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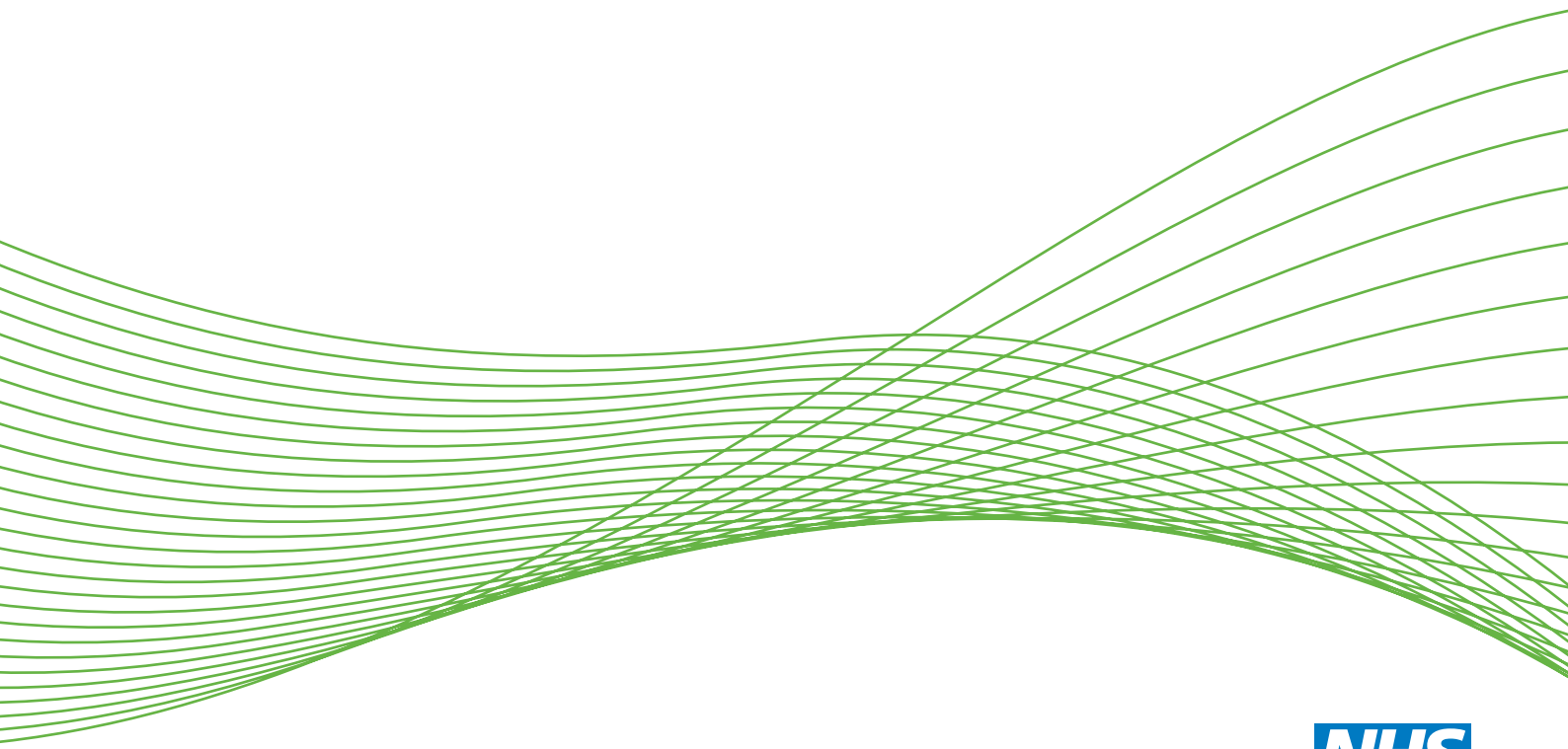

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Abstract

Echocardiography in newly diagnosed atrial fibrillation patients: a systematic review and economic evaluation

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Objective: To investigate the clinical effectiveness and cost-effectiveness of transthoracic echocardiography (TTE) in all patients who are newly diagnosed with atrial fibrillation (AF).

Design: Narrative synthesis reviews were conducted on the prognostic and diagnostic accuracy of TTE for, and prevalence of, pathologies in patients with AF. Databases were searched from inception. MEDLINE searches were conducted from March to August 2010, and reference lists of articles checked. There were 44 diagnostic accuracy studies, five prognostic studies, and 16 prevalence studies accepted into the review. Given the complexity of the many pathologies identified by TTE, the variety of potential changes to clinical management, and paucity of data, the model focused on changes to oral anticoagulation (OAC). The mathematical model assessed the cost-effectiveness of TTE for patients with AF who were not routinely given OAC, assuming, if left atrial abnormality was detected, that the higher risk of stroke warranted OAC; this meant that patients with a $CHADS_2$ (cardiac failure, hypertension, age, diabetes, stroke doubled) score of 0 [dabigatran etexilate (Pradaxa®, Boehringer Ingelheim)/rivaroxaban (Xarelto®, Bayer Schering)] or 0/1 (warfarin) were included. A simplified approach evaluated the additional quality-adjusted life-years (QALYs) required in order for TTE to be perceived as cost-effective at a threshold of £20,000 per QALY.

Setting: Transthoracic echocardiography is usually performed in cardiology clinics but may be used in primary or non-specialist secondary care.

Participants: Patients with newly diagnosed AF.

Intervention: Transthoracic echocardiography.

Main outcome measures: Prognosis, diagnostic sensitivity or specificity of TTE, prevalence of pathologies in patients with AF, cost-effectiveness and QALYs.

Results: Prognostic studies indicated that TTE-diagnosed left ventricular dysfunction, increased left atrial diameter and valvular abnormality were significantly associated with an increased risk of stroke, mortality or thromboembolism. There was a high prevalence (around 25–30%) of ischaemic heart disease, valvular heart disease and heart failure in patients with AF. Diagnostic accuracy of TTE was high, with most pathologies having specificity of ≥ 0.8 and sensitivity of ≥ 0.6. The mathematical model predicted that when the $CHADS_2$ tool is used the addition of TTE in identifying patients with left atrial abnormality appears to be cost-effective for informing some OAC decisions. In the simplified approach a threshold of 0.0033 was required for a TTE to be cost-effective.

Conclusions: When $CHADS_2$ was used, the addition of TTE in identifying patients with left atrial abnormality was cost-effective for informing some OAC decisions. A simple analysis indicates that the number of QALYs required for TTE to be cost-effective is small, and that if benefits beyond those associated with a reduction in stroke are believed probable then TTE is likely to be cost-effective in all scenarios. Our findings suggest that further research would be useful, following up newly diagnosed patients with AF who have undergone TTE, to study treatments given as a result of TTE diagnoses and subsequent cardiovascular events. This could identify additional benefits of routine testing, beyond stroke prevention. Studies assessing the proportion of people with a $CHADS_2$ score of 0 or 1 that have left atrial abnormality would provide better estimates of the cost-effectiveness of TTE, and allow more accurate estimates of the sensitivity and specificity of TTE for identifying left atrial abnormality in AF to be obtained.

Study registration: PROSPERO CRD42011001354.

Funding: The National Institute for Health Research Health Technology Assessment programme.

Contents

Glossary

Antiarrhythmic drugs Pharmacological treatment to correct irregular heartbeats and to slow rapid heartbeats.

Anticoagulant drugs Pharmacological treatment to reduce the risk of blood clotting.

Arrhythmia Abnormality of the normal heart rhythm.

Atrial fibrillation Arrhythmia characterised by rapid and irregular beating of the atria and absence of regular P waves on the electrocardiogram.

Atrial flutter Arrhythmia characterised by 'flutter waves' on the electrocardiogram.

Cardioversion Treatment to restore the heart to normal sinus rhythm using drugs or electric shock.

Electrical cardioversion Treatment to restore the heart to normal sinus rhythm using electric shock.

Electrocardiography Recording of the heart's electrical activity.

Lone atrial fibrillation Atrial fibrillation with no identified cause.

Paroxysmal atrial fibrillation Atrial fibrillation that spontaneously terminates within 7 days, usually within 48 hours.

Permanent atrial fibrillation Established atrial fibrillation that has not terminated, has terminated but recurred, or for which cardioversion has not been attempted.

Persistent atrial fibrillation Atrial fibrillation that does not self-terminate, or lasts >7 days (without cardioversion).

Pharmacological cardioversion Treatment to restore the heart to normal sinus rhythm using drugs.

Rate control Management of arrhythmia that works to control heart rate.

Rhythm control Management of arrhythmia that works to restore and maintain normal sinus rhythm.

Sensitivity Proportion of true-positives, a measure of the accuracy of a diagnostic test.

Sinus rhythm Normal heart rhythm.

Specificity Proportion of true-negatives, a measure of the accuracy of a diagnostic test.

List of abbreviations

2D	two-dimensional
AF	atrial fibrillation
AMI	acute myocardial infarction
AR	aortic regurgitation
AV	atrioventricular
BSE	British Society of Echocardiography
CAF	chronic atrial fibrillation
CARAF	Canadian Registry of Atrial Fibrillation
CEAF	cost-effectiveness acceptability frontier
CHA_2DS_2-VASc	congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 years, and sex category (female)
$CHADS_2$	cardiac failure, hypertension, age, diabetes, stroke doubled
CHF	congestive heart failure
CI	confidence interval
CrI	credible interval
CT	computerised tomography
DES	discrete event simulation
DM	diabetes mellitus
ECG	electrocardiography
ESC	European Society of Cardiology
EVPI	expected value of perfect information
EVPPI	expected value of partial perfect information
FN	false-negative
FP	false-positive
GI	gastrointestinal
GOS	Glasgow Outcome Scale
GP	general practitioner
HR	hazard ratio
HRG	Healthcare Resource Group
ICER	incremental cost-effectiveness ratio
ICH	intracranial haemorrhage
ICM	ischaemic cardiomyopathy
INR	international normalised ratio
LA	left atrial
LAA	left atrial appendage
LAD	left atrial diameter
LV	left ventricular
M-mode	motion-mode echocardiography
MAICER	maximum acceptable incremental cost effectiveness ratio
MI	myocardial infarction
MR	mitral regurgitation
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
MVP	mitral valve prolapse
NCC-CC	National Collaborating Centre for Chronic Conditions
NICE	National Institute for Health and Care Excellence
NSF	National Service Framework
OAC	oral anticoagulant
OR	odds ratio
PE	pulmonary embolism

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QUADAS	quality assessment of studies of diagnostic accuracy included in systematic reviews
RA	right atrial
RAA	right atrial appendage
RCT	randomised controlled trial
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
RR	relative risk
RV	right ventricular
SPAF	Stroke Prevention in Atrial Fibrillation
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TIA	transient ischaemic attack
TN	true-negative
TOE	transoesophageal echocardiography
TP	true-positive
TTE	transthoracic echocardiography
WoS	Web of Science

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Scientific summary

Background

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. AF may be asymptomatic, but may cause palpitations, chest pain, shortness of breath or fainting. If left untreated, AF is a significant risk factor for stroke and other morbidities.

Transthoracic echocardiography (TTE) allows imaging of the heart and blood flow. Echocardiography enables the diagnosis of cardiac abnormalities earlier than would be possible if symptoms were left to develop. Currently, only selected patients with AF are recommended for TTE: those who have clinically suspected heart disease or for whom further information is needed for treatment planning.

Objectives

The assessment investigated the clinical effectiveness and cost-effectiveness of performing routine TTE in all newly diagnosed patients with AF, in comparison with the current practice of selective testing.

Methods

Literature reviews were conducted on the diagnostic accuracy of TTE for clinically important pathologies in AF and their prevalence in patients with AF. A search of MEDLINE, and, for the prevalence review, of 11 other databases was conducted from March to August 2010, and reference lists of relevant articles were checked. For the diagnostic review, the intervention was conventional TTE, and the outcomes sensitivity or specificity. Results were tabulated and discussed in a narrative synthesis.

A mathematical model was constructed to assess the cost-effectiveness of TTE in patients with newly diagnosed AF. It was assumed that TTE would be of benefit only when patient management was changed. It was assumed that if a left atrial abnormality was detected then the patient was at a higher risk of stroke and should receive treatment. The estimated sensitivity and specificity of TTE in identifying left atrial abnormality was incorporated in the model.

A total of 14 separate paired comparisons, comparing a baseline strategy of not using TTE with a comparator strategy that did, were produced. These considered higher- and lower-risk groups, two different age groups, three different types of oral anticoagulant, and both males and females separately.

A simplified approach was also undertaken that evaluated the additional quality-adjusted life-years (QALYs) required in order for TTE to be perceived as cost-effective at a threshold of £20,000 per QALY.

Results

The literature reviews identified 44 diagnostic accuracy studies, five prognostic studies and 16 prevalence studies. Diagnostic accuracy showed high specificities for all selected pathologies, with the majority having specificity of 0.8 or higher, meaning a low proportion of false-positives. Specificity was lower for aortic dissection and pulmonary disease than for other pathologies. For most pathologies there was also quite high sensitivity, with the majority having sensitivity of ≥ 0.6, with the exceptions of atrial thrombi, atrial septal defect and pulmonary embolism (PE), for which sensitivity was lower. Prognostic studies indicated

that TTE-diagnosed left ventricular (LV) dysfunction or increased left atrial diameter (LAD) was associated with significantly increased risks of thromboembolism or mortality. LV dysfunction also had a significantly increased risk of stroke, and valvular abnormality a significantly increased risk of mortality. Not all studies found a significant association between TTE-diagnosed mitral regurgitation (MR) and prognosis; however, there were reported a significantly increased risk of thromboembolism with mild MR, in contrast with a significantly protective effect of severe MR against stroke. Mitral annular calcification and mitral valve prolapse were not found to be associated with thromboembolism and stroke, respectively. There was a high prevalence (around 25–30%) of ischaemic heart disease, valvular heart disease and heart failure in patients with AF in the included prevalence studies.

The results of the mathematical model indicated that it may be cost-effective to use TTE to make the decision about whether to prescribe warfarin to patients with a $CHADS_2$ (cardiac failure, hypertension, age, diabetes, stroke doubled) score of 1, or whether to prescribe rivaroxaban to patients aged ≥65 years with a $CHADS_2$ score of 0.

In the simplified approach, a threshold of 0.0033 was required for a TTE to be cost-effective. This is a very small value, and if a clinician believes there will be some patient gain in addition to providing treatment to reduce stroke risk then TTE is likely to be cost-effective.

Discussion

Diagnostic accuracy of TTE and prevalence of pathologies in patients with AF indicate that routine TTE following AF diagnosis would identify pathologies in many patients, particularly with regard to valvular heart disease, ischaemic heart disease and heart failure. TTE seems to be a sufficient diagnostic tool for screening most pathologies included in this review. For completeness of screening, extra testing for PE by lung scan and for atrial thrombi and atrial septal hypertrophy by transoesophageal echocardiography would reduce risk of false-negatives from TTE. However, it is unclear whether identifying these pathologies, in addition to the many diagnosed by TTE, would lead to improvement above that of TTE screening.

It is clear that TTE has the potential to be cost-effective, and this has been indicated in the analyses that assume that the $CHADS_2$ tool is used. The simplified approach indicates that very few QALYs are required for TTE to be perceived as cost-effective. The modelling undertaken focuses purely on the risks of stroke and of bleed events; if patients will benefit from TTE in other respects it is likely that this diagnostic test would be cost-effective.

Conclusions

Transthoracic echocardiography is a non-invasive procedure with the potential to accurately identify treatable pathologies in patients with AF.

Where the $CHADS_2$ tool is used, the addition of TTE in identifying patients with left atrial abnormality appears to be cost-effective for informing some oral anticoagulation decisions. A simple analysis indicates that the QALYs required for TTE to be cost-effective is small, and that if benefits beyond those associated with a reduction in stroke (at the expense of greater number of bleed) are believed probable then TTE is likely to be cost-effective in all scenarios.

Our findings suggest that further research is needed to follow-up newly diagnosed patients with AF who have undergone TTE, to study treatments given as a result of TTE diagnoses and subsequent cardiovascular events, which could identify additional benefits of routine testing, beyond stroke prevention. Studies assessing the proportion of people with a $CHADS_2$ scores of 0 or 1 that have left atrial abnormality would

provide better estimates of the cost-effectiveness of TTE, and allow more accurate estimates of the sensitivity and specificity of TTE for identifying left atrial abnormality in AF to be obtained.

Study registration

This study is registered as PROSPERO CRD42011001354.

Funding

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

Chapter 1 Background

Atrial fibrillation

Cardiac arrhythmias affect the heart, causing an irregular heartbeat. Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia.[1] It is a form of tachyarrhythmia, meaning an abnormally rapid heartbeat accompanied by an irregular rhythm, and is characterised by uncoordinated atrial activation with consequent deterioration of atrial mechanical function.[2]

Atrial fibrillation:

- does not always cause symptoms but may cause palpitations, chest pain or discomfort, shortness of breath, dizziness, or fainting.[1] In extreme cases there may be loss of consciousness[1]
- is sometimes associated with other arrhythmias, most commonly atrial flutter or atrial tachycardias, but may occur by itself[3]
- is more common in older people, and at the age of 80–89 years, almost 9% of people have AF.[1] With the ageing population and increasing prevalence of chronic heart disease, AF has increased in frequency over the past few years.[2]

Types of atrial fibrillation

The Working Group of Arrhythmia of the European Society of Cardiology (WGA-ESC) and the North American Society of Pacing and Electrophysiology (NASPE) created an international consensus on the classification of AF, applying to episodes of AF lasting more than 30 seconds.[3]

The initial event of AF is the first detected episode.[3] AF may or may not recur after the initial event.[3] AF is considered recurrent on experiencing two or more episodes.[1,3]

Paroxysmal AF is a recurrent form of AF that spontaneously terminates within 7 days, usually within 48 hours.[3]

Persistent AF is a recurrent form of AF that does not self-terminate, or lasts longer than 7 days (without cardioversion).[3] This may be the first presentation of AF, or may follow paroxysmal AF.[3] A patient may have some episodes of paroxysmal AF and some episodes of persistent AF, in which case he or she may be classified according to the most frequent presentation.[2]

Permanent AF is established AF that has not terminated, has terminated but recurred within 24 hours, or for which cardioversion has not been attempted (accepted AF).[3] This may be the first presentation of AF, or may follow self-terminating AF episodes.[3]

Non-valvular (or non-rheumatic) AF refers to cases of AF with the absence of rheumatic valve disease, prosthetic valve or repaired mitral valve.[2]

Aetiology, pathology and prognosis of atrial fibrillation

Atrial fibrillation may occur in the absence of any concomitant disease, in which case it is termed idiopathic AF.[3] Lone AF is a term used to describe AF in patients without concomitant heart disease[3] and with normal echocardiogram.[2] This term is usually applied to younger patients with AF, that is <60 years old.[2] AF may be triggered by atrial flutter or by other atrial tachycardias.[3]

Atrial fibrillation can be caused by other medical conditions, such as cardiovascular disease, diabetes mellitus (DM), obesity or hypertension.[1] Cardiovascular conditions associated with AF include coronary

artery disease, valvular heart disease, heart failure and hypertension.[2] AF may occur following surgery.[1] Alcohol and caffeine may predispose patients to AF.[2] Family history is a risk factor for AF.[4]

Atrial fibrillation occurring in the context of acute myocardial infarction (AMI), cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism (PE), pneumonia, or other acute pulmonary disease is termed secondary AF.[2]

For some patients with secondary AF, after curing the underlying cause the AF is unlikely to recur.[2,3] Examples of these causes include AMI, acute pericarditis, acute myocarditis or acute pulmonary embolus.[3] However, AF may occur independently of other diseases, for example in patients with hypothyroidism, even when the concomitant disorder is being treated.[2]

Atrial fibrillation is associated with atrial fibrosis and loss of atrial muscle mass.[2] A coexistence of normal and fibrosed atrial fibres may explain non-homogeneity of conduction within the condition.[2]

On electrocardiography (ECG), AF is described by the absence of consistent P waves.[1,3] Replacing consistent P waves on the ECG of a patient in AF, are rapid oscillations or fibrillatory waves that vary in size, shape and timing.[1,3] These are generally associated with an irregular ventricular response when atrioventricular (AV) conduction is intact.[1,3]

In AF, the ventricular response depends on AV nodal properties, the level of vagal and sympathetic tone, and drugs that affect AV nodal conduction, such as beta-blockers, non-dihydropyridine calcium channel blockers (calcium antagonists) and digitalis glycosides.[1,3]

Paroxysmal AF can progress to chronic AF (CAF). A study of the Canadian Registry of Atrial Fibrillation (CARAF) found the probability of progression to CAF by 1 year was 8.6% and thereafter there was a slow but steady progression to 24.7% by 5 years.[5] By 5 years, the probability of documented recurrence of any AF (chronic or paroxysmal) was 63.2%.[5] Increasing age, significant aortic stenosis or mitral regurgitation (MR), enlargement of the left atrial (LA) and diagnosis of cardiomyopathy were independently associated with progression to CAF.[5] A more rapid heart rate during AF was associated with decreased risk of progression.[5] If left untreated, AF may sometimes result in a degree of haemodynamic instability that can represent a critical condition that requires immediate intervention to alleviate symptoms of breathlessness, chest pain and loss of consciousness.[1]

An irregular heartbeat makes the heart less efficient at circulating blood around the body. This can increase the risk of blood clots developing within the circulatory system. If left untreated, AF is a significant risk factor for thromboembolic events including stroke.[1]

Atrial fibrillation can be a risk factor for stroke. The rate of ischaemic stroke has been estimated to be two to seven times higher among patients with non-valvular AF than in those without.[2] The risk is greater for those with rheumatic AF.[2]

Guidelines produced by the National Collaborating Centre for Chronic Conditions (NCC-CC) for National Institute for Health and Care Excellence (NICE) on AF define risk of stroke in patients with AF as follows:

High risk Previous ischaemic stroke or transient ischaemic attack (TIA) or thromboembolic event, age ≥75 years with hypertension, diabetes or vascular disease (coronary or peripheral artery disease), clinical evidence of valve disease or heart failure, or impaired left ventricular (LV) function.

Moderate risk Age ≥65 years with no high risk factors, or age <75 years with hypertension, diabetes or vascular disease.

Low risk Age <65 years with no moderate- or high-risk factors.[1]

Several sets of clinical criteria have been proposed for stratifying risk of stroke in patients with AF, including Atrial Fibrillation Investigators (AFI) criteria, Stroke Prevention in Atrial Fibrillation (SPAF) study criteria, and the $CHADS_2$ (cardiac failure, hypertension, age, diabetes, stroke doubled) score, which is a clinical prediction rule for estimating the risk of stroke in patients with non-rheumatic AF.[2]

European Society of Cardiology (ESC) 2010 guidelines[6] recommend a risk factor-based approach for assessing stroke risk in patients with non-valvular AF based on CHA_2DS_2-VASc [congestive heart failure (CHF), hypertension, age ≥75 years (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 years, and sex category (female)]. Valvular AF is considered a major risk factor for stroke.[6]

As well as thromboembolic complications, AF has been associated with an increased risk of dementia, heart failure and death.[4]

An increased mortality rate in AF, compared with that of patients in normal sinus rhythm, has been linked to the severity of underlying heart disease.[2] Among patients with heart failure, AF has been associated with increased mortality rate in some, although not all, studies.[2,7]

Echocardiography may be useful in predicting the prognosis of AF. A retrospective study of PE in CAF identified transthoracic echocardiography (TTE) variables that were associated with acute PE or chronic thromboembolic pulmonary hypertension in AF as increased right ventricular (RV) dimension, higher tricuspid pressure gradient and shorter pulmonary artery acceleration time.[8] CAF was also associated with PE in participants with significantly decreased LV dimension and better LV performance.[8] A study of CARAF found baseline echocardiographic variables were associated with progression to CAF, independently of age, cardiomyopathy and heart rate.[5]

Transthoracic tissue Doppler imaging has associated the ratio of early transmitral flow velocity to early diastolic mitral annular velocity with the prognosis of non-valvular AF, in terms of overall survival, cardiac death and CHF.[9] Cerebral infarction in patients with non-valvular paroxysmal AF has been linked with TTE markers of a lower peak late diastolic flow velocity and a higher early to late ratio for transmitral flow.[10]

Transoesophageal echocardiography has also been used to predict prognosis in patients with AF.[11,12]

Providencia *et al.*[13] investigated TTE and transoesophageal echocardiography (TOE) in combination with the $CHADS_2$ and CHA_2DS_2-VASc scores as means of improving risk stratification for thromboembolic events in a cohort of patients with AF. They found that TTE diagnosed LV systolic function, and LA area measurement may provide a valuable addition to $CHADS_2$ and CHA_2DS_2-VASc scores.[13]

Measurement of atrial fibrillation

Guidelines on the management of AF, published by NICE in 2006, state that diagnosis should be made by ECG.[1] Suspected paroxysmal AF not detected by standard ECG recording can be diagnosed by a 24-hour ambulatory ECG monitor where asymptomatic episodes are suspected or where episodes are <24 hours apart, or by an event recorder ECG in which symptomatic episodes are > 24 hours apart.[1]

On the ECG, AF is described by the absence of consistent P waves.[1,3]

Regular relative risk (RR) intervals on the ECG may occur in some cases of AF, for example, in the presence of heart block associated with conduction disease or drug therapy.[1,3]

Patients with permanent ventricular pacing may require temporary pacemaker inhibition in order to visualise AF activity and diagnose AF.[1,3] A rapid, irregular, sustained, wide QRS complex (combination of Q, R and S waves) tachycardia could suggest AF with conduction via an accessory pathway.[1,3]

Atrial fibrillation is distinguished from atrial flutter on the ECG, as atrial flutter shows a pattern of atrial activity called 'flutter waves' visible on the ECG.[3] AF is distinguished from atrial tachycardia on the ECG, as in atrial tachycardia the P waves are well identified and separated by an isoelectric baseline.[3]

Physical examination suggestive of AF includes irregular pulse, irregular jugular venous pulsations, and variation in the intensity of first heart sound or absence of fourth sound heard previously during sinus rhythm.[2]

Incidence and/or prevalence of atrial fibrillation

Atrial fibrillation is a common cardiac arrhythmia associated with a substantial degree of morbidity and mortality.[14] On average, AF is present in 1–2% of the population.[15,16] Epidemiological data have often come from studies with small populations in developed countries with a minimal representation of ethnic minorities.[17,18] Additional concerns about previous studies have included limited age range of patients and unreliable ascertainment (such as self-reporting and/or examination of hospital records) for AF diagnosis.[15] However, two large studies with lengthy follow-up periods, the Framingham Heart Study in the USA[19] and the Renfrew/Paisley study[16] in the west of Scotland, have been notable sources of incidence data. The Framingham Heart Study estimated 2-yearly incidence rates of 0.9 per 1000 person-years and 1.9 per 1000 person-years in women and men aged 50–59 years, respectively.[19] Incidence rates, over a 4-year period, reported from the Renfrew/Paisley study[16] were 0.44 per 1000 person-years and 1.31 per 1000 person-years for women and men aged 55–64 years. Data from the Framingham study[19] showed that men were 1.5 times more likely to develop AF than women.

Atrial fibrillation affects approximately 6 million people in Europe and 2.3 million of the US population.[20] It is estimated that there are about 650,000 cases of AF in England and Wales, with the greatest number of affected patients aged between 75 and 84 years.[21]

The incidence of AF is closely related to age.[22] Increasing age is more often than not associated with structural and physiological cardiac abnormalities that predispose to the development of AF. In addition, advanced age implies longer exposure to known risk factors. Available epidemiological evidence has demonstrated that AF is more common in those aged ≥50 years: reported rates in 50- to 59-year-olds and those aged between 80 and 89 years were 0.5% and 8.8%, respectively.[23] AF rates double with each successive decade of age, especially after the age of 50 years.[24] The prevalence of AF in patients who are 80–90 years of age is close to 9%,[20] and this trend is often reported.[15,20,25] Factors influencing this include the increasingly ageing population and the greater proportion of patients living with cardiovascular and non-cardiac predisposing risk factors, such as hypertension, obesity and diabetes.[20] An underlying pathology may be absent in 15–30% of patients.[26]

Impact of atrial fibrillation

Significance for patients in terms of ill health (burden of disease)

Atrial fibrillation is a common and significant cause of cardiovascular-related morbidity and mortality. The condition is a major predictor of atrial thrombosis, peripheral embolism and stroke, especially in elderly patients.[16,27,28] Evidence for the Framingham Heart Study noted a four- to fivefold rise in the risk of stroke in patients with AF.[14] The observed increase in risk has been attributed to the presence of LV hypertrophy, which is often associated with long-standing AF.[27] The risk of stroke also increases with age.[14,20]

Coexisting cardiovascular disease and AF significantly reduce quality of life in those patients with symptoms such as palpitations, light-headedness and fatigue. Furthermore, patients with AF with underlying coronary heart disease and chronic lung disease are more likely to suffer from myocardial infarction (MI) and acute respiratory failure.[29] Evidence from a longitudinal cohort study has also suggested an increased risk of dementia in patients with AF.[30]

Atrial fibrillation is also associated with an increase in mortality rate. In the Framingham study,[19] AF was associated with 1.5- to 1.9-fold increase in the risk of mortality, following adjustments for the underlying cardiovascular diseases in affected patients.[31] This conferred risk of death is similar in both men and women and does not vary significantly by age.[31] Data from the Renfrew/Paisley cohort with a 20-year follow-up period demonstrated an increase of 1.8- to 2.8-fold and 1.5- to 2.2-fold in cardiovascular-related death and all-cause death, respectively.[32]

Significance for the NHS

In many developed countries, AF is increasingly becoming a significant public health challenge. It is a major cause of increased hospitalisation in the UK.[18,33] The number of hospital admissions for patients with AF has at least doubled in recent times.[34]

A study of the health and social care-related expenditure on patients with AF in 1995 showed that an estimated £244M, which accounted for 0.62% of the total NHS budget was spent on patients with AF.[35] Of this, half of the cost covered the hospitalisation of patients, whereas 20% of the total expenditure was for the cost of drug prescriptions. An extra £46.4M was used to provide long-term nursing home care following admission. Based on projections of AF expenditure in 1995, it was estimated that direct costs of the condition would be approximately £459M in the year 2000.[35]

Current service provision

The setting for management may vary depending on the nature and the severity of the condition[1,36] [National Service Framework (NSF)/NICE]; however, urgent referral of patients with persisting and complicated arrhythmia is required for prompt and appropriate treatment.

Relevant national guidelines and management of atrial fibrillation

Key guidance documents for the care of patients with AF have been developed by the ESC,[6] American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA),[2,37] NICE[1] and the NSF committee.[36] Recommendations within these guidelines emphasise the importance of early and accurate diagnosis and appropriate management strategies for patients.

Immediate and early 12-lead ECG tracing is advised, even if symptoms have subsided.[1,36] ECG is also recommended in patients with documented AF.[2] The number and duration of ECG monitoring studies are usually based on clinical judgement.[2] Intense and prolonged monitoring is recommended in patients with:[1,2]

- severe symptoms
- documented or suspected underlying disease of cardiac or non-cardiac origin
- complications due to ongoing or previous 'silent' AF
- treatment with antiarrhythmic agents
- treatment related to rate control.

The aim of treatment is to reduce symptoms and avert complications in patients with AF. To achieve this, the goal of treatment may include a number of desirable effects such as the control of ventricular rate, treatment of underlying conditions and the prevention of thromboembolic events. There are a range of options for the management of AF. Available therapies consist of a variety of pharmacological agents including antiarrhythmic and antithrombotic agents as well as the use of alternative non-pharmacological interventions, such as cardioversion. Treatment decisions depend on the type of AF.[1]

For the control of ventricular rate, treatment may consist of a rate control or rhythm control strategy. Rhythm control is the recommended initial therapy for patients with paroxysmal AF, whereas rate control

treatment is the choice of initial treatment for patients with permanent AF.[1] For patients with persistent AF, treatment with rhythm control or rate control strategies may be the initial approach.[1]

Rate control strategies aim to control ventricular rate.[2] Generally, heart rate is considered to be controlled if it is between 60 and 80 beats per minute at rest and between 90 and 115 beats during moderate exercise. Treatment may be tailored to achieve a resting heart rate ≤80 beats per minute (strict rate control) or <110 beats per minute (lenient rate control).[38] A study comparing the two strategies in 614 patients with permanent AF who were followed up for no less than 2 years reported similar clinical outcomes (based on a primary composite outcome of systemic embolism, bleeding, stroke, life-threatening arrhythmic event, hospitalisation and death from cardiovascular causes) for both interventions.[38] Rate control involves drug therapy with a beta-blocker [e.g. metoprolol (Lopresor®, Novartis)], a calcium channel blocker [e.g. verapamil (Calan®, Pfizer)] or a cardiac glycoside [e.g. digoxin (Lanoxin®, GlaxoSmithKline)]. Usually, a combination of different classes of drugs may be required to achieve adequate rate control. Rate control is recommended as initial treatment in elderly patients with minor symptoms.[39–41]

Rhythm control treatments are used to achieve a sinus rhythm. Rhythm control is recommended to be tried first for patients who are symptomatic, present for the first time with lone AF, have CHF or AF secondary to a treated or corrected precipitant, or younger patients.[1] For patients with persistent AF, rhythm control may include cardioversion, followed by antiarrhythmic drug therapy if needed to maintain sinus rhythm. It is important that such patients undergo further investigations to identify coexisting underlying structural cardiac abnormalities.[1] Antiarrhythmic drug therapy usually includes a standard beta-blocker, unless this is ineffective or contraindicated. In this case, alternatives such as flecainide (Tambocor®, Meda), propafenone (Rythmol®, GlaxoSmithKline; Arthmol®, Abbott) sotalol (Sotacor®, Bristol-Myers Squibb) or amiodarone (Cordarone X®, Sanofi-Aventis) can be used.[1] In patients with paroxysmal AF, this antiarrhythmic drug therapy may be used. Alternatively, a patient may be considered for a 'pill-in-the-pocket' strategy if there is no history of infrequent symptomatic episodes of paroxysmal AF, LV dysfunction, valvular or ischaemic heart disease, a systolic blood pressure of >100 mmHg and a resting heart rate of >70 beats per minute.[1] A rhythm control strategy may also be used for postoperative AF after cardiothoracic surgery.[1]

Cardioversion is a method for converting an abnormal heart rate to normal (sinus rhythm).[1,2,36] This may be achieved by pharmacological or electrical interventions. Pharmacological cardioversion involves the use of oral or intravenous agents to achieve a normal and regular heart rate. Examples of treatments include flecainide or intravenous amiodarone. The latter is recommended in patients with structural heart disease.[1] Electrical cardioversion, also referred to as direct-current (DC) cardioversion, involves the delivery of a 'safe' electrical shock to the heart. The electrical current may be delivered across the wall of the chest (external cardioversion) or through a tiny wire introduced into the heart through a peripheral vein (internal cardioversion).[36] Anticoagulation is essential in all patients undergoing elective cardioversion for AF of more than 48 hours' duration or an unknown duration. This is essential because of the associated risk of embolism related to the procedure.[2] In some cases, anticoagulation may need to be continued after cardioversion.[1]

Ablation strategies are indicated for patients with AF who remain symptomatic following antiarrhythmic medication or those for whom pharmacological treatment is contraindicated because of intolerance or existing comorbidity.[42,43] The aim of treatment is to destroy heart muscles that generate abnormal electrical impulses leading to arrhythmic activity. A number of approaches may be used; these include ablation of the AV node, left atrium, right atrium or the focal pulmonary vein. Various energy sources, including ultrasound, microwave, radiofrequency and cryotherapy, are used in ablation techniques. Ablation generally involves the introduction of a fine flexible catheter into the heart via a peripheral vein (usually the femoral vein). However, in some cases, ablation can be used during open cardiac surgery.

Furthermore, AF may be prevented or controlled by the insertion of a pacemaker, an implantable device in contact with the heart by means of flexible wires. Artificial impulses generated by the pacemaker regulate

and maintain the heart rate. Although a number of pacing algorithms and techniques exist, the role of permanent pacing in patients with AF is still uncertain.[44]

Antithrombotic therapy may additionally be given to patients with AF in accordance with risk of stroke. The 2006 recommendations from the NCC-CC state that anticoagulation therapy with warfarin is recommended for patients at high risk of stroke, or to be considered for patients at moderate risk of stroke, unless the patient has contraindications to warfarin. For patients with low risk of stroke, aspirin is recommended.[1] On the other hand, inconsistencies in the evidence regarding the antiplatelet benefits of aspirin require that it is used cautiously in patients with an increased risk of thromboembolism.[1,2]

Risk of stroke is defined as follows:[1]

- *High risk* Previous ischaemic stroke or TIA or thromboembolic event, age ≥ 75 years with hypertension, diabetes or vascular disease (coronary or peripheral artery disease), clinical evidence of valve disease or heart failure, or impaired LV function.
- *Moderate risk* Age ≥ 65 years with no high risk factors, or age < 75 years with hypertension, diabetes or vascular disease.
- *Low risk* Age < 65 years with no moderate or high risk factors.

The 2006 NICE guidelines[1,2] recommend use of warfarin for patients at high risk, and some patients at moderate risk, of stroke. NICE has recently approved both dabigatran etexilate (Pradaxa®, Boehringer Ingelheim) and rivaroxaban (Xarelto®, Bayer Schering) as alternatives for the prevention of stroke in people with AF[45,46] (last accessed January 2012[47]).

European Society of Cardiology 2010 guidelines[6] recommend a risk factor-based approach for patients with non-valvular atrial fibrillation based on CHA_2DS_2-VASc. Valvular AF is considered high risk for stroke.[6]

The CHA_2DS_2-VASc model uses a point system in which two points are allocated where a patient has a history of stroke or TIA, or is aged ≥ 75 years. One point is allocated for each of the following: aged 65–74 years, a history of hypertension, diabetes, recent cardiac failure, vascular disease comprising MI, complex aortic plaque, or peripheral arterial disease, and female sex. ESC 2010 guidelines[6] recommend oral anticoagulant (OAC) for patients with AF with a CHA_2DS_2-VASc score of ≥ 2, OAC or aspirin for those with a score of 1, and either no antithrombotic therapy or aspirin for those with a score of 0. Where oral anticoagulation is prescribed, this is generally a vitamin K agonist adjusted for international normalised ratio (INR) range 2.0–3.0 (target 2.5).[6]

Alternative new OACs, the oral direct thrombin inhibitors (e.g. dabigatran etexilate and AZD0837) and the oral factor Xa inhibitors [rivaroxaban (Xarelto®, Bayer), apixaban (Eliquis®, Pfizer/Bristol-Myers Squibb), edoxaban (Lixiana®, Daiichi Sankyo), betrixaban (Portola Pharmaceuticals), YM150 (Darexaban®, Astellas Pharma)] are described in the 2010 ESC guidelines[6] as investigational agents that may be considered following regulatory approval, if the patient has a low risk of bleeding.[6]

Dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolisation who do not have a prosthetic heart valve or haemodynamically significant valve disease, severe renal failure (creatinine clearance of < 15 ml/minute) or advanced liver disease (impaired baseline clotting function).[48]

Current service cost and anticipated costs associated with intervention

The Healthcare Resource Group (HRG) cost code RA60Z ('Simple Echocardiogram') was used as the cost of TTE. The mean cost of this technology was estimated as £66. A second, more expensive estimate of £425 was listed for HRG code EA45Z Complex Echocardiogram (includes congenital, transoesophageal and fetal echocardiography), which was deemed not appropriate for TTE.

It is important to note that the costs associated with the intervention (indirect costs of TTE) are likely to greatly exceed the current service cost (direct costs of TTE). This is because the associated costs include those of acting on the clinical information provided by the diagnostic test, which may include the costs of surgical intervention, as well as additional costs of long-term medication for some patients who would not otherwise have received such treatments. For example, TTE may indicate that some additional patients should receive OACs. For illustration, the annual costs of both rivaroxaban and dabigatran are both estimated to be in the region of £800, so a single year's additional treatment cost as a result of a clinical indication provided by TTE can be much greater than the cost of TTE itself.

Description of transthoracic echocardiography

Summary of intervention

Aim of transthoracic echocardiography

Transthoracic echocardiography is used to assist the diagnosis and management of a broad range of heart conditions. The commonest indications are for heart failure, murmur, palpitations/arrhythmias/blackouts and hypertension.[49]

Transthoracic echocardiography

The standard adult transthoracic echocardiogram measures structure and function of the heart. It should reliably describe quantitative LV systolic and diastolic function and assess all valves, including minor abnormalities that may progress or need follow-up, basic prosthetic valve function, and common congenital abnormalities cardiomyopathies, as well as detecting the presence and significance of pericardial fluid.[50]

The following cardiac and vascular structures are routinely evaluated as part of a complete adult echocardiographic report: left ventricle, mitral valve, left atrium, aortic valve, aorta, right ventricle, tricuspid valve, right atrium, pulmonary valve, pulmonary artery, pericardium, inferior vena cava and pulmonary veins. LV size is one of the most important components of LV function quantification. Changes in LV dimensions are frequently interpreted as indices of progression or regression of a disease state that affects the left heart.[51]

A complete transthoracic study includes two-dimensional (2D) and, usually, M-mode (motion mode) echocardiography, as well as spectral and colour Doppler techniques. M-mode supplies additional information when indicated; it is obtained by selecting any of the individual sector lines from which a 2D image is constructed. It is useful for quantifying linear dimensions of the cardiac chambers and walls when the correct direction is verified under 2D imaging. Doppler modalities provide functional information on intracardiac flow haemodynamics, including measurement of systolic and diastolic blood flow velocities and volumes, assessment of the severity of valvular lesions, and location and severity of intracardiac shunts. Pulsed-wave Doppler is useful for locating and timing blood flow within the physiological range of velocities. Continuous wave Doppler can accurately measure the highest flow velocities and estimate the gradients across valves or interventricular defects. Colour flow mapping provides a composite picture of flow over a larger area and is most useful for screening valves for regurgitation and stenosis, and detecting the presence of intracardiac shunts. Colour flow M-mode is useful for timing blood flow information.[51]

Transthoracic echocardiography provides comprehensive evaluation of cardiac and vascular structures and function, and can immediately affect the diagnostic and management work-up of the patient. It is accepted that 2D TTE can accurately assess cardiac chamber size, wall thickness, ventricular function, valvular anatomy, and the size of great vessels. Pulsed-wave, continuous wave and colour flow Doppler echocardiography provide measurements of blood flow velocities and assessment of intracardiac pressures and haemodynamics, and can detect and quantify stenosis, regurgitation and other abnormal flow states.[51]

The diagnosis of heart conditions requires the integration of clinical, laboratory and echocardiographic data. The contribution of TTE in the diagnosis of heart conditions depends on the particular condition. It is particularly useful for the assessment and management of valve disease, providing good structural information about the valve and its supporting structures. Doppler provides good information about the severity of the lesion and whether the valve is repairable. The impact of valve lesion on the heart as a whole can also be assessed.[52] The usefulness of TTE in an intensive care setting has been reported by Stanko *et al*.[53] TTE resulted in a change of diagnosis in 29% of studies, and a change of management in 41% of studies.

Indications

According to the British Society of Echocardiography (BSE),[50] TTE is indicated for the following conditions if certain circumstances (relating to seriousness) are fulfilled: heart murmurs, native valvular stenosis, native valvular regurgitation, prosthetic valve assessment, infective endocarditis, ischaemic heart disease, cardiomyopathy, pericardial disease, cardiac masses, pulmonary disease, neurological disease, arrhythmia/palpitations/syncope, echocardiography before cardioversion, hypertension, aortic and major arterial disease, and preoperative echocardiography for elective and semi-urgent surgery.

Various guidelines for the use of TTE for all indications have been reported in recent years. Details of the clinical indications for echocardiography are provided by the BSE.[50] The Bedfordshire and Hertfordshire Cardiac Network[49] describes the effective use of TTE in adults for indications including heart murmur and palpitations, and the National Imaging Board[52] provides guidance relating to a number of cardiac imaging modalities, including echocardiography.

Technical difficulties

Some patients give poor images and the information derived using TTE from these patients can therefore be limited. Furthermore, the accuracy of TTE depends on the experience of the person reporting the images.[52] The risks associated with TTE are extremely low.

Setting and equipment required

Transthoracic echocardiography is a non-invasive imaging technique performed with the use of an ultrasound machine. It provides real-time images, is portable and of low cost.[51] It is usually performed in cardiology clinics and is less used in primary or non-specialist secondary care, and may be undertaken by a cardiologist, BSE-accredited echocardiographer or general practitioner (GP) with special interests.[1]

Current usage in the NHS

A prospective survey of the management of AF in the ESC member countries, conducted in 2005, showed that 78% ($n = 757$) of patients with first-detected AF had been given a transthoracic echocardiogram.[54]

Criteria for use

Patients currently meeting the criteria for recommended TTE in the NICE guidelines[1] for AF comprise:

- younger patients for whom a baseline echocardiogram is important for long-term management
- patients for whom cardioversion (electrical or pharmacological) is being considered
- patients in whom there is a high risk or a suspicion of underlying structural/functional heart disease (such as heart failure or heart murmur) that influences their subsequent management
- patients in need of clinical risk stratification for antithrombotic therapy, where clinical evidence is needed of LV dysfunction or valve disease.

Guidelines from NICE[1] state that TTE is not recommended for patients with AF for whom the need to initiate anticoagulation therapy has already been decided on clinical criteria.

Factors associated with successful screening programmes

Many of the issues facing routine testing of a specific patient group are issues shared by screening programmes, especially the impact of false-positives (FPs) and false-negatives (FNs). The UK National Screening Committee have set criteria for effective screening programmes.[55] These are as follows.

- The condition being screened for should be an important health condition, with adequate clinical and epidemiological understanding, and, where possible, primary prevention interventions should be in place.[55] In addition, the health condition should have a detectable risk factor, disease marker, latent period or early symptomatic stage.[55]
- The diagnostic tool for the health condition should be validated, safe and acceptable to those being screened, with an agreed cut-off level defined to diagnose the health condition.[55] Policies should be in place for further diagnoses and patient choices in the event of a positive diagnosis.[55]
- The health condition should have an effective treatment available, for which early treatment is more advantageous than treatment if the health condition is not diagnosed until a later stage.[55] Appropriate treatment should be widely available.[55]
- The screening programme should be evidence based, clinically and socially acceptable, cost-effective, adequately resourced and should be monitored.[55] Informed consent should be obtained from all participants. Any potential adverse effects from the diagnostic test or subsequent treatment should be outweighed by the benefits of the screening programme.[55]
- False-positives can lead to unnecessary anxiety for the participant. It may lead to further diagnostic tests, some of which may be unpleasant for the participant. If unchecked, subsequent change in treatment may result in adverse effects. From a health provider's perspective, these are associated with costs of unnecessary diagnostic tests and/or treatment provision.
- False-negatives may lead to false reassurance, diagnostic delay and subsequent treatment delay.[56] These may adversely affect the participant, including psychologically.[56] From a health provider's perspective this may be damaging by reducing public confidence in the screening programme or may result in legal action.[56]

Chapter 2 Definition of the decision problem

Decision problem

The purpose of the assessment was to address the question 'What is the clinical effectiveness and cost-effectiveness of performing a routine echocardiogram in all newly diagnosed patients with AF in preventing complications arising from AF, in comparison with current practice of selective testing?'

The population was newly diagnosed patients with AF.

Potential subgroups identified prior to the review were those patients in whom AF was diagnosed when they presented with associated medical conditions (heart failure, stroke or thromboembolism), as opposed to patients in whom AF was the primary diagnosis, whether asymptomatic or based on symptoms not requiring hospital visit, or patients receiving diagnoses of paroxysmal, persistent or permanent AF. Lack of data made analyses of these subgroups impractical.

The technology investigated was TTE.

Conventional TTE was the intervention. Included modes were M-mode, 2D/cross-sectional and the Doppler modes (colour flow mapping, continuous wave, pulsed wave).

Complex or invasive modes of TTE were excluded, such as stress/exercise echocardiography, contrast echocardiography, three-dimensional echocardiography and intraoperative echocardiography. These would not form the routine TTE. Invasive modes, such as contrast TTE requiring application of dobutamine or adenosine, would have a different impact on patients and may have adverse effects, unlike routine TTE, as well as differences in time taken and cost.

We excluded diagnostic assessments that used a combination of tests including TTE.

The intervention was defined as TTE in all newly diagnosed patients with AF. This included patients for whom TTE is not currently recommended, such as patients with AF for whom the need to initiate anticoagulation therapy has already been decided on clinical criteria.

The comparator was current practice, that is only selected subgroups of patients with AF undergoing TTE. These comprise:

- younger patients for whom a baseline echocardiogram is important for long-term management
- patients for whom cardioversion (electrical or pharmacological) is being considered
- patients in whom there is a high risk or a suspicion of underlying structural/functional heart disease (such as heart failure or heart murmur) that influences their subsequent management
- patients in need of clinical risk stratification for antithrombotic therapy.

The decision problem was essentially reduced to the cost-effectiveness of TTE in those patients where there would initially be a decision not to provide anticoagulation treatment (that is those patients with a $CHADS_2$ or CHA_2DS_2-VASC score of 0). In such a group the use of TTE could detect underlying conditions that are associated with a high risk of stroke and for which the use of anticoagulant treatment would be recommended.

Outcomes sought related to selected pathologies in patients with AF identifiable by TTE. Clinical outcome measures were diagnostic accuracy of TTE in identifying pathologies as measured in terms of sensitivity

[proportion of true-positives (TPs)] and specificity [proportion of true-negatives (TNs)] and prognosis of AF populations based on diagnosis of pathology by TTE, and prevalence of these pathologies in AF.

Overall aims and objectives of assessment

The objectives of the review were to:

- investigate, by systematic review, the diagnostic accuracy of TTE for clinically important pathologies in AF
- investigate, by systematic review, the prevalence of these pathologies
- estimate the potential benefits and harms due to altered treatment based on results of TTE
- estimate the incremental cost-effectiveness of routine TTE for newly diagnosed compared with current practice of TTE in selected patients with AF.

Chapter 3 Assessment of clinical effectiveness

Methods for reviewing clinical effectiveness

The purpose of the assessment report was to assess the effectiveness of performing routine echocardiography in all patients with newly diagnosed AF in enabling appropriate treatment for patients based on diagnoses of pathologies from TTE. As no clinical studies screening patients with AF with TTE were identified, the review question was broken down. Critical to the effectiveness of routine screening are the diagnostic accuracy of TTE and the prevalence within the AF population for the pathologies tested. Two systematic reviews were conducted to investigate clinical effectiveness of routine TTE in patients with newly diagnosed AF. These were reviews of:

1. diagnostic accuracy of TTE for clinically relevant pathologies in patients with AF (see *Methods for diagnostic accuracy review*, below)
2. prevalence of clinically relevant pathologies within the AF population (see *Methods for reviewing prevalence of clinically relevant pathologies in atrial fibrillation patients*, below).

Clinically relevant pathologies

In order for routine TTE screening of newly diagnosed patients with AF to be successful, the screening would need to identify pathologies which would not usually be identified by the time of AF diagnosis, and which would result in a change in clinical management. These were not restricted to pathologies affecting decisions about anticoagulation. Factors affecting routine screening programmes are reported in *Chapter 1* (see *Factors associated with successful screening programmes*).

Pathologies were selected according to the following inclusion/exclusion criteria.

Inclusion:

1. The pathology could occur in patients with AF.
2. The pathology is detectable by TTE.
3. A positive diagnosis would lead to a change in clinical management.

Exclusion:

1. The pathology would necessarily be diagnosed prior to AF diagnosis (e.g. congenital abnormalities that would have been diagnosed in infancy) or at the time of AF diagnosis (i.e. would be diagnosed by ECG).
2. The pathology would necessarily be clinically diagnosed without echocardiography.
3. The pathology presents with symptoms that represent indications for which a patient would receive TTE regardless of AF diagnosis, including indications for emergency TTE.

Based on the above inclusion and exclusion criteria, the following pathologies were selected, and for ease of reporting were grouped into the following categories.

1. *Structural heart defects* This category comprised atrial septal defect, ventricular septal defect and rupture of the chordae tendineae or papillary muscle.
2. *Ischaemia or thrombosis* This category comprised atrial and ventricular thrombosis, atherosclerotic heart disease and aneurysm of the heart.
3. *Pulmonary disease* This category comprised PE and hypertension, and cor pulmonale.
4. *Endocarditis* This category comprised infective and non-infective endocarditis.

5. *Valvular heart disease* This category comprised valvular regurgitation/incompetence/insufficiency or stenosis of one or more of the mitral, aortic, tricuspid or pulmonary valves.
6. *Cardiomyopathy* This category comprised hypertrophic obstructive or non-obstructive or dilated cardiomyopathies, and included LV non-compaction.
7. *Heart failure* This category comprised CHF, LV dysfunction or impairment, LA enlargement and RV dysfunction.
8. *Diseases of arteries* This category comprised aortic dissection.
9. *Cardiac masses* This category comprised cardiac tumours or masses.

Examples of excluded pathologies are given in *Appendix 1*.

For some, but not all, of the selected pathologies, TTE/TOE are considered the gold standard for diagnosis (see *Appendix 2*).

Methods for diagnostic accuracy review

Identification of studies

A comprehensive search was undertaken to systematically identify studies assessing the diagnostic accuracy of TTE for the clinically relevant pathologies as described above (see *Clinically relevant pathologies*).

The search strategy comprised the following main elements: searching of an electronic database; contact with experts in the field; and scrutiny of bibliographies of retrieved papers. Owing to the large number of references identified by the search, the search was restricted to MEDLINE. The MEDLINE search strategy is presented in *Appendix 3*.

Literature searches were conducted from March to August 2010. References were collected in a database and duplicates removed.

Inclusion and exclusion criteria

Inclusion

Population

Studies of patients with AF were selected. Where studies of patients with AF were not available for a selected pathology, diagnostic accuracy studies were sought from other adult populations with suspected cardiac conditions. Only populations with AF were considered for prognostic studies.

Intervention

Conventional TTE was the intervention. Included modes were M-mode, 2D/cross-sectional and the Doppler modes (colour flow mapping, continuous wave, pulsed wave).

Comparators

Included comparators were diagnostic techniques appropriate for the selected pathology: autopsy, surgery, cardiac catheterisation, TOE, computerised tomography (CT), magnetic resonance imaging (MRI).

Outcomes

Included outcomes were the diagnostic accuracy of TTE for each pathology in terms of sensitivity (proportion of TPs) or specificity (proportion of TNs). Studies were accepted if they reported sensitivity or specificity, or if they provided sufficient data to calculate sensitivity or specificity. Sensitivity is calculated as the number of TPs divided by the sum of TPs and FNs. Specificity is calculated as the number of TNs divided by the sum of TNs and FPs.

Prognostic accuracy was also included (i.e. TTE diagnosis of pathology predicting later cardiovascular events or mortality in AF populations).

Study types

Diagnostic accuracy studies using TTE to diagnose any of the selected pathologies (see *Clinically relevant pathologies*, above) were sought.

For each pathology, we initially sought studies of diagnostic accuracy with a population of patients with AF. Where sensitivity or specificity data were lacking from studies of AF populations for a particular pathology, studies of populations with other suspected cardiac conditions were sought. Study types were accepted into the review according to the hierarchy of evidence published by Merlin *et al*.[57] For this, level 1 evidence is considered to be systematic reviews of level 2 evidence, with level 2 being diagnostic test accuracy studies with an independent, blinded comparator of a valid reference standard, tested on consecutive patients. Level 3 includes comparative studies with either non-consecutive patients, a comparator that has not been validated or is not blinded, or a case–control design. Level 4 refers to studies of diagnostic yield that do not compare with a reference standard. For studies of AF patients, study types of any of the four levels were included.

