	0.00 (0.00 to 0.31)	1.00 (0.93 to 1.00)
Nemec 1991[116]	7	0	6	19	0.54 (0.25 to 0.81)	1.00 (0.82 to 1.00)
Siostrzonek 1991[134]	9	0	21	120	0.30 (0.15 to 0.49)	1.00 (0.97 to 1.00)
Stendel 2000[133]	10	0	14	68	0.42 (0.22 to 0.63)	1.00 (0.95 to 1.00)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
TTEh vs. TOE (PFO)						
Clarke 2004[143]	12	1	1	96	0.92 (0.64 to 1.00)	0.99 (0.94 to 1.00)
Daniels 2004[140]	48	7	5	196	0.91 (0.79 to 0.97)	0.97 (0.93 to 0.99)
Gonzalez-Alujas 2011[146]	93	0	0	41	1.00 (0.96 to 1.00)	1.00 (0.91 to 1.00)
Ha 2001[137]	25	0	15	96	0.63 (0.46 to 0.77)	1.00 (0.96 to 1.00)
Hubail 2011[112]	7	0	1	35	0.88 (0.47 to 1.00)	1.00 (0.90 to 1.00)
Jax 2010[127]	22	0	24	0	0.48 (0.33 to 0.63)	Not estimable
Kerr 2000[113]	12	0	5	27	0.71 (0.44 to 0.90)	1.00 (0.87 to 1.00)
Madala 2004[115]	9	10	0	45	1.00 (0.66 to 1.00)	0.82 (0.69 to 0.91)
Maffè 2010[150]	55	0	7	13	0.89 (0.78 to 0.95)	1.00 (0.75 to 1.00)
Thanigaraj 2005[123]	34	0	2	58	0.94 (0.81 to 0.99)	1.00 (0.94 to 1.00)
Trevelyan 2006[144]	26	0	8	53	0.76 (0.59 to 0.89)	1.00 (0.93 to 1.00)
Zito 2009[151]	26	0	20	26	0.57 (0.41 to 0.71)	1.00 (0.87 to 1.00)
Sensitivity analysis: TOE vs. TCD (PFO)						
Gonzalez-Alujas 2011[146]	90	1	3	40	0.97 (0.91 to 0.99)	0.98 (0.87 to 1.00)
Sensitivity analysis: TOE vs. TMD (PFO)						
Kerr 2000[113]	17	0	1	26	0.94 (0.73 to 1.00)	1.00 (0.87 to 1.00)
TTE vs. TOE (atrial septal defect)						
Akosah 1998[107]	0	0	5	119	0.00 (0.00 to 0.52)	1.00 (0.97 to 1.00)
Blum 2004[145]	0	0	1	67	0.00 (0.00 to 0.97)	1.00 (0.95 to 1.00)
Kuhl 1999[128]	31	0	20	60	0.61 (0.46 to 0.74)	1.00 (0.94 to 1.00)
Musolino 2003[61]	1	0	3	56	0.25 (0.01 to 0.81)	1.00 (0.94 to 1.00)
TTEh vs. TOE (atrial septal defect)						
Kuhl 1999[128]	46	0	5	60	0.90 (0.79 to 0.97)	1.00 (0.94 to 1.00)
Thanigaraj 2005[123]	7	0	0	87	1.00 (0.59 to 1.00)	1.00 (0.96 to 1.00)
TTE vs. surgical + cardiac catheterisation (atrial septal defect – ostium secundum)						
Shub 1983[121]	93	0	12	0	0.89 (0.81 to 0.94)	Not estimable
TTE vs. surgical + cardiac catheterisation (atrial septal defect – ostium primum)						
Shub 1983[121]	32	0	0	0	1.00 (0.89 to 1.00)	Not estimable
TTE vs. TOE (atrial septal aneurysm)						
Cujec 1991[152]	0	0	2	24	0.00 (0.00 to 0.84)	1.00 (0.86 to 1.00)
Di Tullio 1993[110]	0	0	2	47	0.00 (0.00 to 0.84)	1.00 (0.92 to 1.00)
Mugge 1995[131]	103	0	92	0	0.53 (0.46 to 0.60)	Not estimable
Musolino 2003[61]	0	0	11	49	0.00 (0.00 to 0.28)	1.00 (0.93 to 1.00)
TTEh vs. TOE (atrial septal aneurysm)						
Gonzalez-Alujas 2011[146]	34	0	1	22	0.97 (0.85 to 1.00)	1.00 (0.85 to 1.00)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
TTE vs. TOE (left atrial appendage thrombi)						
Akosah 1998[107]	0	0	18	106	0.00 (0.00 to 0.19)	1.00 (0.97 to 1.00)
Aschenberg 1986[125]	0	0	6	15	0.00 (0.00 to 0.46)	1.00 (0.78 to 1.00)
Cujec 1991[152]	0	0	1	25	0.00 (0.00 to 0.97)	1.00 (0.86 to 1.00)
Fatkin 1996[156]	0	0	4	56	0.00 (0.00 to 0.60)	1.00 (0.94 to 1.00)
Musolino 2003[61]	0	0	1	59	0.00 (0.00 to 0.97)	1.00 (0.94 to 1.00)
Omran 1999[132]	10	0	2	104	0.83 (0.52 to 0.98)	1.00 (0.97 to 1.00)
Pop 1990[142]	0	0	2	17	0.00 (0.00 to 0.84)	1.00 (0.80 to 1.00)
Sallach 2009[120]	0	0	2	116	0.00 (0.00 to 0.84)	1.00 (0.97 to 1.00)
TTEh vs. TOE (left atrial appendage thrombi)						
Sallach 2009[120]	2	0	0	116	1.00 (0.16 to 1.00)	1.00 (0.97 to 1.00)
TTE vs. TOE (SEC)						
Lee 1991[114]	0	0	9	41	0.00 (0.00 to 0.34)	1.00 (0.91 to 1.00)
Omran 1999[132]	4	0	51	61	0.07 (0.02 to 0.18)	1.00 (0.94 to 1.00)
Pop 1990[142]	0	0	2	17	0.00 (0.00 to 0.84)	1.00 (0.80 to 1.00)
TTE vs. TOE (left atrial SEC)						
Black 1991[154]	0	0	75	325	0.00 (0.00 to 0.05)	1.00 (0.99 to 1.00)
Black 1991[155]	0	0	33	67	0.00 (0.00 to 0.11)	1.00 (0.95 to 1.00)
Cujec 1991[152]	0	0	7	19	0.00 (0.00 to 0.41)	1.00 (0.82 to 1.00)
Pearson 1991[118]	0	0	13	66	0.00 (0.00 to 0.25)	1.00 (0.95 to 1.00)
TTEh vs. TOE (left atrial SEC)						
Ha 2000[136]	63	0	9	1	0.88 (0.78 to 0.94)	1.00 (0.03 to 1.00)
TTE vs. TOE (left ventricular SEC)						
Black 1991[155]	0	0	2	98	0.00 (0.00 to 0.84)	1.00 (0.96 to 1.00)
TTE vs. left ventriculography (left ventricular aneurysm)						
Baur 1982[108]	14	0	3	9	0.82 (0.57 to 0.96)	1.00 (0.66 to 1.00)
Li 2009[135]	13	1	3	21	0.81 (0.54 to 0.96)	0.95 (0.77 to 1.00)
TTEh vs. cardiac catheterisation (aortic valve stenosis)						
Lembcke 2009[129]	160	3	0	39	1.00 (0.98 to 1.00)	0.93 (0.81 to 0.99)
TTEf vs. TOE (cardiac vegetations)						
Chirillo 2005[149]	10	22	18	89	0.36 (0.19 to 0.56)	0.80 (0.72 to 0.87)
TTEh vs. TOE (cardiac vegetations)						
Chirillo 2005[149]	23	2	5	109	0.82 (0.63 to 0.94)	0.98 (0.94 to 1.00)
Jassal 2007[5]	16	2	3	15	0.84 (0.60 to 0.97)	0.88 (0.64 to 0.99)
TTE vs. TOE (mitral valve regurgitation)						
Musolino 2003[61]	5	0	0	55	1.00 (0.48 to 1.00)	1.00 (0.94 to 1.00)
Neuman 2003[117]	51	0	3	0	0.94 (0.85 to 0.99)	Not estimable

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
TTEh vs. TOE (mitral valve regurgitation)						
Roldan 2008[119]	8	4	6	62	0.57 (0.29 to 0.82)	0.94 (0.85 to 0.98)
TTE vs. TOE (mitral valve stenosis)						
Musolino 2003[61]	2	0	0	58	1.00 (0.16 to 1.00)	1.00 (0.94 to 1.00)
TTEh vs. TOE (mitral valve prolapse)						
Hirata 2008[111]	39	0	3	0	0.93 (0.81 to 0.99)	Not estimable
TTEh (three-dimensional) vs. TOE (mitral valve prolapse)						
Gutiérrez-Chico 2008[147]	40	0	1	0	0.98 (0.87 to 1.00)	Not estimable
Hirata 2008[111]	40	0	2	0	0.95 (0.84 to 0.99)	Not estimable
TTE vs. TOE (atrial myxoma)						
Vincelj 2001[148]	8	0	2	4	0.80 (0.44 to 0.97)	1.00 (0.40 to 1.00)

Appendix 9 Cost-effectiveness review: literature search strategies, a MEDLINE example

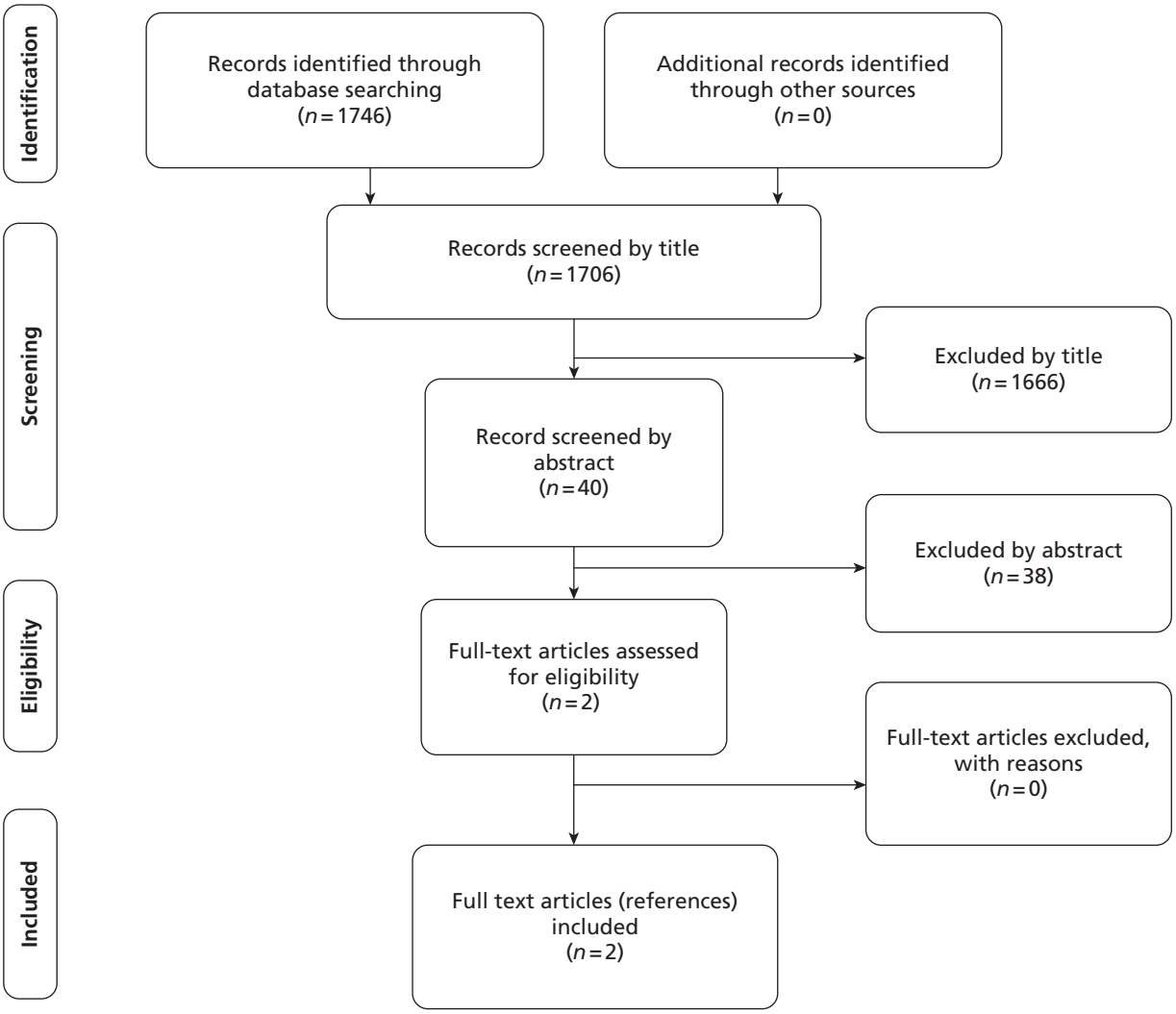
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R).