Prognostic accuracy studies were sought. For these, studies with a population of AF patients were sought. Study types of any of the four levels of prognostic accuracy study types according to the hierarchy of evidence published by Merlin *et al.*[57] were included. For this, level 1 evidence is considered to be systematic reviews of level 2 evidence, with level 2 being prospective cohort studies, level 3 being all-or-none studies, prognostic data from one arm of a controlled trial, or a retrospective cohort study. Level 4 refers to case series, or cohort studies with populations at different stages of disease.

Exclusion

Population

Infants and children were excluded. AF is very rare in infants and children unless concomitant structural or congenital heart disease is present.[1] Any AF presentation in an infant or child would lead to further investigations.

Intervention

Diagnostic assessments that used a combination of tests including TTE were excluded, when data were not available for TTE alone. Invasive or complex modes of TTE were excluded. These comprised stress/exercise echocardiography, contrast echocardiography, three-dimensional echocardiography, intraoperative echocardiography, or handheld echocardiography devices. TOE was excluded.

Study types

Studies looking solely at defining severity of previously confirmed diagnosed conditions, treatment studies (such as the use of echocardiography to assess effects of surgery) and animal studies.

The following publication types were excluded: studies only published in languages other than English, reports published as meeting abstracts only where insufficient details were reported, editorials and opinion pieces.

Study selection was made by one reviewer based on the above inclusion/exclusion criteria, and discussed with a second reviewer where needed.

Data abstraction, critical appraisal strategy and synthesis

Data were extracted by one reviewer using a standardised data extraction form and checked by another reviewer. Discrepancies were resolved by discussion. Where needed, sensitivity was calculated as the number of TPs divided by the sum of the number of TPs and the number of FNs. Specificity was

calculated as the number of TNs divided by the sum of the number of TNs and the number of FPs. Where possible, confidence intervals (CIs) were calculated based on the Gaussian formula from Newcombe:[58] $p \pm 1.96 \times \sqrt{p(1-p)/n}$.

Quality assessment involved assessing the study type according to the hierarchy of Merlin *et al*.[57] This takes into account whether studies of test accuracy use consecutive patients, and whether assessors are blinded to other test results (see study types in *Inclusion and exclusion criteria*, above).

Further quality assessment was based on QUADAS (quality assessment of studies of diagnostic accuracy included in systematic reviews) criteria.[59]

Data extraction forms are in *Appendix 4*. Quality assessment forms are in *Appendix 5*.

Data were tabulated and discussed in a narrative review.

Methods for reviewing prevalence of clinically relevant pathologies in atrial fibrillation patients

Identification of studies

A comprehensive search was undertaken to systematically identify clinical effectiveness literature concerning the prevalence of clinically important pathologies in patients with AF. To obtain the best estimates, the search was restricted to studies with the objective of assessing prevalence.

The search strategy comprised the following main elements: searching of electronic databases; contact with experts in the field; and scrutiny of bibliographies of retrieved papers.

The following databases were searched from inception: MEDLINE; MEDLINE in Process (for latest publications); EMBASE; The Cochrane Library, including the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register (CCTR), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) databases; NIHR Clinical Research Network Portfolio database; National Research Register (NRR) Archive; Web of Science (WoS) Conference Proceedings; Current Controlled Trials (CCT); ClinicalTrials.gov. Searches were not restricted by date or publication type.

The MEDLINE search strategy is presented in *Appendix 3*.

Literature searches were conducted from March to August 2010. References were collected in a database, and duplicates removed.

Inclusion and exclusion criteria

Inclusion

Population

Adult patients diagnosed with AF. Diagnosis of AF may be confirmed by ECG, which may be standard ECG, 24-hour ambulatory ECG or event recorder ECG.

Study types

Epidemiological studies of prevalence of selected pathologies (see *Clinically relevant pathologies*, above) were sought.

Outcome
Prevalence of selected pathologies (see *Clinically relevant pathologies*, above).

Exclusion
The following publication types were excluded: animal studies, editorials, opinion pieces, studies only published in languages other than English, and reports published as meeting abstracts only if insufficient details were reported.

Study selection was made by one reviewer based on the above inclusion/exclusion criteria, and checked with a second reviewer where needed.

Data abstraction, critical appraisal and synthesis
Data were extracted by one reviewer using a standardised data extraction form and checked by another reviewer. Discrepancies were resolved by discussion.

Quality assessment, for studies with the intended outcome of prevalence of a pathology, was based on criteria identified in the STROBE statement (Strengthening the Reporting of Observational Studies in Epidemiology).[60]

Data extraction forms are provided in *Appendix 6*. Quality assessment forms are in *Appendix 7*.

Data from studies designed to detect the prevalence of a particular pathology were tabulated. Owing to heterogeneity of populations, pathologies and comparators, data synthesis was precluded. These data were discussed in a narrative review.

Results

Diagnostic accuracy of transthoracic echocardiography for clinically relevant pathologies

Quantity and quality of research available
The literature search yielded 15,824 article citations when duplicates had been removed. *Figure 1* shows study selection, in a modified version of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.[61] Citations presenting purely economic analyses were not included in this chapter. References excluded at the full paper screening stage ($n = 38$), with reason for exclusion, are presented in *Appendix 8*.

There were 44 diagnostic accuracy studies[62–105] and five prognostic studies[106–110] accepted into the review.

A summary of included diagnostic accuracy studies is presented in *Table 1* and a summary of included prognostic studies is presented in *Table 2*.

Of the 44 included studies,[62–105] there were 17 studies[62,69,72,74,75,77,79,80,82,86,90,91,95,97,100–102] that included AF patients in the population. Of these, for two studies[79,91] all participants had AF. Although two studies[63,71] stated that there were no patients with AF in the population, in other studies it was not reported.

For all categories of pathologies sought, studies of diagnostic accuracy were identified. AF population studies were available for the categories of structural defect, ischaemia/thrombosis, pulmonary disease and valvular heart disease.

Methods of TTE represented were 2D, M-mode, pulsed and continuous wave Doppler, and colour Doppler. All studies had a high percentage of usable, good images from TTE.

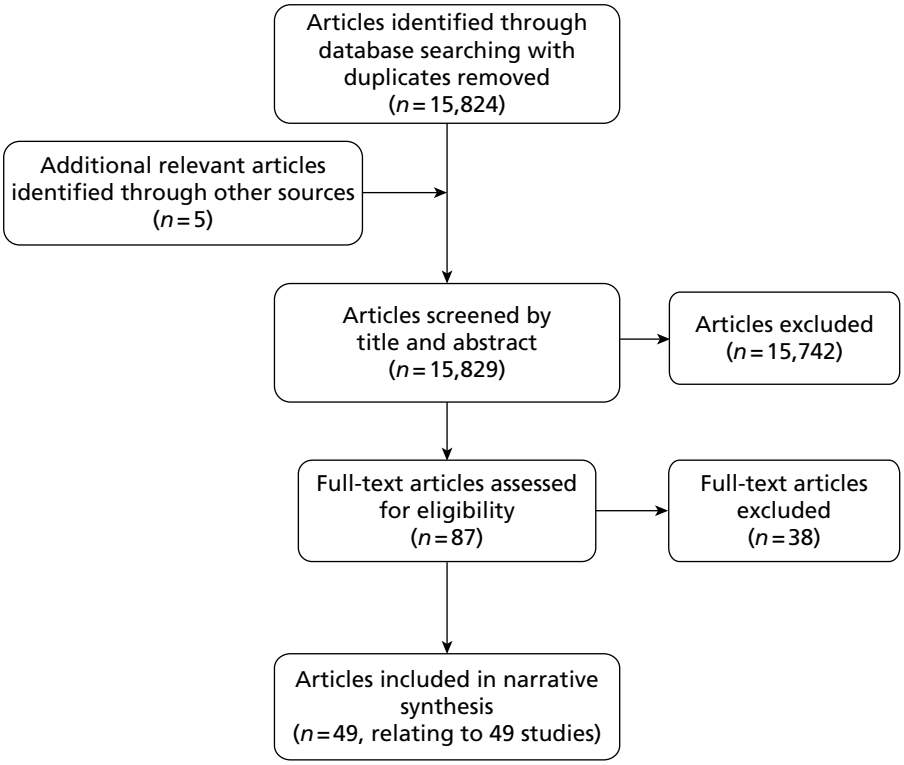

FIGURE 1 Study selection for diagnostic review.

All five prognostic accuracy studies included[106–110] had a population of non-valvular/non-rheumatic AF. Of the categories of pathologies sought, only heart failure and valvular heart disease were represented. Three of the studies were prospective studies[106,107,110] with follow-up ranging from mean 1.3 to 9.6 years. Two of the studies[108,109] were retrospective. The TTE methods represented were 2D, M-mode and colour Doppler.

Quality of included studies

Quality assessment forms are in *Appendix 5*. According to the level of hierarchy proposed by Merlin *et al.*,[57] studies ranged from level 2 (higher quality) to level 3c (lower quality). Twelve studies were of level 2,[64–67,76,80,81,83,88,91,94,102] a study of test accuracy with an independent, blinded comparison with a reference standard among consecutive patients. Six of the studies were level 3a,[68,73,74,84,99,103] i.e. they differed from level 2 only in being among non-consecutive patients. Twenty-two of the studies were level 3b,[62,69,71,72,77–79,82,85–87,89,90,92,93,95,96,98,100,101,104,105] comparisons with a reference standard that did not meet criteria for higher levels of evidence. There were four diagnostic case–control studies, level 3c.[63,70,75,97]

Considering only diagnostic accuracy studies with AF populations, there were three level 2 studies,[80,91,102] one level 3a study,[74] 11 level 3b studies[62,69,72,77,79,82,86,90,95,100,101] and two level 3c studies.[75,97] As all AF population studies were included, and non-AF population studies selected according to hierarchy of evidence, this explains the higher proportion of level 2 and 3a studies with non-AF populations.

For the prognostic studies, one study was level 2,[107] a prospective cohort study; two studies were level 3b;[106,110] and two studies were level 3c,[108,109] retrospective cohort studies.

Selected items from QUADAS were also addressed (see *Appendix 5*). We did not ask about representativeness of patients in the study for participants receiving the test in practice, as this review is concerned with screening patients with AF, and so an AF population, although relevant to this review, would not necessarily reflect quality of the diagnostic studies. All included diagnostic studies were of high quality in terms of all patients receiving TTE and a reference standard, and the reference standard being

TABLE 1 Summary of diagnostic accuracy studies

Study	Category of pathology	No. of participants enrolled in study	Population AF	Type of TTE	Percentage usable TTE images
Acar *et al.* 1991[62]	Ischaemia/ thrombosis	581	44.9% AF	2D TTE	100
Arques *et al.* 2005[63]	Heart failure	40	0%	TTE colour M-mode Doppler	98
Attenhofer Jost *et al.* 2000[64]	Structural defect and valvular heart disease	100	NR (all had heart murmur)	TTE 2D and continuous wave Doppler	100
Barron *et al*. 1988[65]	Valvular heart disease	140	NR	2D and Doppler TTE	100
Bova *et al.* 2003[66]	Pulmonary disease	162	NR	TTE continuous wave Doppler	97
Casella *et al.* 2009[67]	Endocarditis	75	NR	Harmonic imaging TTE	100 (81.5% good image quality)
Cassidy *et al.* 1992[68]	Valvular heart disease	41	NR (systolic murmur 100%)	TTE, M-mode, 2D and Doppler	91
Dittmann *et al.* 1987[69]	Valvular heart disease	55	38% AF	M-mode, pulsed Doppler TTE	100
Enia *et al.* 1989[70]	Disease of arteries	555	NR	TTE	100
Erbel *et al.* 1984[71]	Heart failure	110	0%	2D echocardiography	100
Grossmann *et al*. 2002[72]	Valvular heart disease	68	25% AF	Colour Doppler TTE	100
Groves *et al.* 2004[73]	Valvular heart disease	61	NR	TTE	100 (selected for having usable data)
Guyer *et al.* 1984[74]	Valvular heart disease	38	82% AF	2D TTE	100 (selected for having usable data)
Helmcke *et al.* 1987[75]	Valvular heart disease	160	21% AF	Colour Doppler echocardiography	92
Jassal *et al.* 2007[76]	Endocarditis	36	NR	Harmonic imaging TTE	100 (17% indeterminate diagnosis but included in analysis)
Kaymaz *et al.* 2001[77]	Ischaemia/ thrombosis	474	56.3% AF at time of study	TTE	100
Kishon *et al.* 1993[78]	Structural defect	40	NR (new systolic murmur in 68%)	2D TTE, Doppler colour TTE	100 (15% of VSD images suboptimal, but included in analysis)
Kitayama *et al.* 1997[79]	Ischaemia/ thrombosis	70	100% CAF	TTE M-mode, 2D and pulsed and colour Doppler	100 (10% technically inadequate but included in analysis)
Lanzarini *et al.* 2005[80]	Pulmonary disease	86	13% controlled AF	TTE standard M-mode, 2D and pulsed and continuous wave Doppler	100

continued

TABLE 1 Summary of diagnostic accuracy studies (*continued*)

Study	Category of pathology	No. of participants enrolled in study	Population AF	Type of TTE	Percentage usable TTE images
Maestre *et al.* 2009[81]	Heart failure	216	NR	M-mode and 2D TTE	100
Mugge *et al.* 1995[82]	Ischaemia/ thrombosis	195	14.4% in AF	Colour Doppler TTE	100 (patients selected from group with usable TTE)
Nienaber *et al.* 1993[83]	Disease of arteries	110	NR	Colour, Doppler TTE	100
Nienaber *et al.* 1994[84]	Disease of arteries	35	NR	M-mode, 2D, Doppler TTE	100
Okura *et al.* 2006[85]	Cardiomyopathy	52	NR	2D and Doppler TTE	85
Pochis *et al.* 1992[86]	Structural defect	116	53% atrial fibrillation or flutter, or paroxysmal atrial tachycardia	TTE	92
Reichek *et al.* 1981[87]	Heart failure	34	NR	M-mode echocardiography	100
Reichlin *et al.* 2004[88]	Valvular heart disease	203	NR (all had heart murmur)	Two-colour Doppler TTE (gold standard comparator)	100
Roudat *et al.* 1988[89]	Disease of arteries	673	NR	TTE 2D, M-mode	98
Saraste *et al.* 2005[90]	Ischaemia/ thrombosis	84	4% CAF	Doppler TTE, colour and 2D	100
Sharifi *et al.* 2003[91]	Ischaemia/ thrombosis	112	100% AF (24% CAF)	TTE	100 (patients selected from group with usable TTE)
Sharma *et al.* 1992[92]	Structural defect	53	NR	TTE M-mode (pulsed and continuous wave Doppler and colour flow available only for some patients)	85
Sheiban *et al.* 1987[93]	Cardiac masses	77	NR	2D TTE	100
Shively *et al.* 1991[94]	Endocarditis	62	NR	TTE 2D, M-mode and Doppler colour	100 (at least 68% good quality)
Shrestha *et al.* 1983[95]	Ischaemia/ thrombosis	293	88% patients with thrombus had AF; NR whole population	2D TTE	100
Shub *et al.* 1983[96]	Structural defect	171	NR	TTE 2D, pulsed Doppler	95
Shyu *et al.* 1992[97]	Structural defect	60	77% AF	2D and colour TTE	100

TABLE 1 Summary of diagnostic accuracy studies (*continued*)

Study	Category of pathology	No. of participants enrolled in study	Population AF	Type of TTE	Percentage usable TTE images
Smith *et al.* 1985[98]	Structural defect	12	NR (all post AMI)	Cross-sectional Doppler echocardiography	100
Sparrow *et al.* 2003[99]	Heart failure	737	NR	TTE	87
Stratton *et al.* 1982[100]	Ischaemia/ thrombosis	88	Some AF, per cent NR	2D TTE	89
Veyrat *et al.* 1983[101]	Valvular heart disease	95	40% AF	Pulsed Doppler echocardiography	100
Vigna *et al.* 1993[102]	Ischaemia/ thrombosis	59	59% in AF at time of study	TTE colour Doppler	100
Wong *et al.* 1983[103]	Valvular heart disease	113	NR	2D echocardiography	100
Zanolla *et al.* 1982[104]	Valvular heart disease	43	NR	2D echocardiography	100
Zotz *et al.* 1993[105]	Structural defect	17 (16 for colour Doppler)	NR (all post AMI)	Colour Doppler TTE	100

NR, not reported; VSD, ventricular septal defect.

TABLE 2 Summary of prognostic studies

Study	Category of pathology	No. of participants	Population AF	Prospective or retrospective	Follow-up	Type of TTE
Atrial Fibrillation Investigators 1998[106]	Heart failure and valvular heart disease	1010	Non-valvular AF	Prospective	Mean 1.6 years	TTE 2D, M-mode
Klem *et al.* 2003[107]	Heart failure and valvular heart disease	409	Non-rheumatic AF	Prospective	Mean 9.6 years	TTE
Miyaska *et al.* 2000[108]	Valvular heart disease	173	Non-rheumatic AF	Retrospective	NA	TTE 2D, M-mode
Nakagami *et al.* 1998[109]	Heart failure and valvular heart disease	290	Non-rheumatic AF	Retrospective	Mean 7.4 years	TTE M-mode, 2D and colour Doppler
The Stroke Prevention in Atrial Fibrillation Investigators 1992[110]	Heart failure and valvular heart disease	568	Non-rheumatic AF	Prospective	Mean 1.3 years	M-mode and 2D and Doppler

NA, not applicable.

administered whatever the TTE results, and the reference standard being independent of TTE. More than half of the studies were blinded.

Some studies selected participants on the basis of having usable TTE images, and some excluded indeterminate images from the analysis of sensitivity or specificity, whereas six studies explicitly included

either poorer images in analysis[78,92,96–98,105] or provided separate analyses by the inclusion or exclusion of poor-image-quality TTE.[67]

Diagnostic accuracy results

Eight studies[64,78,86,92,96–98,105] reported diagnostic accuracy of TTE in structural defects (*Table 3*). TTE was presumed the gold standard for one study of ventricular septal defect.[64] Sensitivity ranged from 0.25 for atrial septal hypertrophy[86] to 1 for ostium primum atrial septal defect[96] or ventricular septal rupture.[98] Two studies[86,97] reported specificity, which ranged from 0.9 for rupture of chordae tendineae[97] to 0.909 for atrial septal hypertrophy.[86] Six[78,92,96–98,105] of the eight studies used catheterisation, surgery or autopsy as the comparator diagnostic test, whereas one used clinical cardiac examination,[64] and one used TOE[86] (see *Table 3*).

Nine studies[62,77,79,82,90,91,95,100,102] reported diagnostic accuracy of TTE in ischaemic heart disease (*Table 4*). Sensitivity ranged from 0 for right atrial appendage (RAA)[79] or left atrial appendage (LAA)[102] thrombus to 0.955 for thrombosis of ventricle.[100] Specificity ranged from 0.857 for thrombosis of ventricle[100] to 1 for LA[79] or right atrial (RA)[79] thrombus. Five of the studies[62,77,90,95,100] used surgery or angiography, three used TOE[82,91,102] and one used CT[79] as comparators (see *Table 4*).

Two studies[66,80] reported diagnostic accuracy of TTE in pulmonary disease (*Table 5*). Sensitivity ranged from 0.523 for PE[66] to 1 for pulmonary hypertension.[80] Specificity ranged from 0.6 to 1 for pulmonary hypertension.[80] The study of PE[66] used perfusion lung scan with radiography or pulmonary angiography as a comparator, whereas the study of pulmonary hypertension[80] used catheterisation (see *Table 5*).

Three studies[67,76,94] reported diagnostic accuracy of TTE in endocarditis (*Table 6*). Sensitivity ranged from 0.44[94] to 0.871;[67] specificity ranged from 0.615[67] to 0.98.[94] Two of the studies used TOE as a comparator,[67,76] whereas the other study[94] used information obtained from clinical follow-up (see *Table 6*).

Twelve studies[64,65,68,69,72–75,88,101,103,104] reported diagnostic accuracy of TTE in valvular heart disease (*Table 7*). TTE was presumed gold standard for four studies of MR,[64,68] aortic stenosis,[64,68] mitral valve prolapse (MVP),[64] valvular heart disease,[64,88] aortic regurgitation (AR)[64,68] and tricuspid regurgitation.[73] Sensitivity ranged from 0.222 for mitral stenosis leaflet calcification[103] to 1 for mitral stenosis[104] or mitral regurgitation[75] or severe AR.[69] Specificity ranged from 0.655 for mitral stenosis to 1 for AR or MR. Six of the studies used catheterisation/aortography or radiography/cinefluorography as comparators,[69,74,75,101,103,104] four of the studies used clinical examination,[64,65,68,88] one used TOE[68] and one used CT[73] (see *Table 7*).

One study[85] reported the accuracy of TTE in differentiating between ischaemic and non-ischaemic cardiomyopathy (ICM and non-ICM) (*Table 8*). This study reported a sensitivity of 0.77 and specificity of 0.77 for differentiating between ICM and non-ICM with a comparator of angiography.

Five studies[63,71,81,87,99] reported accuracy of TTE in the diagnosis of heart failure (*Table 9*). TTE was presumed the gold standard for two studies of CHF[81] and LV dysfunction.[99] Sensitivity ranged from 0.737 for CHF[63] to 0.93 for LV hypertrophy.[87] Specificity ranged from 0.75 for CHF[63] to 1 for LV dysfunction.[71] Two of the studies used clinical diagnosis as comparators,[81,99] two studies[63,71] used radiography or catheterisation, and one used autopsy results[87] (see *Table 9*).

Four studies[70,83,84,89] reported diagnostic accuracy of TTE in aortic dissection (*Table 10*). Sensitivity ranged from 0.593[83] to 0.953.[89] Specificity ranged from 0.508[89] to 0.977.[89] Three studies[83,84,89] included surgery, autopsy or angiography as comparators; the other study used aortography[70] (see *Table 10*).

One study[93] reported the diagnostic accuracy of TTE for intracardiac masses (*Table 11*). This study reported sensitivity 0.882 and specificity 0.953, with a comparator of surgery.[93]

TABLE 3 Structural defect

Study	Pathology	No. of patients analysed	Population AF	Intervention	Comparator diagnostic test	Sensitivity of TTE	Specificity of TTE
Attenhofer Jost *et al.* 2000[64]	Ventricular septal defect	100	NR (heart murmur 100%)	TTE	Clinical cardiac examination	TTE as gold standard (presumed sensitivity = 1)	TTE as gold standard (presumed specificity = 1)
Kishon *et al.* 1993[78]	Ventricular septal defect	40	NR (new systolic murmur in 68%)	TTE	Surgery or autopsy	0.68 (95% CI 0.53 to 0.82) (if include suspected by TTE then 0.775)	NC
	Rupture of papillary muscle	22	NR (new systolic murmur in 100%)	TTE	Surgery or autopsy	0.46 (95% CI 0.25 to 0.66) (0.727 if include suspected by TTE)	NC
Pochis *et al.* 1992[86]	Atrial septal hypertrophy	107	53% atrial fibrillation or flutter, or paroxysmal atrial tachycardia	TTE	TOE	0.25 (95% CI 0.17 to 0.33)	0.91 (95% CI 0.85 to 0.96)
Sharma *et al.* 1992[92]	Atrial septal defect, sinus venosus defect	45	NR	TTE	Catheterisation	0.62 (95% CI 0.48 to 0.76)	NC
Shub *et al.* 1983[96]	Atrial septal defect, ostium secundum	105	NR	TTE	Catheterisation or surgery	0.89 (95% CI 0.82 to 0.95)	NC
	Atrial septal defect, ostium primum	32	NR	TTE	Catheterisation or surgery	1	NC
	Atrial septal defect, sinus venosus	16	NR	TTE	Catheterisation or surgery	0.434 (95% CI 0.19 to 0.68)	NC
Shyu *et al.* 1992[97]	Rupture of chordae tendineae	60	77% AF	TTE	Catheterisation or (valve repair) surgery	0.65 (95% CI 0.53 to 0.77)	0.9 (95% CI 0.82 to 0.98)
Smith *et al.* 1985[98]	Ventricular septal rupture	12	NR (all post AMI)	TTE	Catheterisation or autopsy	1	NC
Zotz *et al.* 1993[105]	Ventricular septal rupture	17 (16 for colour Doppler)	NR (all post AMI)	TTE	Surgery or autopsy	0.71 (95% CI 0.49 to 0.92) (if TTE using only conventional view 0.235); by colour Doppler 0.938	NC

NC, not calculable; NR, not reported.

TABLE 4 Ischaemia/thrombosis

Study	Pathology	No. of patients analysed	Population AF	Intervention	Comparator diagnostic test	Sensitivity of TTE	Specificity of TTE
Acar *et al.* 1991[62]	LA thrombus	581	44.9% AF	TTE	Surgery	0.28 (95% CI 0.24 to 0.32) (LA body 0.65, LAA 0.04)	0.99 (95% CI 0.99 to 1.0)
Kaymaz *et al.* 2001[77]	LA thrombus	474	56.3% AF at time of study	TTE	Surgery	0.32 (95% CI 0.28 to 0.37)	0.94 (95% CI 0.91 to 0.96)
Kitayama *et al.* 1997[79]	LA thrombus	70	100% CAF	TTE	CT	0.67 (95% CI 0.55 to 0.78)	1
	RA thrombus	70	100% CAF	TTE	CT	0	1
Mugge *et al.* 1995[82]	Atrial septal aneurysm	195	14.4% in AF	TTE	TOE	0.47 (95% CI 0.41 to 0.53)	NC
Saraste *et al.* 2005[90]	Coronary artery stenosis (significant stenosis/ occlusion in any coronary artery)	84	4% CAF	TTE	Angiography	0.82 (95% CI 0.74 to 0.90)	0.92 (95% CI 0.86 to 0.98)
Sharifi *et al.* 2003[91]	Atrial thrombi	112	100% AF (24% CAF)	TTE	TOE	0.17 (95% CI 0.09 to 0.24) (if includes SEC as well as thrombus 0.714)	1 (if includes SEC as well as thrombus 1)
Shrestha *et al.* 1983[95]	LA thrombus	293	NR whole population, 88% patients with thrombus	TTE	Surgery	0.59 (95% CI 0.53 to 0.64) (LA body 0.75, LAA 0.00)	0.99 (95% CI 0.97 to 1.0)
Stratton *et al.* 1982[100]	Thrombosis of ventricle	78	Some AF, per cent NR	TTE	Surgery or indium-111 platelet imaging	0.86 (95% CI 0.79 to 0.94) (0.955 if includes equivocal diagnoses)	0.95 (95% CI 0.90 to 0.99) (0.857 if includes equivocal diagnoses)
Vigna *et al.* 1993[102]	LA thrombus	59	59% in AF at time of study	TTE	TOE	0.33 (95% CI 0.21 to 0.45) (LA body 0.44, LAA 0.00)	1

NC, not calculable; NR, not reported; SEC, spontaneous echo contrast.

TABLE 5 Pulmonary disease

Study	Pathology	No. of patients analysed	Population AF	Intervention	Comparator diagnostic test	Sensitivity of TTE	Specificity of TTE
Bova *et al.* 2003[66]	PE	152	NR	TTE	Perfusion lung scan with radiography, or pulmonary angiography	0.52 (95% CI 0.44 to 0.60)	0.87 (95% CI 0.82 to 0.93)
Lanzarini *et al.* 2005[80]	Pulmonary hypertension	86	13% controlled AF	TTE	Catheterisation	1 using PAPd/TR; 0.88 using PAPs	0.6 using PAPd/TR; 1 using PAPs

NR, not reported; PAPs, pulmonary artery systolic pressure; PAPd/TR, pulmonary artery diastolic pressure/early phase tricuspid regurgitation.

TABLE 6 Endocarditis

Study	Pathology	No. of patients analysed	Population AF	Intervention	Comparator diagnostic test	Sensitivity of TTE	Specificity of TTE
Casella *et al.* 2009[67]	Native valve infective endocarditis	75	NR	TTE	TOE	0.82 (95% CI 0.65 to 0.93). If indeterminate images excluded ($n = 61$) 0.871 (0.702 to 0.964)	0.62 (95% CI 0.445 to 0.77). If indeterminate images excluded 0.857 (0.673 to 0.960)
Jassal *et al.* 2007[76]	Native valve infective endocarditis	36	NR	TTE	TOE	0.84 (95% CI 0.72 to 0.96)	0.88 (95% CI 0.77 to 0.98)
Shively *et al.* 1991[94]	Endocarditis	66 episodes in 62 patients (four patients referred twice)	NR	TTE	Non-echocardiographic pathological data from the subsequent clinical course	0.44 (95% CI 0.32 to 0.56)	0.98 (95% CI 0.95 to 1.0)

NR, not reported.

TABLE 7 Valvular heart disease

Study	Pathology	No. of patients analysed	Population AF	Intervention	Comparator diagnostic test	Sensitivity of TTE	Specificity of TTE
Attenhofer Jost *et al.* 2000[64]	Mitral regurgitation Aortic stenosis MVP Valvular heart disease, aortic and mitral valve AR	100	NR (all had heart murmur)	TTE	Clinical cardiac examination	TTE as gold standard (presumed sensitivity = 1)	TTE as gold standard (presumed specificity = 1)
Barron 1988 *et al.*[65]	MVP	140	NR	TTE	Auscultation	0.47 (95% CI 0.39 to 0.55)	0.90 (95% CI 0.85 to 0.95)
Cassidy *et al.* 1992[68]	Mitral regurgitation AR Aortic stenosis	37	NR (all had systolic murmur)	TTE	Clinical cardiac examination	TTE as gold standard (presumed sensitivity = 1)	TTE as gold standard (presumed specificity = 1)
Dittmann *et al.* 1987[69]	AR	55	38% AF	TTE	Aortography	Pulsed Doppler 0.93 (95% CI 0.86 to 0.99) (0.87 mild or moderate; 1 severe AR), M-mode 0.62	Pulsed Doppler 1, M-mode 1
Grossmann *et al.* 2002[72]	Mitral regurgitation	68	25% AF	TTE	TOE	0.79 (95% CI 0.69 to 0.89)	1
Groves *et al.* 2004[73]	Tricuspid regurgitation	61	NR	TTE	CT	TTE as gold standard (presumed sensitivity = 1)	TTE as gold standard (presumed specificity = 1)
Guyer *et al.* 1984[74]	Tricuspid stenosis	38	82% AF	TTE	Catheterisation	0.69 (95% CI 0.55 to 0.84)	0.96 (95% CI 0.90 to 1.0)
Helmcke *et al.* 1987[75]	Mitral regurgitation	147	21% AF	TTE	Catheterisation	1	1
Reichlin *et al.* 2004[88]	Valvular heart disease	203	NR (all had heart murmur)	TTE	Clinical cardiac examination (including auscultation)	TTE as gold standard (presumed sensitivity = 1)	TTE as gold standard (presumed specificity = 1)
Veyrat *et al.* 1983[101]	AR	95	40% AF	TTE	Aortography	0.95 (95% CI 0.89 to 1.0)	1

Study	Pathology	No. of patients analysed	Population AF	Intervention	Comparator diagnostic test	Sensitivity of TTE	Specificity of TTE
Wong *et al.* 1983[103]	Aortic stenosis, calcification	113	NR	TTE	Cinefluorography	0.76 (95% CI 0.68 to 0.84)	0.89 (95% CI 0.83 to 0.95)
	Mitral stenosis, annulus calcification					0.77 (95% CI 0.69 to 0.84)	0.94 (95% CI 0.89 to 0.98)
	Mitral stenosis, leaflet calcification					0.22 (95% CI 0.15 to 0.30)	0.93 (95% CI 0.88 to 0.97)
Zanolla *et al.* 1982[104]	Mitral stenosis	43	NR	TTE	Radiography	1	0.66 (95% CI 0.51 to 0.80)

NR, not reported.

TABLE 8 Cardiomyopathy

Study	Pathology	No. of patients analysed	Population AF	Intervention	Comparator diagnostic test	Sensitivity of TTE	Specificity of TTE
Okura *et al.* 2006[85]	Cardiomyopathy, differentiating between ischaemic and non-ischaemic	44	NR	TTE	Angiography	0.77 (95% CI 0.64 to 0.89)	0.77 (95% CI 0.65 to 0.90)

NR, not reported.

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TABLE 9 Heart failure

Study	Pathology	No. of patients analysed	Population AF	Intervention	Comparator diagnostic test	Sensitivity of TTE	Specificity of TTE
Arques *et al.* 2005[63]	CHF	39	0%	TTE	Radiography and clinical signs	0.74 (95% CI 0.60 to 0.88)	0.75 (95% CI 0.61 to 0.89)
Erbel *et al.* 1984[71]	LV dysfunction, ejection fraction	110	0%	TTE	Catheterisation to cineventriculograms	0.81 (95% CI 0.73 to 0.88)	1
Maestre *et al.* 2009[81]	CHF	216	NR	TTE	Clinical criteria	TTE as gold standard (presumed sensitivity = 1)	TTE as gold standard (presumed specificity = 1)
Reichek *et al.* 1981[87]	LV hypertrophy	34	NR	TTE	Autopsy	0.93 (95% CI 0.84 to 1)	0.95 (95% CI 0.88 to 1)
Sparrow *et al.* 2003[99]	LV dysfunction	621	NR	TTE	Clinical diagnosis	TTE as gold standard (presumed sensitivity = 1)	TTE as gold standard (presumed specificity = 1)

NR, not reported.

TABLE 10 Diseases of arteries

Study	Pathology	No. of patients analysed	Population AF	Intervention	Comparator diagnostic test	Sensitivity of TTE	Specificity of TTE
Enia *et al.* 1989[70]	Aortic dissection	555	NR	TTE	Aortography	0.92 (95% CI 0.89 to 0.94)	0.71 (95% CI 0.68 to 0.75)
Nienaber *et al.* 1994[84]	Aortic dissection	35	NR	TTE	Surgery, autopsy or angiography	0.77 (95% CI 0.63 to 0.91)	0.67 (95% CI 0.51 to 0.82)
Nienaber *et al.* 1993[83]	Aortic dissection, thoracic	110	NR	TTE	Surgery, autopsy or angiography	0.59 (95% CI 0.51 to 0.69)	0.83 (95% CI 0.76 to 0.90)
Roudat *et al.* 1988[89]	Aortic dissection	660	NR	TTE	Surgery, autopsy or angiography or CT	0.95 (95% CI 0.94 to 0.97) using dilatation of segment of aorta (0.758 using abnormal linear image in lumen)	0.51 (95% CI 0.47 to 0.55) using dilatation of segment of aorta (0.977 using abnormal linear image in lumen)

NR, not reported.

Prognostic study results

Five studies[106–110] reported prognosis based on TTE-diagnosed pathologies in AF populations.

The pathologies were left atrial diameter (LAD); mitral annular calcification; MVP global, moderate to severe or reduced LV systolic dysfunction; any or severe MR; and valvular abnormality (*Table 12*).

Prognosis was investigated by studies for the types of valvular heart disease, mitral annular calcification, MVP, MR and valvular abnormality. Mitral annular calcification was non-significantly associated with thromboembolism by age-adjusted analysis RR of 0.6 (95% CI 0.2 to 1.5; $p > 0.2$).[110] MVP had a non-significant association with risk of stroke unadjusted RR of 0.29 ($p = 0.22$).[106] For MR, grade 1 MR (compared with no MR) odds ratio (OR) of 2.689 (95% CI 1.039 to 7.189; $p = 0.0434$) was significantly associated with history of thromboembolic events.[108] Severe MR had a non-significant association with risk of stroke (relative to none or mild MR) unadjusted RR of 1.7 ($p = 0.59$),[106] was found to be protective against stroke with hazard ratio (HR) of stroke for increase in MR from mild to severe groups 0.45 (95% CI 0.20 to 0.97) by multivariate analysis (multivariate analysis includes MR, LAD, sex and age),[109] and was non-significantly associated with thromboembolism by age-adjusted analysis RR 0.4 (95% CI 0.1 to 3.0; $p > 0.2$).[110] For MR, the retrospective studies[108,109] found significant associations with prognosis, whereas the prospective studies[106,110] had non-significant results. Any detected valvular abnormalities had a reported HR for mortality: diabetic participants 2.05 (95% CI 1.10 to 3.82; $p = 0.0229$), non-diabetic participants HR 1.88 (95% CI 1.30 to 2.70; $p = 0.0007$).[107] For this study, diabetics and non-diabetic groups differed in that diabetic participants were older and had higher comorbidity, and more of them received oral anticoagulation; there was also a relatively small number of diabetics.[107]

Left atrial diameter had a reported non-significant association with risk of stroke unadjusted RR of 1.02/mm (95% CI 0.99 to 1.06; $p = 0.10$[106]) and was reported to have HR of stroke for every 10-mm increment in LA size of 1.06 (95% CI 0.75 to 1.49) by multivariate analysis (multivariate analysis includes MR, LAD, sex, age).[109] LAD (corrected for body surface area) as a continuous variable by univariate analysis was significantly associated with thromboembolism ($p = 0.01$[110]), and had reported HR for mortality, diabetic participants 1.01 (95% CI 0.97 to 1.05; $p = 0.6445$), HR non-diabetic participants 1.06 (95% CI 1.03 to 1.08; $p < 0.0001$).[107] Moderate to severe LV dysfunction was associated with a significantly higher risk of stroke relative to normal LV function or mild dysfunction,[106] and global LV dysfunction was significantly associated with risk of thromboembolism.[110] Reduced LV function had reported HR for mortality, diabetic participants 1.52 (95% CI 0.85 to 2.70; $p = 0.1598$), HR non-diabetic participants 2.28 (95% CI 1.58 to 3.29; $p < 0.0001$).[107]

Results of prevalence review

Quantity and quality of research available

The literature search yielded 8316 article citations when duplicates had been removed. *Figure 2* shows study selection, in a modified version of the PRISMA flow diagram.[61] References excluded at the full paper screening stage ($n = 15$), with reason for exclusion, are presented in *Appendix 9*.

TABLE 11 Tumours or cardiac masses

Study	Pathology	No. of patients analysed	Population AF	Intervention	Comparator diagnostic test	Sensitivity of TTE	Specificity of TTE
Sheiban *et al.* 1987[93]	Intracardiac masses	77	NR	TTE	Surgery	0.88 (95% CI 0.81 to 0.95)	0.95 (95% CI 0.91 to 1.0)

NR, not reported.

TABLE 12 Prognosis based on TTE-diagnosed pathologies in AF

Study	Pathology	No. of participants	Population AF	Follow-up	Results
Atrial Fibrillation Investigators 1998[106]	Moderate to severe LV systolic dysfunction	1010 (of whom 129 with moderate to severe LV dysfunction)	Non-valvular AF	Mean 1.6 years	Independent predictor of stroke (relative to none or mild LV dysfunction), unadjusted RR of 3.04 ($p<0.001$), multivariate analysis RR of 2.5 (95% CI 1.5 to 4.4; $p<0.001$) (multivariate analysis includes age, previous stroke/TIA, history of diabetes, history of heart failure, history of hypertension)
	LAD	1003			Non-significant association with risk of stroke unadjusted RR of 1.02/mm (95% CI 0.99 to 1.06; $p=0.10$), multivariate analysis $p=0.62$ (multivariate analysis includes age, previous stroke/TIA, history of diabetes, history of heart failure, history of hypertension)
	MVP	991 (of whom 50 with MVP)			Non-significant association with risk of stroke unadjusted RR of 0.29 ($p=0.22$)
	Severe MR	863 (of whom 86 with severe MR)			Non-significant association with risk of stroke (relative to none or mild MR) unadjusted RR of 1.7 ($p=0.59$)
Klem *et al.* 2003[107]	Reduced LV function	409 (reduced LV function, of whom 31 of 73 diabetic, and 98 of 336 non-diabetic)	Non-rheumatic AF	Mean 9.6 years	HR for mortality, diabetic participants 1.52 (95% CI 0.85 to 2.70; $p=0.1598$), non-diabetic participants HR of 2.28 (95% CI 1.58 to 3.29; $p<0.0001$)
	LAD	409 (of whom 73 diabetic, 336 non-diabetic)			HR for mortality, diabetic participants 1.01 (95% CI 0.97 to 1.05; $p=0.6445$), non-diabetic participants HR of 1.06 (95% CI 1.03 to 1.08; $p<0.0001$)
	Valvular abnormality	409 (of whom valvular abnormality in 41 of 73 diabetic, and 136 of 336 non-diabetic)			HR for mortality, diabetic participants 2.05 (95% CI 1.10 to 3.82; $p=0.0229$), non-diabetic participants HR of 1.88 (95% CI 1.30 to 2.70; $p=0.0007$)
Miyaska *et al.* 2000[108]	MR	173 (of whom 104 no MR, 69 grade 1 MR)	Non-rheumatic AF	NA (patient records' study)	Grade 1 MR (compared with no MR) OR of 2.689 (95% CI 1.039 to 7.189; $p=0.0434$) significantly associated with history of thromboembolic events

Study	Pathology	No. of participants	Population AF	Follow-up	Results
Nakagami *et al.* 1998[109]	Severe MR LAD	290	Non-rheumatic AF	Mean 7.4 years	HR of stroke for increase in MR from mild to severe groups 0.45 (95% CI 0.20 to 0.97) (MR protective against stroke) by multivariate analysis (multivariate analysis includes MR, LAD, sex, age) HR of stroke for every 10-mm increment in LA size 1.06 (95% CI 0.75 to 1.49) by multivariate analysis (multivariate analysis includes MR, LAD, sex, age)
The Stroke Prevention in Atrial Fibrillation Investigators 1992[110]	LAD	539	Non-rheumatic AF	Mean 1.3 years	LAD (corrected for body surface area) as a continuous variable by univariate analysis was significantly associated with thromboembolism ($p = 0.01$). By multivariate analysis $p = 0.02$ (multivariate analysis LAD and global LV diameter)
	Mitral annular calcification	568 (of whom 91 with mitral annular calcification)			Non-significantly associated with thromboembolism by age-adjusted analysis RR 0.6 (95% CI 0.2 to 1.5; $p > 0.2$)
	Severe MR	568 (of whom 37 with severe MR)			Non-significantly associated with thromboembolism by age-adjusted analysis RR 0.4 (95% CI 0.1 to 3.0; $p > 0.2$)
	LV dysfunction (global)	568 (of whom 132 with LV dysfunction)			By univariate analysis was significantly associated with thromboembolism (RR 2.9, 95% CI 1.6 to 5.3; $p < 0.001$); by multivariate analysis RR of 2.6 (95% CI 1.4 to 4.9; $p = 0.003$) (multivariate analysis LAD and global LV dysfunction)

NA, not applicable.

There were 16 prevalence studies[28,111–125] accepted into the review. Some of the studies investigated the prevalence of more than one pathology.

A summary of included prevalence studies is presented in *Table 13*.

Prevalence studies were found for the following categories of pathologies: structural defect, ischaemia/thrombosis, valvular heart disease, cardiomyopathy and heart failure.

The assessment of methodological quality of included studies was performed using the recommended guidelines in the checklist for the STROBE statement.[126] Features of the study considered were information regarding the study's rationale and objectives, study design (including methods of recruitment and assessment), reporting of results and measures used to address confounding factors. The criteria and characteristics of individual studies are shown in *Appendix 7*.

Of the 16 studies that provided data for the review of the prevalence of clinically significant pathologies in patients with AF, seven studies[28,112,114,115,119,121,124] were retrospective in design, eight[113,116–118,120,122,123,125] were prospective studies, and one[111] was a case–control study.

Patients with AF were identified mainly by ECG, either at the time of recruitment or from hospital notes such as admissions notes or discharge records. Five studies did not report the methods used to verify the presence or history of AF in eligible patients[112,114,120,124,125] although one study gave details in a prior

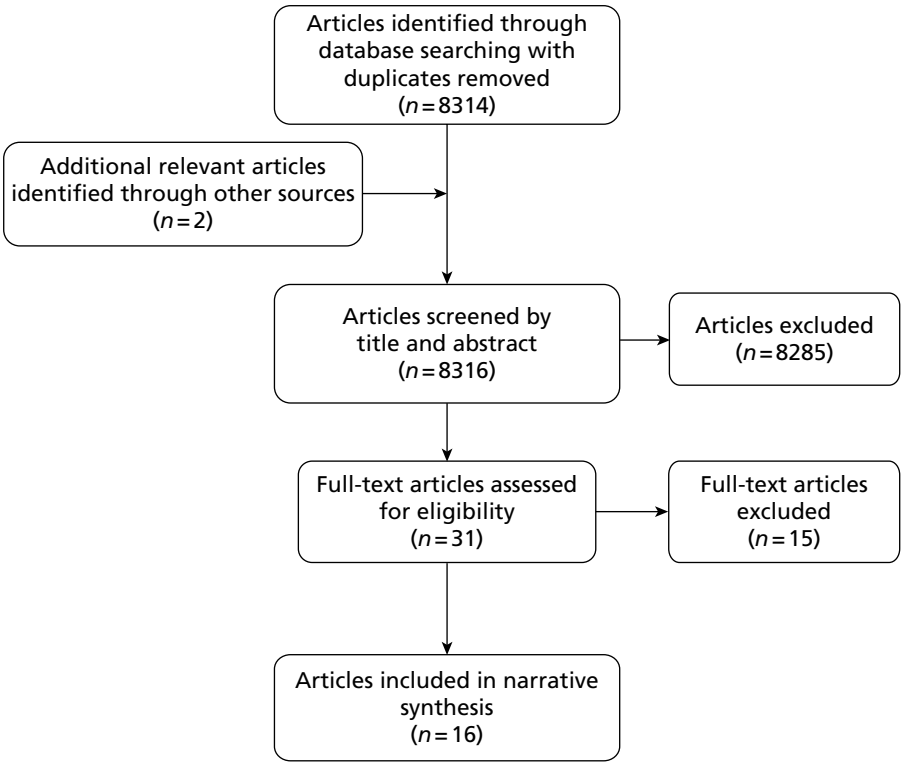


FIGURE 2 Study selection for prevalence review.

TABLE 13 Summary of prevalence studies

Study	Category of pathology	Population sample size	Type of AF of population (where specified)
Agmon *et al.* 2001[111]	Ischaemia/thrombosis	42	AF
Archer *et al.* 1995[112]	Ischaemia/thrombosis	55	Non-rheumatic AF
Blackshear *et al.* 1999[113]	Ischaemia/thrombosis	770	AF
Corrado *et al.* 2004[114]	Ischaemia/thrombosis	41	AF or atrial flutter
Dang *et al.* 2004[115]	Valvular heart disease	737	First hospitalisation associated with AF
de Divitiis *et al.* 1999[28]	Ischaemia/thrombosis	90	AF
Heppell *et al.* 1997[116]	Ischaemia/thrombosis	109	AF
Kleeman *et al.* 2009[117]	Ischaemia/thrombosis	295	Non-valvular AF
Levy *et al.* 1999[118]	Ischaemia/thrombosis and valvular heart disease, and cardiomyopathy and heart failure	756	Chronic, paroxysmal or recent-onset AF
Lip *et al.* 1997[119]	Structural defect and ischaemia/ thrombosis, and valvular heart disease and cardiomyopathy	111	AF
Maltagliati *et al.* 2006[120]	Ischaemia/thrombosis	757	AF or atrial flutter
Narumiya *et al.* 2003[121]	Ischaemia/thrombosis	50	Lone AF (28%) or non-lone AF (72%)
Santiago *et al.* 1994[122]	Ischaemia/thrombosis and valvular heart disease	30	AF
Scherr *et al.* 2009[123]	Ischaemia/thrombosis	732 catheter ablations for AF in 585 patients	AF (catheter ablations)
Shen *et al.* 2002[124]	Ischaemia/thrombosis	182	AF and subtherapeutic INR
Tsai *et al.* 1997[125]	Ischaemia/thrombosis	219	Chronic non-rheumatic AF

publication[98] and the others used candidates for cardioversion giving confidence in accuracy of diagnosis. Although two retrospective studies[28,121] used TOE and TTE in diagnosing the presence of ischaemic heart disease, the methods used to diagnose the presence of coexisting clinically significant cardiac pathologies were not detailed in three studies.[115,118,119] The remaining studies relied on TOE and provided information on diagnostic criteria for pathologies of interest. Detailed descriptions of the assessors evaluating eligible patients regarding pathologies of interest were reported in four studies;[113,114,116,123] for one of these studies,[113] the relevant information was reported in a separate publication.[127] In one study,[116] outcome data were incomplete; the reason was that TOE provided inadequate visualisation of the pathology of interest in a number of patients.

All methodological quality criteria of interest were met in six studies.[111,113,117,122,123,125] At least one of the criteria was not satisfied in three studies,[28,114,116] the criteria were partially met in one study[115] and information was unclear in two studies.[112,120]

Prevalence results

One prevalence study[119] was identified that sought to identify prevalence of atrial septal defect, as presented in *Table 14*. This study, by Lip *et al.*,[119] found a prevalence of 0.9% for atrial septal defect. This study looked at a cross-section of patient records in UK primary care.

Fifteen studies[28,111–114,116–125] investigated the prevalence of pathologies within the category 'ischaemia/thrombosis', as shown in *Table 15*. One study, that by Lip *et al.* 1997,[119] found a 28.8% prevalence of ischaemic heart disease.

The six studies[112,116,117,120,124,125] reporting prevalence of LA thrombus gave differing prevalences, ranging from 3%[117] to 18%.[116] Both of these studies[116,117] used TOE to diagnose thrombi. These six studies differed in terms of sample size and population, with Maltagliati *et al.*[120] including atrial flutter, Shen *et al.*[124] restricting the population to patients with subtherapeutic INR, and Kleeman *et al.*[117] using a population admitted for cardioversion.

Six studies[28,114,120–123] investigated prevalence of LAA thrombi; the lowest reported prevalence was for patients undergoing catheter ablations 1.6%[123] and the highest was 40%,[122] although this study had a small sample size ($n = 30$). Two studies[28,120] looked at RAA thrombus, reporting prevalences of 0.5%[120] and 6.7%.[28] Both of these studies used TOE to diagnose thrombi.

Four studies[115,118,119,122] investigated the prevalence of valvular pathologies (*Table 16*). Two of these studies[115,119] reported prevalence of valvular heart disease as 13.4%[115] to 26.1%,[119] and combining rheumatic and non-rheumatic valvular heart disease from Levy *et al.*[118] would give 18.8% prevalence. Mitral valve disease had a reported prevalence of 10.4%,[115] and Santiago *et al.*[122] reported prevalence of 30% for MR.

Three studies[115,118,119] investigated the prevalence of pathologies within the category cardiomyopathy, as presented in *Table 17*. Dang *et al.*[115] and Lip *et al.*[119] reported prevalences of 4.5%[115] to 5.4%.[119] Levy *et al.*[118] reported a prevalence of 4.5% for hypertrophic cardiomyopathy and of 9.2% for dilated cardiomyopathy.

Two studies[115,118] investigated the prevalence of heart failure, as shown in *Table 18*. Dang *et al.*[115] reported a prevalence of 31.1% and Levy *et al.*[118] reported the prevalence of CHF to be 29.8%.

Discussion of clinical effectiveness

Diagnostic accuracy studies with AF populations were available for the pathologies atrial septal defect, atrial septal aneurysm, rupture of chordae tendineae, atrial thrombosis, ventricular thrombosis, coronary artery stenosis, pulmonary hypertension, aortic and MR, and tricuspid stenosis. Diagnostic accuracy studies without reported AF populations were available for other pathologies, including endocarditis, cardiomyopathy, heart failure, LV dysfunction, aortic dissection and cardiac masses. As the search was limited to MEDLINE, it is possible that the database search will have missed some studies, although additional bibliography and hand-searching identified only a small proportion of articles to be screened, and the database search identified diagnostic studies for almost all the pathologies selected as relevant. Thus diagnostic accuracy data were available for a range of relevant pathologies, although data were not available for all pathologies in an AF population. There was considerable heterogeneity between studies, especially in terms of population and pathology being identified, and in comparator diagnostic technique, with some heterogeneity in the type of TTE used and the study type.

TABLE 14 Prevalence study structural defect

Study	Pathology	Population (*n*, type of AF)	Prevalence (%)
Lip *et al.* 1997[119]	Atrial septal defect	111 AF	0.9

TABLE 15 Prevalence studies: ischaemia/thrombosis

Study	Pathology	Population (*n*, type of AF)	Prevalence (%)
Agmon *et al.* 2001[111]	Aortic atherosclerosis	42 AF	73.8
	Complex aortic atherosclerosis	42 AF	16.7
Archer *et al.* 1995[112]	LA thrombus	55 non-rheumatic AF	9.1
	LV thrombus	55 non-rheumatic AF	3.6
	Atrial septal aneurysm	55 non-rheumatic AF	7.3
Blackshear *et al.* 1999[113]	Aortic atherosclerotic plaque	770 AF	56.6
	Complex aortic atherosclerotic plaque	770 AF	25.1
Corrado *et al.* 2004[114]	LAA thrombus	41 AF or atrial flutter	9.8
de Divitiis *et al.* 1999[28]	LAA thrombus	90 AF	12.2
	RAA thrombus	90 AF	6.7
	Left and/or RAA thrombus	90 AF	13
Heppell *et al.* 1997[116]	LA thrombus	109 AF	18
Kleeman *et al.* 2009[117]	LA thrombus	295 non-valvular AF or atrial flutter	3
Levy *et al.* 1999[118]	Coronary artery disease	756 chronic, paroxysmal or recent-onset AF	16.6
Lip *et al.* 1997[119]	Ischaemic heart disease	111 AF	28.8
Maltagliati *et al.* 2006[120]	LA thrombus	757 AF or atrial flutter	6.3 (if exclude LAA 0.3)
	LAA thrombus	757 AF or atrial flutter	5.5
	RAA thrombus	757 AF or atrial flutter	0.5
Narumiya *et al.* 2003[121]	LAA thrombus	50, of which 14 lone AF, 36 non-lone AF	12 (16.7% non-lone AF; 0% lone AF)
Santiago *et al.* 1994[122]	LAA thrombus	30 AF	40
Scherr *et al.* 2009[123]	LAA thrombus	732 catheter ablations for AF in 585 patients	1.6
Shen *et al.* 2002[124]	LA thrombus	182 AF and subtherapeutic INR	9.9
Tsai *et al.* 1997[125]	LA thrombus	219 chronic non-rheumatic AF	6.8

TABLE 16 Prevalence studies: valvular heart disease

Study	Pathology	Population (*n*, type of AF)	Prevalence (%)
Dang *et al.* 2004[115]	Mitral valve disease	737 first hospitalisation associated with AF	10.4
	All valve diseases	737 first hospitalisation associated with AF	13.4
Levy *et al.* 1999[118]	Valvular heart disease rheumatic	756 chronic, paroxysmal or recent-onset AF (167 paroxysmal, 389 chronic, 200 recent onset)	15.2 (10% paroxysmal, 20% chronic, 12% recent onset)
	Valvular heart disease non-rheumatic (including MVP)	756 chronic, paroxysmal or recent-onset AF (167 paroxysmal, 389 chronic, 200 recent onset)	3.3 (5% paroxysmal, 3% chronic, 3% recent onset)
Lip *et al.* 1997[119]	Valvular heart disease	111 AF	26.1
Santiago *et al.* 1994[122]	MR	30 AF	30

TABLE 17 Prevalence studies: cardiomyopathy

Study	Pathology	Population (*n*, type of AF)	Prevalence (%)
Dang *et al.* 2004[115]	Cardiomyopathy	737 first hospitalisation associated with AF	4.5
Levy *et al.* 1999[118]	Hypertrophic cardiomyopathy	756 chronic, paroxysmal or recent-onset AF (167 paroxysmal, 389 chronic, 200 recent onset)	4.8 (3% paroxysmal, 4% chronic, 9% recent onset)
	Dilated cardiomyopathy	756 chronic, paroxysmal or recent-onset AF (167 paroxysmal, 389 chronic, 200 recent onset)	9.2 (2% paroxysmal, 13% chronic, 9% recent onset)
	Cardiomyopathy (other)	756 chronic, paroxysmal or recent-onset AF	1.2
Lip *et al.* 1997[119]	Cardiomyopathy	111 AF	5.4

TABLE 18 Heart failure

Study	Pathology	Population (*n*, type of AF)	Prevalence (%)
Dang *et al.* 2004[115]	Heart failure	737 first hospitalisation associated with AF	31.1
Levy *et al.* 1999[118]	CHF	756 AF (167 paroxysmal, 389 chronic, 200 recent onset)	29.8 (14% paroxysmal, 43% chronic, 18% recent onset)

Diagnostic accuracy showed high specificities for all selected pathologies, with the majority having specificity of 0.8 or higher, meaning a low proportion of FPs. For most pathologies there was also quite high sensitivity, with the majority having sensitivity of ≥0.6, with the exceptions of atrial thrombi, atrial septal defect and PE. Thus screening may result in considerable FNs for atrial thrombi, atrial septal hypertrophy/defect and PE. In general, sensitivity was lower for atrial thrombi, atrial septal defect and PE than for other pathologies, and specificity was lower for aortic dissection and pulmonary disease than for other pathologies. TTE seems to be a sufficient diagnostic tool for most pathologies included here, but there may need to be extra screening for PE by lung scan, and atrial thrombi and atrial septal hypertrophy by TOE.