Searched: 1948 to present.

1. Stroke/ (39,233)
2. stroke$.mp. (138,756)
3. stroke volume/ (25,237)
4. stroke volume$.mp. (32,752)
5. Cerebrovascular accident.mp. (2591)
6. cerebrovascular event.mp. (471)
7. Cerebrovascular disease.mp. (9405)
8. Ischemic Attack, Transient/ or transient ischemic event.mp. (16,035)
9. transient ischemic attack.mp. (3409)
10. vascular accident.mp. (674)
11. brain emboli$.mp. or Intracranial Embolism/ (2398)
12. cerebral emboli$.mp. (1923)
13. brain infarction.mp. or Brain Infarction/ (3554)
14. cerebral infarction.mp. or Cerebral Infarction/ (21,326)
15. or/1-14 (175,197)
16. Echocardiography.mp. or Echocardiography/ (105,417)
17. transthoracic echocardiography.mp. (4128)
18. Transoesophageal echocardiography.mp. (1369)
19. transesophageal echocardiography.mp. (8092)
20. (echocardiog$ adj (transthorac$ or trans-thorac$ or (trans$ and thorac$))).mp. (427)
21. (echocardiog$ adj (transoesophag$ or trans-oesophag$ or (trans and oesophag$))).mp. (46)
22. (echocardiog$ adj (transesophag$ or trans-esophag$ or (trans and esophag$))).mp. (12,231)
23. 24 hour holter.mp. (1157)
24. twenty four hour holter.mp. (111)
25. telemetr$.mp. (9058)
26. secondary prevention.mp. (9681)
27. cardiac imag$.mp. (1883)
28. cardiac magnetic resonance imaging.mp. (1315)
29. cardiac MR.mp. (349)
30. cardiac MRI.mp. (882)
31. carotid ultrasound.mp. (499)
32. carotid doppler.mp. (210)
33. transcranial doppler.mp. (5296)
34. transcranial doppler.mp. (5296)
35. R? Test Evolution.mp. (2)
36. R? Test.mp. (981)
37. reveal device.mp. (1)
38. implantable loop recorder.mp. (154)
39. diagnostic imag$.mp. (29,793)
40. Ultrasonography/ or diagnostic ultrasound.mp. (59,099)
41. ultrasonic diagnosis.mp. (1607)
42. magnetic resonance imaging.mp. or Magnetic Resonance Imaging/ (253,683)
43. or/16-42 (458,448)

44. exp "Sensitivity and Specificity"/ (324,293)
45. sensitivity.tw. (420,807)
46. ((pre-test or pretest) adj probability).tw. (940)
47. post-test probability.tw. (261)
48. predictive value$.tw. (51,868)
49. likelihood ratio$.tw. (6225)
50. or/44-49 (671,637)
51. 15 and 43 and 50 (3735)
52. from 51 keep 2001-3735 (1735)
53. Economics/ (25,956)
54. "costs and cost analysis"/ (38,507)
55. Cost allocation/ (1887)
56. Cost-benefit analysis/ (49,895)
57. Cost control/ (18,559)
58. Cost savings/ (6894)
59. Cost of illness/ (13,573)
60. Cost sharing/ (1634)
61. "deductibles and coinsurance"/ (1268)
62. Medical savings accounts/ (440)
63. Health care costs/ (20,579)
64. Direct service costs/ (924)
65. Drug costs/ (10,121)
66. Employer health costs/ (1026)
67. Hospital costs/ (6325)
68. Health expenditures/ (11,358)
69. Capital expenditures/ (1889)
70. Value of life/ (5118)
71. exp economics, hospital/ (16,987)
72. exp economics, medical/ (13118)
73. Economics, nursing/ (3833)
74. Economics, pharmaceutical/ (2192)
75. exp "fees and charges"/ (25,020)
76. exp budgets/ (10,802)
77. (low adj cost).mp. (16,143)
78. (high adj cost).mp. (6351)
79. (health?care adj cost$).mp. (2668)
80. (fiscal or funding or financial or finance).tw. (61,105)
81. (cost adj estimate$).mp. (1113)
82. (cost adj variable).mp. (28)
83. (unit adj cost$).mp. (1182)
84. (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (133,214)
85. or/53-84 (378,997)
86. 15 and 43 and 85 (331)

Appendix 10 Cost-effectiveness review: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (adapted) flow chart