All studies had a high percentage of usable, good images from TTE. Although for some studies participants were selected on the basis of having usable TTE images, even for other studies the lowest percentage of usable images was 85%.

In practice, accuracy will depend on the skill of the echocardiographer. Studies of diagnostic accuracy used experienced echocardiographers. It may be that when less-experienced staff are employed, there is lower accuracy. Even with skilled echocardiographers, there may be interobserver variations in the interpretation of images.[128,129–132]

Diagnostic accuracy studies identified were published from 1981 to 2009; with many relatively old studies included, it may be that imaging techniques and equipment have improved since then. This means that the review may underestimate the accuracy of TTE.

Prognostic studies indicated that LV dysfunction as diagnosed by TTE was associated with a significantly increased risk of thromboembolism, stroke or mortality. Increased LAD as assessed by TTE was associated with a significantly increased risk of thromboembolism or mortality; however, it was not significantly associated with stroke when assessed in 10-mm increments. Valvular abnormality carried a significantly increased risk of mortality. MR was not significantly associated with stroke or thromboembolism in two studies; however, two other studies suggested a significantly increased risk of thromboembolism with mild MR, in contrast with a significantly protective effect of severe MR against stroke. There was no significant association found between mitral annular calcification and thromboembolism, or between MVP and

stroke. These findings are consistent with the report of Providencia *et al.*,[13] published after the literature search was conducted, which found that TTE-diagnosed LV systolic function and LA area measurement may provide a valuable addition to $CHADS_2$ and CHA_2DS_2-VASc scores.[13]

Prevalence studies were sought for AF populations, and were not found for all pathologies. Prevalence studies were found for atrial septal defect, atrial septal aneurysm, atrial thrombus, ventricular thrombus, ischaemic heart disease or thrombosis, valvular heart disease, cardiomyopathy and heart failure. The prevalence studies had relevance to the UK. Two of the prevalence studies had UK populations, although the most common setting for the prevalence studies was USA. The wide variations in prevalence rates for specific pathologies may be explained by the degree of heterogeneity in the studies considered in this review. The sources of dissimilarities stem from study designs, characteristics of patients studied and severity of illness (e.g. as assessed by $CHADS_2$ scores). Although in most instances the diagnostic criteria for assessing pathologies of interest were outlined, there was a lack of detail regarding the description of the assessor or observer variability. Many of the studies used TOE to diagnose pathologies, and inadequate reporting of observer variation in transoesophageal echocardiographic examinations has been noted in available literature.[133]

There was a high prevalence (around 25–30%) of ischaemic heart disease, valvular heart disease and heart failure in patients with AF in the included prevalence studies. Cardiomyopathy prevalence was around 5%, and atrial septal defect had a prevalence of $<1\%$.

Studies of AF have reported characteristics of patients with AF, including prevalences of cardiac pathologies. This review found a prevalence study only for atrial septal defect, whereas prevalence of structural heart disease, of any type, thus encompassing many difference pathologies, has been reported in 46%[108] or 54%[114] of patients with AF not experiencing thromboembolic event or LAA thrombus, respectively. Prevalence of ischaemic heart disease found in this review was broadly in line with other reports. Ischaemic heart disease has been reported in 25%[113] or 12%,[134] and coronary disease in 22%,[28] 56% of 188 patients with short-term (<48 hours) AF,[117] or 32% of first-detected AF,[54] 34% paroxysmal AF,[54] 29%[54] persistent AF, 36%[54] permanent AF. Atrial thrombus has been found in 3% AF[135] or 12–20% in post-mortem studies of valvular AF,[136] LA thrombus in 14% of new-onset AF,[137] and LAA thrombus in 12% non-valvular AF or atrial flutter.[138] Results of thrombus prevalence studies within this review fell within these estimates. In the Scherr study[123] all patients with atrial flutter had a larger LAD (>4.5 cm) than those patients without LA thrombi. It was also noted that the prevalence of LAA thrombi increased with increasing $CHADS_2$ score. Although the prevalence of LAA thrombi ranges between 0.3% and 1.4% for those with scores of 0 and 1, the prevalence of this pathology occurs in 5.3% of patients with a score of ≥ 2. Atrial septal aneurysm has been reported in 2%[139] and LV aneurysm in 1% (SPAF Investigators 1992[110]) of patients with AF. This review did not find studies that set out to assess prevalence of pulmonary disease in patients with AF; however, pulmonary disease has been reported in 6% of patients with AF.[134] According to the Framingham heart study,[19] approximately one-third of women with AF and one-fifth of men with AF have valvular heart disease.[19] Results of valvular heart disease prevalence studies within this review were broadly in line with other reported estimates. Valvular heart disease has been reported in 10% of asymptomatic patients with AF and 26% of symptomatic patients with AF,[134] 23% AF,[140] 21% of first-detected AF,[54] 19% paroxysmal AF, 24% persistent AF[54] and 40% permanent AF,[54] with a review estimate of up to 40% AF.[141] Cardiomyopathy has been reported in 8% of first-detected AF,[54] 7% paroxysmal AF,[54] 13% persistent AF[54] and 16% permanent AF.[54] Dilated cardiomyopathy has been found in 11% AF[28] and 17% patients with short-term (<48 hours) AF.[117] Heart failure has been reported in 26% of first-detected AF,[54] 23% paroxysmal AF,[54] 35% persistent AF[54] and 49% permanent AF.[54] According to the Framingham heart study,[19] approximately one-quarter of men and women with AF have heart failure,[19] with up to 42% patients with AF developing CHF during their lifetime.[142] CHF in AF study participants has been reported as 28%[113] or 40%,[122] similar to results of prevalence studies included in this review. This review did not find studies that set out to assess prevalence of aortic dissection in patients with AF; however, aortic dissection has been reported in 7% patients with AF.[122]

Overall, diagnostic accuracy of TTE and prevalence of pathologies in patients with AF indicate that routine TTE following AF diagnosis would identify pathologies in many patients, particularly with regard to valvular heart disease, ischaemic heart disease and heart failure. TTE seems to be a sufficient diagnostic tool for screening most pathologies included in this review. For completeness of screening, extra testing for PE by lung scan, and for atrial thrombi and atrial septal hypertrophy by TOE, would reduce risk of FNs from TTE. However, it is unclear whether identifying these pathologies, in addition to the many diagnosed by TTE, would lead to improvement above that of TTE screening. In practice, some patients may have been diagnosed with a pathology prior to AF diagnosis. Patients may have more than one pathology in addition to AF. In practice, some diagnoses are likely to be checked with other diagnostic tools before treatment change, which will minimise the impact of FPs, although FPs may lead to some unnecessary diagnostic tests.

Chapter 4 Simulating clinical events and estimating cost-effectiveness ratios

Introduction

Key questions that are investigated

The model described here attempts to determine the cost-effectiveness of conducting TTE in all newly diagnosed patients by answering the following two linked questions:

1. Does the added information provided by performing TTE on everyone lead to better long-term clinical outcomes for patients with newly diagnosed AF? (*Clinical effectiveness.*)
2. Is any improvement in long-term clinical outcome [increased quality-adjusted life-years (QALYs)] worth the additional cost of performing TTE tests in all patients? (*Cost-effectiveness.*)

The relationship between information provided by a transthoracic echocardiography and clinical outcomes

With regard to the first question, the added information of performing a TTE in all patients can only lead to improvements in clinical outcomes if it leads to altered patient management. If by performing a TTE in a patient additional information about the structure and function of the heart is revealed, but this new information does not lead to any change in medical strategy, then the new information has not improved the clinical effectiveness of the patient's treatment.

Given this, it is important to identify situations where the identification of particular clinical features through TTE would lead to clear and consistent differences in clinical management. One example of this would be the identification of structural features within the heart that confer a greater risk of stroke than was previously estimated before TTE, where the updated risk level would recommend that pharmaceutical treatment should be provided, contrasting with a decision to not treat prior to the TTE. A further example would be a change in decision regarding surgical interventions; however, given the complexity of this area and paucity of data, our focus in the model has been on the way additional information provided by TTE is likely to change pharmaceutical management.

The decision to prescribe anticoagulants

Introduction

The specific focus of the model is the clinical decision whether or not to prescribe an OAC to a patient. Three types of OAC are considered: warfarin, dabigatran and rivaroxaban. The decision involves balancing competing clinical risks, as these drugs reduce the risk of stroke, but an adverse effect increases the risk of major bleeding events, which, in some cases, can lead to clinical outcomes as, or more, severe than the strokes that the treatment aims to prevent. In patients with an underlying low risk of stroke, the added risks of treatment in terms of bleeding events can outweigh the additional benefit caused by the reduced risk of stroke, and so it is neither clinically effective nor cost-effective to prescribe anticoagulants in this patient group. Within the context of this model, the added clinical benefit of performing TTE in a patient is a direct result of the increased appropriateness of the decision whether or not to prescribe anticoagulants, measured in terms of estimated QALYs.

Uncertainty about appropriate anticoagulants

Introduction

An important point to note is that the choice of OAC available to newly diagnosed patients with AF may affect the cost-effectiveness of the diagnostic technology. Three OACs are currently recommended for this patient group. These are warfarin, dabigatran and rivaroxaban. Each drug differs in terms of costs, clinical effectiveness in preventing strokes, and major bleeding event risks.

Diagnostic strategies

In the context of this clinical decision, TTE is best conceived as part of a diagnostic strategy. Two versions of the diagnostic strategy are compared: a 'baseline' strategy assuming that TTE is not undertaken, and a 'baseline + TTE' strategy that incorporates additional information provided by TTE. The diagnostic strategy will indicate that some patients should receive the drug, and others should not. This indication is appropriate in some cases ('TPs' and 'TNs') and not appropriate in others ('FPs' and 'FNs'), as indicated in *Table 19*. This table focuses purely on the clinical issues; whether additional benefits are worth any additional costs will be detailed later in this report.

The $CHADS_2$ diagnostic tool for assessing the risk of stroke in patients with atrial fibrillation

The main diagnostic tool currently used to make the decision about whether to prescribe anticoagulants in newly diagnosed patients with AF is the $CHADS_2$ instrument.

The $CHADS_2$ instrument produces a risk score for each patient ranging from 0 to 6 points inclusive, according to the criteria shown in *Table 20*.

TABLE 19 The conceptual accuracy associated with TTE

	In reality	
Diagnostic strategy indicates that additional benefit:	**The additional benefit of treatment outweighs additional risk: *patient should receive drug***	**The additional benefit of treatment does not outweigh additional risk: *patient should not receive drug***
Outweighs additional risk **Patient prescribed drug**	Correct decision to prescribe **TP**	Incorrect decision to prescribe **FP**
Does not outweigh additional risk **Do not prescribe drug**	Incorrect decision not to prescribe **FN**	Correct decision not to prescribe **TN**

TABLE 20 The criteria used in performing a $CHADS_2$ assessment

Code	Condition	Points
C	CHF	1
H	Hypertension	1
A	Age ≥ 75 years	1
D	DM	1
S_2	Prior stroke or TIA	2

$CHADS_2$ decision rule and choice of oral anticoagulants

Although dabigatran and rivaroxaban are generally considered to be very similar OACs in terms of costs, clinical effectiveness, and risk of major bleeding events, the indications provided in the NICE guidance for each OAC differ slightly.

The guidance for rivaroxaban states:

- Rivaroxaban is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, people with non-valvular AF with one or more risk factors, such as:
  - CHF
  - hypertension
  - ≥75 years of age
  - DM
  - prior stroke or transient ischaemic attack.[47]

It is noted that this guidance is equivalent to stating that rivaroxaban is recommended for patients with AF with a $CHADS_2$ score of ≥1.

The guidance for dabigatran states that:

- Dabigatran etexilate is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication (i.e. in people with non-valvular AF with one or more of the following risk factors):
  - previous stroke, transient ischaemic attack or systemic embolism
  - LV ejection fraction of <40%
  - symptomatic heart failure of New York Heart Association (NYHA) class 2 or above
  - age ≥75 years
  - age ≥65 years, with one of the following: DM, coronary artery disease or hypertension.[143]

It is noted that an implication of the guidance is that dabigatran is indicated in patients who have a $CHADS_2$ score of ≥1 if they are aged ≥65 years. In people aged <65 years, the correspondence between $CHADS_2$ score and OAC decision is not clear cut. For simplicity, and because the mathematical model developed does not model the progression of each individual disease state that is incorporated in the $CHADS_2$ score, the mathematical model will be run in patients aged ≥65 years only when considering dabigatran as the OAC of choice.

Based on the above NICE recommendations, recent ESC guidance[47] and broad recognition that warfarin carries a higher risk of major bleeding events for most patient groups than either dabigatran or rivaroxaban,[6] different $CHADS_2$ thresholds were used for each OAC, as shown in *Table 21* below.

Comparator strategy: $CHADS_2$ plus transthoracic echocardiography

In our comparator strategy, '$CHADS_2$ + TTE', the decision to coagulate can also be made as a result of TTE identifying a structural feature of LA abnormality that predisposes an individual to a high risk of

TABLE 21 The assumed level of $CHADS_2$ at which specific OAC would be performed

$CHADS_2$ score	Prescribe dabigatran	Prescribe warfarin	Prescribe rivaroxaban
0	No	No	No
1	Yes (≥65 years)	No	Yes
2 or more	Yes	Yes	Yes

stroke.[144] For the purposes of this report we define LA abnormality as a patient having one or more of the following conditions:

- LAA thrombi
- dense spontaneous echo contrast
- LAA low-flow velocities.

These conditions have been chosen as they are the ones used in a recent publication by Provedencia *et al.*,[13] which provides key data for populating the model.

This means the comparator offers two alternative routes by which a decision to recommend OACs can be made:

- a $CHADS_2$ score at or above the threshold required to recommend OACs
- a TTE indicating the presence of LA abnormality.

In effect, this means that some individuals who would not have received OAC with $CHADS_2$ alone will receive OAC following $CHADS_2$ + TTE due to detection of LA abnormality. It is noted that in no instance patients who would have received OAC using $CHADS_2$ alone would have treatment withheld. As such, it has been assumed that TTE will only provide information that can alter patient management when the $CHADS_2$ score does not indicate treatment with OAC. In the remaining patients we have not formally assessed the cost-effectiveness of TTE, noting that costs would be incurred for no assumed gain.

Scenarios modelled

The risks of each of the discrete events modelled in the discrete event simulation (DES) depend on factors such as the OAC chosen, the initial age of the patient when newly diagnosed with AF, gender, and whether or not the patient has another $CHADS_2$ risk factor. Because of this, a number of different scenarios were considered incorporating different combinations of OAC, age, gender, and initial $CHADS_2$ score. A total of 14 scenarios are presented, as described in *Table 22*.

TABLE 22 Summary of the 14 comparisons modelled using the mathematical mode

Scenario	OAC	Age (years)	Initial $CHADS_2$ score	Gender
W_50_0_M	Warfarin	50	0	Male
W_50_0_F				Female
W_50_1_M		50	1	Male
W_50_1_F				Female
W_65_0_M		65	0	Male
W_65_0_F				Female
W_65_1_M		65	1	Male
W_65_1_F				Female
R_50_0_M	Rivaroxaban	50	0	Male
R_50_0_F				Female
R_65_0_M		65	0	Male
R_65_0_F				Female
D_65_0_M	Dabigatran	65	0	Male
D_65_0_F				Female

CHA_2DS_2-VASc score [Congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 years, and sex category (female)]

An alternative variation of the $CHADS_2$ instrument exists, which uses additional information such as gender to make the decision. It was decided not to produce an additional 14 scenarios using CHA_2DS_2-VASc rather than $CHADS_2$ as the baseline strategy for a number of reasons. These include the already large number of scenarios considered; the fact the recent NICE guidance[47] on rivaroxaban and dabigatran relate more clearly to $CHADS_2$ than CHA_2DS_2-VASc scores, and the fact that $CHADS_2$ is the more established of the two instruments.

Detailing the mathematical model

Overall structure of model

An overview of the model is presented in *Figure 3*. The model involves two distinct stages:

1. A short-term stage in which the clinical characteristics of a patient are generated, and the decision whether or not to prescribe an OAC is made for both the baseline and the baseline + TTE strategy.
2. A long-term simulation of the clinical outcomes, and associated costs and utilities, which follow from the patient's clinical characteristics and the decision whether or not to prescribe an OAC.

The cost-effectiveness of TTE in this context results from the differences in the long-term outcomes in a large cohort of individuals following the baseline + TTE diagnostic strategy compared with long-term outcomes in a similar cohort of individuals following the baseline diagnostic strategy.

Key structural assumptions made by the model are:

(a) Patients who have a major clinical bleed while on OAC have treatment with OACs stopped.
(b) Patients who have a stroke receive OAC, unless they have had a prior major clinical bleed.

In populating the model we elected to use data reported by Providencia *et al.*,[13] as this was a recent, internally consistent study, which used the $CHADS_2$ tool and had also conducted TOE. Although the study was not large ($n = 405$) it was deemed to outweigh the limitations associated with using data from heterogeneous studies that would have required numerous assumptions.

Simulating patient characteristics

Introduction

The short-term diagnostic section of the model begins by simulating a series of male and female cohorts aged either 50 or 65 years old with newly diagnosed AF but with none of the following conditions: CHF, hypertension, DM, prior stroke or TIA, or vascular disease. This patient group has been selected as they would have a $CHADS_2$ score of 0 and thus would not be currently recommended treatment with an OAC. Additionally, otherwise identical cohorts of individuals with a $CHADS_2$ score of 1 are considered in the case of warfarin.

A summary of the sources of data used to populate the model is provided in *Appendix 10*.

For this patient group the age at death (assuming no AF- or AF treatment-related mortality) was simulated. The diagnosis, or not, of LA abnormality following TTE was additionally simulated.

Risk of all-cause mortality

The risks of all-cause mortality were estimated separately for males and females using gender-specific UK life table data.[145] These were converted into probabilities of males and females dying in each forthcoming

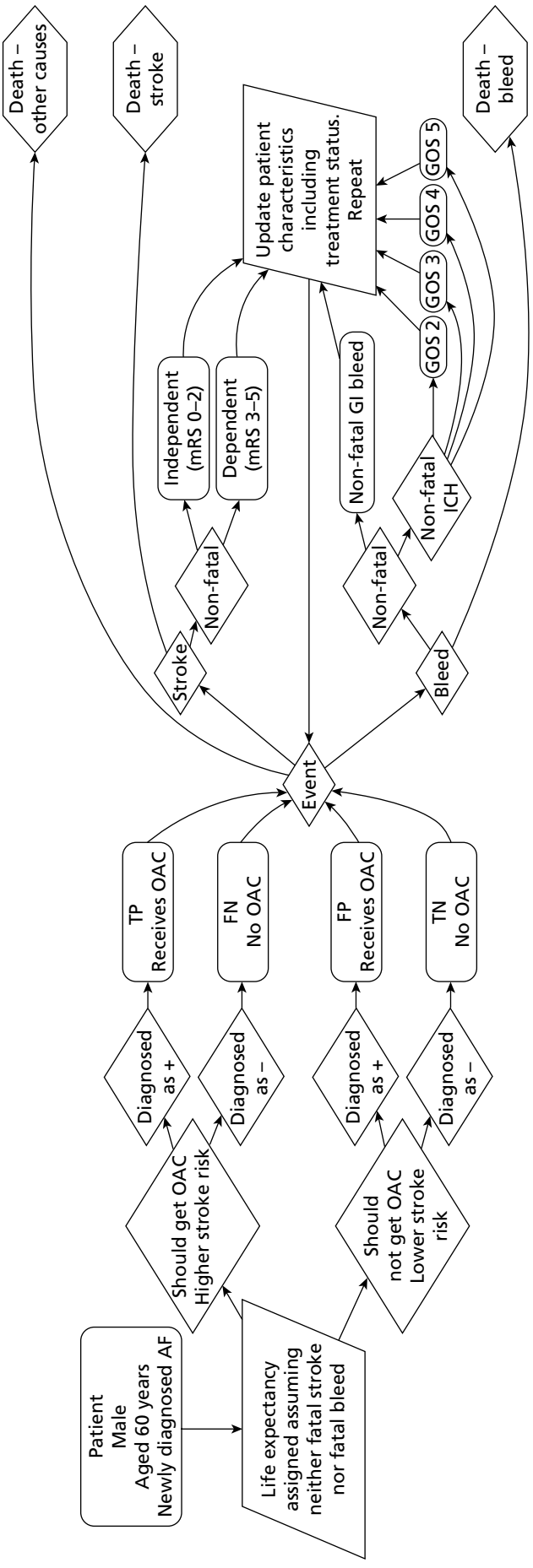


FIGURE 3 Mathematical model. GI, gastrointestinal; GOS, Glasgow Outcome Scale; ICH, intracranial haemorrhage; mRS, modified Rankin Scale.

year assuming initial ages of 50 and 65 years. These produced a range of distributions of death given. For simplicity, it was assumed that all remaining patients would die within their 101st year.

The assumed sensitivity and specificity of transthoracic echocardiography of diagnosing left atrial abnormality

Table 2 in the paper by Providencia *et al.*[13] provides sufficient information to calculate an estimate of sensitivity and specificity of TTE in diagnosing LA abnormality. These data were used to derive *Tables 23* and *24*. Patients were assessed using both TTE and TOE, and for TTE were assigned an echocardiographic risk score depending on how many structural features that are constituents of LA abnormality were identified through TTE. It was assumed that TOE was the gold standard and identified all patients with LA abnormality.

This allows calculation of sensitivity and specificity for this patient group:

- sensitivity = TP/(TP + FN) = 87/(87 + 5) = 0.946 (to three decimal places)
- specificity = TN/(TN + FP) = 83/(83 + 159) = 0.343 (to three decimal places).

The four cells in *Table 25* also allow uncertainty to be estimated for the joint distribution of sensitivity and specificity. One thousand draws from a Dirichlet distribution using the cell counts as parameter values were used to jointly calculate sensitivity and specificity. The resulting joint distribution of sensitivity and specificity estimates is shown in *Figure 4* as a contour plot. A contour plot represents variation in density by joining together points on the surface with equal heights, allowing three-dimensional information to be presented in a monochrome graph. This method of presenting the data was preferred to a scatterplot, as the relative density would have been relatively difficult to ascertain in a scatterplot containing 1000 points. In *Figure 4* the peak density of the plot is, unsurprisingly, close to the point estimates of 0.95 for sensitivity and 0.34 for specificity.

It was assumed that the derived distributions of sensitivity and specificity were applicable to all patients and were thus assumed applicable to patients who had a $CHADS_2$ score of 0.

Data reported in table 2 of Provedencia *et al.*[13] indicate that of 24 patients with a $CHADS_2$ score of 0, two had a LA abnormality. Given the small number of data available (the number in the LA abnormality group being <5) an uninformative prior of 0.5 was added to each paired data set, culminating in an expected 2.5 out of 25 patients expected to have a LA abnormality among those with a $CHADS_2$ score of 0. These values were used to populate beta distributions to allow for uncertainty in the true proportion of patients with LA abnormality within the $CHADS_2 = 0$ score.

TABLE 23 The data used to estimate sensitivity and specificity of TTE in diagnosing LA abnormality

Echocardiographic parameters: score	No. of patients	No. of patients with LA abnormality
0	88	5
≥1	246	87
Total	334	92

TABLE 24 The estimated accuracy of TTE in diagnosing LA abnormality

Feature	Patients with high-risk feature	Patients without high-risk feature
No high-risk feature identified by TTE	FN 5	TN 88 − 5 = 83
High-risk feature identified by TTE	TP 87	FP 246 − 87 = 159

For patients with a $CHADS_2$ score of 0 there were 17 patients out of 79 with a LA abnormality.

Estimating a patient's underlying risk of stroke

This section describes the risk of a stroke. The breakdown of types of stroke and the associated costs and utilities are detailed in later sections.

$CHADS_2$-related stroke risk

We assumed that higher $CHADS_2$ scores were associated with a higher risk of stroke. Our estimates were based on unadjusted stroke risk estimates presented in Friberg *et al.*[146] These estimates are presented in *Table 25* (95% CIs were estimated from beta distributions).

Patients with LAA were assumed to have a risk of stroke independent of $CHADS_2$ score. The risk was set as 8.0% (95% CI 7.26 to 8.31) per annum, as reported in Connelly *et al.*[147] For simplicity, the risk of stroke was assumed to apply throughout the lifetime of the patient.

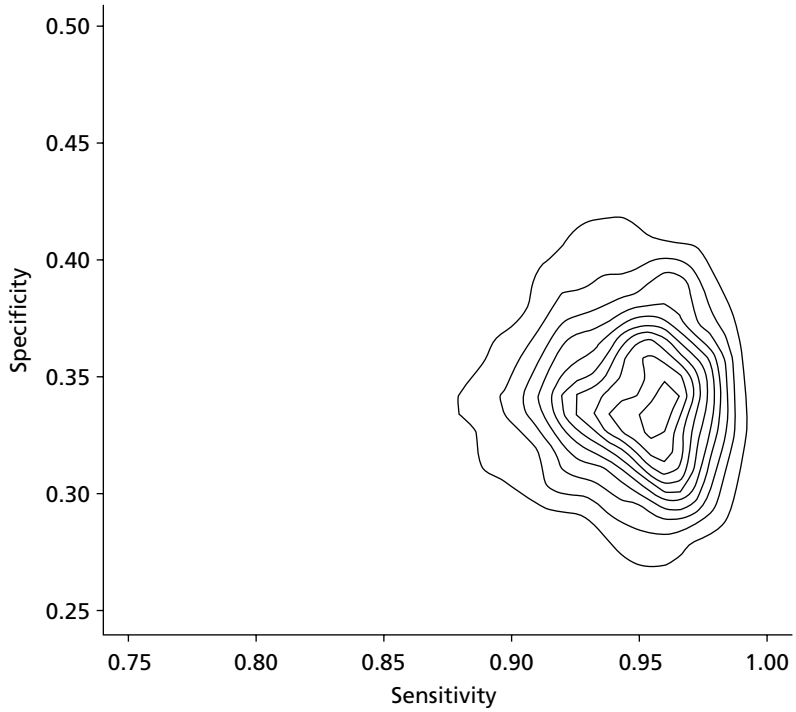


FIGURE 4 Joint distribution of sensitivity and specificity based on 1000 draws from a Dirichlet distribution.

TABLE 25 The assumed risk of stroke associated with $CHADS_2$ score

$CHADS_2$ score	Annual risk (95% CI)
0	0.6 (0.5 to 0.7)
1	3.0 (2.9 to 3.2)
2	4.2 (4.0 to 4.4)
3	7.1 (6.7 to 7.5)
4	11.1 (10.4 to 11.8)

Estimating uncertainty in $CHADS_2$-related stroke risk using $CHADS_2$ score

Introduction

Simulating values In order to ensure no estimated risks were less than zero, we assumed that the above estimates followed a log-normal distribution, producing 10,000 simulated values for the stroke risk associated with each score, as shown in *Figure 5*.

The estimated efficacy of each oral anticoagulant in preventing strokes

Effect of dabigatran on stroke risk

The effect of warfarin in preventing strokes was taken from a 2006 meta-analysis.[148] The effects of dabigatran and rivaroxaban compared with placebo (i.e. no treatment) were estimated using an indirect comparison approach. Estimates for the annual risk ratio of a stroke for patients given 150 mg of dabigatran twice daily compared with warfarin were taken from a paper based on the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study.[147] Data on the effect of rivaroxaban were taken from Patel *et al*.[149]

Overall, 1000 simulated values were sampled from each distribution, with derived values for dabigatran compared with placebo estimated by multiplying the RRs of the sampled warfarin compared with placebo value and the dabigatran compared with warfarin value, to produce a distribution of estimates of the RR of dabigatran compared with placebo (*Figure 6*). An identical methodology was used to produce a distribution of the RR of rivaroxaban compared with placebo.

Table 26 shows summary statistics from these two papers, as well as for the simulated distribution produced by combining the two, whereas the density functions of the three distributions are shown below (*Table 27*).

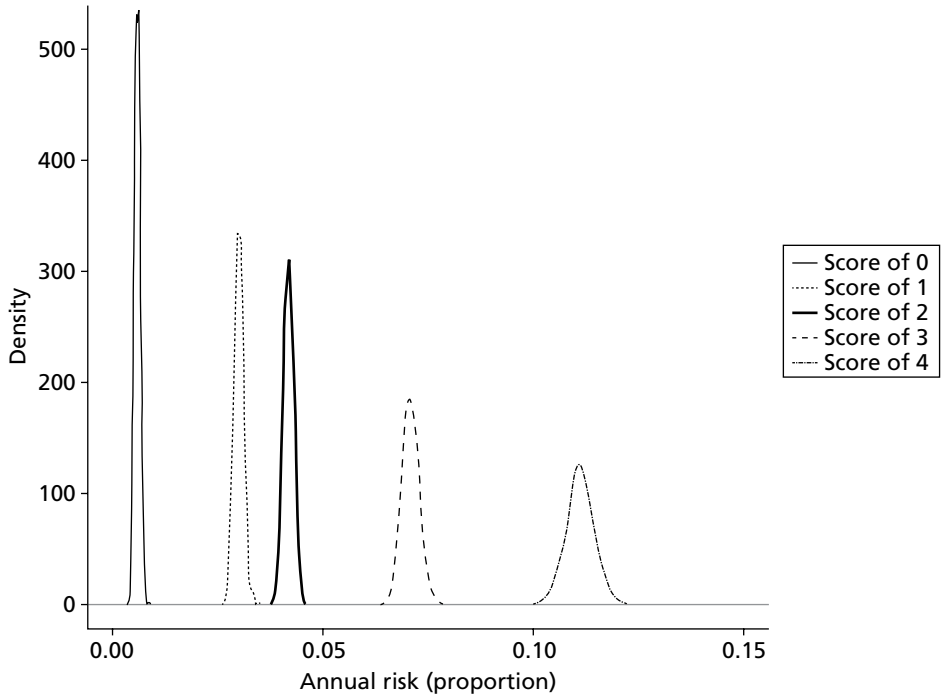


FIGURE 5 The estimated distribution of annual stroke risk by $CHADS_2$ score.

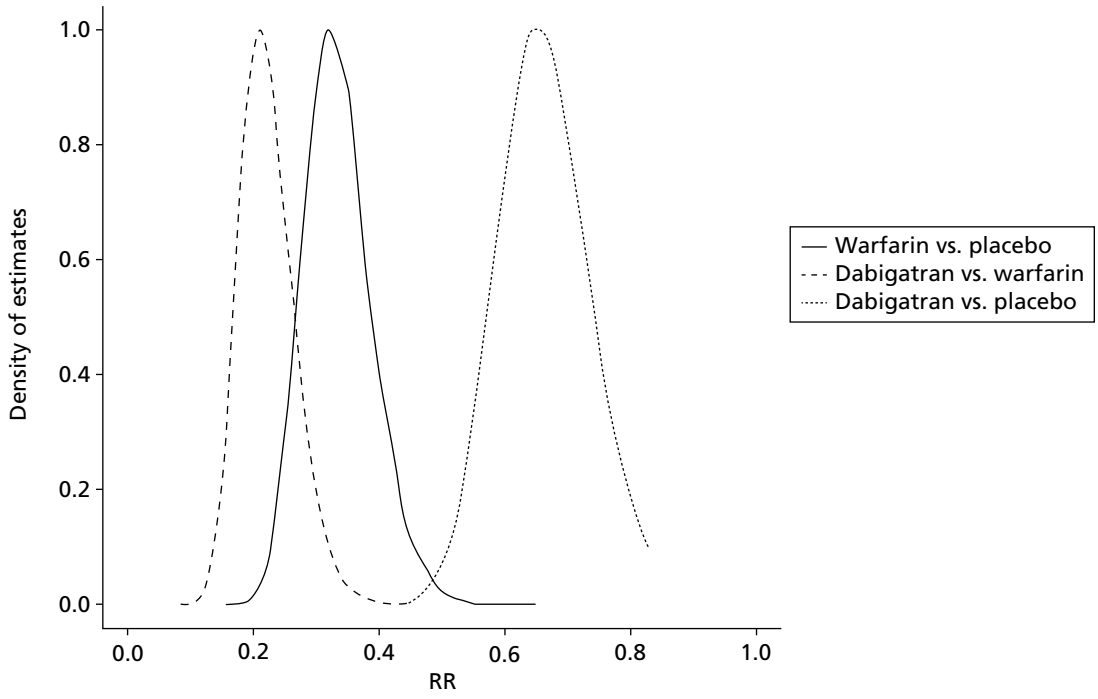


FIGURE 6 The assumed distributions of each OAC vs. placebo.

TABLE 26 Data on the reduction in stroke risk associated with each OAC

Comparison	RR (95% CI or CrI)	Assumed distribution	Source
RR: warfarin vs. placebo	0.33 (0.24 to 0.45)	Log-normal	Lip and Edwards 2006[148]
RR: dabigatran vs. warfarin	0.66 (0.53 to 0.82)	Log-normal	Connolly *et al.* 2009[147]
RR: dabigatran vs. placebo	0.22 (0.15 to 0.32)	Log-normal	Derived from above
RR: rivaroxaban vs. warfarin	0.88 (0.74 to 1.03)	Log-normal	Patel *et al.* 2011[149]
RR: rivaroxaban vs. placebo	0.30 (0.20 to 0.41)	Log-normal	Derived from above

CrI, credible interval.

TABLE 27 Simulated CrIs for the annual risk of bleed on dabigatran

Age group (years)	Central estimate (%)	Presumed sample size	95% CrI
<75	2.12	[a]3618[150]	1.66% to 2.60%
≥75	5.10	[b]2419[150]	4.22% to 5.99%

CrI, credible interval.

a Total participants reported aged <75 years of 10,855. Three arms in trial with equal probability of assignment.

b Total participants reported aged ≥75 years of 7258. Three arms in trial with equal probability of assignment.

The estimated risk of bleed associated with each oral anticoagulant

This section describes the risk of a major bleeding event. The breakdown of types of bleed and the associated costs and utilities are detailed in later sections.

The estimated risk of bleeding associated with dabigatran

The risk of major bleeding events in patients receiving dabigatran was based on results published using data from the RE-LY trial.[150] This reported that major bleeding events occurred at a rate of 2.12% per year in patients given dabigatran and who were <75 years of age, and at a rate of 5.10% in patients aged ≥75 years. A simulation approach, based on the binomial distribution and incorporating information about the different sample sizes of these two age groups within the trial, was used to represent uncertainty around these estimates for use within the probabilistic sensitivity analysis (PSA). *Table 27* presents credible intervals (CrIs) for these two age groups, and *Figure 7* shows these results graphically. CrIs were calculated using a presumed sample size: the paper reports 10,855 participants of <75 years and 7258 participants aged ≥75 years; an equal probability of assignment between the three trial arms was assumed.

The estimated risk of bleeding associated with warfarin

Results from the RE-LY study[150] were used to estimate the annual risk of bleed associated with warfarin, as shown in *Table 28*. The presumed sample sizes used for estimating the risk of bleeding in patients treated with dabigatran were also used in estimating the risk of bleeding associated with warfarin.

The estimated risk of bleeding associated with rivaroxaban

The annual risk of bleeding given rivaroxaban was estimated indirectly by combining estimates of the risk of bleed given warfarin compared with placebo[148] with estimates of the risk of bleed given rivaroxaban compared with warfarin.[149] The central estimates and CrIs are shown in *Table 29*. The presumed sample sizes used for estimating the risk of bleeding in patients treated with dabigatran were also used in estimating the risk of bleeding associated with warfarin.

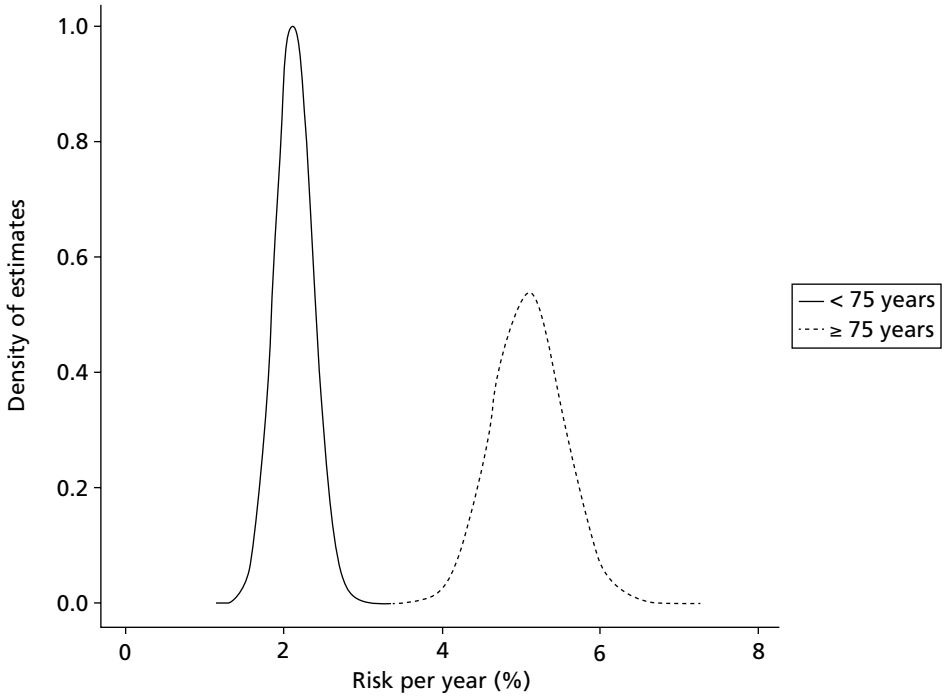


FIGURE 7 Distribution of simulated estimates for the annual risk of bleed on dabigatran.

TABLE 28 The assumed risk of bleeding associated with warfarin treatment

Age group (years)	Central estimate (%)	95% CrI
<75	3.04	2.49% to 3.62%
≥75	4.38	3.60% to 5.21%

TABLE 29 The assumed risk of bleeding associated with rivaroxaban treatment

Age group (years)	Central estimate (%)	95% CrI
<75 years	3.15	2.46% to 3.96%
≥75 years	4.55	3.57% to 5.70%

The assumed costs associated with each oral anticoagulant and with transthoracic echocardiography

Cost of dabigatran

This is assumed to cost £920.43 per year, assuming two 150-mg tablets daily at a cost of £2.52 per day.[142] This cost is fixed within all runs of the PSA.

Cost of rivaroxaban

The cost of rivaroxaban was assumed to be £767 per year, based on 20 mg per day.[151] This price was fixed in all runs.

Cost of warfarin

The annual cost of warfarin includes both drug costs and monitoring costs. The dosage received depends on the results of monitoring, although the costs of different dosages of drugs differ only marginally in comparison with the costs of monitoring. The annual monitoring costs were assumed to be £241 per annum, in line with assumptions made by the appraisal committee in the review of dabigatran.[142] The annual cost of the drug was taken from the *British National Formulary* (BNF) website, and suggested prices varied from 3.1 to 4.8 pence per tablet, depending on dose, equivalent to between £11.22 and £17.87 per year.[152]

Including monitoring costs, this suggests a range for average total costs of between £252.22 and £258.87 per year. The average of this range (£255.54) was used as the central estimate. In the PSA the total costs were assumed to be drawn from a uniform distribution ranging from £252.22 to £258.87.

Cost of transthoracic echocardiography

TTE has been estimated to cost £66 using HRG code RA60Z Simple Echocardiogram.[153] A second, more expensive estimate of £425 was listed for HRG code EA45Z Complex Echocardiogram (including Congenital, Transoesophageal and Fetal Echocardiography), which was deemed not appropriate for TTE. Consideration was given to the use of alternative values for the cost of TTE, such as £100 to allow for variation in cost. However, on viewing the initial results it was seen that a small change in the cost of TTE would not materially alter the cost per QALY. This was due to the main component of incremental costs being the costs associated with prescribing OACs minus any savings in the reduced numbers of stroke plus any additional costs associated with bleeding episodes.

Simulating the patient experience

Introduction

The long-term part of the model uses an individual-level DES approach to simulate health trajectories experienced by a large series of patients who experience competing risks of major health events.

Within a DES, an individual begins in one of a range of discrete states. They remain in this state until the 'next event' occurs. The next event the individual experiences, and the time they remain in their current state, are both determined by the competing risks of possible events that may occur next given the individual's current state. In this DES, the individual begins aged 60 years. They are assumed to be newly diagnosed patients with AF, and not to have previously taken OACs, and thus not to have a risk of experiencing a major bleeding event.

Extended example

Within the DES, the patient who enters the model is assigned a life expectancy using data from national life tables.[145] This produces a time to event against which other competing risks are compared. For example, for a patient aged 60 years and assigned a life expectancy of 75 years, this baseline next event is assigned a value of 15 years (75–60 years).

This value of 15 years is compared against the risk of alternative next events. The two alternative next events in this model are:

- risk of stroke
- risk of major bleeds due to an OAC.

Only if a patient is receiving an OAC do they experience a risk of major bleeds due to that OAC, and so this event will not occur in patients who are not receiving OACs. As previously discussed, taking an OAC reduces the risk of stroke, so patients not treated with an OAC have no risk of bleed but a higher risk of stroke.

In the DES, higher risks are represented by, on average, shorter times to competing next events. For example, if an event has a 20% risk of occurring per year then it has an expected time to occurrence of 5 years (1/0.2). An event with a 50% risk of occurring per year, however, has an expected time to occurrence of just 2 years (1/0.5). As events do not all occur at the expected time to occurrence, and have a range of times to occurrence around this expected time, simulated values for each of these times of events are sampled from exponential distributions parameterised by the expected time to occurrence.

Within the DES, the 'next event' an individual experiences is the event out of a series of candidate events with the shortest simulated time to occurrence. As a hypothetical example, consider *Table 30* for a 60-year-old patient on OACs.

TABLE 30 Hypothetical first 'next event' candidates for a 60-year-old patient in the model

Candidate event name	Annual probability	Sampled time to occurrence (years)	Candidate event selected
Death, not bleed or stroke related	NA (using life table data[145])	15	No
Stroke	0.050	18	No
Bleed	0.100	12	Yes

NA, not applicable.
The shading indicates that the events are not 'the next event' at this stage, and so are not selected.

Out of the three candidate next events, the event with shortest time to occurrence is that of a bleed. This means that the next event the individual experiences is a bleed, and that this event occurs 12 years from the patient's current age. In the model, the candidate's profile is updated to increase their age by 12 years and their most recent event to 'bleed'.

Assuming the bleed is non-fatal (discussed later), this updating of the patient's profile has knock-on effects for the subsequent next events too. As the individual is now 12 years older, the time to occurrence of the baseline candidate 'death due to other causes' has to be reduced by 12 years, from 15 years to 3 years. Having experienced a major side effect from the OAC, it is assumed the individual will no longer be prescribed the drug, as later detailed, so the risk of major bleeds is set to zero. However, in no longer being prescribed the OAC, the risk of stroke is increased. Assuming, for example, the annual risk of stroke increases as a result of this from 5% per year to 12.5% per year, the table of candidate next events that the individual (now 72 years old) could experience is as follows (*Table 31*).

As 'death from other causes' is the next event candidate with the shortest time to occurrence, it is this next event for this individual, and occurs 3 years after the previous event, at the age of 75 years.

Over the course of the 15 years from the age of 60–75 years for which this simulated individual lives, it is assumed that resources are consumed and QALYs accrued. These patterns of resource use and utility depend on the events experienced and the order they are experienced in, which is partly determined both by the patient's underlying risk of stroke and the decision made about whether or not to prescribe OACs, on the basis either of the $CHADS_2$-alone diagnostic strategy or the $CHADS_2$ + TTE diagnostic strategy.

The differences between the costs and utilities following these two diagnostic strategies are considered to result from the addition of TTE to the diagnostic package. As this is just one of a range of ways that information from TTE could improve clinical management of the patient, the estimates provided are thus partial and conservative estimates of the cost-effectiveness of TTE for this patient group.

Dynamic features of the model

Dynamic features of the model include:

- Updating the $CHADS_2$ score when a patient reaches the age of 75 years. This is because being aged ≥75 years is a risk factor within $CHADS_2$, and increases the $CHADS_2$ score by one point. This means the annual risk of stroke increases at the age of 75 years.
- Updating the $CHADS_2$ score by two points when a patient has a first stroke thus resulting in an increased risk of subsequent strokes.
- If a patient suffers a major bleeding event after taking OACs, they stop being prescribed the OACs, leading to the risk of bleeds reducing to zero, but the risk of stroke increasing.
- If a patient experiences a stroke and is not already taking an OAC, they are prescribed OACs, reducing the risk of stroke but increasing the risk of bleeds assuming that the patient had not previously had a bleed event.

TABLE 31 Hypothetical second 'next event' candidates for the above patient, now aged 72 years

Candidate event name	Annual probability	Sampled time to occurrence	Candidate event selected
Death, not bleed or stroke related	NA (using life table data[145])	3 years	Yes
Stroke	0.125	6 years	No
Bleed	0.000	Infinite	No

NA, not applicable.
The shading indicates that the events are not 'the next event' at this stage, and so are not selected.

- The risk of a major bleeding event when taking dabigatran (150 mg twice daily) was also assumed to change at the age of 75 years.
- The life expectancy given a Glasgow Outcome Scale state 2 (GOS2) was reduced to a maximum of 3.4 years.

The outcome following stroke

Not all strokes are the same in their consequences. The immediate outcome following a stroke is divided into three categories:

- death from stroke
- dependent state following stroke
- independent state following stroke.

Determining the category of stroke

This section describes the methods used to estimate the probabilities of different mutually exclusive states following a stroke, and the costs and utilities associated with each of these states.

The outcome following a stroke is estimated using a two-stage process, using data from Rivero-Arias *et al*.[154] This paper[154] reported that, of 1283 patients who had a stroke within the Oxford Vascular Study (OXVASC) cohort, 24.8% (319/1283) were dead within 24 months. Of those who survived, the degree of disability following the stroke was graded according to the modified Rankin Scale (mRS) 24 months after the event in 425 patients. For simplicity, this 24-month state is assumed to be the patient's permanent state until another event occurs, and the patients for whom mRS outcomes were reported were assumed to be representative of those for whom the data were not collected. The mRS has six discrete non-dead states, categorised 0–5, as shown in *Table 32*.

By convention, mRS states 0–2 are categorised as 'independent' states, and states 3–5 as 'dependent' states. Of those with mRS states recorded at 24 months, 74.1% of those living after a stroke were in an independent state, and 25.9% were in a dependent state, as indicated in *Figure 8*.

Uncertainty in the proportion of patients who survive a stroke was represented using a binomial distribution. As it is required for the accurate calculation of utility multipliers associated with dependent and independent states, the proportion of patients in each of the six mRS outcome states was used to parameterise a Dirichlet distribution in order to represent uncertainty in the distribution of non-dead outcome states following a stroke. These values were then converted back into estimated proportions of those alive in dependent and independent states following stroke. Results from the two-state (dead/alive)

TABLE 32 The mRS categories

mRS score	Category	Description
0	No symptoms	No symptoms at all
1	No significant disability	No significant disability despite symptoms; able to perform all usual duties and activities
2	Slight disability	Slight disability; unable to perform all normal activities but able to look after own affairs without assistance
3	Moderate disability	Moderate disability requiring some help but able to walk without assistance
4	Moderately severe disability	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention

Binomial simulation and the six-state (mRS 0–6) Dirichlet simulation were used to estimate uncertainty in the proportions of patient outcomes following stroke in the three mutually exclusive categories: 'dead', 'dependent stroke', and 'independent stroke'. The estimated proportions, together with 95% CrIs, are shown in *Table 33* and graphically in *Figure 9*.

The effect of a stroke on a patient's utility

The utilities associated with independent and dependent states following strokes were estimated from the same data set used to determine the outcome following stroke.[154]

Utility multipliers following a stroke were estimated from data that presented EuroQOL Five Dimension (EQ-5D) mapped utility estimates for the utility associated with each of the six mRS scores. As the mildest of these categories (mRS 0) is a full recovery, this is assumed to represent baseline patient utility. Multipliers for mRS 1–5 were thus calculated by dividing utility estimates of these worse states by the utility estimates of mRS 0. Uncertainty in both nominators and denominators were estimated using a simulation approach, with 10,000 random draws from EQ-5D estimates of each of the states mRS 1–5 divided by 10,000 random draws from the EQ-5D estimates for state mRS 0.

In order to derive estimates of the utility multiplier associated with both dependent and independent strokes, the proportions of each of the constituent mRS states within the dependent and independent stroke categories need to be estimated. Uncertainty in our knowledge of these proportions thus also needs to be represented. This is done as follows:

1. sample from a Dirichlet distribution with all six mRS states (as detailed in *Introduction*, above)
2. divide the six states into the independent stroke category (mRS 0–2) and dependent stroke category (mRS 3–5)

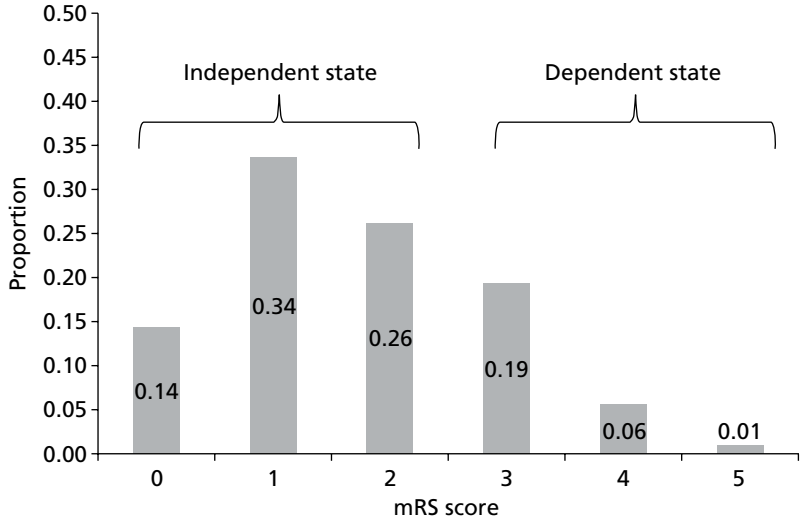


FIGURE 8 Distribution of stroke outcomes at 24 months (survivors at 24 months only).

TABLE 33 Estimated proportions of patient states following a stroke

State	Central estimate	95% CrI
Dead	0.25	0.23 to 0.27
Independent	0.56	0.52 to 0.59
Dependent	0.19	0.16 to 0.23

3. calculate the relative proportion of mRS states 0–2 within the independent stroke category, and relative proportion of mRS states 3–5 within the dependent stroke category
4. use weight utility multiplier estimates of mRS states 0, 1 and 2 in proportion to these states' relative prevalence within the independent stroke category, and weight utility multiplier estimates of mRS states 3, 4 and 5 in proportion to these states' relative prevalence within the dependent stroke category.

As our interest is in the mean utility multiplier for dependent and independent stroke multipliers, the mean values of 10,000 bootstraps of the distributions produced were then calculated in order to estimate both the means and uncertainty around the means. The mean utility multipliers produced are shown in *Table 34*.

For simplicity, it was assumed that patients who had a fatal stroke accrued no further QALYs. This is a limitation as not all patients would have died instantly; however, data that could be used to accurately populate this parameter were not identified.

Comparison with previous utility multiplier estimates

Our estimated utility multipliers are very similar to those presented by Dorman *et al.*[155] for independent strokes, but somewhat higher than those reported in that paper for dependent strokes. This is largely due to the distribution of mRS states within the 'independent stroke' and 'dependent stroke' categories, which for both categories of stroke are weighted towards less severe mRS states (as shown in *Figure 8*). In the case of dependent strokes (mRS 3–5), for example, only around 4% were the worst category mRS 5, which

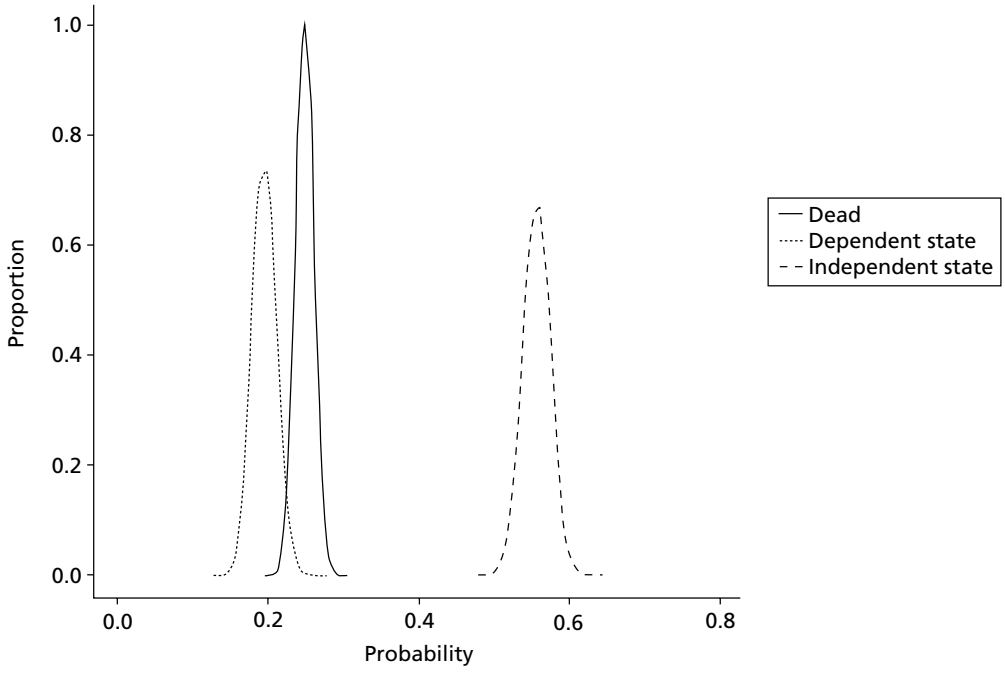


FIGURE 9 The estimated distribution of patients 24 months after a stroke.

TABLE 34 The estimated utility multipliers following a non-fatal stroke

Category	Central utility estimate (95% CrI)
Independent state	0.822 (0.819 to 0.824)
Dependent state	0.482 (0.477 to 0.487)

has an estimated EQ-5D score of around 0, and around 75% were in the least severe category mRS 3, which has an estimated EQ-5D score of >0.5. The discrepancy may reflect improvements in the prognosis following strokes in the decade that separates the studies used.