Appendix 11 Economic evaluation checklist

Drummond *et al.* adapted criteria[158]

Criteria	Meenan *et al.*[37]	McNamara *et al.*[161]
1. Was a well-defined question posed in answerable form?	Yes	Yes
2. Was a comprehensive description of the competing alternatives given?	Yes	Unclear
3. Was the effectiveness of the programme or services established?	Yes	Yes
4. Were all the important and relevant costs and consequences for each alternative identified?	Yes	Unclear
5. Were costs and consequences measured accurately in appropriate physical units?	Yes	Unclear
6. Were the cost and consequences valued credibly?	Yes	Unclear
7. Were costs and consequences adjusted for differential timing?	Not applicable	Not applicable
8. Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Yes
9. Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Unclear
10. Did the presentation and discussion of study results include all issues of concern to users?	Yes	Unclear

Consensus on Health Economic Criteria (CHEC)-list[160]

Criteria	Meenan *et al.*[37]	McNamara *et al.*[161]
1. Is the study population clearly described?	Yes	Yes
2. Are competing alternatives clearly described?	Yes	Yes
3. Is a well-defined research question posed in answerable form?	Yes	Yes
4. Is the economic study design appropriate to the stated objective?	Yes	Yes
5. Is the chosen time horizon appropriate to include relevant costs and consequences?	Yes	Yes
6. Is the actual perspective chosen appropriate?	Yes	Yes
7. Are all important and relevant costs for each alternative identified?	Yes	Unclear
8. Are all costs measured appropriately in physical units?	Yes	Unclear
9. Are costs valued appropriately?	Yes	Unclear
10. Are all important and relevant outcomes for each alternative identified?	Yes	Unclear
11. Are all outcomes measured appropriately?	Yes	Yes
12. Are outcomes valued appropriately?	Not applicable	Yes
13. Is an incremental analysis of costs and outcomes of alternatives performed?	Yes	Yes
14. Are all future costs and outcomes discounted appropriately?	Not applicable	Not applicable
15. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Yes	Unclear
16. Do the conclusions follow from the data reported?	Yes	Yes
17. Does the study discuss the generalisability of the results to other settings and patient/client groups?	No	Unclear
18. Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Yes	Unclear
19. Are ethical and distributional issues discussed appropriately?	No	Unclear

Appendix 12 Stroke survey

1. What guidelines do you use to investigate and manage ischaemic stroke or TIA?

	Investigate	Manage
• Internal guidelines	[ ]	[ ]
• NICE guidelines	[ ]	[ ]
• Royal College of Physicians guidelines	[ ]	[ ]
• Other guidelines	[ ]	[ ]
• Amended guidelines for local use	[ ]	[ ]
• No guidelines	[ ]	[ ]

When a guideline other than unmodified NICE or Royal College of Physicians is used, please enclose a copy.

2. How often are the following tests used to investigate ischaemic stroke or TIA?

	Never	Only young cases	Only if all other tests normal	Only if strong clinical suggestion of cerebral embolism	All cases
12-lead ECG					
Holter monitoring					
Transoesophageal echocardiography (TOE)					
Transthoracic echocardiography (TTE)					
TTE with bubble contrast					
Other (please state)					

Appendix 13 Clinicians' comments

I am afraid, the questions are all or none type, not very differentiating. As a result, it may lead to skewed results. In our institution, all unexplained cases of young stroke (50 yrs or under) gets a TOE and bubble study, and all stroke 50 or under gets a TTE. Additional tests i.e. CT-angio [computerised tomography angiography], contrast carotid, MR angiogram [magnetic resonance angiography] etc. are done according to clinical indication.

Thrombophilia Screen, Vasculitic Screen, Autoantibodies, Carotid doppler, MRA for carotids and vertebrals, CTA, R on T test [a form of ventricular arrhythmia in which the electrocardiographic tracing shows premature ventricular complexes occurring in early diastole], TCD with bubble contrast, Thrombophilia screen, genetic test for CADASIL [cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy] and Fabry's disease etc. tcd sometimes used if paradoxical emb [embolism] thought possible.

[I]ts not either/or it is more subtle and often logical decision making depends on many factors. There are also good reasons why a test might be indicated technically but not done as it has no UTILITY for a particular patient. Too often, thoughtless tests are done, then don't know what to do with the answer!!

[W]e used 7 days holter monitoring for most ischaemic stroke, if the 12 lead ECG showed sinus rhythm to rule out PAF [paroxysmal atrial fibrillation]. It started as a research project, and we may use as routine test, as initial finding shows that up to 12% of patients have PAF [paroxysmal atrial fibrillation] on prolonged monitoring.

[W]e tend to do a bubble contrast TTE and if shunt seen we proceed to TOE.

I found that the questionnaire limited some other options. For example, I do request a transthoracic echo for all young patients and in the case of middle aged and elderly, I arrange an echo for unexplained ischaemic stroke/TIA, and associated co-morbidity.

A Holtoer monitoring is used in unexplained stroke (Ischaemic) for excluding PAF.

Young patients < 50: 1. Antiphsopholipid antibodies 2. Thrombophilia 3. Vasculitis screen 4. Homocystein.

In all young patients, i.e. 50 or less and those aged 50–60 without other significant risk factors, a work up of: ECG, TTE, 24 hour tape, vasculitic and thrombophilia screen are requested. If all these prove normal then consideration is given to TOE being undertaken with patient involvement.

TCD with bubble test. All cases get ECG, the majority get Holter, some get TTE but if we strongly suspect embolic source in young person then we do TCD with bubble and if positive TTE with bubble.

CT angiogram. Other questions don't allow multiple options, e.g. TTE used to investigate all young cases AND those not young but strong clinical suggestion of cerebral embolism. Carotid imaging (doppler, MRA, CTA – not just young patients), Trans-cranial doppler (not just young patients), Lupus anticoagulant, Anticardiolipin antibodies

Thrombophilia/AIP [acute intermittent porphyria]/Cardiolipin in < 55 years. Dopplers in all anterior circulation events if fit for surgery. MRA with fat suppression in all suspected dissections. CTA in some posterior circulation recurrent events. FAST MRI sequencing in (approx. 40% events) when diagnosis unclear or neurology in doubt/questioned.