The assumed costs following stroke

Costs following categories of events were subdivided into one-off costs, such as the cost of admission to an emergency department, and ongoing costs, such as rehabilitation costs, which are assumed to continue indefinitely.

Cost of death due to stroke

The immediate costs associated with death due to a stroke were estimated using values reported in table 6 of a 2002 HTA report.[156] This reported that the mean length of intensive care hospital stay was between 33 and 34 days, and that the mean cost of stay was around £200 per day (95% CI £150 to £500). The mean length of stay was assumed to follow a uniform distribution ranging from 33 to 34 days, and the cost per night to follow a log-normal distribution owing to the asymmetry of the CIs and the fact that a negative cost is implausible.

A total of 10,000 draws from both distributions were combined in a random order to produce a distribution of estimated cost per death. Bootstrapping was used to simulate uncertainty in the mean of this distribution; 1000 draws from this bootstrapped distribution of means was used within the PSA. Costs were then inflation adjusted.[157] The estimated mean costs together with 95% CrIs are presented in *Table 35*.

Cost of dependent state due to stroke

The one-off cost of a patient entering a dependent state due to stroke was estimated using currency code AA22Z ('Non-transient Stroke or Cerebrovascular Accident, Nervous system infections of Encephalopathy') for long-stay non-elective inpatients from the NHS reference costs 2009–10.[153]

The ongoing cost of a patient in a dependent state due to stroke was estimated using data reported in the National Stroke Strategy Impact Assessment,[153] with costs inflation adjusted from 2005–6 to 2009–10 values.[157] A summary of these costs is presented in *Table 36*.

Cost of independent state due to stroke

The one-off cost of a patient entering an independent state due to stroke was estimated using currency code AA22Z ('Non-transient Stroke or Cerebrovascular Accident, Nervous system infections of Encephalopathy') for short-stay non-elective inpatients, from the NHS reference costs 2009–10.[153]

TABLE 35 Estimated mean cost of death due to stroke

Value	Central estimate (£) (95% CrI)
Cost of death due to stroke	9319 (9259 to 9378)

TABLE 36 Estimated mean cost of dependent state due to stroke

Value	Central estimate (£) (95% CrI)
One-off cost of a patient in a dependent state	2830 (2708 to 2952)
Ongoing annual cost of a patient in a dependent state	6386 (5749 to 7023)

The ongoing cost of a patient in an independent state owing to stroke was estimated using data reported in the National Stroke Strategy Impact Assessment,[157] with costs inflation adjusted from 2005–6 to 2009–10 values. A summary of these costs is presented in *Table 37*.

The outcome following major clinical bleed

Determining the category of major clinical bleed

Not all major clinical bleeds are the same in their consequences. The immediate outcome following a bleed is divided into three categories:

- death from major bleed
- non-fatal gastrointestinal (GI) haemorrhage
- non-fatal intracranial haemorrhage (ICH).

There is a wide variation in the effects of an ICH. To represent this variation, outcomes following non-fatal ICH are further subdivided into four distinct states according to the GOS (described later):

- GOS 2 vegetative state
- GOS 3 severely disabled
- GOS 4 moderately disabled
- GOS 5 good recovery.

The probabilities of discrete states following a bleed were calculated using a two-stage approach as described below.

Initial stage

In the model, three possible outcomes are assumed to result from a major bleeding event:

1. death from bleed
2. non-fatal GI haemorrhage
3. non-fatal ICH.

The proportions of these three events are estimated from table 79 of a 2009 HTA monograph,[158] which is derived from a 2003 meta-analysis.[159] Uncertainty about the relative distribution of these three outcomes was represented using a Dirichlet distribution. These results are shown in *Table 38*.

TABLE 37 The estimated mean cost following an independent stroke

Value	Central estimate (£) (95% CrI)
One-off cost of a patient in an independent state	542 (513 to 571)
Ongoing cost of a patient in an independent state	3195 (2871 to 3518)

TABLE 38 Probability of event categories following a major bleeding episode

Event category	Dirichlet distribution value	Central estimate (95% CrI)
Fatal bleed	22.7	0.11 (0.08 to 0.16)
Non-fatal GI	28.4	0.80 (0.74 to 0.84)
Non-fatal ICH	198.9	0.09 (0.06 to 0.13)

If a non-fatal ICH occurs, the effect of this bleed on patient outcome is simulated using data that maps outcomes on to the GOS, which categorises a patient's state after a traumatic brain injury.[160] Uncertainty about the relative distribution of these three outcomes was represented using a Dirichlet distribution. These results are shown in *Table 39* and use data in Holmes *et al*.[161]

A GOS state of 2 is associated with a severely reduced life expectancy. This was taken into account in the model by replicating an assumption in Holmes *et al.*,[161] reducing the life expectancy to 3.4 years where it was otherwise expected to be greater.

Utility multiplier following a major clinical bleed

Utility multiplier following a fatal bleed

It was assumed that the patient would die immediately following a bleeding-related mortality and that no further QALYs would be accrued.

Utility multiplier following a gastrointestinal haemorrhage

The effect of a GI haemorrhage on long-term quality of life is generally considered to be very small. A decision analysis by Goodacre *et al*.[162] assumed that the event resulted in no utility loss. A separate decision analysis model by Meenan *et al*.[163] used a utility multiplier of 0.997. Within the PSA, estimates were sampled from a uniform distribution with upper and lower bounds of 0.997 ± 0.003.

Utility multipliers following an intracranial haemorrhage

The utility following an ICH depends on the GOS state that follows from the haemorrhage. These range from a long-term vegetative state (GOS 2) to a good recovery. Both the GOS and mRS provide ordinal scales of disability and dependence following damage to the brain. By comparing the outcome descriptions for each of the non-fatal GOS states to those of the mRS states described in *Table 39*, we mapped each GOS state on to one or more mRS states. This allowed us to map utility values on to each GOS state using data from the same patient group that was used to inform the stroke utilities.[154] The methods used to derive the utility multipliers for each GOS state are very similar to those used to estimate utility multipliers following stroke, and also make the assumption that the distribution of the mRS states that the GOS states map on to is that reported at 24 months within the Rivero-Arias paper.[154] The assumed mapping between GOS scores and mRS scores, together with the estimated utility multipliers with 95% CrIs, are presented in *Table 40*.

The assumed costs following a major clinical bleed

Costs following categories of events were subdivided into one-off costs (such as the cost of admission to an emergency department) and ongoing costs (such as nursing), which are assumed to continue indefinitely. Mean costs were calculated by adding together distributions from component costs associated with the event then using a bootstrapping approach to identify the mean and uncertainty around the mean of the distribution.

TABLE 39 Probability of GOS categories following non-fatal ICH

Event category	Dirichlet distribution value	Central estimate (95% CrI)
GOS 2	115.5	0.12 (0.10 to 0.14)
GOS 3	140	0.14 (0.12 to 0.16)
GOS 4	79.3	0.08 (0.06 to 0.10)
GOS 5	665.1	0.67 (0.64 to 0.70)

Costs of a fatal major clinical bleed

The costs of a death due to haemorrhage were assumed to be identical to the costs of death due to stroke. This was a mean of £7019 with a 95% CrI of £6975 to £7064.

Costs of a gastrointestinal haemorrhage

The one-off cost of a GI haemorrhage was derived from *NHS Reference Costs 2009–2010*,[153] currency code FZ38E ('Gastrointestinal Bleed with length of stay 2 days or more without major CC') for non-elective inpatients. The central estimate plus 95% CIs are presented in *Table 41*.

Costs of an intracranial haemorrhage

The costs of an ICH were assumed to depend on the effects of the haemorrhage, as assessed using the GOS. As any intracranial bleed was assumed to be more costly than a GI haemorrhage, a cost equal to a GI bleed was added to the one-off costs of each of the GOS states. The specific one-off and ongoing costs associated with each GOS state are presented in *Table 42*.

Further details, including the reference sources and distributions of these component costs, are presented in *Table 43*.

The resulting combined cost estimates were bootstrapped. The bootstrapped estimates are shown in *Table 44*.

TABLE 40 Assumed relationship between GOS and mRS, and estimated utility multipliers for each GOS state

GOS state	Assumed equivalent to	Utility multiplier
GOS 2: vegetative state	mRS 6: dead	0
GOS 3: severely disabled	mRS 4: moderately severely disabled; and mRS 5: severely disabled	0.226 (95% CI 0.221 to 0.231)
GOS 4: moderately disabled	mRS 2: slight disability *and* mRS 3: moderate disability	0.642 (95% CI 0.638 to 0.645)
GOS 5: good recovery	mRS 0: no symptoms *and* mRS 1: no significant disability	0.895 (95% CI 0.892 to 0.898)

TABLE 41 Mean cost estimates for GI bleeds

Value	Central estimate (£) (95% CI)
One-off cost of GI bleed	1261 (1212 to 1310)

TABLE 42 Cost components for GOS states

GOS state	One-off costs	Ongoing costs
GOS 2	GI equivalent costs + GOS 2 intensive care costs + GOS 2 rehabilitation costs	Nursing home costs
GOS 3	GI equivalent costs + intracranial procedures costs	GOS 3 annual care costs
GOS 4	GI equivalent costs + intracranial procedures costs + GOS 4 rehabilitation costs	None
GOS 5	GI equivalent costs	None

TABLE 43 Details and sources of component costs associated with different GOS states

Cost component name	Distribution	Details	Source
GI equivalent costs	Normal ($\mu = 1261$, $\sigma = 25$)	Code FZ38E	Department of Health[153]
GOS 2 intensive care costs	Gamma ($\alpha = 165$, $\beta = 6$)		Holmes[161]
GOS 2 rehabilitation costs	Gamma ($\alpha = 250$, $\beta = 120$)		Holmes[161]
Nursing home costs	52 × gamma ($\alpha = 159$, $\beta = 6$)		Holmes[161]
Intracranial procedures costs	Normal ($\mu = 8829$, $\sigma = 633$)	Code AA17Z	Department of Health[153]
GOS 3 annual care cost	Gamma ($\alpha = 326$, $\beta = 104$)		Holmes[161]
GOS 4 rehabilitation costs	Gamma ($\alpha = 385$, $\beta = 45$)		Holmes[161]

TABLE 44 Estimated costs associated with different GOS outcomes

State	Mean one-off costs (£) (95% CrI)	Mean ongoing cost (£) (95% CrI)
GOS 2	46,785 (40,895 to 53,250)	50,047 (49,645 to 50,434)
GOS 3	10,096 (8849 to 11,363)	33,949 (33,843 to 33,969)
GOS 4	27,419 (22,582 to 32,964)	None
GOS 5	1261 (1211 to 1309)	None

Analyses undertaken

To facilitate the interpretation of results four cohorts of patients were simulated assuming that $CHADS_2$ was the prevalent tool. These four cohorts were patients with a $CHADS_2$ score of 0 (1 when considering warfarin) who:

1. have LA abnormality that was detected by TTE
2. have LA abnormality that was not detected by TTE
3. do not have LA abnormality that was not detected by TTE
4. do not have LA abnormality but where a TTE indicated that LA abnormality was present.

The first two cohorts represent higher risk patients, the remaining two cohorts represent low-risk patients. Cohort 1 represents a TP, cohort 2 represents a FN, cohort 3 represents a TN and cohort 4 represents a FN. For the baseline strategy where TTE is not used, all patients will be in cohorts 2 and 3, with the proportion in cohort 2 equal to the number of patients who actually have LA abnormality.

The results for each cohort were then weighted by the numbers of people in each cohort to form an overall estimation of costs and QALY for the entire population with the given $CHADS_2$ score.

The main results section of the report presents, for each of the 14 pairs of comparisons made: summary statistics of the patient experience simulated in both the no-TTE and TTE strategies; a scatterplot of the output of the PSA;[164] the cost-effectiveness acceptability frontier (CEAF) over willingness-to-pay thresholds ranging from £0/QALY to £50,000/QALY;[165] and mean costs, QALYs and incremental cost-effectiveness ratios (ICERs) estimated from the mathematic models. The CEAF* was used as it incorporates information from both expected value of perfect information (EVPI) analyses and cost-effectiveness acceptability curves in a single measure. (*If there is no solid line in the figure, this indicates that the screening option is not optimal over all willingness-to-pay thresholds ranging from £0/QALY to £50,000/QALY.)

The EVPI was estimated. This provides the maximum level of investment that a funding body would be prepared to pay to eliminate all uncertainty in the decision problem.[166] In calculating EVPI an estimation of the number of patients who will be affected by the decision is required. We have performed a crude estimate that, assuming that the incidence of AF was 1 per 1000 person-years (approximately the pooled rate for women and men aged 55–64 years reported by the Renfrew/Paisley study),[16] there are 6.7 million people aged between 55 and 64 years in England and Wales;[145] 6% of these people are in the $CHADS_2$ 0 category;[13] and the information is relevant for 10 years. These broad estimates indicate that around 70,000 people would benefit from there being no uncertainty regarding whether TTE is cost-effective. Because a large number of subpopulations were considered, this was considered an upper estimate of the population EVPI to consider in each comparison. For illustration, the population EVPI is presented for each comparison assuming population sizes of 25,000, 50,000 and 75,000 people.

A more complex value of information analyses, EVPPI (expected value of partial perfect information), which indicates the maximum level of investment to reduce uncertainty in a subset of one or more parameters,[167] could not be undertaken for computational reasons. This is because each PSA run of 1000 iterations, for each of the 14 groups considered, took approximately 1 hour to run, meaning that EVPPI would take approximately 14,000 hours to run, equivalent to over 1.5 years of uninterrupted computing time.

Instead, to provide further information, sensitivity analyses were undertaken on two key parameters: the proportion of patients with LA abnormality and the joint uncertainty in the sensitivity and specificity of TTE in detecting LA abnormality.

An alternative simplified methodology was also undertaken. This simply divided the assumed cost per QALY threshold £20,000 by the cost of performing a TTE (£66) to provide the threshold QALYs required for TTE to be cost-effective, were it assumed that there would be further benefits than in identifying LA abnormality.

Results

Main clinical effectiveness and cost-effectiveness results: comparison of transthoracic echocardiography and no-transthoracic echocardiography strategies

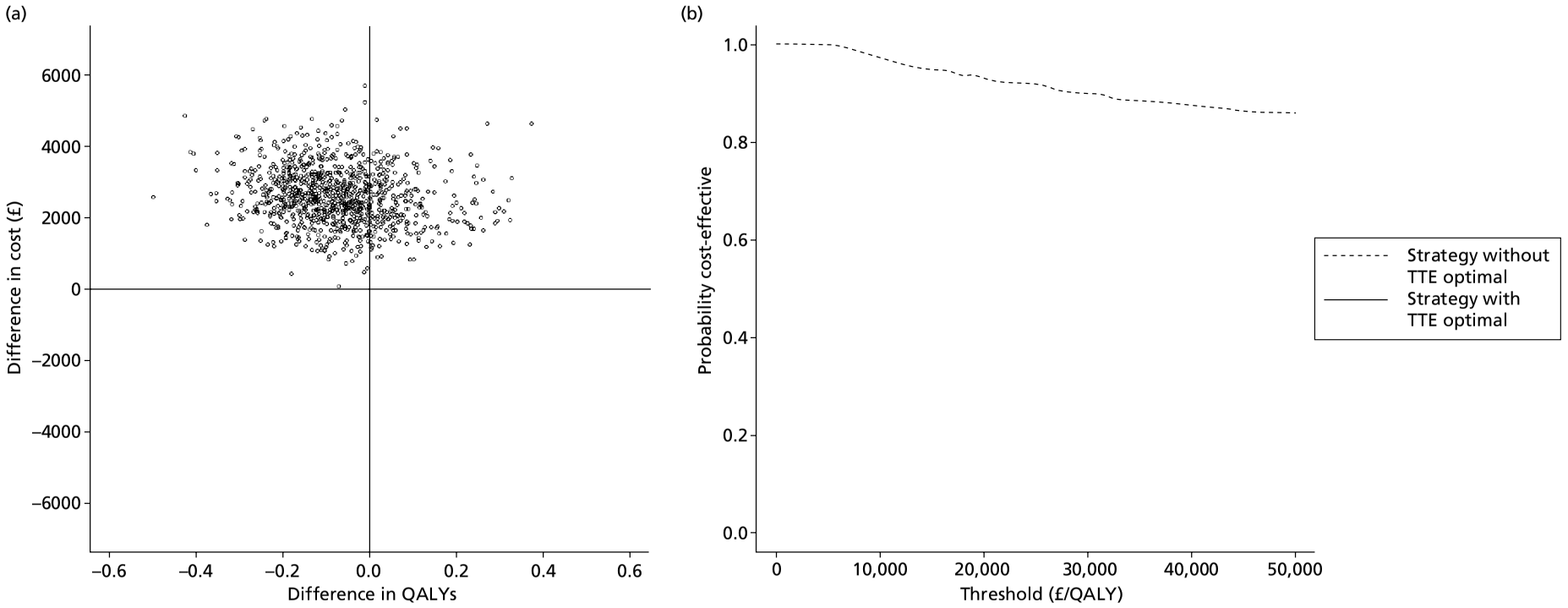
Fifty-year-old males, initial $CHADS_2$ score of 0, informing the decision whether to treat patients with warfarin

Summary results for this treatment option and patient group are shown in *Table 45* and *Figure 10*, below. They indicate that the majority of the PSA scatterplot is in the north-west quadrant, suggesting that the addition of TTE is ruled out by simple dominance in this patient group when using warfarin as the OAC. This is confirmed in the table of results, indicating that the mean cost of conducting full TTE screening is greater than not screening, whereas the mean QALY score is lower. Summary statistics from the patient

TABLE 45 Summary of patient experience simulation comparing TTE and no-TTE strategies in 50-year-old males, with an initial $CHADS_2$ score of 0, in informing the decision whether to treat patients with warfarin

Strategy	Life-years	Cause of death (%)			Average no. of events			
		Stroke	Bleed	Other	Dependent strokes	Independent strokes	ICH	NICH
No initial treatment	28.840	11.7	1.3	87.1	0.120	0.242	0.010	0.075
TTE with those diagnosed with LA abnormality treated	28.928	10.8	1.8	87.4	0.111	0.223	0.014	0.112

NICH, non-intracranial haemorrhage.



(c)

W_50_0_M	Mean cost	Mean QALY
No TTE	£2459	13.60
TTE	£4712	13.51

	Mean	Jackknifed 95% CrI
ICER (£/QALY)	−£26,489	−£26,552 to −£26,408
Interpretation:	Dominated	

FIGURE 10 Probabilistic sensitivity analysis scatterplots, CEAFs and mean ICERs in the W_50_0_M comparison. (a) Scatterplot of difference in costs (£) against difference in QALYs. (b) CEAF (If there is no solid line in the figure, this indicates that the screening option using TTE is not optimal over all willingness-to-pay thresholds ranging from £0/QALY to £50,000/QALY.) (c) Mean costs, QALYs and ICERs.

experience simulation indicate that although the number of deaths from stroke is predicted to reduce as a result of using TTE in this way, the number of deaths due to major bleeding events is predicted to increase.

The CEAF indicates that not screening (dashed line) remains the optimal choice compared with screening (solid line) at willingness-to-pay thresholds varying from £0/QALY to £50,000/QALY. In this case, the addition of TTE is not predicted to be the optional choice at willingness-to-pay thresholds of either £20,000/QALY or £30,000/QALY.

Fifty-year-old females, initial $CHADS_2$ score of 0, treated with warfarin

Summary results for this treatment option and patient group are shown in *Table 46* and *Figure 11*, below. They also indicate that the majority of the PSA scatterplot is in the north-west quadrant, suggesting that the addition of TTE is ruled out by simple dominance in this patient group when using warfarin as the OAC. This is confirmed in the table of results, indicating that the mean cost of conducting full TTE screening is greater than not screening, whereas the mean QALY score is lower. Summary statistics from the patient experience simulation indicate that although the number of deaths from stroke is predicted to reduce as a result of using TTE in this way, the number of deaths due to major bleeding events is predicted to increase.

The CEAF indicates that not screening (dashed line) remains the optimal choice compared with screening (solid line) at willingness-to-pay thresholds varying from £0/QALY to £50,000/QALY. In this case, the addition of TTE is not predicted to be the optional choice at willingness-to-pay thresholds of either £20,000/QALY or £30,000/QALY.

Sixty-five-year-old males, initial $CHADS_2$ score of 0, treated with warfarin

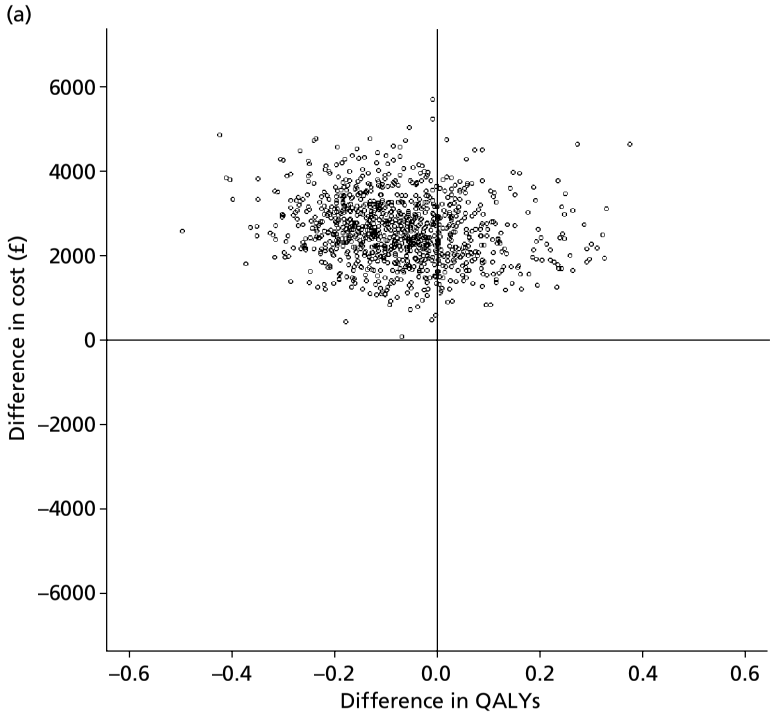
Summary results for this treatment option and patient group are shown in *Table 47* and *Figure 12*. The PSA scatterplot suggests that although the use of TTE is clearly associated with increased costs, it is not associated with substantially increased predicted QALYs. This is confirmed by the table in *Figure 12c*, which shows the TTE strategy to cost almost £1000 more than the no-TTE strategy, but to result in almost no increase in QALYs. Summary statistics from the patient experience simulation indicate that although the number of deaths from stroke is predicted to reduce as a result of using TTE in this way, the number of deaths due to major bleeding events is predicted to increase.

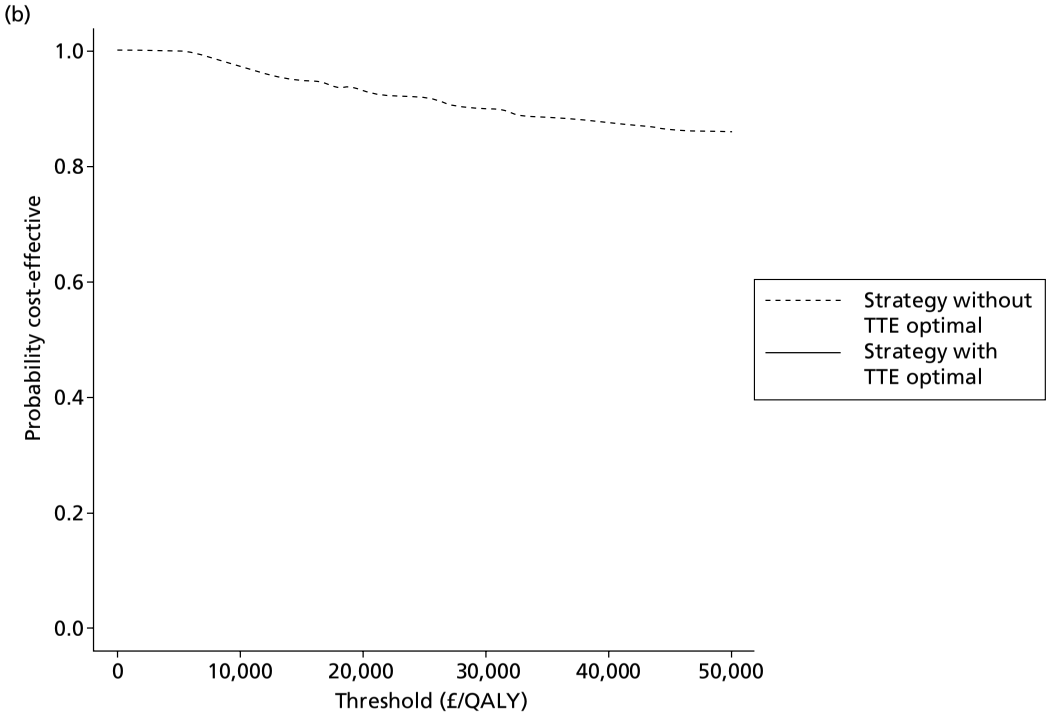
The CEAF indicates that not screening (dashed line) remains the optimal choice compared with screening (solid line) at willingness-to-pay thresholds varying from £0/QALY to £50,000/QALY. In this case, the addition of TTE is not predicted to be the optional choice at willingness-to-pay thresholds of either £20,000/QALY or £30,000/QALY.

TABLE 46 Summary of patient experience simulation comparing TTE and no-TTE strategies in 50-year-old females with initial $CHADS_2$ score of 0, treated with warfarin

		Cause of death (%)			Average no. of events			
Strategy	Life-years	Stroke	Bleed	Other	Dependent Strokes	Independent Strokes	ICH	NICH
No initial treatment	31.633	13.5	1.6	84.9	0.139	0.278	0.012	0.091
TTE with those diagnosed with LA abnormality treated	31.734	12.6	2.1	85.2	0.130	0.259	0.017	0.130

NICH, non-intracranial haemorrhage.





(c)

W_50_0_F	Mean cost	Mean QALY
No TTE	£2815	14.27
TTE	£5405	14.19

	Mean	Jackknifed 95% CrI
ICER (£/QALY)	−£34,078	−£34,175 to −£33,952
Interpretation:	Dominated	

FIGURE 11 Probabilistic sensitivity analysis scatterplots, CEAFs and mean ICERs in the W_50_0_F comparison. (a) Scatterplot of difference in costs (£) against difference in QALYs. (b) CEAF (If there is no solid line in the figure, this indicates that the screening option using TTE is not optimal over all willingness-to-pay thresholds ranging from £0/QALY to £50,000 per QALY.) (c) Mean costs, QALYs and ICERs.

TABLE 47 Summary of patient experience simulation comparing TTE and no-TTE strategies in 65-year-old males with initial $CHADS_2$ score of 0, treated with warfarin

		Cause of death (%)			Average no. of events			
Strategy	Life-years	Stroke	Bleed	Other	Dependent strokes	Independent strokes	ICH	NICH
No initial treatment	17.131	9.0	0.9	90.2	0.087	0.192	0.007	0.052
TTE with those diagnosed with LA abnormality treated	17.204	8.0	1.3	90.7	0.078	0.172	0.010	0.079

NICH, non-intracranial haemorrhage.

Sixty-five-year-old females, initial $CHADS_2$ score of 0, treated with warfarin

Summary results for this treatment option and patient group are shown in *Table 48* and *Figure 13*. The PSA scatter indicates that slightly more of the estimates were in the north-east than the north-west quadrant. The table in part (c) of *Figure 13* shows that the differences in mean costs between strategies are around £1000, but the differences in mean QALYs are less than one-tenth of a QALY. The mean ICER is around £40,000/QALY, and the CEAF indicates that the TTE strategy (solid line) is unlikely to be the optimal decision at standard NICE willingness-to-pay thresholds of £20,000/QALY and £30,000/QALY.

Fifty-year-old males, initial $CHADS_2$ score of 1, treated with warfarin

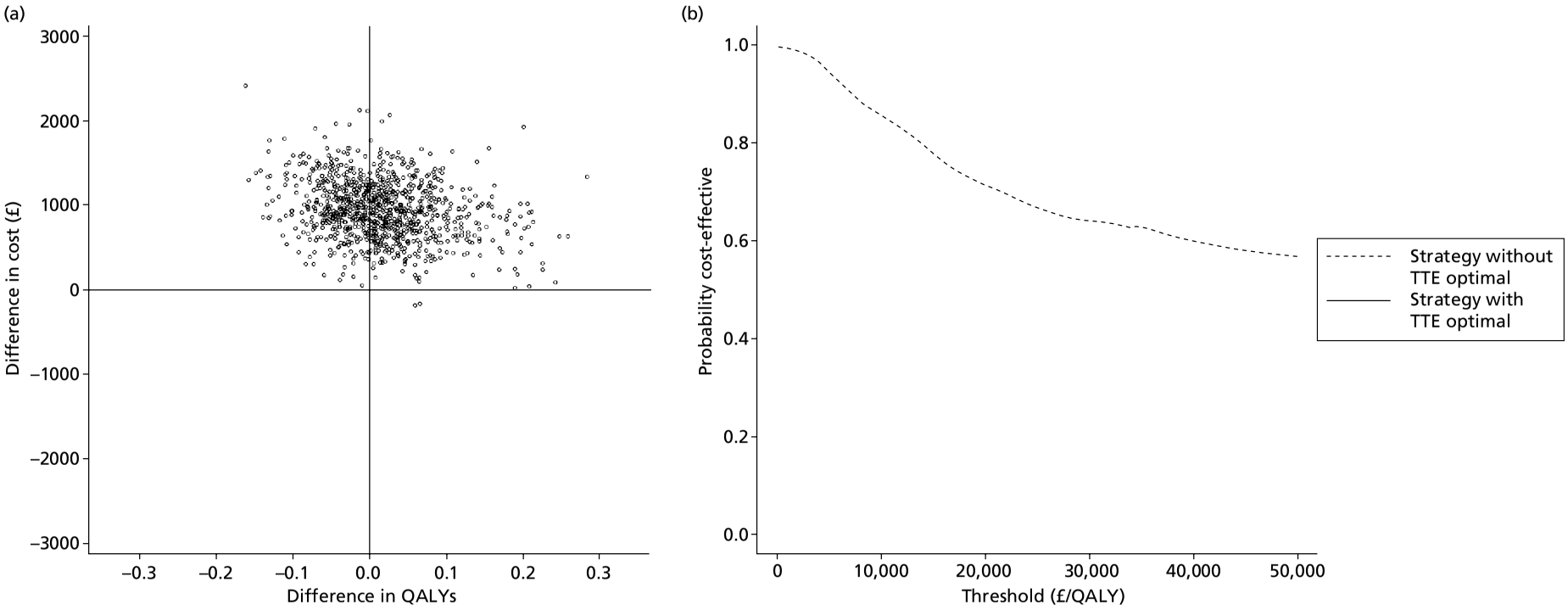
In this patient group and treatment option (*Table 49*) the mathematical model shows that the majority of the estimates from the PSA (as shown in *Figure 14a*) are in the north-east quadrant, indicating that the TTE strategy is both more costly and more effective than the no-TTE strategy. There is a difference in mean QALYs between the two strategies of approximately half a QALY (the table shown in *Figure 14c*) and difference in mean costs of approximately £3000. The mean ICER is estimated to be slightly over £6000/QALY, and the CEAF indicates that, compared with the no-TTE strategy (dashed line), the TTE strategy (solid line) appears optimal at both the £20,000/QALY and £30,000/QALY willingness-to-pay thresholds; at both thresholds the probability that the TTE strategy is more cost-effective is estimated to be >99%.

Fifty-year-old females, initial $CHADS_2$ score of 1, treated with warfarin

In this patient group and treatment option (*Table 50*) the mathematical model shows that the majority of the estimates from the PSA (as shown in *Figure 15a*) are in the north-east quadrant, indicating that the TTE strategy is both more costly and more effective than the no-TTE strategy. There is a difference in mean QALYS between the two strategies of approximately half a QALY (the table in *Figure 15c*) and a difference in mean costs of approximately £3000 . The mean ICER is estimated to be slightly over £7000/QALY, and the CEAF indicates that, compared with the no-TTE strategy (dashed line), the TTE strategy (solid line) appears optimal at both the £20,000/QALY and £30,000/QALY willingness-to-pay thresholds; at both thresholds the probability that the TTE strategy is more cost-effective is estimated to be >99%.

Sixty-five-year-old males, initial $CHADS_2$ score of 1, treated with warfarin

In this patient group and treatment option (*Table 51*) the mathematical model shows that the majority of the estimates from the PSA (as shown in *Figure 16a*) are in the north-east quadrant, indicating that the TTE strategy is both more costly and more effective than the no-TTE strategy. There is a difference in mean QALYs between the two strategies (the table in *Figure 16c*) of approximately one-fifth of a QALY and a difference in mean costs of approximately £2500. The mean ICER is estimated to be around £11,000/QALY, and the CEAF indicates that, compared with the no-TTE strategy (dashed line), the TTE strategy (solid line) appears optimal at both the £20,000/QALY (93% probability most cost-effective) and £30,000/QALY (98.5% probability most cost-effective) willingness-to-pay thresholds.



(c)

W_65_0_M	Mean cost	Mean QALY
No TTE	£1527	9.12
TTE	£2467	9.13

	Mean	Jackknifed 95% CrI
ICER (£/QALY)	£66,793	£66,217 to £67,599
Interpretation:	Neither dominated nor dominating	

FIGURE 12 Probabilistic sensitivity analysis scatterplots, CEAFs and mean ICERs in the W_65_0_M comparison. (a) Scatterplot of difference in costs (£) against difference in QALYs. (b) CEAF (If there is no solid line in the figure, this indicates that the screening option using TTE is not optimal over all willingness-to-pay thresholds ranging from £0/QALY to £50,000 per QALY.) (c) Mean costs, QALYs and ICERs.

TABLE 48 Summary of patient experience simulation comparing TTE and no-TTE strategies in 65-year-old females with initial $CHADS_2$ score of 0, treated with warfarin

		Cause of death (%)			Average no. of events			
Strategy	Life-years	Stroke	Bleed	Other	Dependent strokes	Independent strokes	ICH	NICH
No initial treatment	19.447	10.6	1.1	88.3	0.105	0.225	0.009	0.065
TTE with those diagnosed with LA abnormality treated	19.531	9.6	1.6	88.8	0.096	0.205	0.012	0.095

NICH, non-intracranial haemorrhage.

Sixty-five-year-old females, initial $CHADS_2$ score of 1, treated with warfarin

In this patient group and treatment option (*Table 52*) the mathematical model the majority of the estimates from the PSA (as shown in *Figure 17a*) are in the north-east quadrant, indicating that the TTE strategy is both more costly and more effective than the no-TTE strategy. There is a difference in mean QALYs between the two strategies of approximately one-fifth of a QALY (the table in *Figure 17c*) and a difference in mean costs of approximately £4000. The mean ICER is estimated to be slightly < £15,000/QALY, and the CEAF indicates that, compared with the no-TTE strategy (dashed line), the TTE strategy (solid line) appears optimal at both the £20,000/QALY (73% probability most cost-effective) and £30,000/QALY (92% probability most cost-effective) willingness-to-pay thresholds.

Fifty-year-old males, initial $CHADS_2$ score of 0, treated with rivaroxaban

In this patient group and treatment option (*Table 53*) the mathematical model slightly more of the estimates from the PSA are in the north-west than north-east quadrant, implying that the TTE strategy is likely to be ruled out by simple dominance compared with the no-TTE strategy. This is confirmed by the mean values, which indicate that the TTE strategy is around £2000 more expensive and slightly less effective than the no-TTE strategy. The CEAF (*Figure 18*) indicates that the TTE strategy (solid line) does not appear to be the optimal strategy at all willingness-to-pay thresholds from £0/QALY to £50,000/QALY compared with the no-TTE strategy (dashed line).

Fifty-year-old females, initial $CHADS_2$ score of 0, treated with rivaroxaban

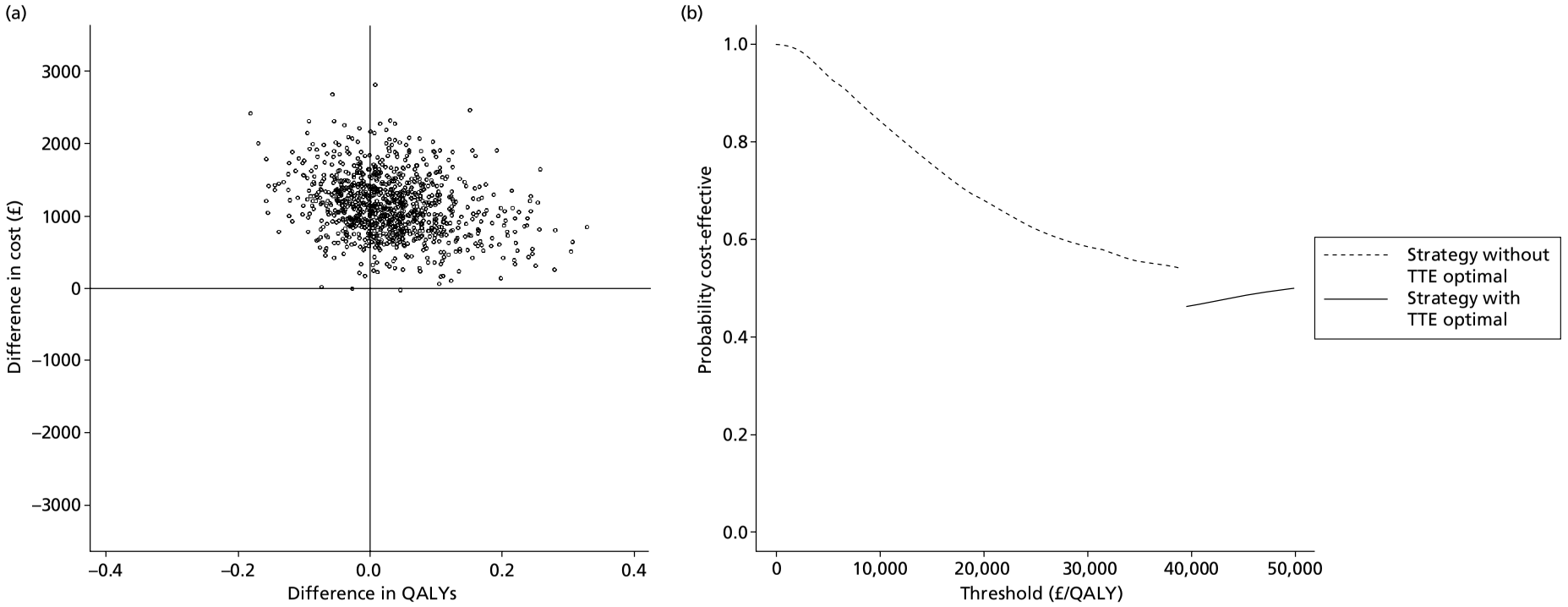
In this patient group and treatment option (*Table 54*) the mathematical model slightly more of the estimates from the PSA are in the north-west than north-east quadrant, implying that the TTE strategy is likely to be ruled out by simple dominance compared with the no-TTE strategy. This is confirmed by the mean values, which indicate that the TTE strategy is around £2500 more expensive and slightly less effective than the no-TTE strategy. The CEAF (*Figure 19*) indicates that the TTE strategy (solid line) does not appear to be the optimal strategy at all willingness-to-pay thresholds from £0/QALY to £50,000/QALY compared with the no-TTE strategy (dashed line).

Sixty-five-year-old males, initial $CHADS_2$ score of 0, treated with rivaroxaban

For this patient group and treatment combination (*Table 55*), the majority of the PSA scatterplot (*Figure 20a*) is either in the north-east or north-west quadrant. Slightly more of the scatterplot appears to be in the north-east quadrant, and the TTE strategy has both a greater mean cost and greater mean QALY estimate than the no-TTE strategy. The mean ICER is slightly over £30,000, and the CEAF (see *Figure 20b*) indicates that the TTE strategy is still not the optimal strategy compared with no TTE at the £30,000/QALY threshold; the TTE strategy is estimated to become optimal only at around £33,700/QALY.

Sixty-five-year-old females, initial $CHADS_2$ score of 0, treated with rivaroxaban

The mathematical model results (*Table 56*) suggest that the TTE strategy is more expensive and slightly more clinically effective, on the average, than the no-TTE strategy, with the PSA scatterplot appearing



(c)

W_65_0_F	Mean cost	Mean QALY
No TTE	£1974	9.94
TTE	£3106	9.97

	Mean	Jackknifed 95% CrI
ICER (£/QALY)	£39,485	£39,291 to £39,754
Interpretation:	Neither dominated nor dominating	

FIGURE 13 Probabilistic sensitivity analysis scatterplots, CEAFs and mean ICERs in the W_65_0_F comparison. (a) Scatterplot of difference in costs (£) against difference in QALYs. (b) CEAF. (c) Mean costs, QALYs and ICERs.

TABLE 49 Summary of patient experience simulation comparing TTE and no-TTE strategies in 50-year-old males with initial $CHADS_2$ score of 1, treated with warfarin

Strategy	Life-years	Cause of death (%)			Average no. of events			
		Stroke	Bleed	Other	Dependent strokes	Independent strokes	ICH	NICH
No initial treatment	25.921	22.6	2.7	74.7	0.235	0.463	0.019	0.156
TTE with those diagnosed with LA abnormality treated	26.250	20.8	3.5	75.7	0.218	0.424	0.025	0.208

NICH, non-intracranial haemorrhage.

slightly more predominant in the north-east than the north-west quadrant. The mean ICER estimate is slightly > £20,000, and the CEAF indicates that the TTE strategy starts to become optimal at a willingness-to-pay threshold of approximately £21,000/QALY (*Figure 21*). If the willingness-to-pay threshold is £30,000 then the TTE strategy is estimated to have a 55% probability of being most cost-effective.

Sixty-five-year-old males, initial $CHADS_2$ score of 0, treated with dabigatran

The mathematical model results (*Table 57*) suggest that the TTE strategy is more expensive and slightly more clinically effective, on the average, than the no-TTE strategy, with the PSA scatterplot appearing slightly more predominant in the north-east than the north-west quadrant. The mean ICER estimate is slightly < £15,000, and the CEAF indicates that the TTE strategy starts to become optimal at a willingness-to-pay threshold of approximately £13,800/QALY (*Figure 22*). If the willingness-to-pay threshold is £20,000, then the TTE strategy is estimated to have a 57% probability of being most cost-effective, and with a willingness-to-pay threshold of £30,000 the TTE strategy has a 65% probability of being most cost-effective.

Sixty-five-year-old females, initial $CHADS_2$ score of 0, treated with dabigatran

The mathematical model results (*Table 58*) suggest that the TTE strategy is more expensive and slightly more clinically effective, on the average, than the no-TTE strategy, with the PSA scatterplot appearing slightly more predominant in the north-east quadrant than in the north-west quadrant. The mean ICER estimate is slightly over £12,000, and the CEAF (*Figure 23*) indicates that the TTE strategy starts to become optimal at a willingness-to-pay threshold of approximately £11,800/QALY. If the willingness-to-pay threshold is £20,000 then the TTE strategy is estimated to have a 64% probability of being most cost-effective, and with a willingness-to-pay threshold of £30,000 the TTE strategy has a 72% probability of being most cost-effective.

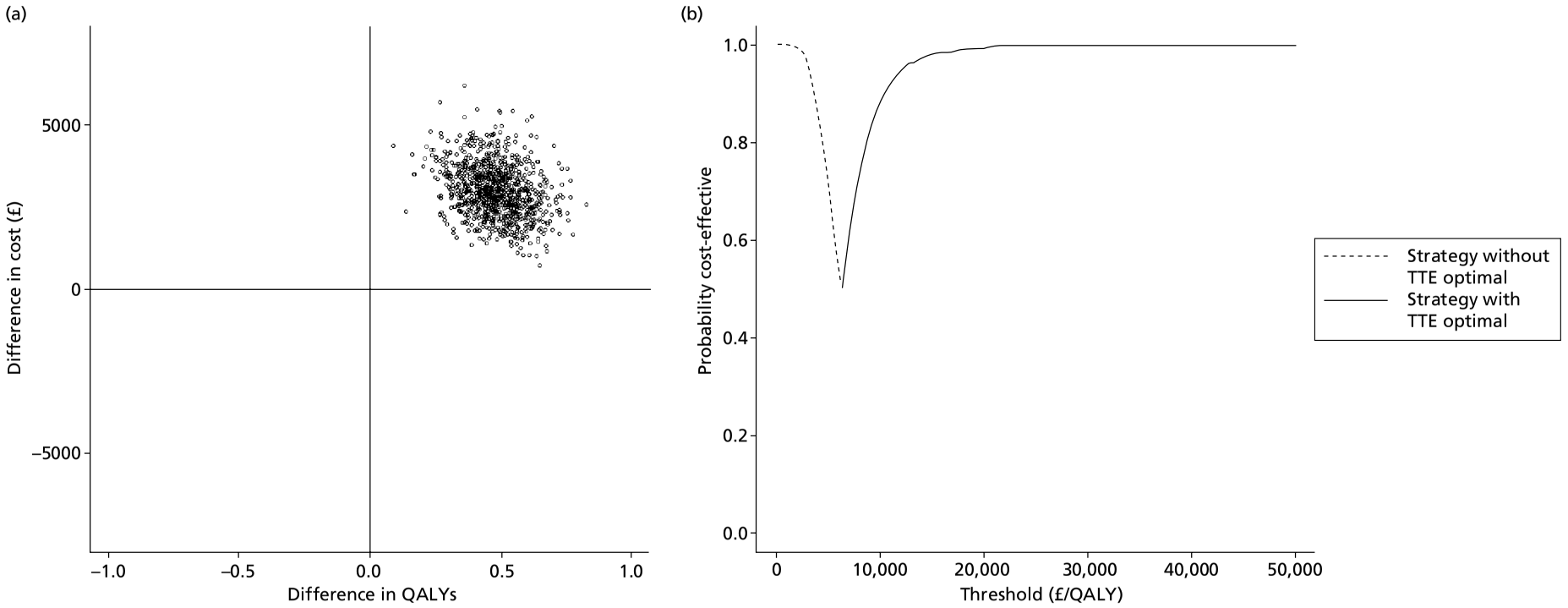
Expected value of perfect information results

The individual EVPI curves for maximum acceptable incremental cost-effectiveness ratios (MAICERs) varying from £0/QALY to £50,000/QALY are presented in *Figure 24*. In this table, the estimated individual EVPI at £20,000/QALY and £30,000/QALY, and corresponding population EVPIs assuming populations ranging from 25,000 to 75,000 people, are also presented for each of the 14 comparisons considered.

Sensitivity of incremental cost-effectiveness ratios to joint sensitivity and specificity of transthoracic echocardiography, and true prevalence of left atrial abnormality

In order to explore the influence of certain parameters on the cost-effectiveness estimates, the effects of changing the sensitivity and specificity estimates, holding all other values at their means, were calculated for each of the 14 comparisons. These are presented in *Appendix 11*.

Additionally, the influence of difference assumptions about the true proportion with LA abnormality was estimated in a similar way. These are presented in *Figure 25* for people aged 50 years with a $CHADS_2$ score



(c)

W_50_1_M	Mean cost	Mean QALY
No TTE	£7334	12.00
TTE	£10,343	12.48

	Mean	Jackknifed 95% CrI
ICER (£/QALY)	£6274	£6269 to £6278
Interpretation:	Neither dominated nor dominating	

FIGURE 14 Probabilistic sensitivity analysis scatterplots, CEAFs and mean ICERs in the W_50_1_M comparison. (a) Scatterplot of difference in costs (£) against difference in QALYs. (b) CEAF. (c) Mean costs, QALYs and ICERs.

TABLE 50 Summary of patient experience simulation comparing TTE and no-TTE strategies in 50-year-old females with initial $CHADS_2$ score of 1, treated with warfarin

Strategy	Life-years	Cause of death (%)			Average no. of events			
		Stroke	Bleed	Other	Dependent strokes	Independent Strokes	ICH	NICH
No initial treatment	28.294	24.6	3.1	72.4	0.259	0.496	0.021	0.181
TTE with those diagnosed with LA abnormality treated	28.660	22.8	3.8	73.4	0.243	0.459	0.027	0.234

NICH, non-intracranial haemorrhage.

of 0, *Figure 26* for people aged 65 years with a $CHADS_2$ score of 0, and in *Figure 27* for people aged either 50 or 65 years with a $CHADS_2$ score of 1.

The figures indicate that, over the range of values considered here, the true prevalence of the LA abnormality could have a significant influence on the ICER in people aged 65 years with a $CHADS_2$ score of 0, suggesting that identifying the true value of this parameter in these patient populations may be more important than in 50-year-olds or people with a $CHADS_2$ score of 1. Among people with a $CHADS_2$ score of 1, it may be more valuable to identify the true value of this parameter in females than in males.

Full incremental analyses

Performing a full incremental analysis was considered beyond the remit of this report, as warfarin, rivaroxaban and dabigatran have all been recommended by NICE through the single technology appraisal process. However, it is recognised that the choice of OAC affects the cost-effectiveness estimates of TTE. The above results can be categorised by patient population, each with differing OAC options considered, as shown in *Table 59*.

A full incremental analysis would require that each with-TTE and without-TTE strategy be compared for each OAC for each patient population. For example, both male and female populations aged 65 years with a $CHADS_2$ score of 0 would involve six comparisons. In addition, because rivaroxaban is effectively recommended by NICE at a $CHADS_2$ score of 1, and dabigatran effectively recommended at a $CHADS_2$ score of 1 in people aged ≥65 years, in these populations it may be appropriate to compare the decision to prescribe warfarin with and without TTE with people who are already receiving either rivaroxaban or dabigatran.

Results from the simplified method

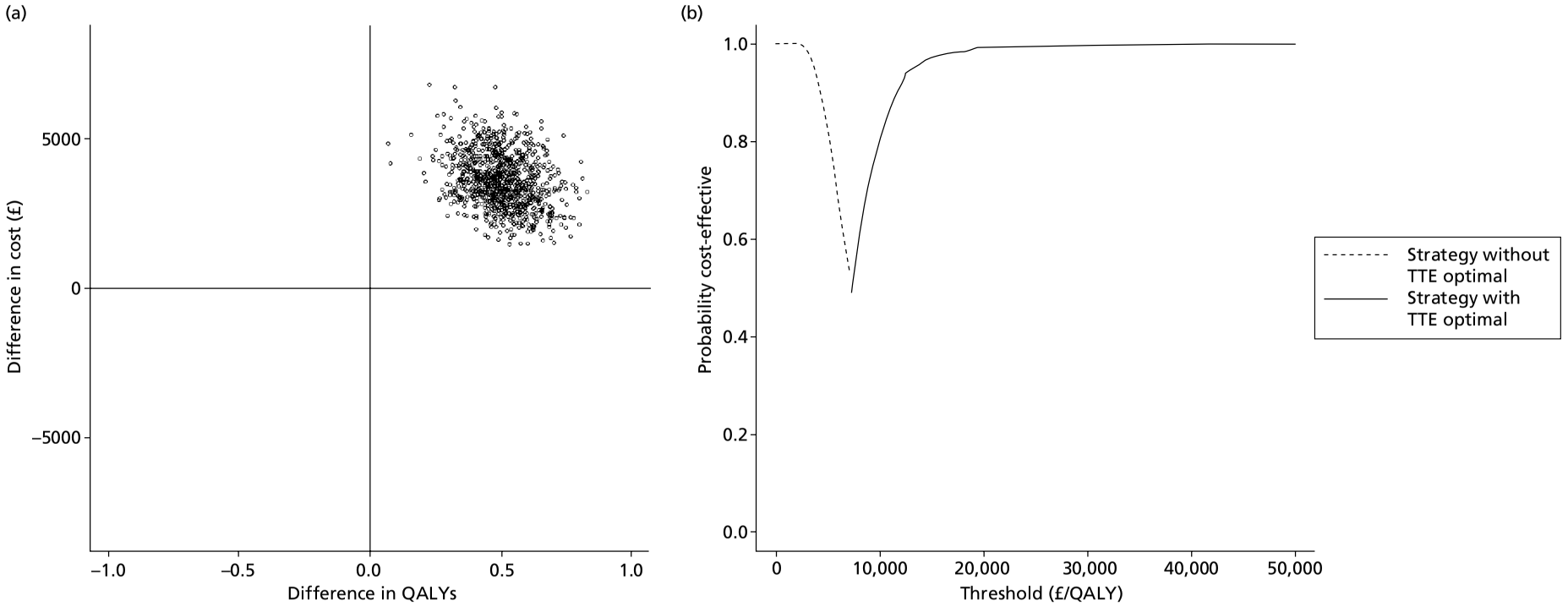
The threshold QALYs required in order that a TTE would be deemed cost-effective was 0.0033 (£20,000/£66).

Interpretation of the results

The series of results presented above can be simplistically summarised as shown in *Table 60*.

These results suggest that:

- In newly diagnosed patients with a $CHADS_2$ score of 1, who are not already receiving warfarin, rivaroxaban, or dabigatran, it may be cost-effective to use TTE to help inform the decision whether to prescribe warfarin.
- In newly diagnosed patients aged ≥65 years, it may be cost-effective to use TTE to help inform the decision about whether to prescribe dabigatran.



(c)

W_50_1_F	Mean cost	Mean QALY
No TTE	£8308	12.54
TTE	£11,919	13.04

	Mean	Jackknifed 95% CrI
ICER (£/QALY)	£7197	£7192 to £7202
Interpretation:	Neither dominated nor dominating	

FIGURE 15 Probabilistic sensitivity analysis scatterplots, CEAFs and mean ICERs in the W_50_1_F comparison. (a) Scatterplot of difference in costs (£) against difference in QALYs. (b) CEAF. (c) Mean costs, QALYs and ICERs.

TABLE 51 Summary of patient experience simulation comparing TTE and no-TTE strategies in 65-year-old males with initial $CHADS_2$ score of 1, treated with warfarin

Strategy	Life-years	Cause of death (%)			Average no. of events			
		Stroke	Bleed	Other	Dependent strokes	Independent strokes	ICH	NICH
No initial treatment	16.176	14.2	1.5	84.4	0.135	0.303	0.012	0.084
TTE with those diagnosed with LA abnormality treated	16.361	12.5	2.1	85.4	0.121	0.265	0.016	0.125

NICH, non-intracranial haemorrhage.

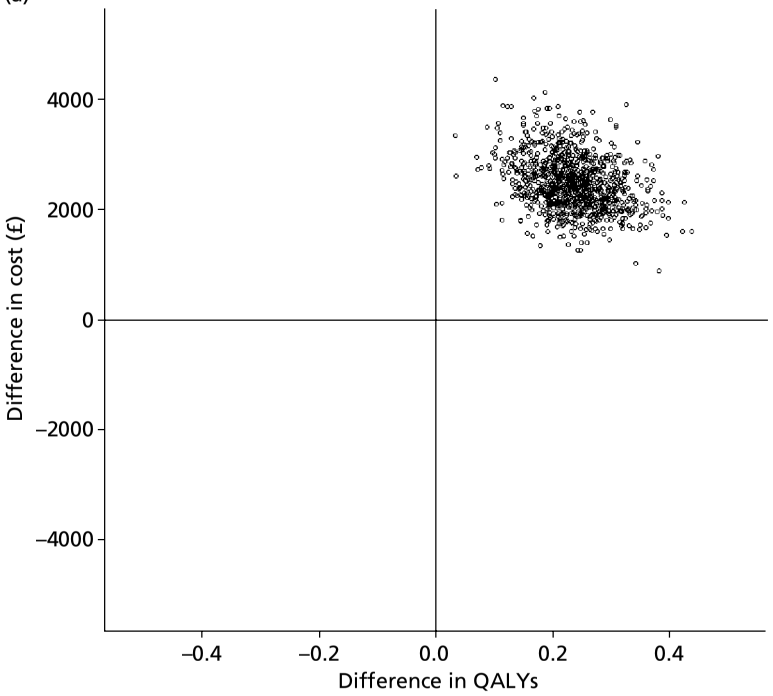
The threshold number of QALYs required for TTE to be cost-effective in the simplified analysis is a very small value and is below the sensitivity of standard preference-based utility measures, such as the EQ-5D. If there was clinical belief that there were benefits aside from identifying LA abnormality that were gained from the TTE then it is possible that TTE would be perceived as cost-effective.