TOE

Thrombophilia screen

Vasculitis screen

Screen for Fabry's disease

MRA or CT angiogram

VRV [ventricular residual volume] if sinus venous thrombosis suspected

Cerebral angiography

All admitted patients have 72 hour cardiac monitoring. Outpatients have 24 hour tapes. If TOE is performed then bubble contrast is considered in all cases by cardiologist.

Appendix 14 Protocol

09/68/01 HTA TAR

Revised Protocol
February 2010

1. Title of the project:

Routine echocardiography in the management of stroke and transient ischemic attack (TIA)

2. Name of TAR team and project 'lead'

TAR team: ScHARR Technology Appraisal Group, University of Sheffield

Project lead: Rachel Jackson, Research Fellow, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

Email: R.Jackson@Sheffield.ac.uk, Tel: 0114 222 0793, Fax: 0114 272 4095

Address for correspondence

All correspondence should be sent to the project lead (R.Jackson@Sheffield.ac.uk), the project administrator (Gill Rooney, G.Rooney@Sheffield.ac.uk) and the managing director of ScHARR-TAG (Eva Kaltenthaler, E.Kaltenthaler@Sheffield.ac.uk).

3. Plain English Summary

Stroke is a serious medical condition in which the blood supply to the brain is disrupted, potentially resulting in disability and mortality. The World Health Organisation defined stroke as 'rapidly developing clinical signs of focal (sometimes global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin' (Hatano, 1976). Symptoms of stroke include numbness, disrupted vision, slurred speech, confusion and headache (Stroke Association, 2009). There are two major types of stroke: ischaemic stroke, in which the blood supply is disrupted due to a narrowing or blockage of the circulatory system; and haemorrhagic stroke, in which blood loss in the brain causes neurological damage. Transient ischaemic attack (TIA) has been defined as 'a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischaemia, without acute infarction' (Easton *et al.*, 2009). In a transient ischaemic attack, symptoms typically subside within a few hours (Stroke Association, 2009). However, people who have experienced a TIA have a high risk of stroke following the event (Coull *et al.*, 2004) and therefore should receive prompt medical attention.

It is estimated that approximately 110,000 people experience a stroke and a further 20,000 individuals have a TIA in England each year (National Audit Office, 2005). It has been reported that 10–15% of TIA patients experience a stroke within 3 months (Easton *et al.*, 2009). Over 56,000 deaths were attributable to stroke in England and Wales in 1999, representing 11% of total deaths for this period (Mant *et al.*, 2004). Stroke places a considerable burden on the economy in England, resulting in direct costs to the NHS of £2.8 billion (Mant *et al.*, 2004).

The identification of the origin of a stroke or TIA can inform treatment and secondary prevention strategies. Embolism of cardiac origin has been estimated to account for approximately 20% of ischaemic strokes (Palacio & Hart, 2002). Imaging technologies such as transthoracic echocardiography (TTE) and transoesophageal echocardiography (TOE) facilitate the detection of potentially-treatable cardiac sources of stroke and TIA. Of the two methods, transthoracic echocardiography is less invasive. Both of these imaging methods are capable of detecting a number of potential cardiac sources of stroke and TIA, including left ventricular/left atrial thrombus (which can be treated by anticoagulation with warfarin), cardiomyopathy (treatable with warfarin or antiplatelet therapy), and patent foramen ovale/atrial septal aneurysm (treatable by anticoagulation, surgical closure, antiplatelet therapy, or by observation) (Yu *et al.*, 2009).

No recommendations relating to the use of echocardiography in the assessment of first episode diagnosed stroke and TIA patients were made within the national clinical guidelines for stroke published by the Royal College of Physicians (2004), the NICE stroke clinical guideline (NICE, 2008) or the National Stroke Strategy (Department of Health, 2007). The use of this technology in the management of stroke and TIA patients in the UK appears to be variable. The British Society of Echocardiography stated that echocardiography was indicated in adult cases of neurological disease in several instances including: a) unexplained stroke or TIA without evidence of prior cerebrovascular disease or without significant risk factors for other cause (with the suggestion that saline contrast echocardiography by TTE or TOE be used), and b) in patients for whom a therapeutic decision will depend on the outcome of echocardiography (eg. anticoagulation). This guidance also stated that echocardiography was not indicated in patients in whom echocardiography would not affect the decision to begin anticoagulation (eg. patients in atrial fibrillation with cerebrovascular event and no suspicion of structural heart disease).

McNamara *et al.* (1997) found in their US-specific cost effectiveness analysis that transthoracic echocardiography (either alone or in sequence with transoesophageal echocardiography) was not cost effective compared with transoesophageal echocardiography. The 2007 update of the 2002 Agency for Healthcare Research and Quality (AHRQ) assessment (Meenan *et al.*, 2007) found that current cost effectiveness evidence was insufficient to justify widespread use of echocardiography in stroke patients in the United States.

The aim of this assessment is to explore the use of transthoracic echocardiography in the assessment of stroke and TIA patients in a UK context.

A related assessment is currently being undertaken by the TAR team in Sheffield entitled 'Echocardiography in newly diagnosed atrial fibrillation patients' (08/45/01).

4 Decision problem

4.1 Purpose of assessment

The aim of this assessment is to answer the following research question: What is the clinical and cost effectiveness of the addition of an echocardiogram to the routine assessment of patients who have had a stroke or transient ischaemic attack (TIA) in the UK?