Limitations in the modelling

Assumptions have been made within the modelling that have simplified the decision problem. Although it is unlikely that these assumptions would change the broad conclusions these are detailed for completeness. The assumptions are that:

1. Within the baseline strategies the decision was assumed to be made on the basis of $CHADS_2$ scores alone. Alternative baseline strategies include the use of CHA_2DS_2-VASc, and $CHADS_2$ or CHA_2DS_2-VASc scores in combination with bleed risk scores, such as Hypertension; Abnormal Liver/Renal Function; Stroke History; Bleeding Disposition; Labile INRs; Elderly; Drugs/Alcohol Usage (HAS-BLED). The baseline strategy could also be that a decision is made on the basis of the individual components within these scores.
2. The dose of dabigatran was set at 150 mg twice daily, rather than allowing some patients to receive a lower dose of 110 mg twice daily. The model could be adapted to reduce the dose when a patient reaches a specified age.
3. The stroke risk associated with patients with left atrial abnormalities is assumed to be constant at 8.0% (95% CI 7.26% to 8.31%) per year. Ideally differential rates by age or by the number (and type) of abnormalities would be used but these data were not identified.
4. The key data on which the economic evaluation was based came from a relatively small study, of fewer than 400 patients. Of these patients, fewer than 25 had a $CHADS_2$ score of 0, and fewer than 80 patients had a $CHADS_2$ score of 1. This has made the assessment of the benefits of TTE uncertain.
5. The risk of death unrelated to bleeding or stroke events was taken from life tables[145] and was not adjusted for the probability of bleeding or stroke mortality. As such, the risk of mortality is likely to be slightly overestimated.
6. The sensitivity and specificity of TTE in identifying LA abnormality was estimated assuming that TOE had perfect sensitivity and specificity. If TOE was not a perfect gold standard then the accuracy of TTE would also change.
7. The full model assumed that the only benefit from TTE would be due to identification of LA abnormality. Any other conditions that may alter patient management have been ignored. To address this limitation a simplified approach was undertaken that calculated the additional QALY gain needed for TTE to be deemed cost-effective.
8. The mathematical model developed does not model the progression of each individual disease state that is incorporated in the $CHADS_2$ score, and so the mathematical model was be run only in patients aged ≥65 years when considering dabigatran as the OAC of choice.

(a)



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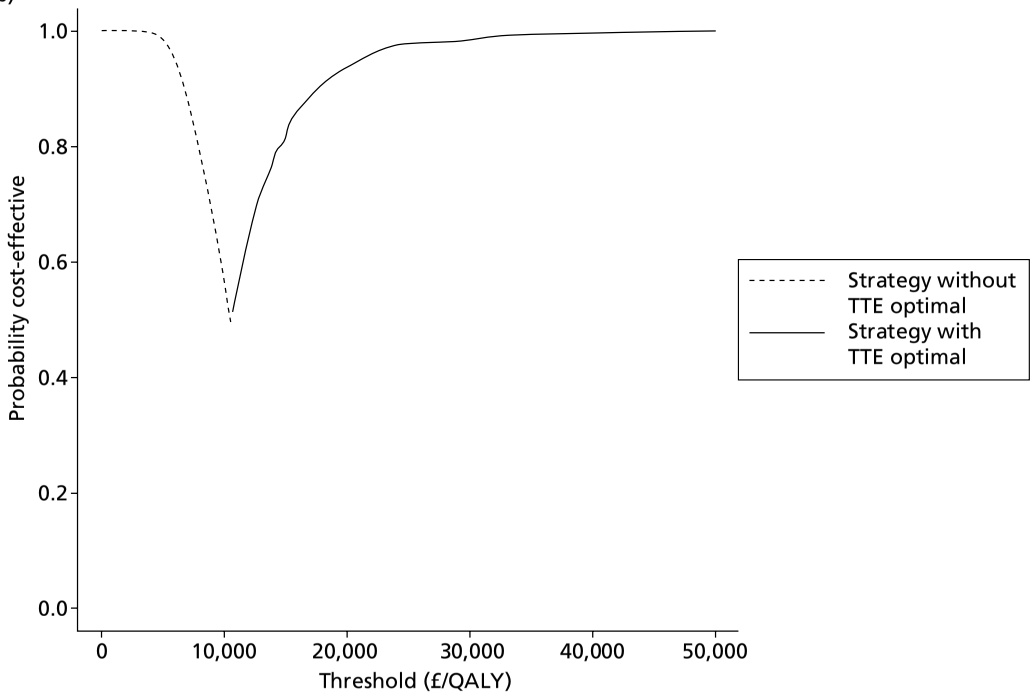


(c)

W_65_1_M	Mean cost	Mean QALY
No TTE	£3242	8.41
TTE	£5737	8.64

	Mean	Jackknifed 95% CrI
ICER (£/QALY)	£10,626	£10,612 to £10,633
Interpretation:	Neither dominated nor dominating	

FIGURE 16 Probabilistic sensitivity analysis scatterplots, CEAFs and mean ICERs in the W_65_1_M comparison. (a) Scatterplot of difference in costs (£) against difference in QALYs. (b) CEAF. (c) Mean costs, QALYs and ICERs.

TABLE 52 Summary of patient experience simulation comparing TTE and no-TTE strategies in 65-year-old females with initial $CHADS_2$ score of 1, treated with warfarin

Strategy	Life-years	Cause of death (%)			Average no. of events			
		Stroke	Bleed	Other	Dependent strokes	Independent strokes	ICH	NICH
No initial treatment	18.340	15.8	1.8	82.4	0.155	0.337	0.013	0.104
TTE with those diagnosed with LA abnormality treated	18.544	14.2	2.5	83.3	0.141	0.300	0.018	0.149

NICH, non-intracranial haemorrhage.

Comparison of our results with those in the published literature

A systematic literature review was conducted to identify, summarise and appraise existing economic studies for evaluating the cost-effectiveness of TTE in patients with AF.

Methodology

Search strategy

A comprehensive literature search was undertaken across five databases: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), WoS, and Cochrane Database of Systematic Reviews (CDSR). Details of the full search strategy are provided in *Appendix 12*.

Inclusion/exclusion criteria

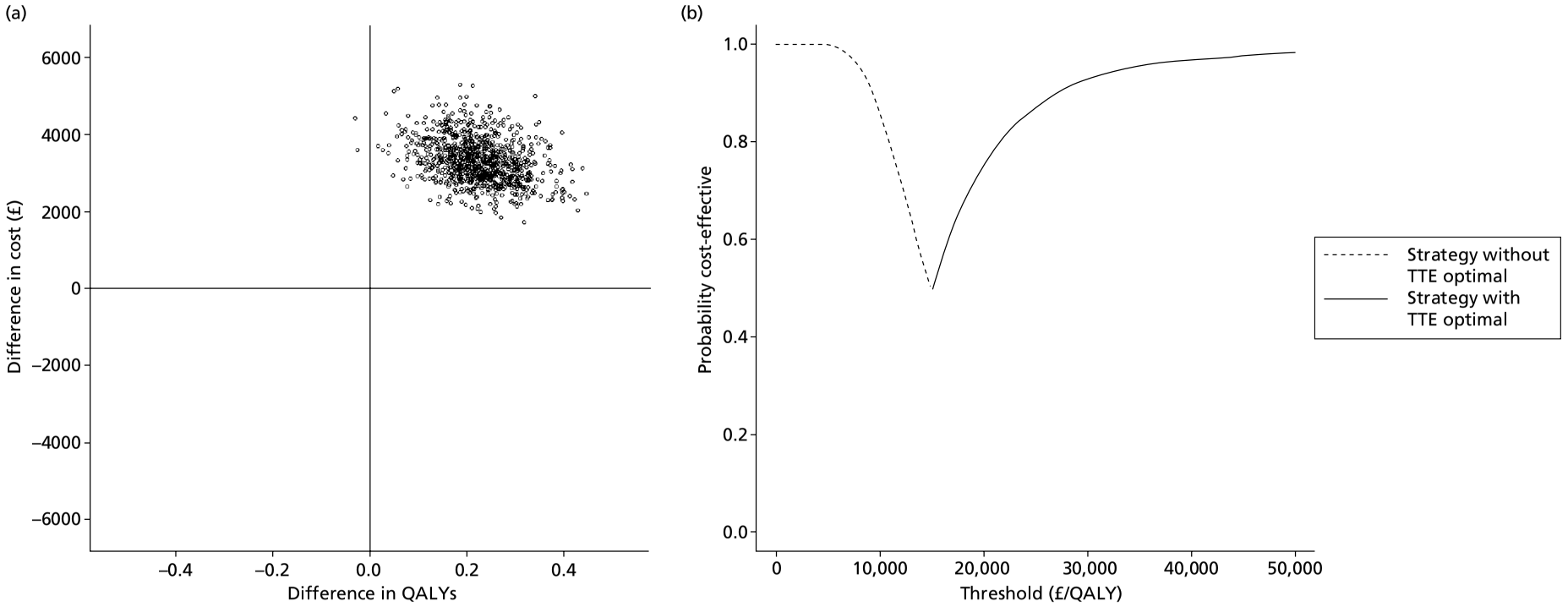
The inclusion criteria for this systematic review were as follows:

- *Population* Patients with AF.
- *Intervention* Transthoracic echocardiogram.
- *Comparators* Conventional therapy.
- *Setting* Interventions delivered within any geographical jurisdiction.
- *Outcomes* Cost per QALY.
- *Study designs* Studies reporting a full economic evaluation, with results expressed in terms of both costs and health outcomes.

Studies were excluded from this review if:

- the patients suffered from cardiac problems other than AF
- the intervention was not transthoracic echocardiogram
- they reported only costs or outcomes
- they were not of full economic evaluation, such as cost-minimisation analysis
- they were not published papers, such as editorials, commentaries and letters
- they were not published in the English language.

All of the potentially relevant citations were imported to Reference Manager Software, version 12 (Thomson ResearchSoft, San Francisco, CA, USA) and duplicates were removed. The titles and abstracts of the unique studies were then screened according to the predetermined inclusion criteria as outlined above. Any disagreements concerning possible inclusion of papers were resolved by discussion among the researchers of the team, or through retrieval and subsequent examination of the full study publication. Full papers of all the potentially relevant citations were retrieved for an in-depth assessment concerning study inclusion in the review.



(c)

W_65_1_F	Mean cost	Mean QALY
No TTE	£3929	9.15
TTE	£7248	9.38

	Mean	Jackknifed 95% CrI
ICER (£/QALY)	£14,953	£14,941 to £14,964
Interpretation:	Neither dominated nor dominating	

FIGURE 17 Probabilistic sensitivity analysis scatterplots, CEAFs and mean ICERs in the W_65_1_F comparison. (a) Scatterplot of difference in costs (£) against difference in QALYs. (b) CEAF. (c) Mean costs, QALYs and ICERs.

TABLE 53 Summary of patient experience simulation comparing TTE and no-TTE strategies in 50-year-old males with initial $CHADS_2$ score of 0, treated with rivaroxaban

Strategy	Life-years	Cause of death (%)			Average no. of events			
		Stroke	Bleed	Other	Dependent strokes	Independent strokes	ICH	NICH
No initial treatment	28.861	11.5	1.3	87.2	0.117	0.239	0.010	0.075
TTE with those diagnosed with LA abnormality treated	28.963	10.5	1.8	87.6	0.108	0.219	0.014	0.113

NICH, non-intracranial haemorrhage.

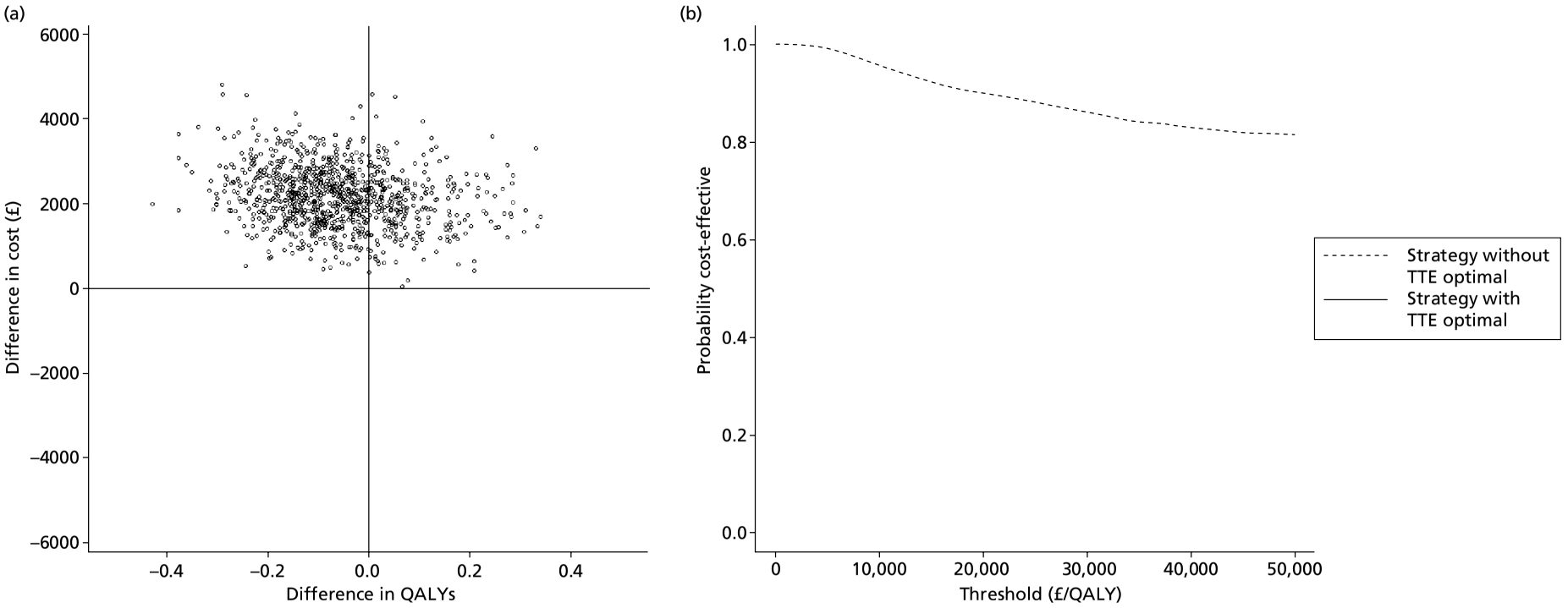
Data extraction and evidence synthesis

Data concerning the characteristics of the population, interventions, comparators, outcomes, study location, time horizon, costs, outcomes and the perspective of the evaluations undertaken were extracted from the included study. These were then tabulated and discussed in a narrative manner.

Results of the systematic review

Number of studies identified and included

In total, 1038 studies were identified through the systematic searches. Following the removal of duplicate citations, 881 unique studies were retrieved. Of these, 43 potentially relevant citations were retrieved for a more detailed inspection. Further, 26 studies were excluded and 17 studies were retrieved for double screening. After double screening, 17 studies were excluded as they failed to satisfy one or more of the inclusion criteria.



(c)

R_50_0_M	Mean cost	Mean QALY
No TTE	£2449	13.61
TTE	£4614	13.54

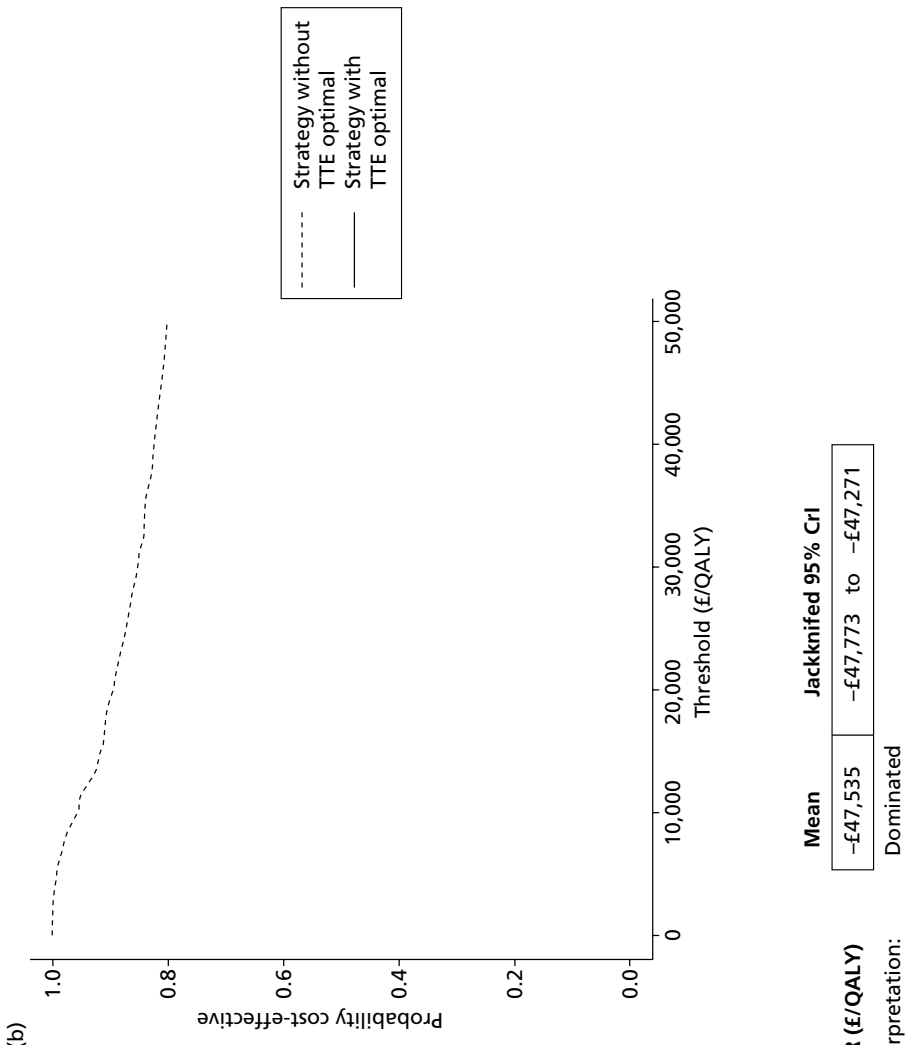
	Mean	Jackknifed 95% CrI
ICER (£/QALY)	−£34,060	−£34,170 to −£33,910
Interpretation:	Dominated	

FIGURE 18 Probabilistic sensitivity analysis scatterplots, CEAFs and mean ICERs in the R_50_0_M comparison. (a) Scatterplot of difference in costs (£) against difference in QALYs. (b) CEAF (If there is no solid line in the figure, this indicates that the screening option using TTE is not optimal over all willingness-to-pay thresholds ranging from £0/QALY to £50,000 per QALY.) (c) Mean costs, QALYs and ICERs.

TABLE 54 Summary of patient experience simulation comparing TTE and no-TTE strategies in 50-year-old females with initial $CHADS_2$ score of 0, treated with rivaroxaban

		Cause of death (%)			Average no. of events			
Strategy	Life-years	Stroke	Bleed	Other	Dependent strokes	Independent strokes	ICH	NICH
No initial treatment	31.657	13.3	1.6	85.1	0.136	0.275	0.012	0.091
TTE with those diagnosed with LA abnormality treated	31.772	12.4	2.1	85.5	0.127	0.255	0.017	0.130

NICH, non-intracranial haemorrhage.



(c)

R_50_0_F	Mean cost	Mean QALY
No TTE	£2779	14.27
TTE	£5315	14.22

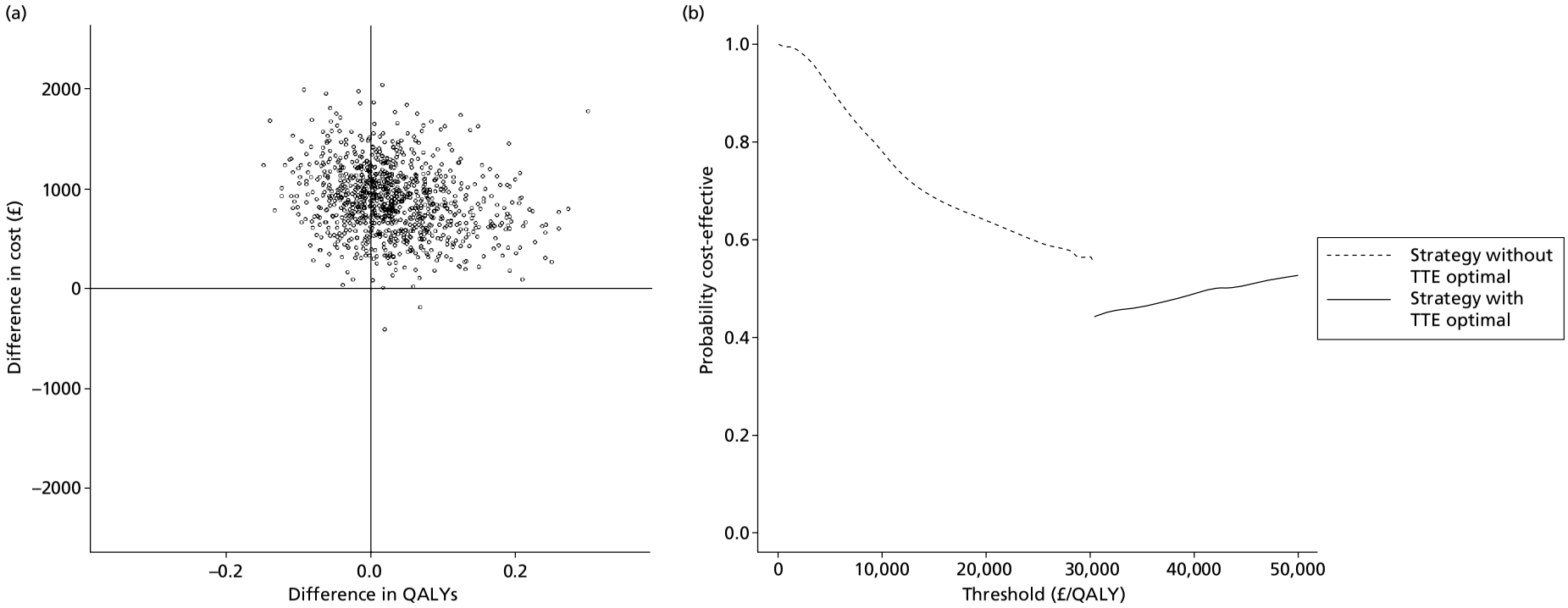
	Mean	Jackknifed 95% CrI
ICER (£/QALY)	−£47,535	−£47,773 to −£47,271
Interpretation:	Dominated	

FIGURE 19 Probabilistic sensitivity analysis scatterplots, CEAFs and mean ICERs in the R_50_0_F comparison. (a) Scatterplot of difference in costs (£) against difference in QALYs. (b) CEAF (If there is no solid line in the figure, this indicates that the screening option using TTE is not optimal over all willingness-to-pay thresholds ranging from £0/QALY to £50,000 per QALY.) (c) Mean costs, QALYs and ICERs.

TABLE 55 Summary of patient experience simulation comparing TTE and no-TTE strategies in 65-year-old males with initial $CHADS_2$ score of 0, treated with rivaroxaban

Strategy	Life-years	Cause of death (%)			Average no. of events			
		Stroke	Bleed	Other	Dependent strokes	Independent strokes	ICH	NICH
No initial treatment	17.141	8.8	0.9	90.3	0.085	0.190	0.007	0.052
TTE with those diagnosed with LA abnormality treated	17.221	7.8	1.3	90.9	0.076	0.169	0.010	0.080

NICH, non-intracranial haemorrhage.



(c)

R_65_0_M	Mean cost	Mean QALY
No TTE	£1510	9.12
TTE	£2393	9.15

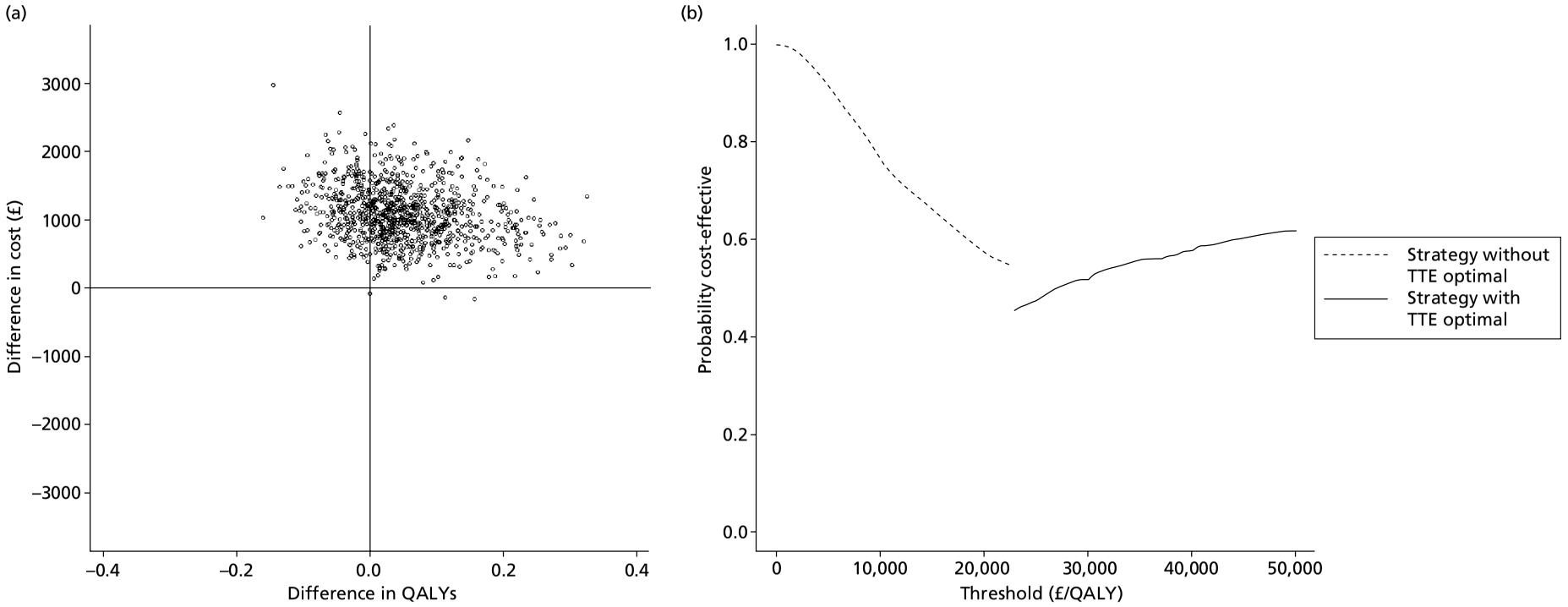
	Mean	Jackknifed 95% CrI
ICER (£/QALY)	£30,310	£30,179 to £30,487
Interpretation:	Neither dominated nor dominating	

FIGURE 20 Probabilistic sensitivity analysis scatterplots, CEAFs and mean ICERs in the R_65_0_M comparison. (a) Scatterplot of difference in costs (£) against difference in QALYs. (b) CEAF. (c) Mean costs, QALYs and ICERs.

TABLE 56 Summary of patient experience simulation comparing TTE and no-TTE strategies in 65-year-old females with initial $CHADS_2$ score of 0, treated with rivaroxaban

Strategy	Life-years	Cause of death (%)			Average no. of events			
		Stroke	Bleed	Other	Dependent strokes	Independent strokes	ICH	NICH
No initial treatment	19.460	10.5	1.1	88.4	0.103	0.223	0.009	0.066
TTE with those diagnosed with LA abnormality treated	19.554	9.4	1.6	89.0	0.093	0.201	0.012	0.096

NICH, non-intracranial haemorrhage.



(c)

R_65_0_F	Mean cost	Mean QALY
No TTE	£1955	9.95
TTE	£3039	9.99

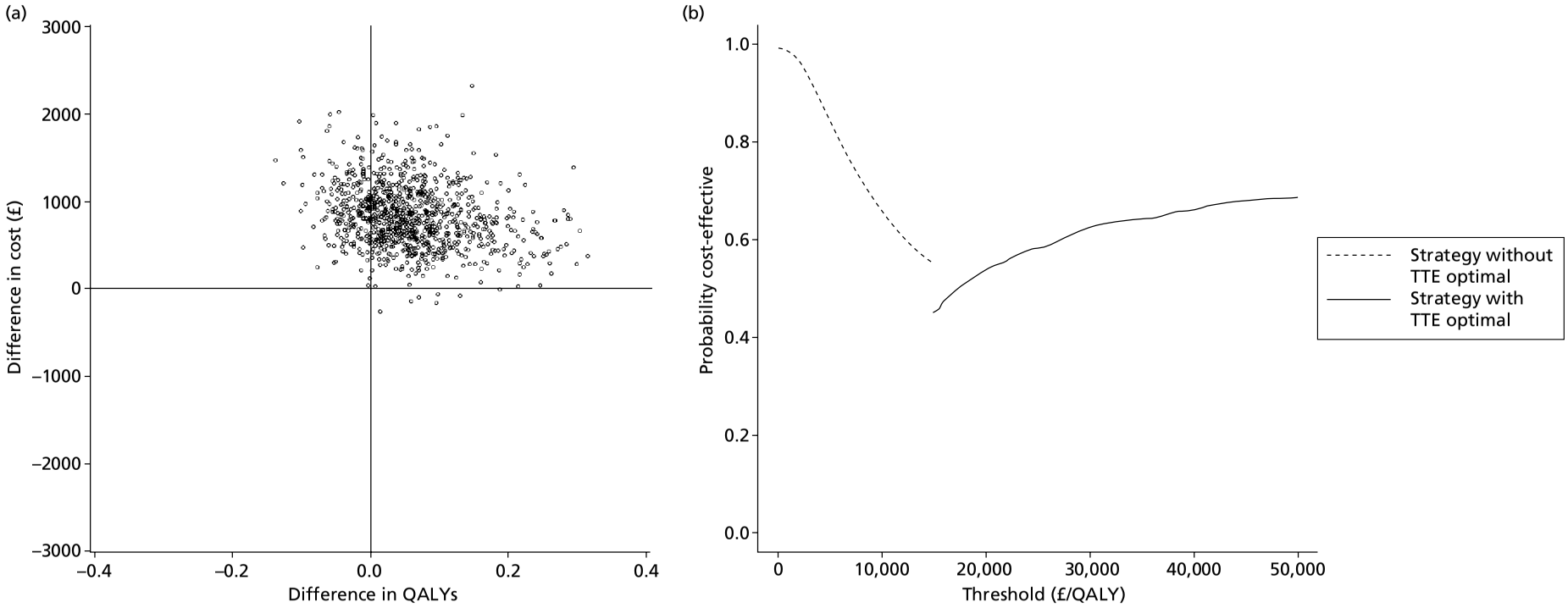
	Mean	Jackknifed 95% CrI
ICER (£/QALY)	£22,751	£22,681 to £22,844
Interpretation:	Neither dominated nor dominating	

FIGURE 21 Probabilistic sensitivity analysis scatterplots, CEAFs and mean ICERs in the R_65_0_F comparison. (a) Scatterplot of difference in costs (£) against difference in QALYs. (b) CEAF. (c) Mean costs, QALYs and ICERs.

TABLE 57 Summary of patient experience simulation comparing TTE and no-TTE strategies in 65-year-old males with initial $CHADS_2$ score of 0, treated with dabigatran

Strategy	Life-years	Cause of death (%)			Average no. of events			
		Stroke	Bleed	Other	Dependent strokes	Independent strokes	ICH	NICH
No initial treatment	17.158	8.6	0.9	90.5	0.081	0.188	0.007	0.053
TTE with those diagnosed with LA abnormality treated	17.251	7.5	1.3	91.2	0.072	0.163	0.010	0.081

NICH, non-intracranial haemorrhage.



(c)

D_65_0_M	Mean cost	Mean QALY
No TTE	£1489	9.13
TTE	£2321	9.18

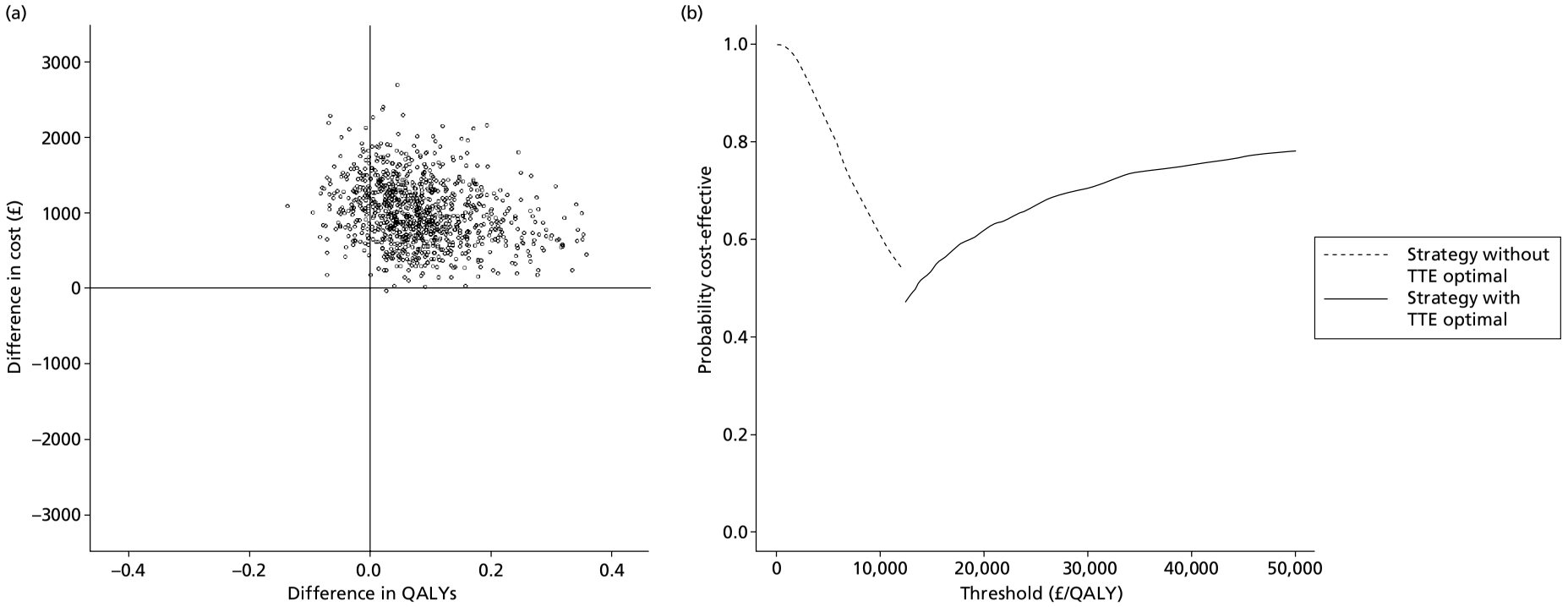
	Mean	Jackknifed 95% CrI
ICER (£/QALY)	£14,728	£14,693 to £14,782
Interpretation:	Neither dominated nor dominating	

FIGURE 22 Probabilistic sensitivity analysis scatterplots, CEAFs and mean ICERs in the D_65_0_M comparison. (a) Scatterplot of difference in costs (£) against difference in QALYs. (b) CEAF. (c) Mean costs, QALYs and ICERs.

TABLE 58 Summary of patient experience simulation comparing TTE and no-TTE strategies in 65-year-old females with initial $CHADS_2$ score of 0, treated with dabigatran

Strategy	Life-years	Cause of death (%)			Average no. of events			
		Stroke	Bleed	Other	Dependent strokes	Independent strokes	ICH	NICH
No initial treatment	19.485	10.2	1.1	88.7	0.099	0.220	0.009	0.066
TTE with those diagnosed with LA abnormality treated	19.598	9.0	1.6	89.4	0.089	0.195	0.012	0.097

NICH, non-intracranial haemorrhage.

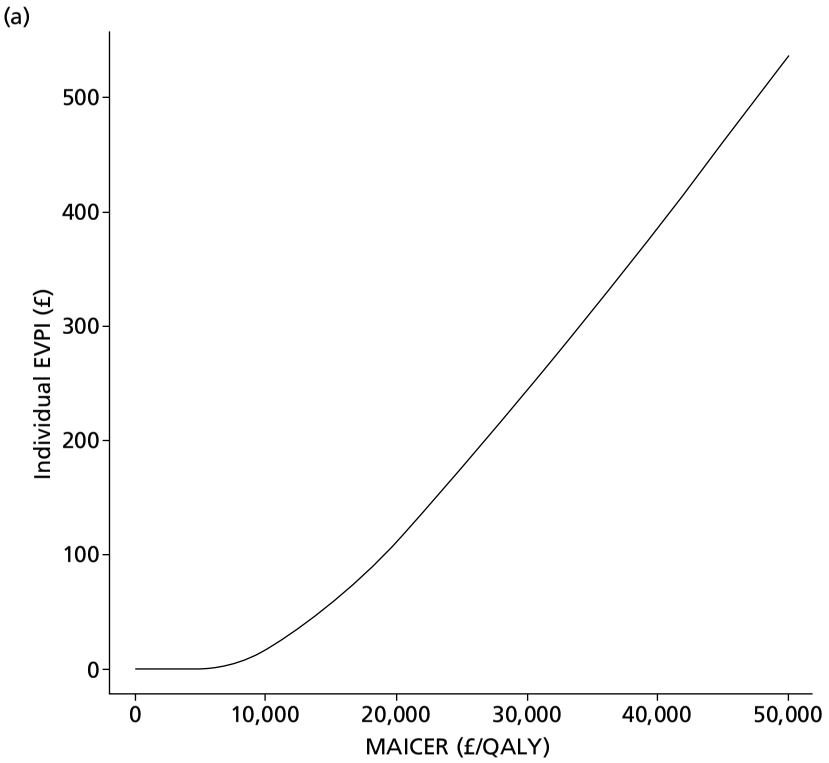


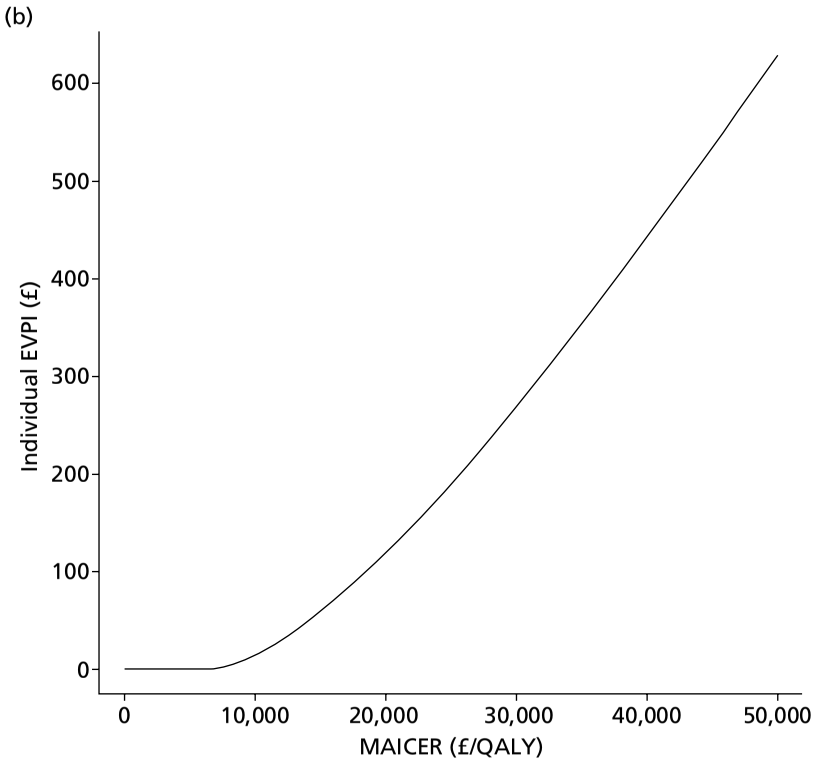
(c)

D_65_0_F	Mean cost	Mean QALY
No TTE	£1942	9.95
TTE	£2946	10.01

	Mean	Jackknifed 95% CrI
ICER (£/QALY)	£12,314	£12,290 to £12,348
Interpretation:	Neither dominated nor dominating	

FIGURE 23 Probabilistic sensitivity analysis scatterplots, CEAFs and mean ICERs in the D_65_0_F comparison. (a) Scatterplot of difference in costs (£) against difference in QALYs. (b) CEAF. (c) Mean costs, QALYs and ICERs.



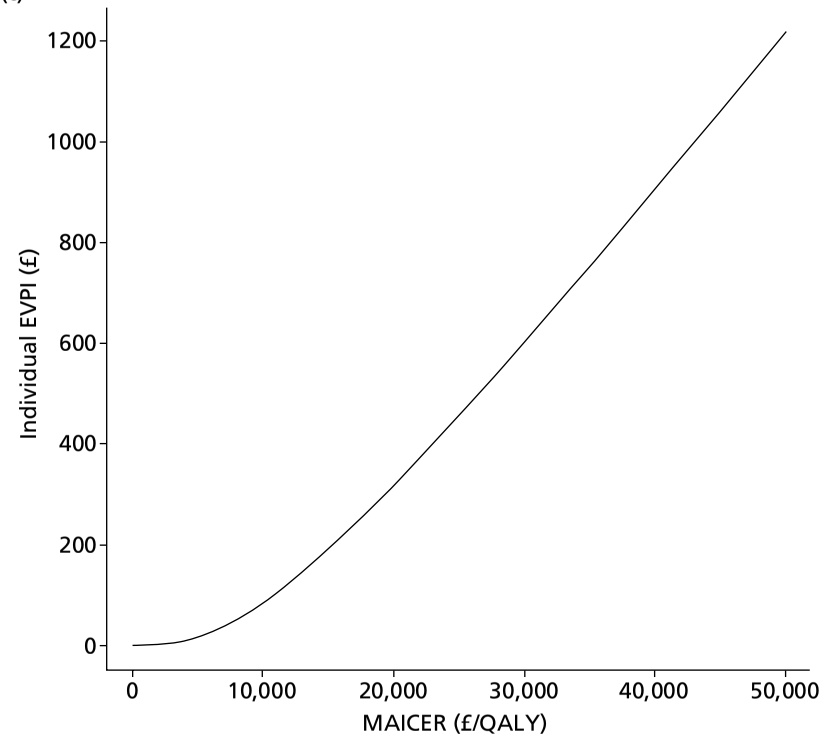


MAICER	Individual EVPI (£)	Population EVPI (£M)		
		25,000	50,000	75,000
£20,000/QALY	111	2.78	5.55	8.33
£30,000/QALY	244	6.09	12.18	18.26

MAICER	Individual EVPI (£)	Population EVPI (£M)		
		25,000	50,000	75,000
£20,000/QALY	120	2.99	5.98	8.97
£30,000/QALY	269	6.72	13.44	20.15

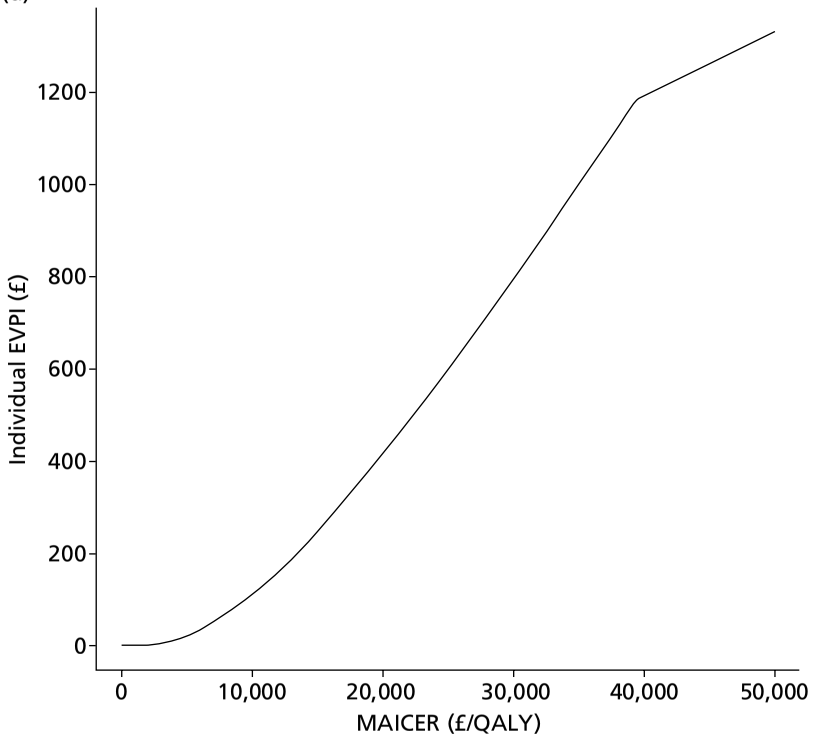
FIGURE 24 Relationship between individual EVPI and MAICER for all 14 comparisons, together with individual and population EVPIs at MAICERs of £20,000/QALY and £30,000/QALY. (a) W_50_0_M; (b) W_50_0_F; (c) W_65_0_M; (d) W_65_0_F; (e) W_50_1_M; (f) W_50_1_F; (g) W_65_1_M; (h) W_65_1_F; (i) R_50_0_M; (j) R_50_0_F; (k) R_65_0_M; (l) R_65_0_F; (m) D_65_0_M; (n) D_65_0_F. (*continued*)

(c)

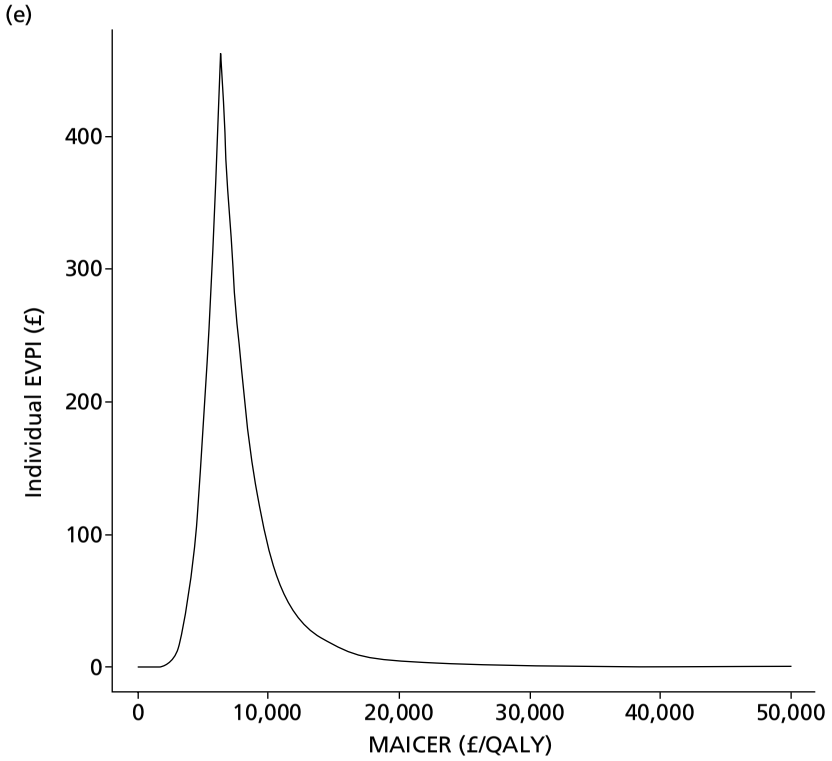


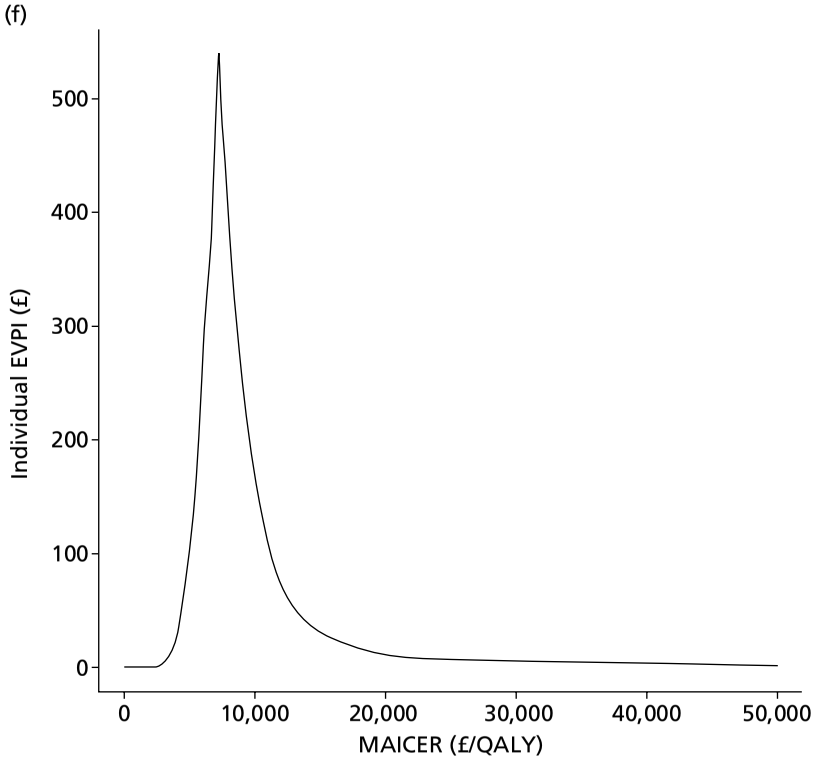
MAICER	Individual EVPI (£)	Population EVPI (£M)		
		25,000	50,000	75,000
£20,000/QALY	315	7.89	15.77	23.66
£30,000/QALY	601	15.03	30.06	45.09

(d)



MAICER	Individual EVPI (£)	Population EVPI (£M)		
		25,000	50,000	75,000
£20,000/QALY	413	10.33	20.66	30.99
£30,000/QALY	796	19.91	39.82	59.73



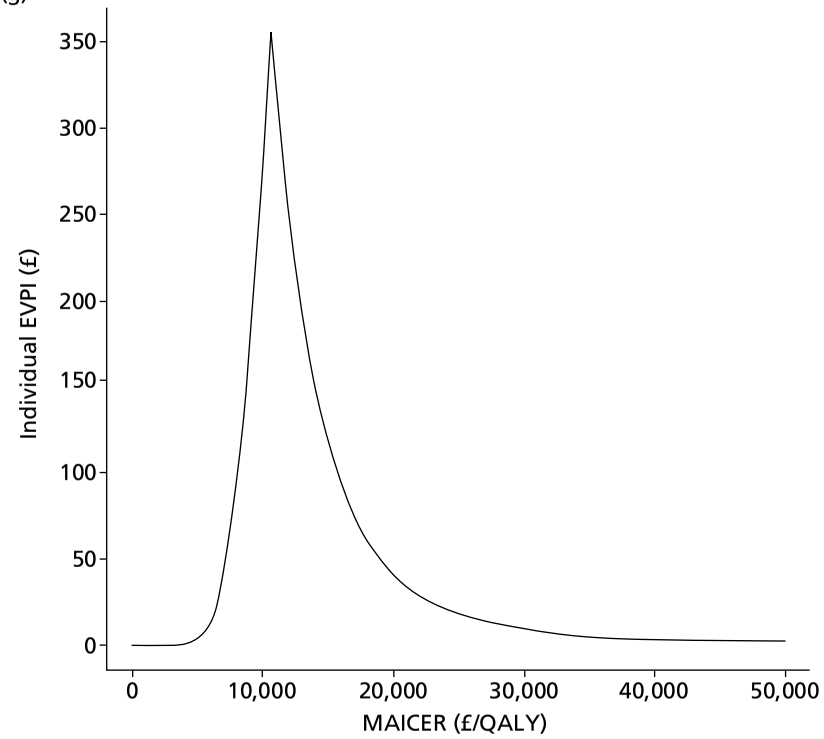


MAICER	Individual EVPI (£)	Population EVPI (£M)		
		25,000	50,000	75,000
£20,000/QALY	4	0.10	0.20	0.30
£30,000/QALY	2	0.04	0.08	0.12

MAICER	Individual EVPI (£)	Population EVPI (£M)		
		25,000	50,000	75,000
£20,000/QALY	12	0.29	0.59	0.88
£30,000/QALY	5	0.12	0.25	0.37

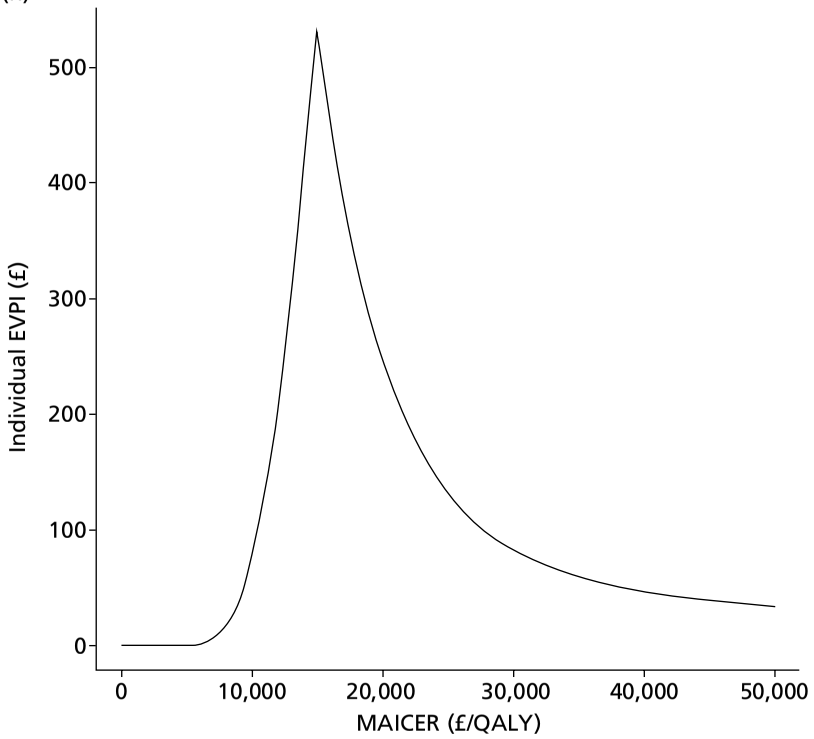
FIGURE 24 Relationship between individual EVPI and MAICER for all 14 comparisons, together with individual and population EVPIs at MAICERs of £20,000/QALY and £30,000/QALY. (a) W_50_0_M; (b) W_50_0_F; (c) W_65_0_M; (d) W_65_0_F; (e) W_50_1_M; (f) W_50_1_F; (g) W_65_1_M; (h) W_65_1_F; (i) R_50_0_M; (j) R_50_0_F; (k) R_65_0_M; (l) R_65_0_F; (m) D_65_0_M; (n) D_65_0_F. (*continued*)

(g)

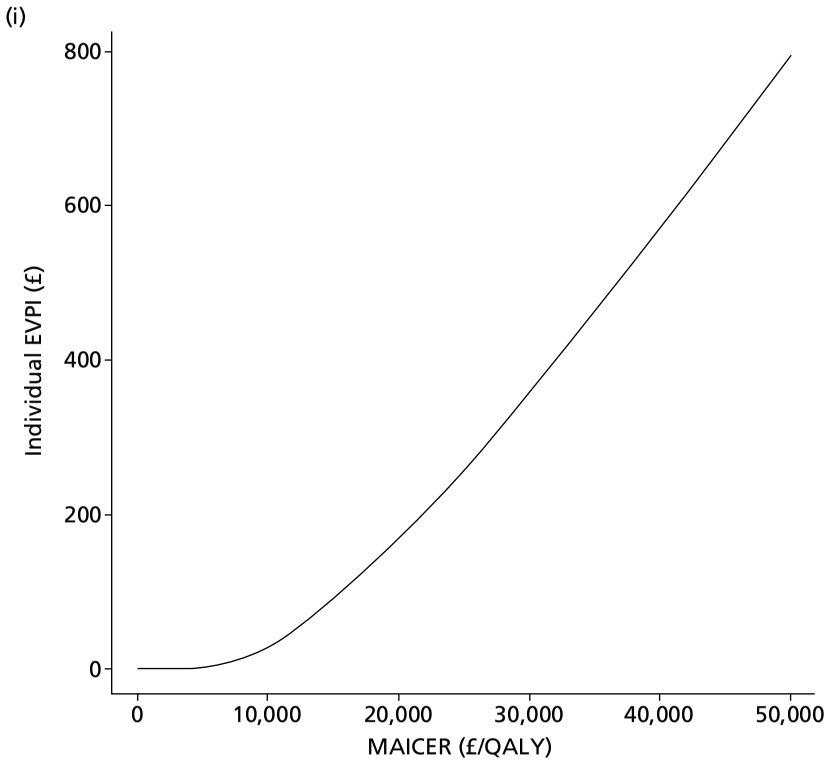


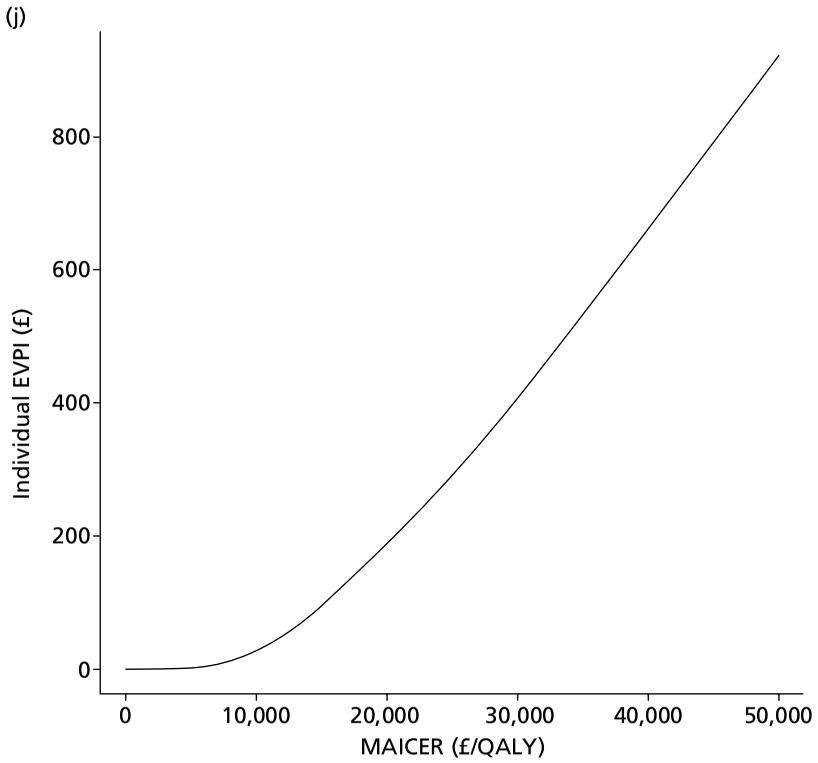
MAICER	Individual EVPI (£)	Population EVPI (£M)		
		25,000	50,000	75,000
£20,000/QALY	41	1.03	2.05	3.08
£30,000/QALY	9	0.24	0.47	0.71

(h)



MAICER	Individual EVPI (£)	Population EVPI (£M)		
		25,000	50,000	75,000
£20,000/QALY	249	6.22	12.43	18.65
£30,000/QALY	82	2.06	4.12	6.18



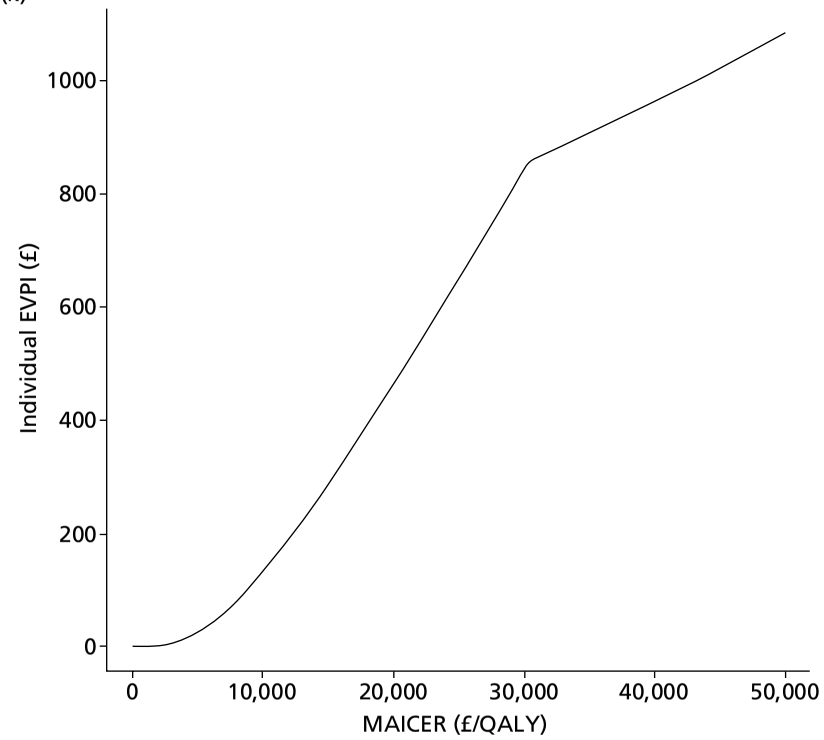


MAICER	Individual EVPI (£)	Population EVPI (£M)		
		25,000	50,000	75,000
£20,000/QALY	169	4.22	8.43	12.66
£30,000/QALY	355	8.89	17.77	26.66

MAICER	Individual EVPI (£)	Population EVPI (£M)		
		25,000	50,000	75,000
£20,000/QALY	189	4.73	9.45	14.18
£30,000/QALY	409	10.22	20.43	30.65

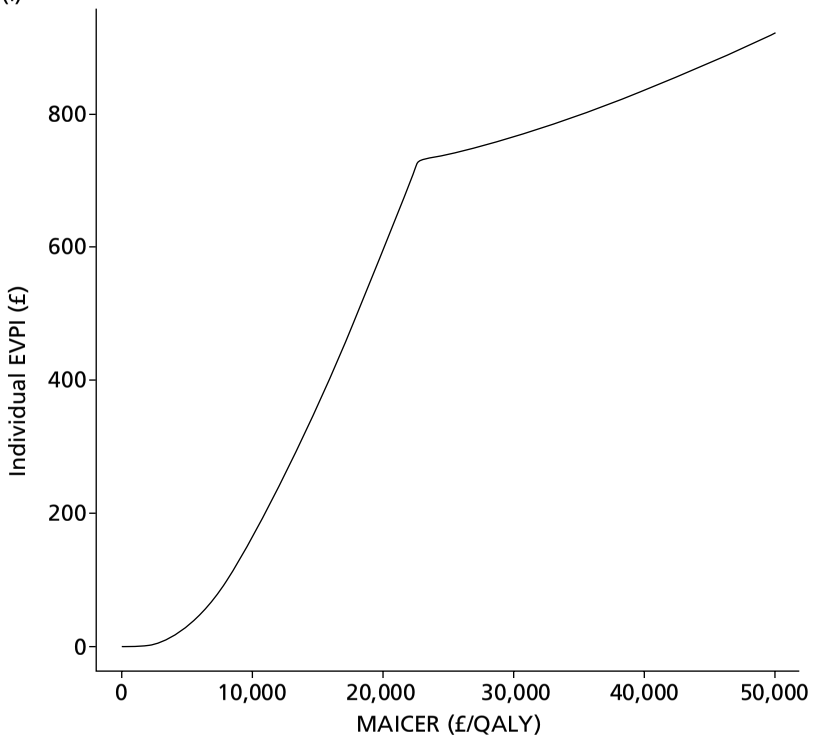
FIGURE 24 Relationship between individual EVPI and MAICER for all 14 comparisons, together with individual and population EVPIs at MAICERs of £20,000/QALY and £30,000/QALY. (a) W_50_0_M; (b) W_50_0_F; (c) W_65_0_M; (d) W_65_0_F; (e) W_50_1_M; (f) W_50_1_F; (g) W_65_1_M; (h) W_65_1_F; (i) R_50_0_M; (j) R_50_0_F; (k) R_65_0_M; (l) R_65_0_F; (m) D_65_0_M; (n) D_65_0_F. (*continued*)

(k)

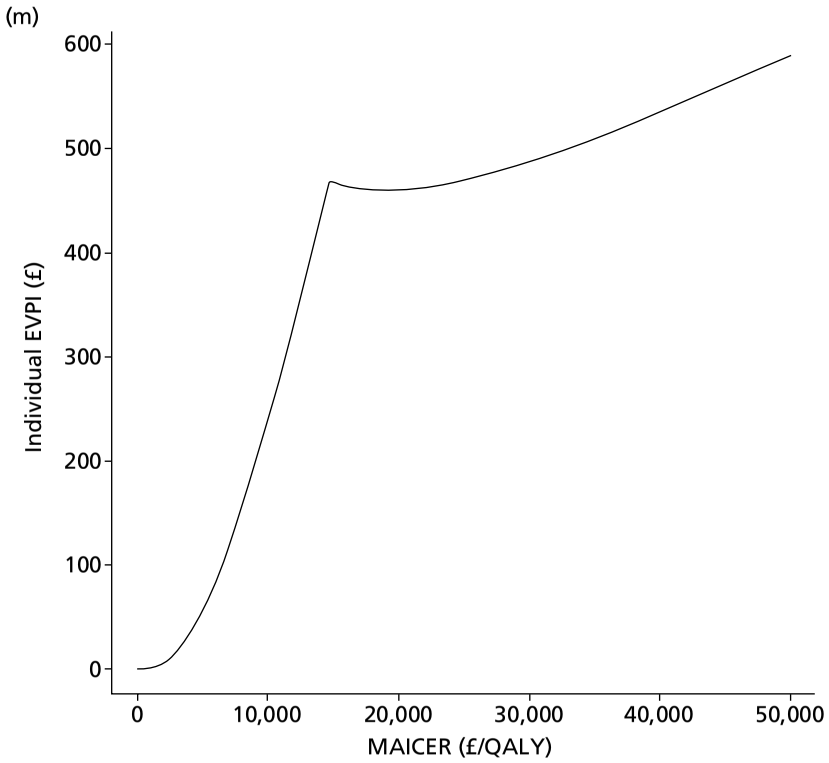


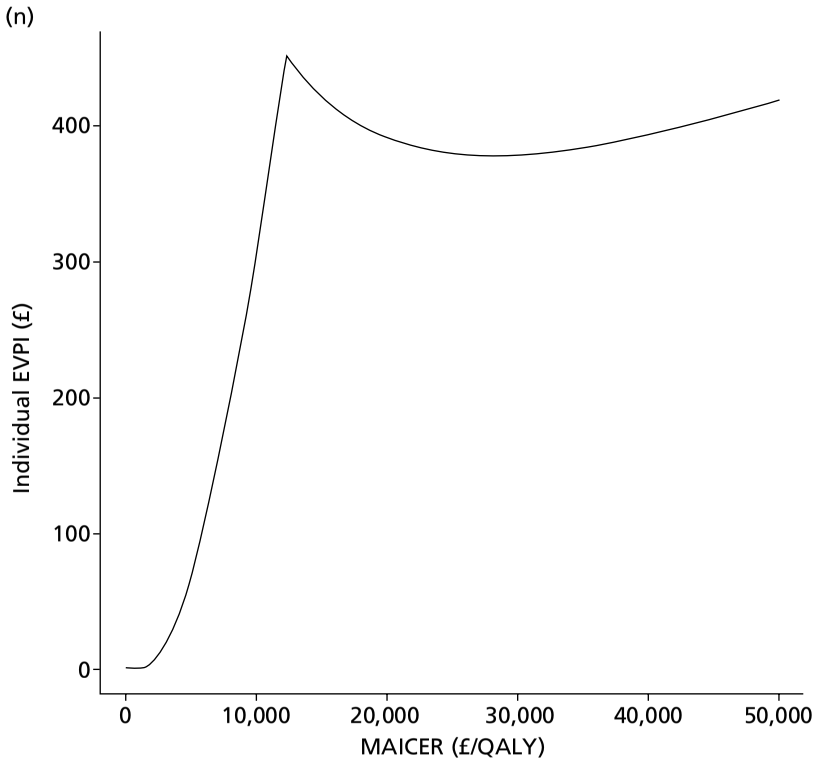
MAICER	Individual EVPI (£)	Population EVPI (£M)		
		25,000	50,000	75,000
£20,000/QALY	464	11.61	23.22	34.83
£30,000/QALY	845	21.12	42.25	63.37

(l)



MAICER	Individual EVPI (£)	Population EVPI (£M)		
		25,000	50,000	75,000
£20,000/QALY	597	14.93	29.87	44.80
£30,000/QALY	770	19.25	38.51	57.76





MAICER	Individual EVPI (£)	Population EVPI (£M)		
		25,000	50,000	75,000
£20,000/QALY	461	11.53	23.05	34.58
£30,000/QALY	487	12.18	24.36	36.55

MAICER	Individual EVPI (£)	Population EVPI (£M)		
		25,000	50,000	75,000
£20,000/QALY	392	9.79	19.58	29.37
£30,000/QALY	378	9.46	18.92	28.38

FIGURE 24 Relationship between individual EVPI and MAICER for all 14 comparisons, together with individual and population EVPIs at MAICERs of £20,000/QALY and £30,000/QALY. (a) W_50_0_M; (b) W_50_0_F; (c) W_65_0_M; (d) W_65_0_F; (e) W_50_1_M; (f) W_50_1_F; (g) W_65_1_M; (h) W_65_1_F; (i) R_50_0_M; (j) R_50_0_F; (k) R_65_0_M; (l) R_65_0_F; (m) D_65_0_M; (n) D_65_0_F. (*continued*)

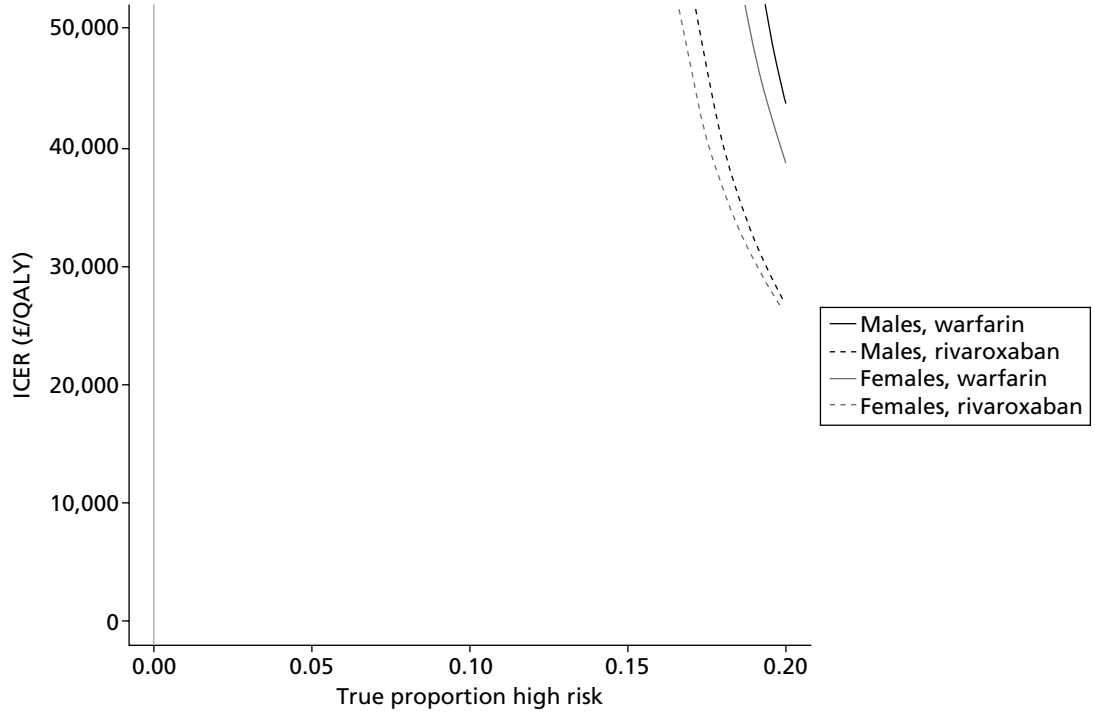


FIGURE 25 Effect of true proportion of population with LA abnormality on estimated ICER in 50-year-olds who have a $CHADS_2$ score of 0.

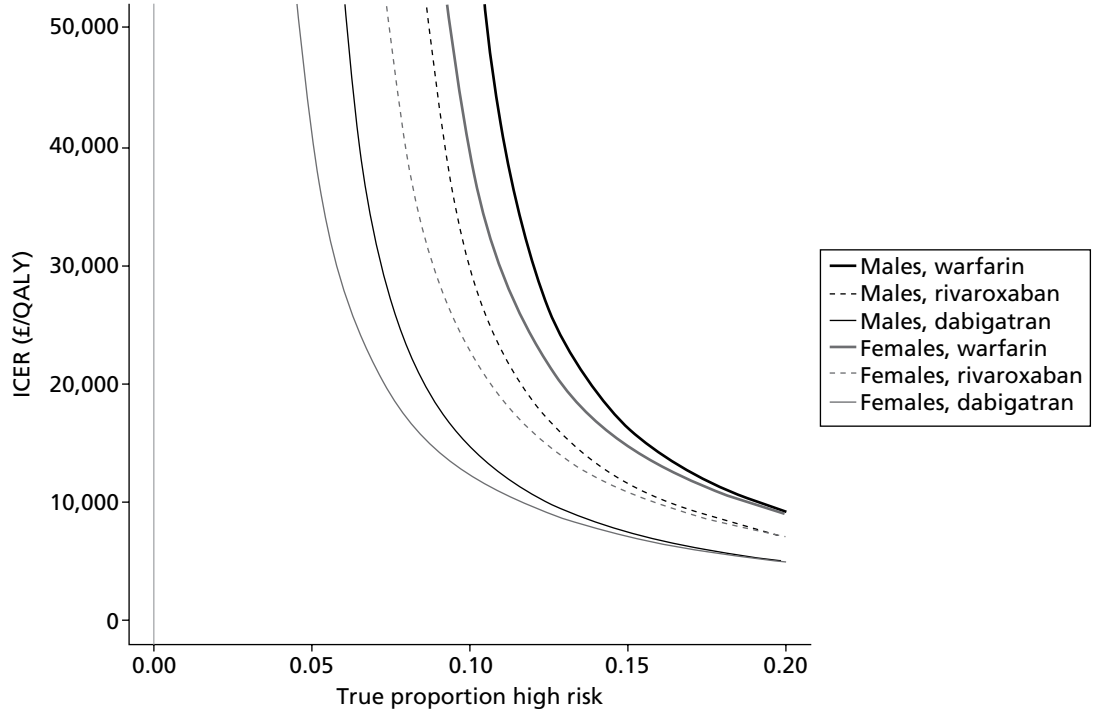


FIGURE 26 Effect of true proportion of population with LA abnormality on estimated ICER in 65-year-olds who have a $CHADS_2$ score of 0.

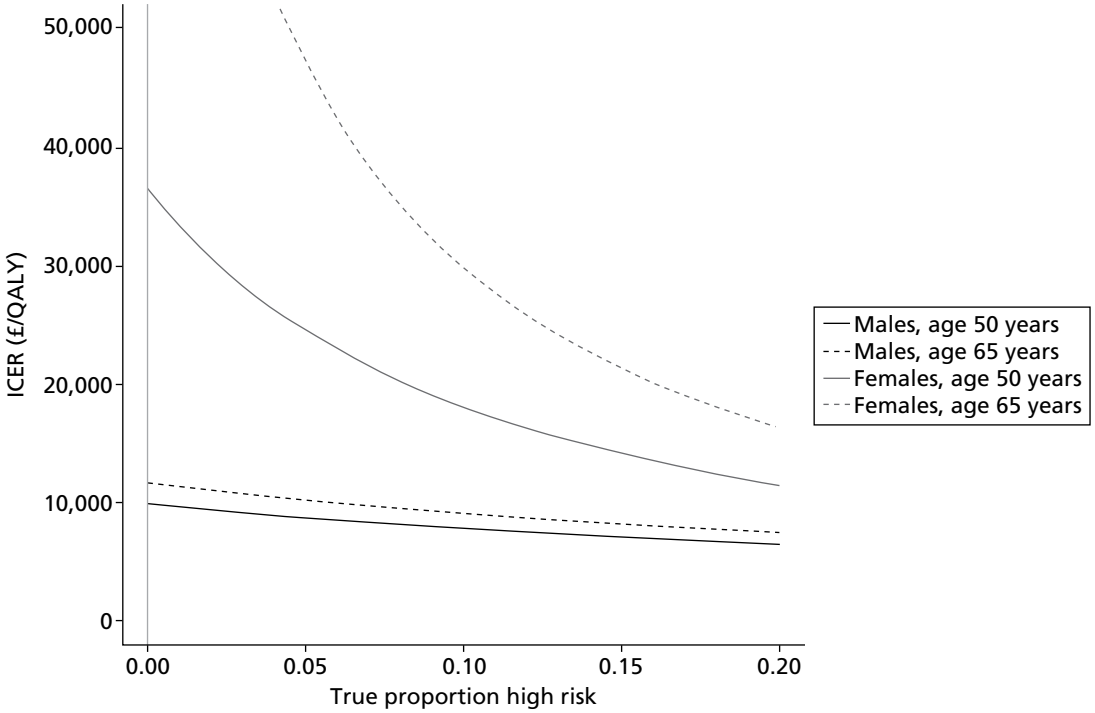


FIGURE 27 Effect of true proportion of population with LA abnormality on estimated ICER in people aged either 50 or 65 years who have a $CHADS_2$ score of 1.

TABLE 59 Summary of patient populations modelled

Patient population	OACs considered
Males, age 50 years, $CHADS_2$ score of 0	Warfarin, rivaroxaban
Females, age 50 years, $CHADS_2$ score of 0	Warfarin, rivaroxaban
Male, age 65 years, $CHADS_2$ score of 0	Warfarin, rivaroxaban, dabigatran
Females, age 65 years, $CHADS_2$ score of 0	Warfarin, rivaroxaban, dabigatran
Males, age 50 years, $CHADS_2$ score of 1	Warfarin
Females, age 50 years, $CHADS_2$ score of 1	Warfarin
Male, age 65 years, $CHADS_2$ score of 1	Warfarin
Females, age 65 years, $CHADS_2$ score of 1	Warfarin

TABLE 60 Qualitative summary of main results

Age (years)	Gender	$CHADS_2$ score of 1	OAC	Ruled out by simple dominance	Likely to be cost-effective at £20,000/QALY
50	Male	No	Warfarin	Yes	No
	Female				
65	Male	No	Warfarin	No	No
	Female				No (possibly at £30,000/QALY)
50	Male	Yes	Warfarin	No	Yes
	Female				
65	Male	Yes	Warfarin	No	Yes
	Female				
50	Male	No	Rivaroxaban	Yes	No
	Female				
65	Male	No	Rivaroxaban	No	No (possibly at £30,000/QALY)
	Female				Maybe
65	Male	No	Dabigatran	No	Yes
	Female				

Chapter 5 Assessment of factors relevant to the NHS and other parties

The assessment of newly diagnosed patients with AF using a TTE is unlikely to cause a significant impact on either the NHS or other parties. TTEs are relatively easily available, as well as both safe and non-invasive for patients, with staff who are trained in their use likely to be already available in hospitals.

The additional resources required are relatively small, at an estimated £66 per TTE performed. It is likely that additional bed-days are made available owing to the reduction in stroke following appropriate management, although there is likely to be an increase in bleed-related admissions.

Chapter 6 Discussion and conclusions

Statement of principal findings

Diagnostic accuracy showed high specificities for all selected pathologies, with the majority having specificity of ≥0.8, meaning a low proportion of FPs. Specificity was lower for aortic dissection and pulmonary disease than for other pathologies. For most pathologies there was also quite high sensitivity, with the majority having sensitivity of ≥0.6, with the exceptions of atrial thrombi, atrial septal defect and PE, for which sensitivity was lower. There was a high prevalence (around 25–30%) of ischaemic heart disease, valvular heart disease and heart failure in patients with AF in the included prevalence studies. TTE seems to be a sufficient diagnostic tool for most pathologies included here, but there may need to be extra screening for PE by lung scan, and atrial thrombi and atrial septal hypertrophy by TOE, to avoid FNs for these pathologies.

The results of the mathematical model indicated that in newly diagnosed patients with a $CHADS_2$ score of 1, who are not already receiving warfarin, rivaroxaban, or dabigatran, it may be cost-effective to use TTE to help inform the decision whether to prescribe warfarin. In newly diagnosed patients aged ≥65 years it may be cost-effective to use TTE to help inform the decision about whether to prescribe dabigatran. A simplified approach indicated that only a small number of QALYs (0.0033) was required to deem a TTE to be cost-effective, and that incidental benefits may provide more than this number of QALYs.

Strengths and limitations of the assessment

A range of studies were identified that were of good quality and of relevance to UK populations.

It is possible that some studies were missed owing to limiting to studies published in the English language, and only one database being searched for diagnostic accuracy studies.

Data here are not a substitute for a trial of routine screening. In practice, the many different pathologies that could be identified may lead to many different treatment strategies. Patients may have more than one pathology in addition to AF, and may have been diagnosed with other conditions prior to AF diagnosis. It is also important that personnel performing these examinations receive adequate training to minimise bias and improve the quality of screening procedures. The outcome of screening in terms of treatment modification and subsequent prognostic impact will be complex. Receiving diagnoses may result in the patient making lifestyle changes as well as being provided with more appropriate medical treatment. In addition, there may be an emotional impact on patients in terms of undergoing testing, receiving additional diagnoses or being reassured where comorbidities are not diagnosed. Patients need to be provided with information about screening – including implications and limitations – before deciding whether to consent to testing. A trial of routine TTE screening in patients with newly diagnosed AF could address the impact on patients, which may go beyond simple changes in medical treatment, although any such trial would be costly owing to the large sample size and long length of follow-up needed to investigate outcomes including mortality; however, given the benefits and lack of adverse effects of TTE, it is unclear how useful additional evidence from a trial would be.

Our literature review identified no economic evaluations of TTE in patients with AF so it is believed that this is the first. One strength of the modelling is that it uses recent data assessing the sensitivity and specificity of TTE in identifying LA abnormality in patients categorised by $CHADS_2$ score with confirmation provided by TOE. A limitation is that this study had a relatively small data set ($n = 405$) and was undertaken in Portugal, with the population not necessarily representative of a UK population.

A further strength is the simplified approach that was also undertaken. This showed that the QALYs required for TTE to be cost-effective were very small (<0.005). Such values could be provided by many factors not incorporated into the mathematical model, and if clinicians believe that benefits other than those associated with reduced stroke rates (albeit at an increased risk of bleeding) are likely then it is probable that TTE is cost-effective.

Analyses have also been undertaken using different OACs with the conclusions remaining constant.

Uncertainties

There are a number of uncertainties within the economic evaluation of TTE. We elected to model the problem using data provided in Providencia *et al.*,[13] as this was a recent, internally consistent study using the $CHADS_2$ tool, and it had also conducted TOE. However, the study was not large ($n = 405$). This meant that data on the specificity and sensitivity of TTE in identifying LA abnormality were sparse. Using TTE could only affect the decisions in the low risk categories: $CHADS_2 = 0$, and $CHADS_2 = 1$. The number of patients in these categories was small, each fewer than 80 patients, with three values of fewer than 25 patients

A key uncertainty is whether there are other benefits that are accrued from a TTE other than identifying LA abnormality. If these exist, and produce even small QALY gains (>0.0033) then TTE would be cost-effective in all scenarios.

Other relevant factors

As TTE is relatively easily available, and is a safe and non-invasive diagnostic, no other relevant factors were identified.

Implications for service provision

Our conclusions have few implications for service provision. Should TTE be recommended for those patients with $CHADS_2$ scores of 0 or 1 then this is unlikely to place a great burden on hospitals who are likely to have staff trained in the use of TTE machines. Capacity will depend on scheduling the use of existing TTE equipment and extra staff time needed.

Suggested research priorities

Following up patients with newly diagnosed AF who have undergone TTE to study treatments given as a result of TTE diagnoses and subsequent cardiovascular events could identify potential benefits of routine testing, beyond stroke prevention.

Our conclusions regarding the cost-effectiveness of TTE have been limited by the available data relating to the proportion of people with $CHADS_2$ scores of 0 or 1 who have LA abnormality. These proportions have been shown to markedly affect the cost per QALY and there are few data available. In obtaining such data more accurate estimates of the sensitivity and specificity of TTE in identifying LA abnormality should be collected.

Any additional benefit of TTE beyond those associated with treatment for stroke prevention also needs to be researched. Even small gains would equate to TTE being perceived as cost-effective.

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References

1. The National Collaborating Centre for Chronic Conditions. *Atrial fibrillation: national clinical guideline for management in primary and secondary care*. 2006. URL: www.nice.org.uk/nicemedia/live/10982/30055/30055.pdf.
2. Fuster V, Ryden LE, Cannom, DS, Crijns HJ, Curtis AB, Ellenbogen KA, *et al.* 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation. *Circulation* 2011;**123**:e269–367. http://dx.doi.org/10.1161/CIR.0b013e318214876d
3. Levy S, Camm AJ, Saksena S, Aliot E, Breithardt G, Crijns H, *et al.* International consensus on nomenclature and classification of atrial fibrillation. *Europace* 2003;**5**:119–22. http://dx.doi.org/10.1053/eupc.2002.0300
4. Estes NAM, Sacco RL, Al-Khatib SM, Ellinor PT, Bezanson J, Alonso A, *et al.* American Heart Association Atrial Fibrillation Research Summit. *Circulation* 2011;**124**:363–72. http://dx.doi.org/10.1161/CIR.0b013e318224b037
5. Kerr CR, Humphries KH, Talajic M, Klein GJ, Connolly SJ, Green M, *et al.* Progression to chronic atrial fibrillation after the initial diagnosis of paroxysmal atrial fibrillation: results from the Canadian Registry of Atrial Fibrillation. *Am Heart J* 2005;**149**:489–96. http://dx.doi.org/10.1016/j.ahj.2004.09.053
6. Developed with the special contribution of the European Heart Rhythm Association (EHRA), Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS), Task FM, Camm AJ, Kirchhof P, Lip GYH, *et al.* Guidelines for the management of atrial fibrillation. *Eur Heart J* 2010;**31**:2369–429.
7. Olson JM, Samad BA, Alam M. Prognostic value of pulse-wave tissue Doppler parameters in patients with systolic heart failure. *Am J Cardiol* 2008;**102**:722–5. http://dx.doi.org/10.1016/j.amjcard.2008.04.054
8. Pizko P, Lewczuk J, Lenatowska L, Jagas J, Romaszkiewicz R, Blaszczyk D, *et al.* Pulmonary thromboembolism in 102 consecutive patients with chronic atrial fibrillation. Diagnostic value of echocardiography. *Kardiol Pol* 2007;**65**:246–51.
9. Okura H, Takada Y, Kubo T, Iwata K, Mizoguchi S, Taguchi H, *et al.* Tissue Doppler-derived index of left ventricular filling pressure, E/E', predicts survival of patients with non-valvular atrial fibrillation. *Heart* 2006;**92**:1248–52. http://dx.doi.org/10.1136/hrt.2005.082594
10. Sakabe K, Fukuda N, Fukuda Y, Morishita S, Shinohara H, Tamura Y, *et al.* Transthoracic echocardiography during sinus rhythm identifies elderly patients with nonvalvular paroxysmal atrial fibrillation at high risk of cerebral infarction. *Int J Cardiol* 2009;**136**:346–8. http://dx.doi.org/10.1016/j.ijcard.2008.04.065
11. Thambidorai SK, Murray RD, Parakh K, Shah TK, Black IW, Jasper SE, *et al.* Utility of transesophageal echocardiography in identification of thrombogenic milieu in patients with atrial fibrillation (an ACUTE ancillary study). *Am J Cardiol* 2005;**96**:935–41. http://dx.doi.org/10.1016/j.amjcard.2005.05.051
12. Bernhardt P, Schmidt H, Hammerstingl C, Luderitz B, Omran H. Patients at high risk with atrial fibrillation: a prospective and serial follow-up during 12 months with transesophageal echocardiography and cerebral magnetic resonance imaging. *J Am Soc Echocardiogr* 2005;**18**:919–24. http://dx.doi.org/10.1016/j.echo.2005.01.028

13. Providencia R, Botelho A, Trigo J, Quintal N, Nascimento J, Mota P, *et al.* Possible refinement of clinical thromboembolism assessment in patients with atrial fibrillation using echocardiographic parameters. *Europace* 2012;**14**:36–45. http://dx.doi.org/10.1093/europace/eur272

14. Kannel WB, Benjamin EJ. Current perceptions of the epidemiology of atrial fibrillation. *Cardiol Clin* 2009;**27**:13–vii.

15. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, *et al.* Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001;**285**:2370–5. http://dx.doi.org/10.1001/jama.285.18.2370

16. Stewart S, Hart CL, Hole DJ, McMurray JJ. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. *Heart* 2001;**86**:516–21. http://dx.doi.org/10.1136/heart.86.5.516

17. Ryder KM, Benjamin EJ. Epidemiology and significance of atrial fibrillation. *Am J Cardiol* 1999;**84**:131–8R. http://dx.doi.org/10.1016/S0002-9149(99)00713-4

18. Stewart S. Epidemiology and economic impact of atrial fibrillation. *J Cardiovasc Nurs* 2004;**19**:94–102.

19. Kannel WBW. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998;**82**:2N–9N. http://dx.doi.org/10.1016/S0002-9149(98)00583-9

20. Kannel WB, Benjamin EJ. Status of the epidemiology of atrial fibrillation. *Med Clin N Am* 2008;**92**:17–40. http://dx.doi.org/10.1016/j.mcna.2007.09.002

21. Majeed A, Moser K, Carroll K. Trends in the prevalence and management of atrial fibrillation in general practice in England and Wales, 1994–1998: analysis of data from the general practice research database. *Heart* 2001;**86**:284–8. http://dx.doi.org/10.1136/heart.86.3.284

22. Murphy NF, Simpson CR, Jhund PS, Stewart S, Kirkpatrick M, Chalmers J, *et al.* A national survey of the prevalence, incidence, primary care burden and treatment of atrial fibrillation in Scotland. *Heart* 2007;**93**:606–12. http://dx.doi.org/10.1136/hrt.2006.107573

23. Lip GY, Beevers DG. ABC of atrial fibrillation. History, epidemiology, and importance of atrial fibrillation. *BMJ* 1995;**311**:1361–3. http://dx.doi.org/10.1136/bmj.311.7016.1361

24. Wolf PAB. Secular trends in the prevalence of atrial fibrillation: the Framingham study. *Am Heart J* 1996;**131**:790–5. http://dx.doi.org/10.1016/S0002-8703(96)90288-4

25. Lip GY, Bawden L, Hodson R, Rutland E, Snatchfold J, Beevers DG. Atrial fibrillation amongst the Indo-Asian general practice population. The West Birmingham Atrial Fibrillation Project. *Int J Cardiol* 1998;**65**:187–92.

26. Rienstra M, Hagens VE, van Veldhuisen DJ, Bosker HA, Tijssen JG, Kamp O, *et al.* Clinical characteristics of persistent lone atrial fibrillation in the RACE study. *Am J Cardiol* 2004;**94**:1486–90. http://dx.doi.org/10.1016/j.amjcard.2004.08.024

27. Aronow WS, Ahn C, Kronzon I, Gutstein H. Association of left ventricular hypertrophy and chronic atrial fibrillation with the incidence of new thromboembolic stroke in 2,384 older persons. *Am J Cardiol* 1999;**84**:468–9, A9.

28. de Divitiis M, Omran H, Rabahieh R, Rang B, Illien S, Schimpf R, *et al.* Right atrial appendage thrombosis in atrial fibrillation: its frequency and its clinical predictors. *Am J Cardiol* 1999;**84**:1023–8. http://dx.doi.org/10.1016/S0002-9149(99)00492-0

29. Chugh SS, Blackshear JL, Shen WK, Hammill SC, Gersh BJ. Epidemiology and natural history of atrial fibrillation: clinical implications. *J Am Coll Cardiol* 2001;**37**:371–8. http://dx.doi.org/10.1016/S0735-1097(00)01107-4

30. Miyasaka Y, Barnes ME, Petersen RC, Cha SS, Bailey KR, Gersh BJ, *et al.* Risk of dementia in stroke-free patients diagnosed with atrial fibrillation: data from a community-based cohort. *Eur Heart J* 2007;**28**:1962–7. http://dx.doi.org/10.1093/eurheartj/ehm012

31. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death. *Circulation* 1998;**98**:946–52. http://dx.doi.org/10.1161/01.CIR.98.10.946

32. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002;**113**:359–64. http://dx.doi.org/10.1016/S0002-9343(02)01236-6

33. Mitra R, Leatham EW. Admissions with atrial fibrillation: disease patterns and outcomes in a District General Hospital. *QJM* 2005;**98**:153–4. http://dx.doi.org/10.1093/qjmed/hci021

34. Stewart S, MacIntyre K, MacLeod MM, Bailey AE, Capewell S, McMurray JJ. Trends in hospital activity, morbidity and case fatality related to atrial fibrillation in Scotland, 1986–1996. *Eur Heart J* 2001;**22**:693–701. http://dx.doi.org/10.1053/euhj.2000.2511

35. Stewart S, Murphy NF, Walker A, McGuire A, McMurray JJ. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. *Heart* 2004;**90**:286–92. http://dx.doi.org/10.1136/hrt.2002.008748

36. National Service Framework. *National Service Framework for Coronary Heart Disease. Chapter 8: arrhythmias and sudden cardiac death*. 2005. URL: www.cardiomyopathy.org/assets/files/NSF%20Chapter%208.pdf (accessed November 2011).

37. Fuster V, Ryden L, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, *et al.* ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation. *Circulation* 2006;**114**:700–52. http://dx.doi.org/10.1161/CIRCULATIONAHA.106.177031

38. Van Gelder I, Groenveld H, Crijns H, Tuininga Y, Tijssen J, Alings A, *et al.* Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med* 2010;**362**:1363–73. http://dx.doi.org/10.1056/NEJMoa1001337

39. AFFIRM Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;**347**:1825–33. http://dx.doi.org/10.1056/NEJMoa021328

40. Van Gelder I, Hagens VE, Bosker H, Kingma H, Kamp O, Kingma T, *et al.* A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002;**347**:1834–40. http://dx.doi.org/10.1056/NEJMoa021375

41. Roy D, Talajic M, Nattel S, Wyse D, Dorian P, Lee K, *et al.* Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med* 2008;**358**:2667–77. http://dx.doi.org/10.1056/NEJMoa0708789

42. National Institute for Health and Care Excellence (NICE). NICE guidelines. *Cryoablation for atrial fibrillation in association with other cardiac surgery*. London: NICE; 2006.

43. Camm A, Kirchhof P, Lip G, Schotten U, Savelieva I, Ernst S, *et al.* Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;**31**:2369–429. http://dx.doi.org/10.1093/eurheartj/ehq278

44. American Heart Association (AHA) Science Advisory, Knight BP, Gersh BJ, Carlson M, Friedman P, McNamara R, *et al.* Role of permanent pacing to prevent atrial fibrillation: science advisory from the American Heart Association Council on Clinical Cardiology (Subcommittee on Electrocardiography and Arrhythmias) and the Quality of Care and Outcomes Research Interdisciplinary Working

Group, in collaboration with the Heart Rhythm Society. *Circulation* 2005;**111**:240–3. http://dx.doi.org/10.1161/01.CIR.0000151800.84945.47

45. National Institute for Health and Care Excellence (NICE). *Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation*. London: NICE; 2012.

46. National Institute for Health and Care Excellence (NICE). *Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation.* London: NICE; 2012.

47. National Institute for Health and Care Excellence (NICE). *Atrial fibrillation (stroke prevention) – rivaroxaban*. London: NICE; 2012.

48. Wann LS, Curtis AB, Ellenbogen KA, Estes NAM, Ezekowitz MD, Jackman WM, *et al.* 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on dabigatran): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2011;**57**:1330–7. http://dx.doi.org/10.1016/j.jacc.2011.01.010

49. Bayliss J (for Bedfordshire and Hertfordshire Cardiac Network). Bedfordshire and Hertfordshire Cardiac Network guidance. *Effective use of transthoracic echocardiography (TTE) in adults – summary*. 2006. URL: www.bhhsnetwork.nhs.uk/UserFiles/File/StandardsGuidelines/Beds&Herts_Echo_guidelines_v2_Brief.pdf (accessed November 2011).

50. British Society of Echocardiography. *Clinical indications for echocardiography*. 2009. URL: http://cdn1.cache.twofourdigital.net/u/bsecho/media/10465/clinical_indications_for_echocardiography.pdf (accessed November 2011).

51. Evangelista A, Flachskampf FA, Lancellotti P, Badano LP, Aguilar R, Monaghan MJ, *et al.* European Association of Echocardiography recommendations for standardization of performance, digital storage and reporting of echocardiographic studies. *Eur J Echocardiogr* 2008;**9**:438–48. http://dx.doi.org/10.1093/ejechocard/jen174

52. National Imaging Board. *Cardiac imaging: a report from the National Imaging Board*. 2010. URL: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_114380 (accessed November 2011).

53. Stanko L, Jacobsohn E, Tam J, De Wet C, Avidan M. Transthoracic echocardiography: impact on diagnosis and management in tertiary care intensive care units. *Anaesth Intensive Care* 2005;**33**:492–6.

54. Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D, Davies DW, *et al.* Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J* 2005;**26**:2422–34. http://dx.doi.org/10.1093/eurheartj/ehi505

55. UK National Screening Committee. Screening Criteria set by the UK National Screening Committee. 2011. URL: www.scotland.gov.uk/Topics/Health/health/cancer/Cancer-Screening/criteria (accessed November 2011).

56. Petticrew M, Sowden A, Lister-Sharp D, Wright K. False-negative results in screening programmes: systematic review of impact and implications. *Health Technol Assess* 2000;**4**(5).

57. Merlin T, Weston A, Tooher R. Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Med Res Meth* 2009;**9**:(34). http://dx.doi.org/10.1186/1471-2288-9-34

58. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stats Med* 1998;**17**:857–72. http://dx.doi.org/10.1002/(SICI)1097-0258(19980430)17:8<857::AID-SIM777>3.0.CO;2-E

59. Whiting P, Rutjes A, Reitsma J, Bossuyt P, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Meth* 2003;**3**:(25). http://dx.doi.org/10.1186/1471-2288-3-25

60. Elm EV, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, *et al.* Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;**335**:806–8. http://dx.doi.org/10.1136/bmj.39335.541782.AD

61. Moher D, Liberati A, Tetzlaff J, Altman DG, the PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Ann Intern Med* 2009;**151**:65–94.

62. Acar J, Cormier B, Grimberg D, Kawthekar G, Iung B, Scheuer B, *et al.* Diagnosis of left atrial thrombi in mitral stenosis – usefulness of ultrasound techniques compared with other methods. *Eur Heart J* 1991;**12**(Suppl. B):70–6. http://dx.doi.org/10.1093/eurheartj/12.suppl_B.70

63. Arques S, Roux E, Sbragia P, Gelisse R, Ambrosi P, Pieri B, *et al.* Comparative accuracy of color M-mode and tissue Doppler echocardiography in the emergency diagnosis of congestive heart failure in chronic hypertensive patients with normal left ventricular ejection fraction. *Am J Cardiol* 2005;**96**:1456–9. http://dx.doi.org/10.1016/j.amjcard.2005.07.051

64. Attenhofer Jost CH, Turina J, Mayer K, Seifert B, Amann FW, Buechi M, *et al.* Echocardiography in the evaluation of systolic murmurs of unknown cause. *Am J Med* 2000;**108**:614–20. http://dx.doi.org/10.1016/S0002-9343(00)00361-2

65. Barron JT, Manrose DL, Liebson PR. Comparison of auscultation with two-dimensional and Doppler echocardiography in patients with suspected mitral valve prolapse. *Clin Cardiol* 1988;**11**:401–6. http://dx.doi.org/10.1002/clc.4960110608

66. Bova C, Greco F, Misuraca G, Serafini O, Crocco F, Greco A, *et al.* Diagnostic utility of echocardiography in patients with suspected pulmonary embolism. *Am J Emerg Med* 2003;**21**:180–3. http://dx.doi.org/10.1016/S0735-6757(02)42257-7

67. Casella F, Rana B, Casazza G, Bhan A, Kapetanakis S, Omigie J, *et al.* The potential impact of contemporary transthoracic echocardiography on the management of patients with native valve endocarditis: a comparison with transesophageal echocardiography. *Echocardiography* 2009;**26**:900–6. http://dx.doi.org/10.1111/j.1540-8175.2009.00906.x

68. Cassidy TP, Hardwick DJ, Norris CA. Aortic stenosis in elderly people: an evaluation of clinical and echocardiographic diagnosis. *Age Ageing* 1992;**21**:440–4. http://dx.doi.org/10.1093/ageing/21.6.440

69. Dittmann H, Karsch KR, Seipel L. Diagnosis and quantification of aortic regurgitation by pulsed Doppler echocardiography in patients with mitral valve disease. *Eur Heart J* 1987;**8**(Suppl. C):53–7. http://dx.doi.org/10.1093/eurheartj/8.suppl_C.53

70. Enia F, Ledda G, Lo MR, Matassa C, Raspanti G, Stabile A, *et al.* Utility of echocardiography in the diagnosis of aortic dissection involving the ascending aorta. *Chest* 1989;**95**:124–9. http://dx.doi.org/10.1378/chest.95.1.124

71. Erbel R, Schweizer P, Krebs W, Meyer J, Effert S, Erbel R, *et al.* Sensitivity and specificity of two-dimensional echocardiography in detection of impaired left ventricular function. *Eur Heart J* 1984;**5**:477–89.

72. Grossmann G, Wohrle J, Kochs M, Giesler M, Hombach V, Hoher M, *et al.* Quantification of mitral regurgitation by the proximal flow convergence method – comparison of transthoracic and transesophageal echocardiography. *Clin Cardiol* 2002;**25**:517–24. http://dx.doi.org/10.1002/clc.4960251108

73. Groves AM, Win T, Charman SC, Wisbey C, Pepke-Zaba J, Coulden RA, *et al.* Semi-quantitative assessment of tricuspid regurgitation on contrast-enhanced multidetector CT. *Clin Radiol* 2004;**59**:715–19. http://dx.doi.org/10.1016/j.crad.2004.02.007

74. Guyer DE, Gillam LD, Foale RA, Clark MC, Dinsmore R, Palacios I, *et al.* Comparison of the echocardiographic and hemodynamic diagnosis of rheumatic tricuspid stenosis. *J Am Coll Cardiol* 1984;**3**:1135–44. http://dx.doi.org/10.1016/S0735-1097(84)80170-9

75. Helmcke F, Nanda NC, Hsiung MC, Soto B, Adey CK, Goyal RG, *et al.* Color Doppler assessment of mitral regurgitation with orthogonal planes. *Circulation* 1987;**75**:175–83. http://dx.doi.org/10.1161/01.CIR.75.1.175

76. Jassal DS, Aminbakhsh A, Fang T, Shaikh N, Embil JM, Mackenzie GS, *et al.* Diagnostic value of harmonic transthoracic echocardiography in native valve infective endocarditis: comparison with transesophageal echocardiography. *Cardiovasc Ultrasound* 2007;**5**:20. http://dx.doi.org/10.1186/1476-7120-5-20

77. Kaymaz C, Ozdemir N, Kirma C, Sismanoglu M, Daglar B, Ozkan M, *et al.* Location, size and morphological characteristics of left atrial thrombi as assessed by echocardiography in patients with rheumatic mitral valve disease. *Eur J Echocardiogr* 2001;**2**:270–6. http://dx.doi.org/10.1053/euje.2001.0093

78. Kishon Y, Iqbal A, Oh JK, Gersh BJ, Freeman WK, Seward JB, *et al.* Evolution of echocardiographic modalities in detection of postmyocardial infarction ventricular septal defect and papillary muscle rupture: study of 62 patients. *Am Heart J* 1993;**126**:667–75. http://dx.doi.org/10.1016/0002-8703(93)90417-8

79. Kitayama H, Kiuchi K, Endo T, Hayakawa H, Kitayama H, Kiuchi K, *et al.* Value of cardiac ultrafast computed tomography for detecting right atrial thrombi in chronic atrial fibrillation. *Am J Cardiol* 1997;**79**:1292–5. http://dx.doi.org/10.1016/S0002-9149(97)00107-0

80. Lanzarini L, Fontana A, Campana C, Klersy C, Lanzarini L, Fontana A, *et al.* Two simple echo-Doppler measurements can accurately identify pulmonary hypertension in the large majority of patients with chronic heart failure. *J Heart Lung Transplant* 2005;**24**:745–54. http://dx.doi.org/10.1016/j.healun.2004.03.026

81. Maestre A, Gil V, Gallego J, Aznar J, Mora A, Martin-Hidalgo A, *et al.* Diagnostic accuracy of clinical criteria for identifying systolic and diastolic heart failure: cross-sectional study. *J Eval Clin Pract* 2009;**15**:55–61. http://dx.doi.org/10.1111/j.1365-2753.2008.00954.x

82. Mugge A, Daniel WG, Angermann C, Spes C, Khandheria BK, Kronzon I, *et al.* Atrial septal aneurysm in adult patients: a multicenter study using transthoracic and transesophageal echocardiography. *Circulation* 1995;**91**:2785–92. http://dx.doi.org/10.1161/01.CIR.91.11.2785

83. Nienaber CA, von Kodolitsch Y, Nicolas V, Siglow V, Piepho A, Brockhoff C, *et al.* The diagnosis of thoracic aortic dissection by noninvasive imaging procedures. *N Engl J Med* 1993;**328**:1–9. http://dx.doi.org/10.1056/NEJM199301073280101

84. Nienaber CA, von Kodolitsch Y, Brockhoff CJ, Koschyk DH, Spielmann RP. Comparison of conventional and transesophageal echocardiography with magnetic resonance imaging for anatomical mapping of thoracic aortic dissection. A dual noninvasive imaging study with anatomical and/or angiographic validation. *Int J Card Imag* 1994;**10**:1–14. http://dx.doi.org/10.1007/BF01151576

85. Okura H, Fuyuki H, Kubo T, Iwata K, Taguchi H, Toda I, *et al.* Noninvasive diagnosis of ischemic and nonischemic cardiomyopathy using coronary flow velocity measurements of the left anterior descending coronary artery by transthoracic Doppler echocardiography. *J Am Soc Echocardiogr* 2006;**19**:552–8. http://dx.doi.org/10.1016/j.echo.2005.12.013

86. Pochis WT, Saeian K, Sagar KB. Usefulness of transesophageal echocardiography in diagnosing lipomatous hypertrophy of the atrial septum with comparison to transthoracic echocardiography. *Am J Cardiol* 1992;**70**:396–8. http://dx.doi.org/10.1016/0002-9149(92)90629-D

87. Reichek N, Devereux RB. Left ventricular hypertrophy: relationship of anatomic, echocardiographic and electrocardiographic findings. *Circulation* 1981;**63**:1391–8. http://dx.doi.org/10.1161/01.CIR.63.6.1391

88. Reichlin S, Dieterle T, Camli C, Leimenstoll B, Schoenenberger RA, Martina B. Initial clinical evaluation of cardiac systolic murmurs in the ED by noncardiologists. *Am J Emerg Med* 2004;**22**:71–5. http://dx.doi.org/10.1016/S0735-6757(03)00093-7

89. Roudaut RP, Billes MA, Gosse P, Deville C, Baudet E, Fontan F, *et al.* Accuracy of M-mode and two-dimensional echocardiography in the diagnosis of aortic dissection: an experience with 128 cases. *Clin Cardiol* 1988;**11**:553–62. http://dx.doi.org/10.1002/clc.4960110809

90. Saraste M, Vesalainen RK, Ylitalo A, Saraste A, Koskenvuo JW, Toikka JO, *et al.* Transthoracic Doppler echocardiography as a noninvasive tool to assess coronary artery stenoses – a comparison with quantitative coronary angiography. *J Am Soc Echocardiogr* 2005;**18**:679–85. http://dx.doi.org/10.1016/j.echo.2004.09.016

91. Sharifi M, Parhizgar A, Gupta P, Mehdipour M, Emrani F, Baldwin D. Is transesophageal echocardiography necessary before D.C. cardioversion in patients with a normal transthoracic echocardiogram? *Echocardiography* 2007;**24**:397–400. http://dx.doi.org/10.1111/j.1540-8175.2007.00400.x

92. Sharma S, Krishnan U. Diagnosis of the sinus venosus defect by echocardiography and angiocardiography. *Indian Heart J* 1992;**44**:395–8.

93. Sheiban I, Casarotto D, Trevi G, Benussi P, Marini A, Accardi R, *et al.* Two-dimensional echocardiography in the diagnosis of intracardiac masses: a prospective study with anatomic validation. *Cardiovasc Intervent Radiol* 1987;**10**:157–61. http://dx.doi.org/10.1007/BF02577993

94. Shively BK, Gurule FT, Roldan CA, Leggett JH, Schiller NB, Shively BK, *et al.* Diagnostic value of transesophageal compared with transthoracic echocardiography in infective endocarditis. *J Am Coll Cardiol* 1991;**18**:391–7. http://dx.doi.org/10.1016/0735-1097(91)90591-V

95. Shrestha NK, Moreno FL, Narciso FV, Torres L, Calleja HB. Two-dimensional echocardiographic diagnosis of left-atrial thrombus in rheumatic heart disease. A clinicopathologic study. *Circulation* 1983;**67**:341–7. http://dx.doi.org/10.1161/01.CIR.67.2.341

96. Shub C, Dimopoulos IN, Seward JB, Callahan JA, Tancredi RG, Schattenberg TT, *et al.* Sensitivity of two-dimensional echocardiography in the direct visualization of atrial septal defect utilizing the subcostal approach: experience with 154 patients. *J Am Coll Cardiol* 1983;**2**:127–35. http://dx.doi.org/10.1016/S0735-1097(83)80385-4

97. Shyu KG, Lei M, Hwang J, Lin SC, Kuan P, Lien WP. Morphologic characterization and quantitative assessment of mitral regurgitation with ruptured chordae tendineae by transesophageal echocardiography. *Am J Cardiol* 1992;**70**:1152–6. http://dx.doi.org/10.1016/0002-9149(92)90047-3

98. Smith G, Endresen K, Sivertssen E, Semb G. Ventricular septal rupture diagnosed by simultaneous cross-sectional echocardiography and Doppler ultrasound. *Eur Heart J* 1985;**6**:631–6.