4.2 Clear definition of the intervention

Transthoracic echocardiography (TTE) is an ultrasound imaging technique utilising beams of sound transmitted at frequencies of 2.5–5 MHz. A transducer is placed on the chest, allowing the structures of the heart and velocity of blood flow to be visualised (Patient UK, 2009). TTE may be used to determine cardiac sources of stroke or TIA and facilitate treatment and secondary prevention strategies.

4.3 Place of the intervention in the treatment pathway(s)

The assessment will investigate the effects of undertaking TTE in the routine assessment of all first episode diagnosed stroke and TIA patients in secondary care. Typically, once a stroke has been established as being ischaemic in nature via brain imaging (CT or MRI scanning), further imaging technologies may then be employed to determine the underlying aetiology of the episode and inform patient management. If data are available, the cost effectiveness of performing TTE in specific population subgroups will be determined.

4.4 Relevant comparators

Current UK diagnostic protocol (to be identified by researchers). As data available on current practice within the UK from clinical guidelines and the existing literature are limited, we propose to collect information on current UK diagnostic protocols. Managing staff at stroke units across the UK will be approached and a copy of any current stroke diagnostic protocol(s) will be requested. Clinical advisors to the team will be involved in the identification of an appropriate sample. If necessary, professional bodies may be requested to further advise on recruitment. Following collection of diagnostic protocols, the comparator will then be selected in conjunction with clinical advisors. Comparators may include transoesophageal echocardiography, 24 hour Holter monitoring or cardiac monitoring via telemetry (used alone or in combination with TTE and each other).

4.5 Population and relevant subgroups

Patients who have had an ischaemic stroke or TIA (but have no other indication for a TTE) (NB: Echocardiography in newly diagnosed atrial fibrillation patients is being considered in a separate Health Technology Assessment). If data are available, the effectiveness of performing TTE in specific population subgroups (eg. by age, ethnicity) will be described. Such subgroups are to be defined following the completion of Review 1.

4.6 Key factors to be addressed

The objectives of the review are:

1. To investigate by systematic review the prevalence of cardiac sources of stroke and TIA (limited to those detectable by TTE) (Review 1)
2. To investigate by systematic review the diagnostic accuracy of TTE for these cardiac sources (Review 2)
3. To estimate the potential benefits and harms arising from the alteration of treatment based on results of TTE
4. To estimate the incremental cost effectiveness of providing routine TTE to all first episode diagnosed stroke and TIA patients in secondary care
5. To estimate the incremental cost effectiveness of providing routine TTE to subgroups within the first episode diagnosed stroke and TIA patient population in secondary care (where data are available). Subgroups are to be defined based on the findings of Review 1.

5. Report methods for synthesis of evidence of clinical effectiveness

5.1 Description of reviews

Two systematic evidence reviews (Review 1: Prevalence of cardiac sources of stroke and TIA; Review 2: Diagnostic accuracy of TTE for cardiac sources of stroke and TIA) will be undertaken informed by the general principles recommended in the PRISMA (formerly QUOROM) statement (Moher *et al.*, 2009).

Review 1: Prevalence of cardiac sources of embolism in stroke and TIA

Prevalence of cardiac sources of embolism in stroke and TIA will be investigated using epidemiological studies. Cardiac sources will be restricted to those identifiable by TTE. These include left ventricular/left atrial thrombus, patent foramen ovale and atrial septal aneurysm (Yu *et al.*, 2009). It is proposed that conditions that may be associated with cardioembolic stroke such as recent myocardial infarction, dilated

cardiomyopathy, infective endocarditis and atrial fibrillation be excluded since they are typically clinically apparent without echocardiography or are present with symptoms that represent other indications for echocardiography (as per Meenan *et al.*, 2007).

Review 2: Diagnostic accuracy of TTE for cardiac sources of embolism in stroke and TIA

Diagnostic accuracy of TTE will be investigated using studies comparing the identification of cardiac sources of stroke or TIA by TTE with other diagnostic tools. Outcomes relating to screening performance will be described. TTE may be compared against a diagnostic gold standard or alternative imaging method for the detection of cardiac sources of stroke or TIA (eg. transoesophageal echocardiography) within the literature. To inform the economic evaluation, these will need to be synthesised into a consistent evidence base. Studies relating to the prognostic value of TTE (ie. the ability of TTE results to predict subsequent stroke or TIA outcomes) will also be identified. A structured search defined on ad hoc criteria will be undertaken to identify adverse events as a result of the tests under study. Whilst no physical harms appear to be associated with the use of transthoracic echocardiography, there is the potential for the occurrence of adverse events as a result of local anaesthetic or sedation procedures used during the insertion of the transducer probe in transoesophageal echocardiography. Furthermore, patient harms may result as a consequence of diagnostic inaccuracies and resulting inappropriate care.

5.2 Identifying and systematically reviewing clinical effectiveness evidence

Population

The population will be the same for both reviews

Inclusion

First episode diagnosed ischaemic stroke and TIA patients

Interventions

Transthoracic echocardiography (TTE) in the routine assessment of first episode diagnosed stroke and TIA patients in secondary care

Comparators

Current UK diagnostic protocol (to be identified by researchers). Clarification of the care pathway and current UK diagnostic practice is required. As data available on current practice within the UK from clinical guidelines and the existing literature are limited, we propose to collect information on current UK diagnostic protocols. Managing staff at stroke units across the UK will be approached and a copy of any current stroke diagnostic protocol(s) will be requested. Clinical advisors to the team will be involved in the identification of an appropriate sample. If necessary, professional bodies may be requested to further advise on recruitment. Following collection of diagnostic protocols, the comparator will then be selected in conjunction with clinical advisors. Comparators may include transoesophageal echocardiography, 24 hour Holter monitoring or cardiac monitoring via telemetry (used alone or in combination with TTE and each other).