99. Sparrow N, Adlam D, Cowley A, Hampton JR. The diagnosis of heart failure in general practice: implications for the UK National Service Framework. *Eur J Heart Fail* 2003;**5**:349–54. http://dx.doi.org/10.1016/S1388-9842(03)00046-1

100. Stratton JR, Lighty GW Jr, Pearlman AS, Ritchie JL. Detection of left ventricular thrombus by two-dimensional echocardiography: sensitivity, specificity, and causes of uncertainty. *Circulation* 1982;**66**:156–66. http://dx.doi.org/10.1161/01.CIR.66.1.156

101. Veyrat C, Lessana A, Abitbol G, Ameur A, Benaim R, Kalmanson D, *et al.* New indexes for assessing aortic regurgitation with two-dimensional Doppler echocardiographic measurement of the regurgitant aortic valvular area. *Circulation* 1983;**68**:998–1005. http://dx.doi.org/10.1161/01.CIR.68.5.998

102. Vigna C, de Rito V, Criconia GM, Russo A, Testa M, Fanelli R, *et al.* Left atrial thrombus and spontaneous echo-contrast in nonanticoagulated mitral stenosis. A transesophageal echocardiographic study. *Chest* 1993;**103**:348–52. http://dx.doi.org/10.1378/chest.103.2.348

103. Wong M, Tei C, Shah PM. Sensitivity and specificity of two-dimensional echocardiography in the detection of valvular calcification. *Chest* 1983;**84**:423–7. http://dx.doi.org/10.1378/chest.84.4.423

104. Zanolla L, Marino P, Nicolosi GL, Peranzoni PF, Poppi A, Zanolla L, *et al.* Two-dimensional echocardiographic evaluation of mitral valve calcification. Sensitivity and specificity. *Chest* 1982;**82**:154–7. http://dx.doi.org/10.1378/chest.82.2.154

105. Zotz RJ, Dohmen G, Genth S, Erbel R, Dieterich HA, Meyer J. Transthoracic and transesophageal echocardiography to diagnose ventricular septal rupture: importance of right heart infarction. *Coron Artery Dis* 1993;**4**:911–17. http://dx.doi.org/10.1097/00019501-199310000-00011

106. Atrial Fibrillation Investigators. Echocardiographic predictors of stroke in patients with atrial fibrillation: a prospective study of 1066 patients from 3 clinical trials. *Arch Intern Med* 1998;**158**:1316–20. http://dx.doi.org/10.1001/archinte.158.12.1316

107. Klem I, Wehinger C, Schneider B, Hartl E, Finsterer J, Stollberger C, *et al.* Diabetic atrial fibrillation patients: mortality and risk for stroke or embolism during a 10-year follow-up. *Diabetes Metabol Res Rev* 2003;**19**:320–8. http://dx.doi.org/10.1002/dmrr.386

108. Miyasaka Y, Tsuji H, Tokunaga S, Nishiue T, Yamada K, Watanabe J, *et al.* Mild mitral regurgitation was associated with increased prevalence of thromboembolic events in patients with nonrheumatic atrial fibrillation. *Int J Cardiol* 2000;**72**:229–33.

109. Nakagami H, Yamamoto K, Ikeda U, Mitsuhashi T, Goto T, Shimada K, *et al.* Mitral regurgitation reduces the risk of stroke in patients with nonrheumatic atrial fibrillation. *Am Heart J* 1998;**136**:528–32. http://dx.doi.org/10.1016/S0002-8703(98)70231-5

110. The Stroke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation: II. Echocardiographic features of patients at risk. *Ann Intern Med* 1992;**116**:6–12.

111. Agmon Y, Khandheria BK, Meissner I, Schwartz GL, Petterson TM, O'Fallon WM, *et al.* Association of atrial fibrillation and aortic atherosclerosis: a population-based study. *Mayo Clin Proc* 2001;**76**:252–9. http://dx.doi.org/10.4065/76.3.252

112. Archer SL, James KE, Kvernen LR, Cohen IS, Ezekowitz MD, Gornick CC. Role of transesophageal echocardiography in the detection of left atrial thrombus in patients with chronic nonrheumatic atrial fibrillation. *Am Heart J* 1995;**130**:287–95. http://dx.doi.org/10.1016/0002-8703(95)90442-5

113. Blackshear JL, Pearce LA, Hart RG, Zabalgoitia M, Labovitz A, Asinger RW, *et al.* Aortic plaque in atrial fibrillation: prevalence, predictors, and thromboembolic implications. *Stroke* 1999;**30**:834–40. http://dx.doi.org/10.1161/01.STR.30.4.834

114. Corrado GB. Prevalence of atrial thrombi in patients with atrial fibrillation/flutter and subtherapeutic anticoagulation prior to cardioversion. *Eur J Echocardiogr* 2004;**5**:257–61.

115. Dang D, Patel R. Atrial fibrillation in a multiethnic inpatient population of a large public hospital. *J Natl Med Assoc* 2004;**96**:1438–44.

116. Heppell RM, Berkin KE, McLenachan JM, Davies JA. Haemostatic and haemodynamic abnormalities associated with left atrial thrombosis in non-rheumatic atrial fibrillation. *Heart* 1997;**77**:407–11.

117. Kleemann T, Becker T, Strauss M, Schneider S, Seidl K. Prevalence of left atrial thrombus and dense spontaneous echo contrast in patients with short-term atrial fibrillation <48 hours undergoing cardioversion: value of transesophageal echocardiography to guide cardioversion. *J Am Soc Echocardiogr* 2009;**22**:1403–8. http://dx.doi.org/10.1016/j.echo.2009.09.015

118. Levy S, Maarek M. Characterization of different subsets of atrial fibrillation in general practice in France: The ALFA study. *Circulation* 1999;**99**:3028–35. http://dx.doi.org/10.1161/01.CIR.99.23.3028

119. Lip GY, Golding DJ, Nazir M, Beevers DG, Child DL, Fletcher RI, *et al.* A survey of atrial fibrillation in general practice: the West Birmingham Atrial Fibrillation Project. *Br J General Practice* 1997;**47**:285–9.

120. Maltagliati AG. Usefulness of transoesophageal echocardiography before cardioversion in patients with atrial fibrillation and different anticoagulant regimens. *Heart* 2006;**92**:933–8.

121. Narumiya T, Sakamaki T, Sato Y, Kanmatsuse K. Relationship between left atrial appendage function and left atrial thrombus in patients with nonvalvular chronic atrial fibrillation and atrial flutter. *Circ J* 2003;**67**:68–72. http://dx.doi.org/10.1253/circj.67.68

122. Santiago D, Warshofsky M, Li MG, Di Tullio M, Coromilas J, Reiffel J, *et al.* Left atrial appendage function and thrombus formation in atrial fibrillation-flutter: a transesophageal echocardiographic study. *J Am Coll Cardiol* 1994;**24**:159–64. http://dx.doi.org/10.1016/0735-1097(94)90557-6

123. Scherr D, Dalal D, Chilukuri K, Dong J, Spragg D, Henrikson CA, *et al.* Incidence and predictors of left atrial thrombus prior to catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol* 2009;**20**:379–84. http://dx.doi.org/10.1111/j.1540-8167.2008.01336.x

124. Shen X, Li H, Rovang K, Holmberg MJ, Mooss AN, Mohiuddin SM. Prevalence of intra-atrial thrombi in atrial fibrillation patients with subtherapeutic international normalized ratios while taking conventional anticoagulation. *Am J Cardiol* 2002;**90**:660–2.

125. Tsai LM, Lin LJ, Teng JK, Chen JH. Prevalence and clinical significance of left atrial thrombus in nonrheumatic atrial fibrillation. *Int J Cardiol* 1997;**58**:163–9. http://dx.doi.org/10.1016/S0167-5273(96)02862-8

126. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;**61**:344–9. http://dx.doi.org/10.1016/j.jclinepi.2007.11.008

127. Stroke Prevention in Atrial Fibrillation Investigators. The Stroke Prevention in Atrial Fibrillation III randomized clinical trial: background, design and patient characteristics of the Stroke Prevention in Atrial Fibrillation III study. *J Stroke Cerebrovasc Dis* 1996;**6**:341–53.

128. Higashiue S, Watanabe H, Yokoi Y, Takeuchi K, Yoshikawa J. Simple detection of severe coronary stenosis using transthoracic Doppler echocardiography at rest. *Am J Cardiol* 2001;**87**:1064–8. http://dx.doi.org/10.1016/S0002-9149(01)01462-X

129. Garg R, Khaja A, Madsen R, Alpert MA, Tejwani L, Aggarwal K, *et al.* Observer variation in the echocardiographic measurement of maximum atrial septal excursion: a comparison of M-mode with two-dimensional or transesophageal echocardiography. *Echocardiography* 2009;**26**:1122–6. http://dx.doi.org/10.1111/j.1540-8175.2009.00964.x

130. Hirata K, Pulerwitz T, Sciacca R, Otsuka R, Oe Y, Fujikura K, *et al.* Clinical utility of new real time three-dimensional transthoracic echocardiography in assessment of mitral valve prolapse. *Echocardiography* 2008;**25**:482–8. http://dx.doi.org/10.1111/j.1540-8175.2008.00630.x

131. Miniati M, Monti S, Pratali L, Di Ricco G, Marini C, Formichi B, *et al.* Value of transthoracic echocardiography in the diagnosis of pulmonary embolism: results of a prospective study in unselected patients. *Am J Med* 2001;**110**:528–35. http://dx.doi.org/10.1016/S0002-9343(01)00693-3

132. Chamoun AJ, McCulloch M, Xie T, Shah S, Ahmad M. Real-time three-dimensional echocardiography versus two-dimensional echocardiography in the diagnosis of left ventricular apical thrombi: preliminary findings. *J Clin Ultrasound* 2003;**31**:412–18. http://dx.doi.org/10.1002/jcu.10199

133. Shiga T, Wajima Z, Inoue T, Ogawa R. Survey of observer variation in transesophageal echocardiography: comparison of anesthesiology and cardiology literature. *J Cardiothorac Vasc Anesth* 2003;**17**:430–42. http://dx.doi.org/10.1016/S1053-0770(03)00146-0

134. Frykman V, Frick M, Jensen-Urstad M, Ostergren J, Rosenqvist M. Asymptomatic versus symptomatic persistent atrial fibrillation: clinical and noninvasive characteristics. *J Intern Med* 2001;**250**:390–7. http://dx.doi.org/10.1046/j.1365-2796.2001.00893.x

135. Rozenberg V, Boccara F, Benhalima B, Lamisse N, Buyukoglu B, Cohen A, *et al.* Comparison of echocardiographic markers of embolism in atrial flutter and fibrillation: frequency of protruding atherosclerotic plaques in the thoracic aorta. *Echocardiography* 2000;**17**:555–62. http://dx.doi.org/10.1046/j.1540-8175.2000.00555.x

136. DiPasquale G, Urbinati S, Pinelli G. New echocardiographic markers of embolic risk in atrial fibrillation. *Cerebrovasc Dis* 1995;**5**:315–22. http://dx.doi.org/10.1159/000107874

137. Rubin DN, Katz SE, Riley MF, Douglas PS, Manning WJ. Evaluation of left atrial appendage anatomy and function in recent-onset atrial fibrillation by transesophageal echocardiography. *Am J Cardiol* 1996;**78**:774–8. http://dx.doi.org/10.1016/S0002-9149(96)00419-5

138. Black IW, Hopkins AP, Lee LC, Walsh WF. Evaluation of transesophageal echocardiography before cardioversion of atrial fibrillation and flutter in nonanticoagulated patients. *Am Heart J* 1993;**126**:375–81. http://dx.doi.org/10.1016/0002-8703(93)91054-I

139. Rostagno C, Galanti G, Bertini G, Olivo G, Gensini GF. Doppler echocardiography in suspected lone atrial fibrillation. *Angiology* 1998;**49**:637–40. http://dx.doi.org/10.1177/000331979804900808

140. Levy S. Epidemiology and classification of atrial fibrillation. *J Cardiovasc Electrophysiol* 1998;**9**(Suppl. 8):S78–82.

141. Tops LF, Schalij MJ, Bax JJ. Imaging and atrial fibrillation: the role of multimodality imaging in patient evaluation and management of atrial fibrillation. *Eur Heart J* 2010;**31**:542–51. http://dx.doi.org/10.1093/eurheartj/ehq005

142. Tsang TS, Miyasaka Y, Barnes ME, Gersh BJ. Epidemiological profile of atrial fibrillation: a contemporary perspective. *Prog Cardiovasc Dis* 2005;**48**:1–8. http://dx.doi.org/10.1016/j.pcad.2005.06.001

143. National Institute for Health and Care Excellence (NICE). *Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. NICE technology appraisal guidance 249*. 2012. URL: www.nice.org.uk/nicemedia/live/13677/58470/58470.pdf (accessed 28 September 2012).

144. The Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography. Transesophageal echocardiographic correlates of thromboembolism in high-risk patients with nonvalvular atrial fibrillation. *Ann Intern Med* 1998;**128**:639–47.

145. Office for National Statistics (ONS). *Life tables*. URL: www.ons.gov.uk/ons/rel/lifetables/interim-life-tables/2008-2010/index.html (accessed February 2012).

146. Friberg L, Rosenqvist M, Lip G. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J* 2012;**33**:1500–10. http://dx.doi.org/10.1093/eurheartj/ehr488

147. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–51. http://dx.doi.org/10.1056/NEJMoa0905561

148. Lip G, Edwards S. Stroke prevention with aspirin, warfarin and ximelagatran in patients with non-valvular atrial fibrillation: a systematic review and meta-analysis. *Thromb Res* 2006;**118**:321–33. http://dx.doi.org/10.1016/j.thromres.2005.08.007

149. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–91. http://dx.doi.org/10.1056/NEJMoa1009638

150. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, *et al.* Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation* 2011;**123**:2363–72. http://dx.doi.org/10.1161/CIRCULATIONAHA.110.004747

151. London New Drugs Group. *A briefing paper on dabigatran and rivaroxaban: what we know so far*. UK Medicines Information (UKMi); 2012. URL: www.medicinesresources.nhs.uk/upload/Dabigatran_and_rivaroxaban_briefing_Jan12.pdf (accessed April 2013).

152. British Medical Association and Royal Pharmaceutical Society of Great Britain. British national formulary. London: BMA and RPS; 2011. URL: www.medicinescomplete.com/mc/bnf/current/PHP1497-warfarin-non-proprietary.htm

153. Department of Health (DoH). *NHS reference costs 2009–2010*. London: DoH; 2010.

154. Rivero-Arias O, Ouellet M, Gray A, Wolstenholme J, Rothwell P, Luengo-Fernandez R. Mapping the modified Rankin Scale (mRS) Measurement into the Generic EuroQol (EQ-5D) Health Outcome. *Med Decis Making* 2010;**30**:341–54. http://dx.doi.org/10.1177/0272989X09349961

155. Dorman P, Dennis M, Sandercock P. Are the modified 'simple questions' a valid and reliable measure of health related quality of life after stroke? *J Neurol Neurosurg Psychiatr* 2000;**69**:487–93. http://dx.doi.org/10.1136/jnnp.69.4.487

156. Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, *et al.* A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS. *Health Technol Assess* 2002;**6**(26).

157. Curtis L. *Unit costs of health and social care 2010*. Canterbury: PSSRU, University of Kent; 2011.

158. Simpson E, Stevenson M, Rawdin A, Papaioannou D. Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis. *Health Technol Assess* 2009;**13**(2).

159. Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism. *Ann Intern Med* 2003;**139**:893–900.

160. Haselsberger K, Pucher R, Auer LM. Prognosis after acute subdural or epiduralhaemorrhage. *Acta Neurochir (Wien)* 1988;**90**:111–16. http://dx.doi.org/10.1007/BF01560563

161. Holmes M, Goodacre S, Stevenson M, Pandor A, Pickering A. The cost-effectiveness of diagnostic management strategies for adults with minor head injury. *Injury* 2012;**43**:1423–31. http://dx.doi.org/10.1016/j.injury.2011.07.017

162. Goodacre S, Stevenson M, Wailoo A, Sampson F, Sutton AJ, Thomas S. How should we diagnose suspected deep-vein thrombosis? *QJM* 2006;**99**:377–88. http://dx.doi.org/10.1093/qjmed/hcl051

163. Meenan RT, Saha S, Chou R, Swarztrauber K, Pyle Krages K, O'Keeffe-Rosetti MC, *et al.* Cost-effectiveness of echocardiography to identify intracardiac thrombus among patients with first stroke or transient ischemic attack. *Med Decis Making* 2007;**27**:161–77. http://dx.doi.org/10.1177/0272989X06297388

164. National Institute for Health and Care Excellence (NICE). *Guide to the methods of technology appraisals*. London: NICE; 2008.

165. Fenwick E, Claxton K, Sculpher MJ. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001;**10**:779–87. http://dx.doi.org/10.1002/hec.635

166. Claxton K, Posnett J. An economic approach to clinical trial design and research priority-setting. *Health Econ* 1996;**5**:513–24. http://dx.doi.org/10.1002/(SICI)1099-1050(199611)5:6<513::AID-HEC237>3.0.CO;2-9

167. Felli JC, Hazen BG. Sensitivity analysis and the expected value of perfect information. *Med Decis Making* 1998;**18**:95–109. http://dx.doi.org/10.1177/0272989X9801800117

168. Spain MG, Smith MD, Graybum PA, Harlamert EA, Demaria AN. Quantitative assessment of mitral regurgitation by Doppler color flow imaging: angiographic and hemodynamic correlations. *J Am Coll Cardiol* 1989;**13**:585–90. http://dx.doi.org/10.1016/0735-1097(89)90597-4

169. Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography. Transesophageal echocardiography in atrial fibrillation: standards for acquisition and interpretation and assessment of interobserver variability. *J Am Soc Echocardiogr* 1996;**9**:556–66.

170. Abbasi AS, Allen MW, DeCristofaro D, Ungar I. Detection and estimation of the degree of mitral regurgitation by range-gated pulsed doppler echocardiography. *Circulation* 1980;**61**:143–7. http://dx.doi.org/10.1161/01.CIR.61.1.143

171. Aghassi P, Aurigemma GP, Folland ED, Tighe DA. Catheterization-Doppler discrepancies in nonsimultaneous evaluations of aortic stenosis. *Echocardiography* 2005;**22**:367–73. http://dx.doi.org/10.1111/j.1540-8175.2005.04006.x

172. Agricola E, Meris A, Oppizzi M, Bombardini T, Pisani M, Fragasso G, *et al.* Rest and stress echocardiographic predictors of prognosis in patients with left ventricular dysfunction and functional mitral regurgitation. *Int J Cardiol* 2008;**124**:247–9. http://dx.doi.org/10.1016/j.ijcard.2006.11.234

173. Alkadhi H, Desbiolles L, Husmann L, Plass A, Leschka S, Scheffel H, *et al.* Aortic regurgitation: assessment with 64-section CT. *Radiology* 2007;**245**:111–21. http://dx.doi.org/10.1148/radiol.2451061523

174. Assey ME, Usher BW. Echocardiography in diagnosing and managing aortic valve endocarditis. *South Med J* 1981;**74**:558–65. http://dx.doi.org/10.1097/00007611-198105000-00014

175. Babic UU, Popovic Z, Vucinic M, Djurisic Z, Pejcic P, Grujicic S, *et al.* Selective coronary angiography versus two-dimensional echocardiography for diagnosis of left atrial thrombi. *Angiology* 1991;**42**:889–98. http://dx.doi.org/10.1177/000331979104201104

176. Badran HM, Mostafa A, Serage A, Fareed W, Abdelfatah E, Fathe A. Arterial mechanics in ischemic versus nonischemic cardiomyopathy: clinical and diagnostic impact. *Echocardiography* 2009;**26**:785–800. http://dx.doi.org/10.1111/j.1540-8175.2008.00888.x

177. Blanchard D, Diebold B, Peronneau P, Foult JM, Nee M, Guermonprez JL, *et al.* Non-invasive diagnosis of mitral regurgitation by Doppler echocardiography. *Br Heart J* 1981;**45**:589–93. http://dx.doi.org/10.1136/hrt.45.5.589

178. Blot-Souletie N, Hebrard A, Acar P, Carrie D, Puel J. Comparison of accuracy of aortic valve area assessment in aortic stenosis by real time three-dimensional echocardiography in biplane mode

versus two-dimensional transthoracic and transesophageal echocardiography. *Echocardiography* 2007;**24**:1065–72. http://dx.doi.org/10.1111/j.1540-8175.2007.00526.x

179. Bogren HG, Demaria AN, Mason DT. Imaging procedures in the detection of cardiac tumors, with emphasis on echocardiography: a review. *Cardiovasc Intervent Radiol* 1980;**3**:107–25. http://dx.doi.org/10.1007/BF02552329

180. Buchner S, Debl K, Poschenrieder F, Feuerbach S, Riegger GA, Luchner A, *et al.* Cardiovascular magnetic resonance for direct assessment of anatomic regurgitant orifice in mitral regurgitation. *Circ Cardiovasc Imaging* 2008;**1**:148–55. http://dx.doi.org/10.1161/CIRCIMAGING.107.753103

181. Casiglia E, Schiavon L, Tikhonoff V, Bascelli A, Martini B, Mazza A, *et al.* Electrocardiographic criteria of left ventricular hypertrophy in general population. *Eur J Epidemiol* 2008;**23**:261–71. http://dx.doi.org/10.1007/s10654-008-9234-6

182. Charron P, Dubourg O, Desnos M, Isnard R, Hagege A, Millaire A, *et al.* Diagnostic value of electrocardiography and echocardiography for familial hypertrophic cardiomyopathy in a genotyped adult population. *Circulation* 1997;**96**:214–19. http://dx.doi.org/10.1161/01.CIR.96.1.214

183. Chen YZ, Sherrid MV, Dwyer EM Jr. Value of two-dimensional echocardiography in evaluating coronary artery disease: a randomized blinded analysis. *J Am Coll Cardiol* 1985;**5**:911–17. http://dx.doi.org/10.1016/S0735-1097(85)80432-0

184. Egeblad H, Berning J, Saunamaki K, Jacobsen JR, Wennevold A. Assessment of rheumatic mitral valve disease. Value of echocardiography in patients clinically suspected of predominant stenosis. *Br Heart J* 1983;**49**:38–44. http://dx.doi.org/10.1136/hrt.49.1.38

185. Fleischmann KE, Goldman L, Robiolio PA, Lee RT, Johnson PA, Cook EF, *et al.* Echocardiographic correlates of survival in patients with chest pain. *J Am Coll Cardiol* 1994;**23**:1390–6. http://dx.doi.org/10.1016/0735-1097(94)90382-4

186. Gonzalez-Torrecilla E, Garcia-Fernandez MA, Perez-David E, Bermejo J, Moreno M, Delcan JL, *et al.* Predictors of left atrial spontaneous echo contrast and thrombi in patients with mitral stenosis and atrial fibrillation. *Am J Cardiol* 2000;**86**:529–34. http://dx.doi.org/10.1016/S0002-9149(00)01007-9

187. Hsiao SH, Chang SM, Lee CY, Yang SH, Lin SK, Chiou KR, *et al.* Usefulness of tissue Doppler parameters for identifying pulmonary embolism in patients with signs of pulmonary hypertension. *Am J Cardiol* 2006;**98**:685–90. http://dx.doi.org/10.1016/j.amjcard.2006.03.053

188. Irani WN, Grayburn PA, Afridi I, Irani WN, Grayburn PA, Afridi I. A negative transthoracic echocardiogram obviates the need for transesophageal echocardiography in patients with suspected native valve active infective endocarditis. *Am J Cardiol* 1996;**78**:101–3. http://dx.doi.org/10.1016/S0002-9149(96)00236-6

189. Khanna D, Vengala S, Miller AP, Nanda NC, Lloyd SG, Ahmed S, *et al.* Quantification of mitral regurgitation by live three-dimensional transthoracic echocardiographic measurements of vena contracta area. *Echocardiography* 2004;**21**:737–43. http://dx.doi.org/10.1111/j.0742-2822.2004.40027.x

190. Khumri TM, Idupulapati M, Rader VJ, Nayyar S, Stoner CN, Main ML, *et al.* Clinical and echocardiographic markers of mortality risk in patients with atrial fibrillation. *Am J Cardiol* 2007;**99**:1733–6. http://dx.doi.org/10.1016/j.amjcard.2007.01.055

191. Kruger S, Haage P, Hoffmann R, Breuer C, Bucker A, Hanrath P, *et al.* Diagnosis of pulmonary arterial hypertension and pulmonary embolism with magnetic resonance angiography. *Chest* 2001;**120**:1556–61. http://dx.doi.org/10.1378/chest.120.5.1556

192. Lembcke A, Thiele H, Lachnitt A, Enzweiler CN, Wagner M, Hein PA, *et al.* Precision of forty slice spiral computed tomography for quantifying aortic valve stenosis: comparison with

echocardiography and validation against cardiac catheterization. *Investig Radiol* 2008;**43**:719–28. http://dx.doi.org/10.1097/RLI.0b013e318184d7c5

193. Meng Q, Lai H, Lima J, Tong W, Qian Y, Lai S, *et al.* Echocardiographic and pathologic characteristics of primary cardiac tumors: a study of 149 cases. *Int J Cardiol* 2002;**84**:69–75. http://dx.doi.org/10.1016/S0167-5273(02)00136-5

194. Miyatake K, Izumi S, Okamoto M, Kinoshita N, Asonuma H, Nakagawa H, *et al.* Semiquantitative grading of severity of mitral regurgitation by real-time two-dimensional Doppler flow imaging technique. *J Am Coll Cardiol* 1986;**7**:82–8. http://dx.doi.org/10.1016/S0735-1097(86)80263-7

195. Mogelvang R, Sogaard P, Pedersen SA, Olsen NT, Marott JL, Schnohr P, *et al.* Cardiac dysfunction assessed by echocardiographic tissue Doppler imaging is an independent predictor of mortality in the general population. *Circulation* 2009;**119**:2679–85. http://dx.doi.org/10.1161/CIRCULATIONAHA.108.793471

196. Nitta M, Takamoto T, Taniguchi K, Hultgren HN. Diagnostic accuracy of continuous wave Doppler echocardiography in severe aortic stenosis in the elderly. *Japanese Heart J* 1988;**29**:169–78. http://dx.doi.org/10.1536/ihj.29.169

197. Pechacek LW. Comparison of two-dimensional echocardiography, radionuclide ventriculography and cineangiography in detecting surgically documented left ventricular thrombi. *Texas Heart Inst J* 1984;**11**:118–27.

198. Peteiro J, Bendayan I, Marinas J, Campos R, Bouzas B, Castro-Beiras A, *et al.* Prognostic value of mitral regurgitation assessment during exercise echocardiography in patients with left ventricular dysfunction: a follow-up study of 1.7+/–1.5 years. *Eur J Echocardiogr* 2008;**9**:18–25.

199. Roe MT, Abramson MA, Li J, Heinle SK, Kisslo J, Corey GR, *et al.* Clinical information determines the impact of transesophageal echocardiography on the diagnosis of infective endocarditis by the duke criteria. *Am Heart J* 2000;**139**:945–51. http://dx.doi.org/10.1067/mhj.2000.104762

200. Sallach JA, Puwanant S, Drinko JK, Jaffer S, Donal E, Thambidorai SK, *et al.* Comprehensive left atrial appendage optimization of thrombus using surface echocardiography: the CLOTS multicenter pilot trial. *J Am Soc Echocardiogr* 2009;**22**:1165–72. http://dx.doi.org/10.1016/j.echo.2009.05.028

201. Stafford WJ, Petch J, Radford DJ. Vegetations in infective endocarditis. Clinical relevance and diagnosis by cross sectional echocardiography. *Br Heart J* 1985;**53**:310–13. http://dx.doi.org/10.1136/hrt.53.3.310

202. Steckelberg JM, Murphy JG, Ballard D, Bailey K, Tajik AJ, Taliercio CP, *et al.* Emboli in infective endocarditis: the prognostic value of echocardiography. *Ann Intern Med* 1991;**114**:635–40.

203. Stevens SM, Farzaneh-Far R, Na B, Whooley MA, Schiller NB. Development of an echocardiographic risk-stratification index to predict heart failure in patients with stable coronary artery disease: the Heart and Soul study. *JACC Cardiovasc Imag* 2009;**2**:11–20. http://dx.doi.org/10.1016/j.jcmg.2008.08.004

204. Takamoto T, Kim D, Urie PM, Guthaner DF, Gordon HJ, Keren A, *et al.* Comparative recognition of left ventricular thrombi by echocardiography and cineangiography. *Br Heart J* 1985;**53**:36–42. http://dx.doi.org/10.1136/hrt.53.1.36

205. Thuny F, Di Salvo G, Belliard O, Avierinos JF, Pergola V, Rosenberg V, *et al.* Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study. *Circulation* 2005;**112**:69–75. [Erratum published in *Circulation* 2005;**112**:e125] http://dx.doi.org/10.1161/CIRCULATIONAHA.104.493155

206. Visser CA, Kan G, David GK, Lie KI, Durrer D. Two dimensional echocardiography in the diagnosis of left ventricular thrombus. A prospective study of 67 patients with anatomic validation. *Chest* 1983;**83**:228–32. http://dx.doi.org/10.1378/chest.83.2.228

207. Willens HJ, Chirinos JA, Schob A, Veerani A, Perez AJ, Chakko S, *et al.* The relation between mitral annular calcification and mortality in patients undergoing diagnostic coronary angiography. *Echocardiography* 2006;**23**:717–22. http://dx.doi.org/10.1111/j.1540-8175.2006.00300.x

208. Colkesen Y, Acil T, Demircan S, Sezgin AT, Ozin B, Muderrisoglu H, *et al.* Echocardiographic features of patients with paroxysmal atrial fibrillation. *Int J Cardiovasc Imag* 2008;**24**:159–63. http://dx.doi.org/10.1007/s10554-007-9247-3

209. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey K, Seward J, *et al.* Coronary ischemic events after first atrial fibrillation: risk and survival. *Am J Med* 2007;**120**:357–63. http://dx.doi.org/10.1016/j.amjmed.2006.06.042

210. Simpson EL, Stevenson MD, Rawdin A, Papaioannou D. Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis. *Health Technol Assess* 2009:**13**(2).

211. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010;**13**:509–18. http://dx.doi.org/10.1111/j.1524-4733.2010.00700.x

212. National Institute for Health and Care Excellence (NICE). *Atrial fibrillation – dabigatran etexilate (TA249)*. URL: www.nice.org.uk/TA249 (accessed March 2012).

213. Department of Health (DoH). *Impact assessment: national stroke strategy*. 2007. URL: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_081054.pdf (accessed April 2013).

Appendix 1 Inclusion and exclusion of pathologies

TABLE 61 Included pathologies

Category		Pathologies
1	Structural defect	Atrial septal defect, ventricular septal defect, rupture of chordae tendineae or papillary muscle
2	Ischaemia/ thrombosis	LA thrombus (includes LAA thrombus), RA thrombus (includes RAA thrombus), thrombosis of ventricle, atherosclerotic heart disease (coronary artery atherosclerosis/disease/stenosis), aneurysm of heart
3	Pulmonary disease	PE, pulmonary hypertension, cor pulmonale
4	Endocarditis	Endocarditis
5	Valvular heart disease	Valvular regurgitation or stenosis of mitral, aortic or tricuspid valve, valvular heart disease, pulmonary valve disease, mitral valve disease or prolapse
6	Cardiomyopathy	Hypertrophic obstructive or non-obstructive or dilated cardiomyopathy, LV non-compaction
7	Heart failure	CHF, LA enlargement, LV or RV dysfunction or impairment
8	Diseases of arteries	Aortic dissection
9	Cardiac masses	Cardiac tumours or masses

Atrial septal defect and hypertrophic cardiomyopathy were included as although ECG may indicate their diagnoses, it would not provide a definitive diagnosis. LA enlargement could be diagnosed by ECG but AF may make this diagnosis less accurate.

Although newly diagnosed AF in stroke patients was not excluded, stroke in a non-AF population was excluded. Echocardiography in stroke is the subject of a HTA report (unpublished at time of going to press www.hta.ac.uk/project/2243.asp).

Excluded pathologies

The following is not intended as an exhaustive list of every cardiac pathology but provides examples of pathologies fitting exclusion criteria.

Pathologies excluded because they would be diagnosed prior to atrial fibrillation diagnosis, or at time of atrial fibrillation diagnosis

Transposition of great arteries, Fallot's tetralogy, AV septal defect, aortic atresia, hypoplasia of aorta, Marfan syndrome, sinus of Valsalva aneurysm, aortic coarctation, myocardial infarction unrecognised (diagnosed by ECG).

Pathologies excluded because they would be clinically diagnosed without echocardiography

Acute myocardial infarction, acute heart failure, coronary thrombosis, haemopericardium, pericarditis.

Pathologies excluded because they present with symptoms that represent indications for echocardiography (including indications for emergency transthoracic echocardiography)

Myocardial rupture, cardiac tamponade.

Appendix 2 Diagnosis of pathologies

Diagnostic tools used for pathologies are reported in *Table 62*.

Personal communications (in date order) from Professor John Chambers, Guy's and St Thomas' Hospital, 7 July 2011; Dr Rick Steeds, University Hospital (Queen Elizabeth) NHS Foundation Trust, 8 July 2011; and Dr Guy Lloyd, Eastbourne Hospital, 11 July 2011.

TABLE 62 Diagnosis of pathologies

Category		Pathology	Diagnostic tools
1	Structural defect	Atrial septal defect	TTE or TOE primary tool for investigation
		Ventricular septal defect	TTE primary tool for investigation
		Rupture of chordae tendineae or papillary muscle	TTE or TOE considered gold standard
2	Ischaemia/ thrombosis	LA thrombus (includes LAA thrombus)	TOE primary tool for investigation
		RA thrombus (includes RAA thrombus)	TTE or TOE primary tool for investigation
		Thrombosis of ventricle	TTE or TOE primary tool for investigation, may be used with contrast cardiac MRI
		Coronary artery atherosclerosis	For this, TTE/TOE would not be used for the primary investigation. TTE may be used in addition to other tests such as ECG, X-ray, blood tests, coronary angiography, MRI
		Aneurysm of heart	TTE primary tool for investigation, may be used with contrast cardiac MRI
3	Pulmonary disease	PE	For this, TTE/TOE would not be used for the primary investigation. PE is diagnosed on the history, serum fibrin degradation products levels and lung imaging with TTE providing additional risk stratification
		Pulmonary hypertension	For this, TTE/TOE would not be used for the primary investigation. RHC would be used. TTE may be used in addition to RHC
		Cor pulmonale	TTE or TOE primary tool for investigation
4	Endocarditis	Endocarditis	TTE or TOE primary tool for investigation

continued

TABLE 62 Diagnosis of pathologies (*continued*)

Category		Pathology	Diagnostic tools
5	Valvular heart disease	Valvular regurgitation – mitral (mitral valve regurgitation, incompetence, insufficiency)	TTE or TOE considered gold standard
		Stenosis – mitral	TTE or TOE considered gold standard
		Mitral valve disease	TTE or TOE considered gold standard
		Valvular regurgitation – aortic	TTE or TOE considered gold standard
		Stenosis – aortic	TTE considered gold standard
		Valvular regurgitation – tricuspid	TTE considered gold standard
		Stenosis – tricuspid	TTE considered gold standard
		Valvular heart disease	TTE considered gold standard
		Pulmonary valve disease	TTE considered gold standard
6	Cardiomyopathy	Hypertrophic obstructive or non-obstructive or dilated	TTE primary tool for investigation, may be used with cardiac MRI
		LV non-compaction	TTE primary tool for investigation, may be used with cardiac MRI
7	Heart failure	CHF	TTE primary tool for investigation, may be used with cardiac MRI
		LV dysfunction or impairment	TTE primary tool for investigation, may be used with cardiac MRI or multigated acquisition scan
		LA enlargement	TTE primary tool for investigation
		RV dysfunction	TTE primary tool for investigation, may be used with three-dimensional TTE or cardiac MRI or first-pass nuclear medicine study
8	Diseases of arteries	Aortic dissection	For this, TTE/TOE would not be used for the primary investigation. CT or MRI may be used
9	Cardiac masses	Cardiac tumours or masses	TTE primary tool for investigation, may be used with cardiac MRI

RHC, right heart catheterisation.

Appendix 3 Search strategies

Prevalence

Database

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1950 to present>

Search strategy

1. heart valve diseases/ or heart valve problems.mp. or valvular heart disease.mp. (17,404)
2. ((aortic or aorta or mitral or pulmonary or triscuspid or valvular) and (regurgitation or stenosis or incompetence or insufficiency)).mp. (83,008)
3. heart valve regurgitation.mp. (12)
4. heart valve stenosis.mp. (9)
5. mitral valve disease.mp. (1891)
6. heart defects, congenital/ or congenital heart disease.mp. (40,373)
7. congenital heart malformation.mp. (106)
8. heart septal defects, atrial/ or atrial septal defect.mp. (9383)
9. heart septum defect.mp. (2)
10. heart ventricle septum defect.mp. (0)
11. heart septal defects, ventricular/ or ventricular septal defect.mp. (12,797)
12. heart atrium septal defect.mp. (0)
13. aortic coarctation/ or coarctation of the aorta.mp. (9)
14. aorta coarctation.mp. (72)
15. heart valve diseases/ or heart valve problems.mp. or valvular heart disease.mp. (17,404)
16. valvular defects.mp. (167)
17. valvular heart disease.mp. or Heart Valve Diseases/ (17,403)
18. aortic valve disease.mp. (1465)
19. aorta valve disease.mp. (1)
20. mitral valve disease.mp. (1891)
21. pulmonary valve disease.mp. (26)
22. ductus ateriosus, pulmonary/ or patent ductus arteriosus.mp. (5025)
23. cardiomyopathies/ or cardiomyopath$.mp. (54,399)
24. hypertension, pulmonary/ or primary pulmonary hypertension.mp. (19,785)
25. aortic diseases/ or aortic disease.mp. or aorta disease.mp. (11,798)
26. aortic aneurysm/ or aortic aneurysm.mp. or aorta aneurysm.mp. (33,140)
27. (aortic dissection or aorta dissection).mp. (5836)
28. intramural haematoma.mp. (150)
29. aortic rupture/ or aortic rupture.mp. or aorta rupture.mp. (7213)
30. aortic dilation.mp. (141)
31. aortic pathology.mp. (340)
32. cardiomyopathy, dilated/ or dilated cardiomyopthy.mp. or congestive cardiomyopathy.mp. (11,825)
33. cardiomyopathy, hypertrophic/ or hypertrophic cardiomyopathy.mp. (11,890)
34. Heart failure/ or heart failure.mp. (104,920)
35. hypertrophy, left ventricular/ or left ventricular hypertrophy.mp. or left ventricular impairment.mp. (15,400)
36. heart left ventricle hypertrophy.mp. (0)
37. congestive heart failure.mp. (27,387)
38. endocarditis/ or endocarditis.mp. (26,716)
39. pericarditis/ or pericarditis.mp. (11,273)
40. myocardial ischemia/ or ischemic heart disease.mp. or heart muscle ischemia.mp. (39,971)

41. (angina or angina pectoris or angina pectoris, variant or angina, unstable or ludwig's angina or microvascular angina).mp. (54,437)
42. coronary thrombosis/ or coronary thrombosis.mp. (5820)
43. (atherosclerotic heart disease or atherosclerotic cardiovascular disease).mp. (1343)
44. Myocardial Infarction/co (22,261)
45. (chordae tenineae adj rupture).mp. (0)
46. (papillary muscle$ adj rupture).mp. (297)
47. heart papillary muscle rupture.mp. (0)
48. (thrombosis adj atrium).mp. (0)
49. heart atrium thrombosis.mp. (0)
50. (thrombosis adj auricular appendage).mp. (0)
51. (thrombosis adj ventricle).mp. (0)
52. Thrombosis/ or heart ventricle thrombosis.mp. (47,650)
53. left ventricular aneurysm/ or heart aneurysm/ or left ventricular aneurysm.mp. or heart left ventricle anuerysm.mp. (6200)
54. (aneurysm/ or aneurysm.mp.) and (ventricular mural or coronary artery or coronary vessels or aortic).mp. (40,602)
55. (coronary artery anuerysm or aorta anuerysm).mp. (0)
56. heart neoplasms/ or heart masses.mp. or cardiac masses.mp. (11,718)
57. heart tumo?r.mp. (91)
58. pulmonary embolism/ or pulmonary embolism.mp. or lung embolism.mp. (32,491)
59. lung disease/ or pulmonary disease.mp. (79,806)
60. hypertension, pulmonary/ or pulmonary hypertension.mp. (26,664)
61. cor pulmonale.mp. (3437)
62. heart murmurs/ or heart murmur$.mp. (3344)
63. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 (622,101)
64. exp epidemiologic studies/ (1,222,832)
65. exp epidemiology/ (17,055)
66. epidemiology.tw. (73,246)
67. exp prevalence/ (135,244)
68. prevalence.ti. (60,865)
69. exp incidence/ (134,727)
70. incidence.ti. (58,881)
71. 64 or 65 or 66 or 67 or 68 or 69 or 70 (1,481,934)
72. 63 and 71 (102,242)
73. atrial fibrillation/ (25,007)
74. af.tw. (13,864)
75. atrial fibrillation.tw. (26,363)
76. 73 or 74 or 75 (40,470)
77. 72 and 76 (3488)

Diagnostic

1. heart valve diseases/ or heart valve problems.mp. or valvular heart disease.mp. (17,116)
2. ((aortic or aorta or mitral or pulmonary or triscuspid or valvular) and (regurgitation or stenosis or incompetence or insufficiency)).mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (81,348)
3. heart valve regurgitation.mp. (11)

4. heart valve stenosis.mp. (9)
5. heart valve stenosis.mp. (9)
6. mitral valve disease.mp. (1831)
7. heart defects, congenital/ or congenital heart disease.mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (39,689)
8. congenital heart malformation.mp. (99)
9. heart septal defects, atrial/ or atrial septal defect.mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (9244)
10. heart septum defect.mp. (2)
11. heart ventricle septum defect.mp. (0)
12. heart septal defects, ventricular/ or ventricular septal defect.mp. (12,594)
13. heart atrium septal defect.mp. (0)
14. aortic coarctation/ or coarctation of the aorta.mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (9)
15. aorta coarctation.mp. (71)
16. Heart valve diseases/ (15,539)
17. valvular defects.mp. (165)
18. valvular heart disease.mp. or Heart Valve Diseases/ (17,115)
19. aortic valve disease.mp. (1410)
20. aorta valve disease.mp. (1)
21. mitral valve disease.mp. (1831)
22. pulmonary valve disease.mp. (24)
23. ductus ateriosus, pulmonary/ or patent ductus arteriosus.mp. (4919)
24. cardiomyopathies/ or cardiomyopath$.mp. (52,978)
25. hypertension, pulmonary/ or primary pulmonary hypertension.mp. (19,366)
26. aortic diseases/ or aortic disease.mp. or aorta disease.mp. (11,598)
27. aortic aneurysm/ or aortic aneurysm.mp. or aorta aneurysm.mp. (32,524)
28. (aortic dissection or aorta dissection).mp. (5672)
29. intramural haematoma.mp. (150)
30. aortic rupture/ or aortic rupture.mp. or aorta rupture.mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (7122)
31. aortic dilation.mp. (126)
32. aortic pathology.mp. (329)
33. cardiomyopathy, dilated/ or dilated cardiomyopthy.mp. or congestive cardiomyopathy.mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (11,481)
34. cardiomyopathy, hypertrophic/ or hypertrophic cardiomyopathy.mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (11,642)
35. Heart failure/ or heart failure.mp. (101,953)
36. hypertrophy, left ventricular/ or left ventricular hypertrophy.mp. or left ventricular impairment.mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (14,894)
37. heart left ventricle hypertrophy.mp. (0)
38. congestive heart failure.mp. (26,691)
39. endocarditis/ or endocarditis.mp. (26,285)
40. pericarditis/ or pericarditis.mp. (11,130)
41. myocardial ischemia/ or ischemic heart disease.mp. or heart muscle ischemia.mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (38,960)
42. (angina or angina pectoris or angina pectoris, variant or angina, unstable or ludwig's angina or microvascular angina).mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (53,232)
43. coronary thrombosis/ or coronary thrombosis.mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (5635)

44. (atherosclerotic heart disease or atherosclerotic cardiovascular disease).mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (1298)
45. Myocardial Infarction/co [Complications] (21,843)
46. (chordae tenineae adj rupture).mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (0)
47. (papillary muscle$ adj rupture).mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (295)
48. heart papillary muscle rupture.mp. (0)
49. (thrombosis adj atrium).mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (0)
50. heart atrium thrombosis.mp. (0)
51. (thrombosis adj auricular appendage).mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (0)
52. (thrombosis adj ventricle).mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (0)
53. Thrombosis/ or heart ventricle thrombosis.mp. (46,892)
54. left ventricular aneurysm/ or heart aneurysm/ or left ventricular aneurysm.mp. or heart left ventricle anuerysm.mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (6131)
55. (aneurysm/ or aneurysm.mp.) and (ventricular mural or coronary artery or coronary vessels or aortic).mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (39,871)
56. (coronary artery anuerysm or aorta anuerysm).mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (0)
57. heart neoplasms/ or heart masses.mp. or cardiac masses.mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (11,574)
58. heart tumo?r.mp. (89)
59. pulmonary embolism/ or pulmonary embolism.mp. or lung embolism.mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (31,929)
60. lung disease/ or pulmonary disease.mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (78,271)
61. hypertension, pulmonary/ or pulmonary hypertension.mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (25,991)
62. cor pulmonale.mp. (3404)
63. heart murmurs/ or heart murmur$.mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] (3300)
64. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 (609,155)
65. Echocardiography/ (54,742)
66. echocardiography.mp. (98,874)
67. tte.mp. or tte.tw. (1026)
68. transthoracic echocardiography.mp. (3633)
69. (echocardiog$ adj (transthorac$ or trans-thorac$ or (trans$ and thorac$))).mp. (408)
70. 65 or 66 or 67 or 68 or 69 (99,048)
71. prognosis.sh. (281,258)
72. diagnosed.tw. (240,154)
73. cohort:.mp. (196,722)
74. predictor:.tw. (132,468)
75. death.tw. (335,379)
76. exp models, statistical/ (168,145)
77. 71 or 72 or 73 or 74 or 75 or 76 (1,175,870)

78. exp 'Sensitivity and Specificity'/ (299,564)
79. sensitivity.tw. (389,280)
80. specificity.tw. (245,482)
81. ((pre-test or pretest) adj probability).tw. (833)
82. post-test probability.tw. (237)
83. predictive value$.tw. (47,609)
84. likelihood ratio$.tw. (5527)
85. 78 or 79 or 80 or 81 or 82 or 83 or 84 (764,660)
86. 77 or 85 (1,827,791)
87. 64 and 70 and 86 (17,997)
88. limit 87 to (humans and 'all adult (19 plus year s)') (12,787)

Appendix 4 Data abstraction tables: diagnostic review

Diagnostic studies data extraction

Study	**Author**	Acar J *et al.*[62]
	Date	1991
	Pathology(ies) for which accuracy measured	Thrombosis, LA thrombi
Population	**Population AF**	44.9% AF
	Population details	Total of 581 patients who subsequently underwent mitral valve surgery for mitral stenosis
Methods	**TTE details**	2D TTE, Aloka echocardiograph (Aloka Co., Tokyo, Japan) used for first 276 patients, and a Hewlett-Packard 77020A (Hewlett-Packard Co., Andover, MA, USA) for the last 305 with a 2.5-MHz transducer
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	Surgery
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	Transthoracic 2D echocardiography detected 12 out of 43 thrombi. The sensitivity was 28% and specificity 99%. Sensitivity was 65% (11/17) for LAC thrombi but only 4% (1/26) for LAA thrombi

LAC, left atrial cavity.

Study	**Author**	Arques[63]
	Date	2005
	Pathology(ies) for which accuracy measured	CHF
Population	**Population AF**	No history of arrhythmia
	Population details	Twenty chronic hypertensive patients normal with LV ejection fractions who met Vasan's criteria for definite diastolic heart failure, control group of 20 gender- and age-matched hypertensive patients with non-cardiac cause of acute dyspnoea
Methods	**TTE details**	TTE colour M-mode Doppler [E/Vp index (ratio of peak E mitral velocity to Vp velocity)] tissue Doppler [E/Ea ratio (ratio of peak E mitral velocity to peak Ea velocity by tissue Doppler)]. Aloka SSD 550 PHD ultrasound system (Aloka Co., Tokyo, Japan) with a 2.5-MHz harmonic transducer
	Was TTE the reference/ gold standard?	No (clinical diagnostic criteria as reference)
	Diagnostic comparator(s) details	Clinical and radiographic signs of pulmonary congestion, a LV ejection fraction at least 50% on admission, a favourable response to diuretics and nitrates, and an invasive LV end-diastolic pressure of >15 mmHg
Results	**Usable TTE (as percentage of those having TTE)**	19/20 = 95%
	Study results	The colour M-mode Doppler E/Vp index in diagnosing CHF had a sensitivity of 73.7%, a specificity of 75%, and accuracy of 74.3% for the optimal cut-off of 1.5. Showing that tissue Doppler was more reproducible and precise than colour M-mode. The optimal cut-off value was 1.5 for E/Vp ($n = 39$; area under the curve 0.82, 95% CI 0.69 to 0.95, $p = 0.001$; sensitivity 73.7%, specificity 75%, accuracy 74.3%)

Study	**Author**	Attenhofer Jost[64]
	Date	2000
	Pathology(ies) for which accuracy measured	Aortic stenosis, MVP, combined aortic and mitral valve disease, ventricular septal defect (also MR and AR, for which there is higher-level evidence available)
Population	**Population AF**	NR (all had heart murmur)
	Population details	A total of 100 consecutive patients referred for systolic murmur
Methods	**TTE details**	TTE 2D and continuous wave Doppler performed using a Hewlett-Packard 2500 (Hewlett-Packard Co., Andover, MA, USA) or Vingmed CFM 800 (GE Vingmed Ultrasound, Horten, Norway) system
	Was TTE the reference/gold standard?	Yes
	Diagnostic comparator(s) details	Clinical cardiac examination
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	TTE as gold standard

NR, not reported.

Study	**Author**	Barron *et al.*[65]
	Date	1988
	Pathology(ies) for which accuracy measured	MVP
Population	**Population AF**	NR
	Population details	A total of 140 consecutive patients with suspected MVP
Methods	**TTE details**	2D echocardiography and Doppler studies performed using a Hewlett-Packard 7702A phased-array unit with 2.5- and 3.5-MHz transducers
	Was TTE the reference/ gold standard?	No – but data included if echocardiography is assumed standard
	Diagnostic comparator(s) details	Auscultation
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	With auscultation as the reference standard for MVP, 2D echocardiography has a sensitivity of 47% and a specificity of 89%

NR, not reported.

Study	**Author**	Bova[66]
	Date	2003
	Pathology(ies) for which accuracy measured	PE
Population	**Population AF**	NR
	Population details	Consecutive patients referred for PE, or inpatients developing signs of PE = 162 with usable data (from 252 enrolled)
Methods	**TTE details**	TTE continuous wave Doppler. Echocardiography was performed using a Hewlett-Packard 5500 echocardiograph (Hewlett-Packard Co., Andover, MA, USA) with 2.5-MHz transducer
	Was TTE the reference/ gold standard?	No (perfusion lung scan, with back-up angiography where unclear, as reference)
	Diagnostic comparator(s) details	Lung scan angiography, perfusion lung scan
Results	**Usable TTE (as percentage of those having TTE)**	97
	Study results	Using RV dilatation provided a very low sensitivity for PE (31%; 95% CI 21% to 41%) and high specificity (94%; 95% CI 89% to 99%). Twenty of 68 (29%) cases of PE were correctly diagnosed. Maximal tricuspid regurgitant velocity had sensitivity and specificity values of 51% (95% CI 38% to 64%) and 88% (95% CI 81% to 95%), respectively, and 17% of patients did not have positive diagnostic results for PE by this criterion. Thus, PE was correctly diagnosed in 28 of 68 patients (41%). Using both criteria gave a 29% (95% CI 19% to 39%) sensitivity and a 96% (95% CI 92% to 100%) specificity; 135 patients had diagnostic results and 16 of 68 patients (23%) with PE were correctly identified. Utilising either criterion yielded a 52% (95% CI 40% to 64%) sensitivity and 87% (95% CI 80% to 95%) specificity. A total of 152 patients had diagnostic results and 34 of the 68 (50%) patients with PE were identified

NR, not reported.

Study	**Author**	Casella[67]
	Date	2009
	Pathology(ies) for which accuracy measured	Native valve infective endocarditis
Population	**Population AF**	No AF
	Population details	A total of 75 patients referred to echocardiography centre – suspected endocarditis
Methods	**TTE details**	Harmonic TTE was performed using a Philips Sonos 2400, 5500, 7500 or iE33 cardiac ultrasound system (Philips Healthcare, Andover, MA, USA), with a 1.3- to 1.5-MHz transducer
	Was TTE the reference/ gold standard?	No (TOE as reference)
	Diagnostic comparator(s) details	TOE
Results	**Usable TTE (as percentage of those having TTE)**	100 (81.5% good image quality)
	Study results	Of the 75 patients in this study, 33 were found to be positive by TOE. The sensitivity for detection of infective endocarditis by TTE was 81.8%. It provided good image quality in 81.5% of cases; in these patients sensitivity was even greater (89.3%). TPR of TTE was 81.8% (95% CI 64.5% to 93.0%) and TNR was 61.5% (95% CI 44.6% to 76.6%) when indeterminate studies were considered in analysis. As expected, TTE accuracy improved when indeterminate results were excluded. TPR was 87.1% (95% CI 70.2% to 96.4%), whereas TNR was 85.7% (95% CI 67.3% to 96.0%). TPR was different according to native valve involved (86.6% for mitral valve, 71.4% for aortic valve)

TNR, true negative rate; TPR, true positive rate.

Study	**Author**	Cassidy[68]
	Date	1992
	Pathology(ies) for which accuracy measured	Aortic stenosis (also MR and AR, for which there is higher-level evidence available)
Population	**Population AF**	NR (systolic murmur)
	Population details	Elderly patients admitted to ward and referred for systolic murmur, 37 with usable echocardiography (out of 41)
Methods	**TTE details**	TTE, M-mode 2D and Doppler (manufacturer details not reported)
	Was TTE the reference/ gold standard?	Yes
	Diagnostic comparator(s) details	Clinical diagnosis
Results	**Usable TTE (as percentage of those having TTE)**	91
	Study results	Forty-one patients were studied in two 6-month periods. Overall, clinical and echocardiography diagnosis agreed in 75% of cases but the clinical diagnosis of aortic stenosis was poor in the initial period. Adapting from the lessons learnt in this initial period in a repeat of the study, the sensitivity of clinical diagnosis of aortic stenosis improved from 0.38 to 0.75

NR, not reported.

Study	**Author**	Dittmann[69]
	Date	1987
	Pathology(ies) for which accuracy measured	AR in mitral valve disease
Population	**Population AF**	38% ($n = 21$)
	Population details	A total of 55 consecutive patients with aortic and/or mitral valve disease
Methods	**TTE details**	M-mode echocardiography and pulsed Doppler echocardiography were performed using the Toshiba SSH-40A and the Toshiba SDS-21A (Toshiba Corp., Tokyo, Japan), with an ultrasound frequency of 2.4 MHz. The pulse repetition frequency of the range gated Doppler signal was 4 or 6 KHz, depending on the depth of the sample volume
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	Cardiac catheterisation – supravalvular angiography
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	In 13 of 55 patients (three with mitral stenosis, three with mitral incompetence, three with combined mitral lesions, three with aortic stenosis, one with aortic and mitral stenosis) neither angiography nor PDE showed AR (specificity 100%). Apart from three patients with poor echocardiography quality, PDE correctly detected AR in 39 of 42 patients (sensitivity 93%). Clinical examination (62%), M-mode (62%) and both methods combined (81%) were significantly less sensitive than PDE, especially in mild AR ($p < 0.008$). The PDE degree of AR closely correlated with angiography (corrected contingency coefficient 0.91). Differentiation between AR III and IV was not possible [the severity of AR was determined angiographically, graded I (mild) to IV (severe)]. Mitral valve disease did not affect quantification of AR ($n = 20$ patients)

PDE, pulsed Doppler echocardiography.