Search strategy

The search strategy for both reviews will comprise the following main elements: searching of electronic databases; contact with experts in the field; scrutiny of bibliographies of retrieved papers. The electronic databases to be searched will include MEDLINE; MEDLINE in Process (for latest publications); EMBASE; Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, CINAHL, DARE, NHS EED and HTA databases; NHS EED; NIHR Clinical Research Network Portfolio database, NRR (National Research Register) Archive, Web of Science Proceedings, Science Citation Index; Current Controlled Trials, Clinical Trials.gov, FDA website, EMEA website, and relevant conference proceedings.

The draft search strategy is presented in *Appendix 1*.

Study selection

In both reviews, citations will be imported into reference management software and screened for inclusion. The following publication types will be excluded: studies which are only published in languages other than English; studies based on animal models; preclinical and biological studies; narrative reviews, editorials, opinions; and reports published as meeting abstracts only (where insufficient methodological details are reported to allow critical appraisal of study quality). Titles and abstracts will be examined for inclusion by one reviewer. Two reviewers will independently make decisions on inclusion of studies at full text stage and any discrepancies resolved by discussion.

Data extraction strategy

In both reviews, data will be extracted independently by one reviewer (with no blinding to authors or journal) using a standardised form and checked by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

Quality assessment strategy

Quality assessment will be subject to the types of studies identified but will be undertaken using appropriate and established tools (eg. checklists specifically designed for quality assessment of diagnostic studies such as the QUADAS checklist (QUality Assessment of Diagnostic Accuracy Studies; Whiting *et al.*, 2003, see *Appendix 2*). The quality assessment of epidemiological studies is likely to be based on the STROBE statement (Elm *et al.*, 2007) (see *Appendix 2*). Quality assessment will be confirmed by a second reviewer.

Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review. For the review of diagnostic accuracy of TTE in the detection of cardiac sources of stroke or TIA, we will combine data to provide pooled estimates of diagnostic performance where appropriate.

Further information needed

Further clinical data needed for economic modelling will be sought from clinical guidelines and advice from clinical experts. If a large group of data are required, non systematic searches may be undertaken. If studies of prognostic accuracy (ie. the ability of TTE to predict later outcomes in stroke and TIA) are not available, it may be necessary to find data on the risk of later events arising from each clinically important pathology. In considering how each clinically important pathology is treated, details of current NHS practice and data on the benefits and harms of these treatments in the relevant population will be required.

6. Report methods for synthesising evidence of cost effectiveness

6.1 Identifying and systematically reviewing published cost effectiveness studies

The sources detailed in section 5 will be used to identify studies of the cost effectiveness of TTE in the management of first episode diagnosed stroke and TIA patients. An economic search filter will be incorporated into the search strategy to identify relevant studies. Identified economic literature will be critically appraised and quality assessed using the critical appraisal checklist for economic evaluations proposed by Drummond *et al.* (2005). Existing cost effectiveness analyses will also be used to identify sources of evidence to inform structural modelling assumptions and parameter values for the economic model.

6.2 Development of a health economic model

A de novo economic evaluation of the cost effectiveness of TTE in the assessment of first episode diagnosed stroke and TIA patients in secondary care will be conducted. A model will be developed to identify whether the routine testing of all patients (who do not already have an indication for TTE) would result in more cost effective treatment of patients with stroke and TIA compared with current practice. Cost effectiveness modelling will take account of potential benefits and harms of altered treatment, and (if data allow) will identify any subgroups of patients in whom TTE is most likely to be cost effective.

The primary outcome from the model will be an estimate of the incremental cost per additional quality-adjusted life-year (QALY) gained associated with the use of TTE in the assessment of first episode diagnosed stroke and TIA patients. A lifetime time horizon will be used in order to reflect the chronic effects of stroke and the ongoing risk of further cerebrovascular events and potential mortality. The perspective used will be that of the National Health Services and Personal Social Services. Costs and QALYS will be discounted at 3.5% as recommended in current guidelines (NICE, 2008). Modelling assumptions will be taken from the literature, supplemented by clinical expert opinion where required.

The ScHARR modelling team have published papers using different modelling techniques (such as discrete event simulation (Stevenson *et al.*, In press a; Stevenson *et al.*, In press b; Michaels *et al.*, 2009), transition state modelling (Wardlaw *et al.*, 2009) and meta-modelling (Stevenson *et al.*, 2004)). The model structure and software used to construct the model will be determined following data collection in order that the most appropriate technique is used for this particular assessment. Clinical experts will be consulted at the conceptual stage to ensure that the structure of the model is appropriate to clinical practice. The model will include estimates of the effects of TTE on the management of different types of stroke and TIA patients, as well as costs of intervention and subsequent downstream costs associated with appropriate and inappropriate care. If data allow, this approach will enable an analysis of whether the cost effectiveness of the use of TTE in the routine assessment of stroke and TIA patients differs between patient groups.

Ideally, health related quality-of-life evidence will be available directly from the review literature. In the absence of such evidence, the mathematical model may use indirect evidence on quality of life from alternative sources. Quality-of-life data will be reviewed and used to generate the quality adjustment weights required for the model. In addition to the reviewed literature, national sources (eg. NHS reference costs (Department of Health), national unit costs (Curtis, 2008), British National Formulary (http://bnf.org)) will be used to estimate resource use and costs for use in the economic model.

It is anticipated that there may be limited evidence for some of the parameters that will be included in the economic model. Therefore, the uncertainty around the parameter estimates will be modelled to take this into account. The uncertainty in the central value for each required parameter will be represented by a distribution, enabling probabilistic sensitivity analysis to be undertaken. This will allow an assessment of the uncertainty to be made. If resources allow, the cost effectiveness of collecting further information will be explicitly explored using Expected Value of Sample Information techniques (Stevenson *et al.*, In Press; Stevenson & Lloyd-Jones, In Press).

7. Expertise in this TAR team

TAR centre

The School of Health and Related Research (ScHARR) is one of the four Schools that comprise the Faculty of Medicine at the University of Sheffield. ScHARR brings together a wide range of medical and health-related disciplines, including public health, general practice, mental health, epidemiology, health economics, management sciences, medical statistics, operational research, and information science. The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the effectiveness and cost

effectiveness of healthcare interventions for the NHS R&D Health Technology Assessment Programme on behalf of a range of policy makers, including the National Institute for Health and Clinical Excellence.

Team members' contributions

Rachel Jackson (Research Fellow, ScHARR) has experience in systematic reviews of health technologies. She will act as the project lead and lead reviewer on this assessment. She has compiled the study protocol.

Sophie Whyte (Research Associate, ScHARR) has experience in cost-effectiveness analysis. She will undertake the review of cost effectiveness evidence and development of the cost effectiveness model.

Munira Essat (Research Associate, ScHARR) will assist in the systematic reviewing of clinical evidence.

Angie Rees (Information Specialist, ScHARR) is experienced in conducting searches for health technology assessments. She will develop the search strategy and undertake the electronic literature searches.

Matt Stevenson (Senior Research Fellow, ScHARR) assisted in the drafting of the study protocol. He will provide support to the cost effectiveness modelling where appropriate and will oversee the project.

Clinical advisors (including echocardiography and stroke specialists) have been approached by the research team and are to be confirmed.

8. Competing interests of authors

None

9. Timetable/milestones

Milestone	Date
Draft protocol	30th October 2009
Final protocol	5th February 2010
Progress report	29th April 2011
Assessment report	31st May 2011

10. Appendices

Appendix 1: Draft search strategy

Review 1: Prevalence of cardiac sources of stroke and transient ischaemic attack

1. Stroke
2. Cerebrovascular accident
3. Cerebrovascular event
4. Transient ischaemic attack
5. TIA
6. vascular accident.mp.
7. cva.mp.
8. stroke.mp.

9. or/1–8
10. Cardiac source$
11. Cardiac origin$
12. Cardioemboli$
13. Cardiogenic
14. Patent foramen ovale
15. Atrial thromb$/clot$
16. Ventricular thromb$/clot$
17. Cardiac thromb$/clot
18. Cardiac embol$
19. Cardiomyopath$
20. Hypertroph$
21. Atrial sept$
22. Cardiac mass$
23. Cardiac vegetation$
24. Endocarditis
25. or/10–24
26. 9 and 25
27. Exp Epidemiologic studies
28. Exp Epidemiology
29. epidemiology.tw
30. Exp Prevalence
31. prevalence.ti
32. Exp Incidence
33. incidence.ti
34. ep.fs
35. or/27–34
36. 26 and 35

Review 2: Diagnostic accuracy of TTE for cardiac sources of embolism in stroke and TIA

1. Stroke$
2. Cerebrovascular accident$
3. Cerebrovascular event$
4. Transient ischaemic attack$
5. TIA$
6. vascular accident.mp.
7. cva.mp.
8. stroke.mp.
9. or/1–8
10. Echocardiography
11. Transthoracic echocardiography
12. TTE
13. Transoesophageal echocardiography
14. Transesophageal echocardiography
15. TOE
16. TEE
17. 24/Twenty four h$Holter
18. Telemetr$
19. Secondary prevention
20. Cardiac imag$
21. or/10–20

22. Exp sensitivity and specificity
23. Sensitivity.tw
24. Specificity.tw
25. ((pre-test ot pretest) adj probability).tw
26. Post-test probability
27. Predictive value$.tw
28. Likelihood ratio$
29. exp diagnosis/
30. di.fs.
31. diagnos$.tw.
32. exp predictive value of tests/
33. value.ti.
34. accuracy.ti.
35. correlat$.ti.
36. or/22–35
37. 9 and 21 and 36

Appendix 2: Draft data extraction

Forms are to be adapted from the following tools:

QUADAS (quality assessment of studies of diagnostic accuracy) (Whiting *et al.*, 2003)

Was the spectrum of patients described in the paper and was it chosen adequately?
Were selection criteria described clearly?
Was the method of population recruitment consecutive?
Was the setting of the study relevant?
In light of current technology, was the reference standard chosen appropriate to verify test results?
Was there an abnormally long time period between the performance of the test under evaluation and the confirmation of the diagnosis with the reference standard?
Was the execution of the index test described in sufficient detail to permit replication of the test?
Was the execution of the reference standard described in sufficient detail to permit replication of the test?
Did the whole sample, or a random selection of the sample, receive verification using a reference standard of diagnosis?
Did all patients receive the same reference standard regardless of the index test result?
Were the results of the index test incorporated in the results of the reference standard?
Were the index test results interpreted blind to the results of the reference standard?
Were the reference standard results interpreted blind to the results of the index test?
Was clinical data available when test results were interpreted?
Were uninterpretable/indeterminate/intermediate results reported and included in the results?
Were reasons for drop-out from the study reported?

STROBE (Strengthening the reporting of observational studies in epidemiology) (Elm *et al.*, 2007)

Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study* – Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. *Case–control study* – Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. *Cross-sectional study* – Give the eligibility criteria, and the sources and methods of selection of participants (*b*) *Cohort study* – For matched studies, give matching criteria and number of exposed and unexposed. *Case–control study* – For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) *Cohort study* – If applicable, explain how loss to follow-up was addressed. *Case–control study* – If applicable, explain how matching of cases and controls was addressed. *Cross-sectional study* – If applicable, describe analytical methods taking account of sampling strategy (*e*) Describe any sensitivity analyses
Results		
Participants	13*	(*a*) Report numbers of individuals at each stage of study – eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (*b*) Give reasons for non-participation at each stage (*c*) Consider use of a flow diagram
Descriptive data	14	(*a*) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (*b*) Indicate number of participants with missing data for each variable of interest (*c*) *Cohort study* – Summarise follow-up time (eg, average and total amount)
Outcome data	15	*Cohort study* – Report numbers of outcome events or summary measures over time. *Case–control study* – Report numbers in each exposure category, or summary measures of exposure. *Cross-sectional study* – Report numbers of outcome events or summary measures

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done – eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

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