Study	**Author**	Enia[70]
	Date	1989
	Pathology(ies) for which accuracy measured	Aortic dissection involving the ascending aorta
Population	**Population AF**	NR
	Population details	A total of 46 consecutive patients clinically suspected of having aortic dissection. Control group of 509 consecutive unselected patients who underwent both aortography and echocardiography during same period (included valve disease, coronary artery disease, congenital heart disease, cardiomyopathy)
Methods	**TTE details**	Echocardiography performed using a Picker 80 CI and Aloka SSD-800 (Aloka Co., Tokyo, Japan) echocardiography systems
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	Aortography and clinical signs in a group clinically suspected of having aortic dissection
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	The TTE diagnosis of aortic dissection (using three echocardiography signs) had a sensitivity of 48% and a specificity of 100%. For echocardiography markers individually, aortic root enlargement had a high sensitivity (91%) but a moderate PPV (64%) and efficiency (70%). Aortic wall thickening had lower sensitivity (78%) and higher PPV (75%) and efficiency (76%). Intimal flap had very low sensitivity (56%); its PPV and efficiency were 62% and 6%, respectively

NR, not reported; PPV, positive predictive value.

Study	**Author**	Erbel[71]
	Date	1984
	Pathology(ies) for which accuracy measured	LV function
Population	**Population AF**	No AF
	Population details	A total of 110 patients with suspected coronary artery disease, congestive cardiomyopathy and valvular heart disease
Methods	**TTE details**	2D echocardiography was performed using a Diasonics 3400R real-time, phased-array sector scanner, with a 2.25-MHz transducer
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	Catheterisation – cineventriculograms
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	LV ejection fraction had a sensitivity of 81%, and a specificity of 100%. End-diastolic volume had a sensitivity of 80% and a specificity of 88%. Positive predictive accuracy was 86%, and negative predictive accuracy was 82%. For end-systolic volume, sensitivity was 94% and specificity 85%. For stroke volume, sensitivity was 30%, and specificity 98%

Study	**Author**	Grossmann[72]
	Date	2002
	Pathology(ies) for which accuracy measured	MR
Population	**Population AF**	25% AF
	Population details	A total of 68 consecutive patients; 57 with MR diagnosed by TTE or TOE; 11 had no signs of MR by TTE or TOE
Methods	**TTE details**	Colour Doppler TTE was performed using a Toshiba SSH-160A or SSH-140A (Toshiba Corp., Tokyo, Japan) with a 3.75-MHz transducer
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	TOE, cardiac catheterisation
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	In the 11 patients without MR, no flow convergence region was present during TTE and TOE. Among the 57 patients with MR, a proximal flow convergence region could be imaged in 45 (79%) by TTE vs. 50 (88%) by TOE (p = non-significant)

Study	**Author**	Groves[73]
	Date	2004
	Pathology(ies) for which accuracy measured	Tricuspid regurgitation
Population	**Population AF**	NR
	Population details	A total of 86 consecutive patients being investigated for possible pulmonary artery hypertension
Methods	**TTE details**	TTE (comparator) (manufacturer details not reported)
	Was TTE the reference/ gold standard?	Yes for diagnosis (RHC for grading severity)
	Diagnostic comparator(s) details	Multidetector CT, RHC
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	With respect to RHC data, the correlation between severity assessment of tricuspid regurgitation between CT and echocardiography using the Cohen's kappa-weighted coefficient was 0.56 (moderately good agreement), and the correlation between mean pulmonary pressure and tricuspid regurgitation grading on echocardiography was $r = 0.685$ ($p < 0.001$). When using TTE as gold standard, CT assessment of tricuspid regurgitation had a sensitivity of 90.4% and a specificity of 100% in detecting echocardiographic tricuspid regurgitation. For tricuspid regurgitation that was graded as more than trivial by echocardiography, sensitivity of CT was 100%

NR, not reported; RHC, right heart catheterisation.

Study	**Author**	Guyer[74]
	Date	1984
	Pathology(ies) for which accuracy measured	Rheumatic tricuspid stenosis
Population	**Population AF**	31/38 = 82%
	Population details	A total of 38 patients with rheumatic valvular disease who had undergone cardiac catheterisation and echocardiography
Methods	**TTE details**	2D TTE performed using either a Smith Kline Instruments Ekosector 10 or an ATL Mark III scanner (Advanced Technology Laboratories, Bellevue, WA, USA)
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	RHC and LHC
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	Tricuspid stenosis was defined echocardiographically as diastolic anterior leaflet doming, thickening and restricted excursion of the other two tricuspid leaflets, and decreased separation of the leaflet tips. Using these criteria, the sensitivity and specificity of the echocardiogram in detecting tricuspid stenosis were 69% and 96%, respectively, in the group of 38 patients who had both echocardiographic and haemodynamic evaluations. However, when the smaller group of 17 patients who had simultaneous RA and RV pressure recordings were considered separately, there was complete agreement between the echocardiographic and haemodynamic data

LHC, left heart catheterisation; RHC, right heart catheterisation.

Study	**Author**	Helmcke[75]
	Date	1987
	Pathology(ies) for which accuracy measured	MR
Population	**Population AF**	31/82 study group = 38%; none of control group (overall 21%)
	Population details	A total of 82 patients with angiographically proven MR. Control group of 65 with normal mitral valvular function
Methods	**TTE details**	Colour Doppler echocardiography performed using an Irex-Aloka 880 and a 2.5- or 3.5-MHz transducer. Pulse repetition frequencies of 4, 6 or 8 Hz were available. A frequency of 4 Hz was routinely used, which allowed measurement of velocities up to 60 cm/second
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	Cardiac catheterisation/angiography
Results	**Usable TTE (as percentage of those having TTE)**	152/160 = 95%
	Study results	Sixty-five patients had no MR by both colour Doppler and angiography and 82 patients had MR by both techniques. Thus the sensitivity and specificity of colour Doppler for the detection of MR was 100%

Study	**Author**	Jassal[76]
	Date	2007
	Pathology(ies) for which accuracy measured	Endocarditis
Population	**Population AF**	NR
	Population details	A total of 36 consecutive inpatients with an intermediate likelihood of endocarditis
Methods	**TTE details**	Harmonic imaging TTE performed using a Vivid 7 (GE Medical Systems, Milwaukee, WI, USA) and a 1.5- to 1.7-MHz transducer
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	TOE
Results	**Usable TTE (as percentage of those having TTE)**	83% diagnostic (17% indeterminate)
	Study results	TTE was diagnostic in 30 individuals (83%); positive in 16 patients and negative in 14 patients using TOE as the reference standard. Six patients (17%) were indeterminate for the detection of vegetations by TTE. By TOE, 19 were positive, 1 was indeterminate, 16 were negative. Calculating sensitivity and specificity without including indeterminate images, the sensitivity of TTE with reference to TOE was 16 out of 19 positive (84%), and the specificity of TTE with reference to TOE was 14 out of 16 (88%)

NR, not reported.

Study	**Author**	Kaymaz[77]
	Date	2001
	Pathology(ies) for which accuracy measured	Thrombosis, LA thrombi
Population	**Population AF**	56.3% AF at time of study
	Population details	A total of 474 consecutive patients with rheumatic mitral valve disease
Methods	**TTE details**	TTE was performed by a Vingmed CFM 800 echocardiography system with a 3.25-MHz transducer
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	TOE
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	Preoperative transthoracic echocardiography diagnosed thrombi in the LA in 34 (32%) of the patients in whom thrombi in the LA or in both LA and LAA were detected intraoperatively. None of the thrombi confined to LAA were visualised by preoperative transthoracic echocardiography. Of the 418 transthoracic echocardiographic examinations considered as negative for thrombi, 347 were TN and 71 were FN. Preoperative transthoracic echocardiographic assessment was FP for thrombi in 22 patients. According to these results, the sensitivity, specificity, PPV, NPV, and the diagnostic accuracy of transthoracic echocardiography were 32%, 94%, 61%, 83% and 80%, respectively

NPV, negative predictive value; PPV, positive predictive value.

Study	**Author**	Kishon[78]
	Date	1993
	Pathology(ies) for which accuracy measured	VSD and PR, post MI
Population	**Population AF**	NR (new systolic murmur in 68% VSD and 100% PR)
	Population details	62 patients AMI complicated by rupture of either the ventricular septum (40) or the papillary muscle (22), diagnosis of rupture was confirmed either at operation or at autopsy, an echocardiographic study was performed before surgery or death. All patients were studied by 2D echo, and 26 were studied by Doppler technique, nine were studied by TOE
Methods	**TTE details**	All patients examined by 2D TTE with wide-angled scanners (mechanical or phased array) with 2.25- or 3.5-MHz transducers (26 patients additionally studied by pulsed wave Doppler and colour Doppler TTE on commercially available systems)
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	TOE, cardiac catheterisation, cases confirmed by operation or autopsy
Results	**Usable TTE (as percentage of those having TTE)**	100 (6/40 = 15% of VSD images suboptimal, but included in analysis)
	Study results	2D TTE correctly detected 27 of 40 VSD patients (and suspected four more), and 10 of 22 PR patients. Colour Doppler TTE was not available for all participants. Doppler/colour TTE detected 19 out of 20 VSD and 0 out of 6 PR

NR, not reported; PR, papillary muscle rupture; VSD, ventricular septal defect.

Study	**Author**	Kitayama[79]
	Date	1997
	Pathology(ies) for which accuracy measured	RA thrombi and LA thrombi
Population	**Population AF**	100% CAF
	Population details	70 consecutive, CAF
Methods	**TTE details**	TTE M-mode, 2D and pulsed and colour Doppler were performed using a Toshiba Sonolayer SSH-140A with a 2.5- or 3.75-MHz transducer
	Was TTE the reference/ gold standard?	No (study says no gold standard)
	Diagnostic comparator(s) details	Cardiac ultrafast CT (unclear time between TTE and CT)
Results	**Usable TTE (as percentage of those having TTE)**	90
	Study results	TTE detected 4 out of 6 LA thrombi and 0 out of 5 RA thrombi detected by CT

Study	**Author**	Lanzarini[80]
	Date	2005
	Pathology(ies) for which accuracy measured	Pulmonary hypertension
Population	**Population AF**	13% controlled AF
	Population details	A total of 86 consecutive patients with chronic heart failure
Methods	**TTE details**	TTE standard M-mode, 2D and pulsed and continuous wave Doppler performed using a System Five (GE Vingmed Ultrasound, Horten, Norway) device and a 2.5- to 3.5-MHz phased-array transducer
	Was TTE the reference/ gold standard?	No (cardiac catheterisation as reference)
	Diagnostic comparator(s) details	Cardiac catheterisation as reference
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	The proportion of cases identified correctly as having pulmonary hypertension was highest for PAPs (88%) and mean PAP (85%) in addition to acceleration time of pulmonary artery systolic flow (ACT) (79%) and pulmonary artery diastolic pressure obtained utilising the early phase of the tricuspid regurgitation spectral flow (PAPd/TR) (75%). PAPd/TR performed better in the validating sample in terms of diagnostic ability, with high sensitivity and specificity (100% and 60%) and positive and NPVs (PPV 80%, NPV 100%). PAPs, mean PAP, ACT and PAPd/TR confirmed their prevailing diagnostic ability (A-ROC from 0.74 to 0.86) in identifying pulmonary hypertension with fair to high feasibility (67% to 91%) and an OR indicative of strong association. ACT and PAPd/TR, the two parameters with the highest feasibility, allowed us to identify 46 of 49 (94%) hypertensive cases

ACT, acceleration time of pulmonary artery systolic flow; A-ROC, area under the ROC curve; NPV, negative predictive value; PAP, pulmonary artery pressure; PAPd/TR, pulmonary artery diastolic pressure/early phase tricuspid regurgitation; PAPs, pulmonary artery systolic pressure; PPV, positive predictive value; ROC, receiver operating characteristic.

Study	**Author**	Maestre[81]
	Date	2009
	Pathology(ies) for which accuracy measured	LV dysfunction, heart failure
Population	**Population AF**	NR
	Population details	A total of 216 consecutive patients with a suspected diagnosis of HF. Group 1 = 63 TTE indicated systolic dysfunction. Group 2 = 101 TTE indicated diastolic dysfunction. Group 3 = 52 with normal values on TTE
Methods	**TTE details**	Mode M and 2D TTE (this was the standard reference comparator) (manufacturer details not reported)
	Was TTE the reference/ gold standard?	Yes
	Diagnostic comparator(s) details	Clinical criteria
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	With TTE as gold standard the Framingham clinical criteria are very sensitive (92%) and moderately specific (79%)

HF, heart failure; NR, not reported.

Study	**Author**	Mugge[82]
	Date	1995
	Pathology(ies) for which accuracy measured	ASA
Population	**Population AF**	14.4% in AF
	Population details	A total of 195 patients with ASA diagnosis confirmed by TOE
Methods	**TTE details**	Colour Doppler TTE (manufacturer details not reported)
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	TOE (colour or contrast TOE) within 24 hours of TTE
Results	**Usable TTE (as percentage of those having TTE)**	100 (database study, part of inclusion criteria that had to have usable TTE and TOE images)
	Study results	TTE as gold standard. The Framingham clinical criteria are very sensitive (92%) and moderately specific (79%)

ASA, atrial septal aneurysm.

Study	**Author**	Nienaber[83]
	Date	1993
	Pathology(ies) for which accuracy measured	Thoracic aortic dissection
Population	**Population AF**	NR
	Population details	A total of 110 patients with clinically suspected aortic dissection
Methods	**TTE details**	Colour, Doppler TTE performed using sector scanners (V3400 R CV60, Diasonics Inc., Palo Alto, CA, USA; or Hewlett-Packard 77065 or Hewlett-Packard Sonos 1000, Hewlett-Packard Co., Andover, MA, USA) with 2.25- to 3.5-MHz transducers
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	TOE, CT, MRI, interoperative findings, autopsy or contrast angiography
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	TTE had a sensitivity of 59.3%. The specificity of TTE was 83%

NR, not reported.

Study	**Author**	Nienaber[84]
	Date	1994
	Pathology(ies) for which accuracy measured	Aortic dissection
Population	**Population AF**	NR
	Population details	A total of 35 consecutive patients with suspected dissection of the thoracic aorta
Methods	**TTE details**	M-mode, 2D and Doppler TTE performed using sector scanners [V3400 R CV60, Hewlett-Packard 77065 equipped with a 77570 Mitsubishi video copy processor (Mitsubishi, Kyoto, Japan) and Hewlett-Packard Sonos 1000] with 2.25- and 3.5-MHz transducers
	Was TTE the reference/gold standard?	No
	Diagnostic comparator(s) details	TOE, MRI, gold standard of intraoperative findings ($n = 17$), necropsy ($n = 4$) or contrast angiography ($n = 22$)
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	TTE evaluation identified 20 of 26 patients with confirmed evidence of thoracic aortic dissection and was FN in six patients (two type A and four type B dissections). Moreover, there were three FP findings by TTE resulting in a sensitivity of 76.9%, a specificity of 66.7% and an accuracy of 74.3% for the detection of thoracic aortic dissection irrespective of its location

NR, not reported.

Study	**Author**	Okura[85]
	Date	2006
	Pathology(ies) for which accuracy measured	Cardiomyopathy
Population	**Population AF**	NR
	Population details	A total of 52 consecutive patients (44 with usable data) who presented LV dilatation and diffuse LV systolic dysfunction. Group 1 = 13 patients given the diagnosis of ICM by coronary angiography. Group 2 = 31 non-ICM
Methods	**TTE details**	TTE 2D and Doppler, with patients in the left lateral decubitus position, using Vivid 7 (GE Medical Systems, Milwaukee, WI, USA) with M3s (1.5–4-MHz) and M7 (12-MHz) phased-array transducer
	Was TTE the reference/ gold standard?	Echocardiography markers
	Diagnostic comparator(s) details	Coronary angiogram
Results	**Usable TTE (as percentage of those having TTE)**	85
	Study results	Differentiating between ICM and non-ICM, 2D TTE markers peak DSVR less than 1.8 or mean DSVR less than 1.8 had a sensitivity of 77% and a specificity of 77% to differentiate ICM and non-ICM

DSVR, diastolic/systolic velocity ratio; NR, not reported.

Study	**Author**	Pochis[86]
	Date	1992
	Pathology(ies) for which accuracy measured	Atrial septal hypertrophy
Population	**Population AF**	53% AF or flutter, or paroxysmal atrial tachycardia
	Population details	A total of 158 consecutive patients referred for TOE, TTE available for 116
Methods	**TTE details**	TTE and TOE used ultrasound systems Acuson 128XP/10 (Acuson Corp., Mountain View, CA, USA) with a single-plane probe and General Electric RT6800 (General Electric, Milwaukee, WI, USA) with a bi-plane probe
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	TOE
Results	**Usable TTE (as percentage of those having TTE)**	107/116 = 92%
	Study results	107 patients had both TTE and TOE. TTE sensitivity 25%, specificity 91%, PPV 18%, NPV 94%

NPV, negative predictive value; PPV, positive predictive value.

Study	**Author**	Reichek[87]
	Date	1981
	Pathology(ies) for which accuracy measured	LVH
Population	**Population AF**	NR
	Population details	34 patients with TTE and ECGs compared with post-mortem data (tested TTE) (study also includes later study testing of ECG with 142 patients, but not of relevance to this review)
Methods	**TTE details**	M-mode echocardiography performed with a Smith Kline 20A echograph, a Honeywell 1856 recorder and a 2.25-MHz transducer
	Was TTE the reference/ gold standard?	No, postmortem as gold standard (but TTE used as gold standard for assessing accuracy of ECG)
	Diagnostic comparator(s) details	ECG, surgical findings, autopsy
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	Echocardiographic LV mass correlated well with postmortem LV weight ($r = 0.96$) and accurately diagnosed LVH (sensitivity 93%, specificity 95%). M-mode echocardiographic LV mass is superior to ECG criteria for clinical diagnosis of LVH

LVH, left ventricular hypertrophy; NR, not reported.

Study	**Author**	Reichlin[88]
	Date	2004
	Pathology(ies) for which accuracy measured	Valvular heart disease
Population	**Population AF**	NR (all had heart murmur)
	Population details	203 consecutive patients with systolic murmur, presenting to ED
Methods	**TTE details**	2-colour Doppler TTE (gold standard comparator) performed using a Toshiba Sonolayer SSH-140A
	Was TTE the reference/ gold standard?	Yes
	Diagnostic comparator(s) details	Initial clinical evaluation including auscultation
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	With TTE as gold standard the sensitivity and specificity of the initial clinical routine evaluation in diagnosing echocardiographic valvular heart disease were 82% (70–86%) and 69% (60–76%), respectively

ED, emergency department; NR, not reported.

Study	**Author**	Roudaut[89]
	Date	1988
	Pathology(ies) for which accuracy measured	Aortic dissection
Population	**Population AF**	NR
	Population details	673 patients with clinical suspicion of aortic dissection
Methods	**TTE details**	2D and M-mode TTE was performed using a Varian V 3000 or a Roche Kontron RT400-phased array sector scanner
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	Angiography, CT, surgery/autopsy
Results	**Usable TTE (as percentage of those having TTE)**	90% of aortic dissection group (though poor quality 10% included in sensitivity analysis)
	Study results	Two echocardiographic features were found to support a diagnosis of aortic dissection: a dilatation of at least one segment of the aorta (sensitivity 95%, specificity 51%) and a typical abnormal linear intraluminal echocardiography corresponding to the intimal flap (sensitivity 67%, specificity 100%). These features were found to have a high sensitivity in type I aortic dissection (88%), although in types II and III the sensitivity was much lower. TTE is extremely sensitive in the diagnosis of ascending aortic dissection, but much less so in the diagnosis of descending aortic dissection

NR, not reported.

Study	**Author**	Saraste[90]
	Date	2005
	Pathology(ies) for which accuracy measured	Coronary artery stenosis
Population	**Population AF**	4% CAF
	Population details	84 consecutive patients referred for diagnostic coronary angiography because of suggested significant CAD
Methods	**TTE details**	Ultrasound apparatus Sequoia C 256 (Acuson Corp., Mountain View, CA, USA) and standard 3.5-MHz transducer. Doppler colour mapping with data post-processing mix function. All possible standard and non-standard windows and views, 2D mode image used to identify coronary arteries
	Was TTE the reference/ gold standard?	No (angiography as reference)
	Diagnostic comparator(s) details	Coronary angiography
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	TTE for significant coronary artery stenosis had a sensitivity of 82%, and a specificity of 92%. For proximal artery stenosis the sensitivity was 74%, and the specificity was 90%. For left anterior descending coronary artery stenosis the sensitivity was 73%, and the specificity was 92%. For left circumflex coronary artery stenosis the sensitivity was 38%, and the specificity was 99%. For right coronary artery stenosis the sensitivity was 63%, and the specificity was 96%

CAD, coronary artery disease.

Study	**Author**	Sharifi[91]
	Date	2007
	Pathology(ies) for which accuracy measured	Atrial thrombi
Population	**Population AF**	100% AF
	Population details	112 patients with AF (of whom 32 normal TTE, 80 abnormal TTE) of whom 27 had CAF (24%)
Methods	**TTE details**	TTE performed using a Philips Sonos 5500 system
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	TOE (within 2 months after TTE)
Results	**Usable TTE (as percentage of those having TTE)**	100 (although patients selected from group with usable TTE)
	Study results	Based on their transthoracic echocardiographic study, they were divided into two groups: Group 1 consisted of patients with a normal transthoracic echocardiogram and Group 2, those with an abnormal study. Results: Thrombi or spontaneous echocardiography contrast were found in 14 of 112 patients (16%). All, however, were detected in Group 2 patients. There was no patient with a normal transthoracic echocardiogram who had thrombus on his/her transoesophageal echocardiogram. Of the six patients with thrombus detected by TOE, only one had thrombus found by TTE, whereas of all 14 patients who had spontaneous echocardiography contrast on TOE, 10 had spontaneous echocardiography contrast on their transthoracic echocardiogram

Study	**Author**	Sharma[92]
	Date	1992
	Pathology(ies) for which accuracy measured	Atrial septal defect (sinus venosus defect)
Population	**Population AF**	NR
	Population details	A total of 53 patients, but eight unusable images; analysed 45 patients with sinus venosus defect, with echocardiographic and catheterisation studies providing a definitive diagnosis
Methods	**TTE details**	TTE M-mode and cross-sectional using Diasonics 3400R phased array sector scanner for earlier part of study. TTE M-mode and cross-sectional, pulsed and continuous wave Doppler and colour flow mapping using Aloka SSD-730 (Aloka Co., Tokyo, Japan) for later part of study
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	TOE, cineangiography (cardiac catheterisation)
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	TTE correctly detected 28 of 45 confirmed cases. Doppler TTE introduced in later years detected 17 of 26 cases

NR, not reported.

Study	**Author**	Sheiban[93]
	Date	1987
	Pathology(ies) for which accuracy measured	Intracardiac masses
Population	**Population AF**	NR
	Population details	77 patients with suspected intracardiac mass
Methods	**TTE details**	2D echocardiograph was performed using a wide-angle mechanical sector scanner (Hoffrel-System 202/514 or Diasonics CV 400) with a 3.5-MHz transducer
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	Surgery
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	2D detected intracardiac masses with a sensitivity of 88.2% and a specificity of 95.3%

NR, not reported.

Study	**Author**	Shively 1991[94]
	Date	1991
	Pathology(ies) for which accuracy measured	Endocarditis
Population	**Population AF**	NR
	Population details	62 patients with 66 episodes of suspected endocarditis
Methods	**TTE details**	TTE 2D, M-mode and Doppler colour performed using a 77020A system (Hewlett-Packard) with 2.5- and 5-MHz transducers
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	Surgery
Results	**Usable TTE (as percentage of those having TTE)**	100 (82% good quality image of tricuspid valve, 89% good quality image of mitral valve, 68% good quality image of aortic valve)
	Study results	TTE compared with pathologic or non-echocardiographic data from the subsequent clinical course, sensitivity of 44% and specificity of 98% (also tested TOE which had higher sensitivity 94% and specificity 100%)

NR, not reported.

Study	**Author**	Shrestha[95]
	Date	1983
	Pathology(ies) for which accuracy measured	LA thrombus (in rheumatic heart disease)
Population	**Population AF**	NR for whole population, for those with thrombus 45/51 = 88%
	Population details	A total of 293 patients with rheumatic heart disease with LA thrombus confirmed at surgery
Methods	**TTE details**	2D echocardiography was performed using a Toshiba real-time, phased array sector scanner (Sonolayergraph model SSH-1-A, Toshiba Corp., Tokyo, Japan). The transducer has 32 elements, each with 2.4-MHz frequency
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	Surgery
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	Of the 293 patients, 33 had LA thrombi by 2D echocardiographic criteria. This diagnosis was confirmed at surgery and histopathological study in 30 patients (specificity 98.8%). A thrombus was not found in three patients. In 21 other patients, LA thrombi were present but were not detected by 2D echocardiography (sensitivity 58.8%); 10 of these 21 had thrombi in the LA cavity. In 11 patients, thrombi were located in the LAA, all of which were missed by 2D echocardiography. Excluding these 11 LAA thrombi, the sensitivity of 2D echocardiography for detecting LA cavity thrombi was 75.0%

NR, not reported.

Study	**Author**	Shub[96]
	Date	1983
	Pathology(ies) for which accuracy measured	Atrial septal defect
Population	**Population AF**	NR
	Population details	A total of 154 patients with documented atrial septal defect (by catheter or surgery) with satisfactory echocardiography
Methods	**TTE details**	TTE 2D, subcostal, was performed using 80° phased-array scanning systems (Varian-Diasonics) with 2.25- and 3.5-MHz transducers and a mechanical sector scanner (Advanced Technology Laboratories, Bellevue, WA, USA) with 3- and 5-MHz transducers
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	Catheterisation or surgery, contrast echocardiography (only for 71 patients)
Results	**Usable TTE (as percentage of those having TTE)**	145/154 = 94%
	Study results	TTE successfully diagnosed 93 (89%) of the 105 ostium secundum atrial septal defects, all 32 (100%) ostium primum defects and 7 (44%) of the 16 sinus venosus defects. A defect was not visualised (FN response) in 12 patients (11%) with an ostium secundum defect, and in nine patients (56%) with a sinus venosus defect. Sensitivity for secundum was 89%, for primum was 100% and for sinus venosus defect was 44%. Specificity was not calculable as all patients had confirmed atrial septal defect

NR, not reported.

Study	**Author**	Shyu[97]
	Date	1992
	Pathology(ies) for which accuracy measured	Ruptured chordae tendineae
Population	**Population AF**	Some AF
	Population details	Group 1 = 40 adult patients suspected of having a flail mitral valve leaflet with ruptured chordae tendineae who underwent both TTE and TOE before surgery, who went on to undergo surgery Group 2 = 20 control patients with moderate or severe MR and negligible mitral stenosis due to other causes who underwent TTE, TOE and subsequent mitral valve surgery
Methods	**TTE details**	2D Doppler TTE, Toshiba SSH-65A Aloka 870 ultrasound system (Toshiba Corp., Tokyo, Japan) with 2.5- or 3.75-MHz precordial transducer, in standard parasternal and apical transducer positions. Colour Doppler TTE assessed MR by criteria of Spain *et al.*[168]
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	TOE (within 2 days of TTE), cardiac catheterisation (most within 1 week of TTE)
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	With reference to cardiac catheterisation, TTE had a sensitivity of 65% and specificity of 90% and NPV of 56% for diagnosis of ruptured chordae tendineae

NPV, negative predictive value.

Study	**Author**	Smith[98]
	Date	1985
	Pathology(ies) for which accuracy measured	VSR (in patients with AMI)
Population	**Population AF**	NR
	Population details	13 patients with ventricular septal rupture
Methods	**TTE details**	Cross-sectional Doppler echocardiography performed using an IREX system IIIB (Ramsey, NJ, USA) 2D phased array sector scanner with a 2.5-MHz transducer (Ramsey, NJ, USA)
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	Catheterisation or autopsy
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	Using simultaneous cross-sectional echocardiography and Doppler ultrasound detected all 13 cases of VSR, sensitivity 100%. If cross-sectional echocardiography was used alone, 6 of the 13 cases could be visualised

NR, not reported; VSR, ventricular septal rupture.

Study	**Author**	Sparrow[99]
	Date	2003
	Pathology(ies) for which accuracy measured	LV systolic dysfunction
Population	**Population AF**	NR
	Population details	A total of 621 patients prescribed loop diuretics in general practices
Methods	**TTE details**	TTE using a phased-array sector scanner (Vingmed CFM 700, GE Vingmed Ultrasound, Horten, Norway)
	Was TTE the reference/ gold standard?	Yes
	Diagnostic comparator(s) details	Clinical diagnosis made in primary care
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	TTE as gold standard. General practice/clinical diagnoses showed high FP rates. Individual or combinations of clinical features did not accurately predict LV systolic dysfunction

NR, not reported.

Study	**Author**	Stratton[100]
	Date	1982
	Pathology(ies) for which accuracy measured	LV thrombus
Population	**Population AF**	Percentage NR but some patients had AF
	Population details	A total of 78 patients with suspected LV thrombus
Methods	**TTE details**	2D echocardiography performed using either a wide-angle, phased-array sector scanner (Toshiba Corp., Tokyo, Japan; 45 patients) or a wide-angle, mechanical sector scanner (Advanced Technology Laboratories, Bellevue, WA, USA; 33 patients)
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	Surgical findings/indium-111 platelet imaging
Results	**Usable TTE (as percentage of those having TTE)**	78/88 = 89%
	Study results	Echocardiogram was positive for thrombus in 22 patients, equivocal in seven and negative in 49. For detection of thrombus, a positive or equivocal echocardiogram had a sensitivity of 95% (21 of 22), a specificity of 86% (48 of 56), and a predictive value of 72% (21 of 29); the predictive value of a negative study was 98% (48 of 49). Considering positive and equivocal studies separately, the predictive value of a positive study was 86% (19 of 22), whereas that of an equivocal study was only 29% (two of seven)

Study	**Author**	Veyrat[101]
	Date	1983
	Pathology(ies) for which accuracy measured	AR
Population	**Population AF**	38/95 = 40% overall
	Population details	A total of 83 patients with suspected AR; control group of 12 normal subjects
Methods	**TTE details**	Pulsed Doppler echocardiography performed using an ATL 851 (Advanced Technology Laboratories, Bellevue, WA, USA) with a pulsed Doppler 3-MHz velocimeter and a 2D 90° wide-angle mechanical sector scan with a single transducer for both techniques
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	Angiography/aortography, some surgical findings
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	A group of 12 normal subjects and 83 patients, including 40 patients with AR proven by aortography, were investigated; 38 patients with AR were diagnosed by Doppler echocardiography (diagnostic sensitivity 95%, specificity 100%)

Study	**Author**	Vigna[102]
	Date	1993
	Pathology(ies) for which accuracy measured	LA thrombus
Population	**Population AF**	59% in AF at time of study
	Population details	A total of 59 consecutive non-anticoagulated mitral stenosis patients (35 AF, 24 SR)
Methods	**TTE details**	TTE colour Doppler performed using an Aloka 870 SDS system (Aloka Co., Tokyo, Japan) and a 2.5- or 3.5-MHz transducer
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	TOE within 24 hours of TTE
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	LA thrombus was found by TTE in four patients (6.7%) and by TOE in 12 (20.3%) ($p<0.01$). Of the 12 patients with LA thrombus at TOE, 11 were in AF. Thrombus was found in LA body by TTE in four patients (6.7%) and by TOE in nine (15.2%) (p = non-significant). LAA thrombus was found by TOE in four patients (6.7%) and by TTE in none ($p<0.01$). One patient had two thrombi: one in the LA body and the other in the LAA

SR, sinus rhythm.

Study	**Author**	Wong[103]
	Date	1983
	Pathology(ies) for which accuracy measured	Mitral and aortic valve stenosis valvular calcification
Population	**Population AF**	NR
	Population details	A total of 81 patients with valvular abnormalities from 113 elderly volunteers (some undergoing cardiac investigations)
Methods	**TTE details**	2D echocardiography performed using a phased-array system (Varian 3000)
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	35-mm cinefluorograms (radiological)
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	Echocardiographic sensitivity for detecting calcium in both the mitral annulus and aortic valve was 76%; specificity was 89–94%. Detection in the mitral leaflets was low and due to the smallness of the target and high sensitivity of the standard. Thus, an easily performed ultrasonic technique can screen moderate calcification of the mitral annulus and aortic valve with a predictive accuracy of 80%

NR, not reported.

Study	**Author**	Zanolla[104]
	Date	1982
	Pathology(ies) for which accuracy measured	Mitral stenosis, mitral valve calcification
Population	**Population AF**	NR
	Population details	A total of 43 patients with rheumatic disease of the mitral valve by surgery
Methods	**TTE details**	2D echocardiography was performed using a commercially available 30° mechanical sector scanner (Eko Sector 1, Smith Kline Instruments)
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	Radiography of surgically excised valves
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	There were 14 TPs, 19 TNs, 10 FPs and no FNs for 2D echocardiography, with a sensitivity of 100% and a specificity of 65%. It is concluded that 2D echocardiography is an extremely sensitive method for assessing mitral valve calcification, and is prospectively useful also in planning reconstruction vs. replacement in mitral valve surgery. Nevertheless, the consistent number of FPs affecting 2D echocardiography represents a definite limit to the specificity

NR, not reported.

Study	**Author**	Zotz[105]
	Date	1993
	Pathology(ies) for which accuracy measured	VSR (in patients with AMI)
Population	**Population AF**	NR
	Population details	A total of 17 consecutive patients presenting a new systolic murmur after the onset of AMI, caused by a subsequently diagnosed rupture of the interventricular septum
Methods	**TTE details**	Standard and Colour Doppler TTE, performed immediately after myocardial rupture suspected, ultrasound system Toshiba SSH 160A with 2.5-MHz transducer, standard and unconventional views
	Was TTE the reference/ gold standard?	No
	Diagnostic comparator(s) details	Surgery or autopsy, also contrast echocardiography and TOE
Results	**Usable TTE (as percentage of those having TTE)**	100
	Study results	Conventional TTE identified VSR in 4/17; using unconventional views 12/17; and colour Doppler 15/16

NR, not reported; VSR, ventricular septal rupture.

Prognostic studies data extraction

Study	**Author**	Atrial Fibrillation Investigators[106]
	Date	1998
	Pathology(ies) for which prognosis measured	LV dysfunction, LAD, MVP, MR
Population	**Population details**	All participants non-valvular AF
Methods	**TTE details**	TTE 2D, M-mode (manufacturer details not reported)
Results	**Results**	During a mean follow-up of 1.6 years, 78 ischaemic strokes occurred (annual rate 4.7%). Moderate to severe LV systolic dysfunction shown via 2D echocardiography was a strong independent predictor of stroke (relative risk 2.5; $p = 0.001$) in the 1010 patients in whom echocardiographic values for LV function were available. LAD by M-mode echocardiography did not predict stroke (relative risk, 1.02/mm; $p = 0.10$). MR or MVP or LV mass were not significantly associated with stroke

Study	**Author**	Klem[107]
	Date	2003
	Pathology(ies) for which prognosis measured	Reduced LV function, LAD, valvular abnormality
Population	**Population details**	A total of 336 patients with non-rheumatic AF and 73 patients with non-rheumatic AF and also diabetes (for both groups, selected from 409 eligible of 474 consecutive patients)
Methods	**TTE details**	TTE (details in prior publication)
Results	**Results**	Mean follow-up 115 months (9.6 years). Reduced LV function diabetic HR 1.52 (0.85 to 2.70), $p = 0.1598$; non-diabetic HR 2.28 (1.58 to 3.29), $p < 0.0001$; LAD diabetic HR 1.01 (0.97 to 1.05), $p = 0.6445$; non-diabetic HR 1.06 (1.03 to 1.08), $p < 0.0001$; valvular abnormality diabetic HR 2.05 (1.10 to 3.82), $p = 0.0229$; non-diabetic HR 1.88 (1.30 to 2.70), $p = 0.0007$

Study	**Author**	Miyaska[108]
	Date	2000
	Pathology(ies) for which prognosis measured	MR
Population	**Population details**	All participants non-rheumatic AF
Methods	**TTE details**	TTE 2D, M-mode performed by Aloka 870 SSD (Aloka Co., Tokyo, Japan) with a 3.5-MHz transducer
Results	**Results**	Of 69 patients (30%) with grade 1 MR, and 104 patients (45%) with no MR patients with grade 1 MR had significantly higher prevalence of thromboembolic events (28%) than those with MR grade 2 or higher (8%, $p = 0.006$) or those with no MR (11%, $p = 0.007$). A history of previous thromboembolic events were compared between 173 patients with grade 1 MR and those with no MR using the logistic regression analysis adjusted for age, sex, administration of warfarin, and presence of hypertension, DM, structural heart disease, enlarged left atrium (>40 mm), CAF, and grade 1 MR. Grade 1 MR (OR 2.689, 95% CI 1.039 to 7.189, $p = 0.0434$) and no warfarin administration (OR 0.045, 95% CI 0.002 to 0.242, $p = 0.0036$) were significantly associated with the history of thromboembolic events. The presence of mild MR in non-rheumatic AF was associated with higher prevalence of thromboembolic events

Study	**Author**	Nakagami[109]
	Date	1998
	Pathology(ies) for which prognosis measured	Degree of MR and LAD
Population	**Population details**	A total of 290 patients with non-rheumatic AF
Methods	**TTE details**	TTE M-mode, 2D and colour Doppler performed using a Toshiba 160A system (Toshiba Corp., Tokyo, Japan) with a 2.3- or 3.75-MHz transducer
Results	**Results**	Among these patients, 68 had a stroke during the follow-up (rate of stroke per year of follow-up 3.2%). In 95 patients with LAD of >48 mm, the incidence of stroke (9%) in the severe MR group (moderate or severe, $n = 43$) was significantly lower than that (25%) of the mild MR group (none, trivial, or mild; $n = 52$) ($\chi^2 = 3.95$, $p = 0.047$). The relative risk of stroke for increase in MR from mild to severe groups, for every 10-mm increment in LA size, for sex, and for every increase of 10 years of age was 0.45 (95% CI 0.20 to 0.97), 1.06 (95% CI 0.75 to 1.49), 0.98 (95% CI 0.55 to 1.72) and 1.33 (95% CI 1.04 to 1.71), respectively Within 7.4 years' follow-up, MR was protective against stroke if LAD was large (≥48 mm). For LAD of <47 mm, the incidence of stroke had no association with the degree of MR In 95 patients with LAD of ≥48 mm, the incidence of stroke (9%) in the severe MR group (moderate or severe, $n = 43$) was significantly lower than that (25%) in the mild MR group (none, trivial, or mild, $n = 52$) ($\chi^2 = 3.95$, $p = 0.047$). In other groups with LAD of <47 mm, the incidence of stroke had no association with the degree of MR

Study	**Author**	The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators[110]
	Date	1992
	Pathology(ies) for which prognosis measured	Mitral annular calcification, severe MR, LV dysfunction and LAD
Population	**Population details**	A total 568 non-rheumatic AF, inpatient or outpatient, placebo arm of RCT (SPAF study)
Methods	**TTE details**	M-mode and 2D TTE and Doppler (TTE conducted locally then sent to a central registry, Hennepin County Medical Centre)
Results	**Results**	Mean 1.3 years' follow-up, risk of ischaemic stroke or thromboembolism, global LV dysfunction RR 2.6, $p = 0.003$; LA size, $p = 0.02$; LA 2.4 cm/m^2, RR = 1.6; LA 2.9 cm/m^2, RR = 2.7

RCT, randomised controlled trial.

Appendix 5 Quality assessment: diagnostic review

Level in hierarchy of evidence based on Merlin *et al.*:[57]

1. Systematic review of level 2 studies.

2. Study of test accuracy and methodology, including an independent, blinded comparison with a valid reference standard, conducted among consecutive persons with a defined clinical presentation.

3a. Study of test accuracy, with an independent, blinded comparison with a valid reference standard, conducted among non-consecutive persons with a defined clinical presentation.

3b. Study comparing diagnosis with a reference standard that does not meet the criteria for level 2 or 3a.

3c. Diagnostic case–control study.

4. Study of diagnostic yield (no reference standard).

Study	**Author**	Acar *et al.*[62]
	Date	1991
	Pathology(ies) (for which accuracy measured)	Thrombosis, LA thrombi
	Population AF	44.9% AF
Study design	**Study design details**	Comparison of TTE against surgery for the diagnosis of LA thrombi in mitral stenosis (also some cases TOE and angiography) in patients who subsequently underwent mitral valve surgery
	Study design level in hierarchy[57]	3b comparison with reference standard
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	No
	Were the reference standard results interpreted without knowledge of the results of the index test?	No
	Were uninterpretable or indeterminate test results reported?	None reported, all cases used in analysis

Study	**Author**	Arques[63]
	Date	2005
	Pathology(ies) (for which accuracy measured)	CHF
	Population AF	No history of arrhythmia
Study design	**Study design details**	Case–control study, comparison of test accuracy of M-mode TTE and tissue Doppler TTE, with blinding of observers Cases = hypertensive patients with diastolic HF. Controls = gender- and age-matched hypertensive patients All assessments at time of admission
	Study design level in hierarchy[57]	3c
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	Yes

HF, heart failure.

Study	**Author**	Attenhofer Jost[64]
	Date	2000
	Pathology(ies) (for which accuracy measured)	Aortic stenosis, MVP, combined aortic and mitral valve disease, ventricular septal defect (also MR and AR, for which there is higher-level evidence available)
	Population AF	NR (all had heart murmur)
Study design	**Study design details**	Prospective comparison of accuracy, consecutive, blinded, clinical examination immediately before TTE, TTE as reference standard
	Study design level in hierarchy [57]	2
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	TTE as reference standard
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	None reported, all cases used

NR, not reported.

Study	**Author**	Barron *et al.*[65]
	Date	1988
	Pathology(ies) (for which accuracy measured)	MVP
	Population AF	NR
Study design	**Study design details**	Comparison of auscultation and echocardiography, consecutive patients, echocardiographer blinded to auscultatory findings, auscultation immediately prior to or after TTE
	Study design level in hierarchy [57]	2
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unknown
	Were uninterpretable or indeterminate test results reported?	None reported, all cases used

NR, not reported.

Study	**Author**	Bova[66]
	Date	2003
	Pathology(ies) (for which accuracy measured)	PE
	Population AF	NR
Study design	**Study design details**	Prospective comparison of test accuracy of TTE with reference angiography, consecutive patients, blinded, TTE soon after reference standard
	Study design level in hierarchy [57]	2
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	Yes

NR, not reported.

Study	**Author**	Casella[67]
	Date	2009
	Pathology(ies) (for which accuracy measured)	Native valve infective endocarditis
	Population AF	No AF
Study design	**Study design details**	Blinded comparison in consecutive patients, TTE and TOE within 7 days
	Study design level in hierarchy[57]	2
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	Yes (all used in analysis, separate analysis excluding poor image quality)

Study	**Author**	Cassidy[68]
	Date	1992
	Pathology(ies) (for which accuracy measured)	Aortic stenosis (also MR and AR, for which there is higher-level evidence available)
	Population AF	NR (systolic murmur)
Study design	**Study design details**	Prospective comparison of accuracy, over two time periods unclear if consecutive within time period, blinded
	Study design level in hierarchy [57]	3a
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	TTE as reference standard
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	Yes

NR, not reported.

Study	**Author**	Dittmann[69]
	Date	1987
	Pathology(ies) (for which accuracy measured)	AR in mitral valve disease
	Population AF	38% ($n = 21$)
Study design	**Study design details**	Comparison of pulsed Doppler echo, M-mode echo, clinical signs and cardiac catheterisation, consecutive patients, TTE 1 day before catheterisation
	Study design level in hierarchy [57]	3b comparison with reference standard
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Unknown
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unknown
	Were uninterpretable or indeterminate test results reported?	Yes (states no exclusions for inadequate examinations)

Study	**Author**	Enia[70]
	Date	1989
	Pathology(ies) (for which accuracy measured)	Aortic dissection involving the ascending aorta
	Population AF	NR
Study design	**Study design details**	Case–control, prospective comparison of TTE and aortography in two groups of patients Cases = clinical suspicion of aortic dissection consecutive patients Controls = patients with TTE and aortography, consecutive
	Study design level in hierarchy [57]	3c
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	No
	Were the reference standard results interpreted without knowledge of the results of the index test?	No
	Were uninterpretable or indeterminate test results reported?	None reported, all tests used

NR, not reported.

Study	**Author**	Erbel[71]
	Date	1984
	Pathology(ies) (for which accuracy measured)	LV function
	Population AF	No AF
Study design	**Study design details**	Retrospective comparison of diagnostic accuracy of four echocardiography markers by catheterisation and echocardiography, TTE the day before catheterisation
	Study design level in hierarchy [57]	3b comparison with reference standard
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Unknown
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unknown
	Were uninterpretable or indeterminate test results reported?	None reported, all used

Study	**Author**	Grossmann[72]
	Date	2002
	Pathology(ies) (for which accuracy measured)	MR
	Population AF	25% AF
Study design	**Study design details**	Comparison of TTE and TOE with the some patients having catheterisation for the detection and quantification of MR using the proximal flow convergence method. Consecutive patients, TTE and TOE performed during same examination
	Study design level in hierarchy [57]	3b comparison with reference standard
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes (if TOE reference standard, rather than catheterisation)
	Did patients receive the same reference standard regardless of the index test result?	Yes (if TOE reference standard, rather than catheterisation)
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	No
	Were the index test results interpreted without knowledge of the results of the reference standard?	No
	Were the reference standard results interpreted without knowledge of the results of the index test?	No
	Were uninterpretable or indeterminate test results reported?	None reported

Study	**Author**	Groves[73]
	Date	2004
	Pathology(ies) (for which accuracy measured)	Tricuspid regurgitation
	Population AF	NR
Study design	**Study design details**	Retrospective comparison of CT, TTE and RHC for the detection of tricuspid regurgitation; 61 selected patients (out of 86 consecutive); CT, TTE and RHC within 6 weeks of each other
	Study design level in hierarchy [57]	3a
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	TTE as reference standard
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	NA (selected for having usable examinations)

NA, not applicable; NR, not reported; RHC, right heart catheterisation.

Study	**Author**	Guyer[74]
	Date	1984
	Pathology(ies) (for which accuracy measured)	Rheumatic tricuspid stenosis
	Population AF	31/38 = 82%
Study design	**Study design details**	Retrospective comparison of echocardiography and cardiac catheterisation in selected patients with both examinations; catheterisation with 1 year of TTE
	Study design level in hierarchy [57]	3a
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	NA (selected for having both examinations)

NA, not applicable.

Study	**Author**	Helmcke[75]
	Date	1987
	Pathology(ies) (for which accuracy measured)	MR
	Population AF	31/82 with MR = 38%. None without MR (overall 21%)
Study design	**Study design details**	Comparison of colour Doppler echocardiography and cardiac catheterisation angiography in those with and without MR
	Study design level in hierarchy[57]	3c
Items from QUADAS[59]	**Were selection criteria clearly described?**	No
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	Yes

Study	**Author**	Jassal[76]
	Date	2007
	Pathology(ies) (for which accuracy measured)	Endocarditis
	Population AF	NR
Study design	**Study design details**	Prospective comparison of accuracy, selected population of likely endocarditis from consecutive patients, blinded, TTE within 24 hours of TOE
	Study design level in hierarchy[57]	2
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	Yes (indeterminate TTE included in analysis)

NR, not reported.

Study	**Author**	Kaymaz[77]
	Date	2001
	Pathology(ies) (for which accuracy measured)	Thrombosis, LA thrombi
	Population AF	56.3% AF at time of study
Study design	**Study design details**	Comparison of TTE and TOE measurements of LA thrombi (before surgery) against intraoperative findings. Consecutive patients, TTE and TOE within 1–5 days prior to surgery
	Study design level in hierarchy[57]	3b comparison with reference standard
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	No
	Were the reference standard results interpreted without knowledge of the results of the index test?	No
	Were uninterpretable or indeterminate test results reported?	None reported (all included in analysis)

Study	**Author**	Kishon[78]
	Date	1993
	Pathology(ies) (for which accuracy measured)	VSD and papillary muscle rupture, post MI
	Population AF	NR (new systolic murmur in 68% VSD and 100% papillary rupture)
Study design	**Study design details**	Retrospective comparison of surgery and post-mortem examination against TTE and TOE data
	Study design level in hierarchy[57]	3b
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	No
	Were the reference standard results interpreted without knowledge of the results of the index test?	No
	Were uninterpretable or indeterminate test results reported?	Yes (included in analysis)

NR, not reported; VSD, ventricular septal defect.

Study	**Author**	Kitayama[79]
	Date	1997
	Pathology(ies) (for which accuracy measured)	RA thrombi and LA thrombi
	Population AF	100% CAF
Study design	**Study design details**	Comparison of TTE and CT, consecutive patients (unclear if blinded)
	Study design level in hierarchy[57]	3b
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	No (according to Kitayama *et al.*[79])
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Unknown
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unknown
	Were uninterpretable or indeterminate test results reported?	Yes (included in analysis)

Study	**Author**	Lanzarini[80]
	Date	2005
	Pathology(ies) (for which accuracy measured)	Pulmonary hypertension
	Population AF	13% controlled AF
Study design	**Study design details**	Prospective comparison of test accuracy of TTE with reference cardiac catheterisation within 24 hours, consecutive patients, blinded
	Study design level in hierarchy[57]	2
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	None reported, all cases used

Study	**Author**	Maestre[81]
	Date	2009
	Pathology(ies) (for which accuracy measured)	LV dysfunction, heart failure
	Population AF	NR
Study design	**Study design details**	Comparison of clinical criteria and TTE, cross-sectional survey, 216 of 255 consecutive patients meeting criteria
	Study design level in hierarchy[57]	2
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	TTE as reference standard
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	None reported, all used

NR, not reported.

Study	**Author**	Mugge[82]
	Date	1995
	Pathology(ies) (for which accuracy measured)	ASA
	Population AF	14.4% in AF
Study design	**Study design details**	Database comparison of TOE and TTE, in patients with confirmed ASA (by TOE), TTE and TOE within 24 hours of each other
	Study design level in hierarchy[57]	3b comparison with reference standard
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	No
	Were the reference standard results interpreted without knowledge of the results of the index test?	No
	Were uninterpretable or indeterminate test results reported?	NA (selection for having both examinations)

ASA, atrial septal aneurysm; NA, not applicable.

Study	**Author**	Nienaber[83]
	Date	1993
	Pathology(ies) (for which accuracy measured)	Thoracic aortic dissection
	Population AF	NR
Study design	**Study design details**	Blinded comparison of TTE, TOE, CT, MRI validated against clinical findings to assess their reliability in diagnosis of dissection of the thoracic aorta. (All patients undergoing two imaging procedures, all patients validated by angiography, surgery or autopsy)
	Study design level in hierarchy[57]	2
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	None reported, all used

NR, not reported.

Study	**Author**	Nienaber[84]
	Date	1994
	Pathology(ies) (for which accuracy measured)	Aortic dissection
	Population AF	NR
Study design	**Study design details**	Comparison of the diagnostic accuracy of TTE and TOE with MRI for the exact morphological evaluation and anatomical mapping of the thoracic aorta, blinded
	Study design level in hierarchy[57]	3a
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	None reported, all used

NR, not reported.

Study	**Author**	Okura[85]
	Date	2006
	Pathology(ies) (for which accuracy measured)	Cardiomyopathy
	Population AF	NR
Study design	**Study design details**	Consecutive patients, non-blinded, TTE and angiography with 1 week of each other
	Study design level in hierarchy[57]	3b
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	No
	Were the reference standard results interpreted without knowledge of the results of the index test?	No
	Were uninterpretable or indeterminate test results reported?	Yes

NR, not reported.

Study	**Author**	Pochis[86]
	Date	1992
	Pathology(ies) (for which accuracy measured)	Atrial septal hypertrophy
	Population AF	53% AF or flutter, or paroxysmal atrial tachycardia
Study design	**Study design details**	Retrospective comparison of TTE and TOE in the detection of lipomatous hypertrophy of the atrial septum. Assessors blinded to other results
	Study design level in hierarchy[57]	3b – comparison with reference standard
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	Yes

Study	**Author**	Reichek[87]
	Date	1981
	Pathology(ies) (for which accuracy measured)	LV hypertrophy
	Population AF	NR
Study design	**Study design details**	Retrospective comparison of various diagnostic measures in patient groups
	Study design level in hierarchy[57]	3b comparison with reference standard
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Unknown
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unknown
	Were uninterpretable or indeterminate test results reported?	None reported

NR, not reported.

Study	**Author**	Reichlin[88]
	Date	2004
	Pathology(ies) (for which accuracy measured)	Valvular heart disease
	Population AF	NR (all had heart murmur)
Study design	**Study design details**	Prospective comparison of initial clinical evaluation and TTE in the evaluation of systolic murmurs in the diagnosis of valvular heart disease; independent blinded assessors; 203 patients selected from 852 consecutive patients; TTE within 24 hours of clinical evaluation
	Study design level in hierarchy[57]	2
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	TTE as reference standard
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	NA (TTE as gold standard)

NA, not applicable; NR, not reported.

Study	**Author**	Roudaut[89]
	Date	1988
	Pathology(ies) (for which accuracy measured)	Aortic dissection
	Population AF	NR
Study design	**Study design details**	Retrospective comparison of TTE, angiography, CT or autopsy/surgery
	Study design level in hierarchy[57]	3b comparison with reference standard
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	No
	Were the reference standard results interpreted without knowledge of the results of the index test?	No
	Were uninterpretable or indeterminate test results reported?	Yes (excluded from analysis $n = 13$ of 673)

NR, not reported.

Study	**Author**	Saraste[90]
	Date	2005
	Pathology(ies) (for which accuracy measured)	Coronary artery stenosis
	Population AF	4% CAF
Study design	**Study design details**	Prospective comparison of diagnostic measures. Coronary angiography performed a day after TTE by a cardiologist blinded to results of TTE. TTE all performed by same physician
	Study design level in hierarchy[57]	3b – study of test accuracy, includes reference standard
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	None reported, all images used in calculation of sensitivity/specificity

Study	**Author**	Sharifi[91]
	Date	2007
	Pathology(ies) (for which accuracy measured)	Atrial thrombi
	Population AF	100% AF
Study design	**Study design details**	Blinded comparison of consecutive patients
	Study design level in hierarchy[57]	2
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	NA (selected for usable data)

NA, not applicable.

Study	**Author**	Sharma[92]
	Date	1992
	Pathology(ies) (for which accuracy measured)	Atrial septal defect (sinus venosus defect)
	Population AF	NR
Study design	**Study design details**	Retrospective comparison of TTE, TOE and cardiac catheterisation in the demonstration of sinus venosus defect
	Study design level in hierarchy[57]	3b
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	No
	Were the reference standard results interpreted without knowledge of the results of the index test?	No
	Were uninterpretable or indeterminate test results reported?	Yes (eight cases with inadequate TTE or angiography were excluded from analysis)

NR, not reported.

Study	**Author**	Sheiban[93]
	Date	1987
	Pathology(ies) (for which accuracy measured)	Intracardiac masses
	Population AF	NR
Study design	**Study design details**	Prospective comparison of 2D echocardiography and surgery
	Study design level in hierarchy[57]	3b comparison with reference standard
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Unknown
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unknown
	Were uninterpretable or indeterminate test results reported?	None reported, all used

NR, not reported.

Study	**Author**	Shively[94]
	Date	1991
	Pathology(ies) (for which accuracy measured)	Endocarditis
	Population AF	NR
Study design	**Study design details**	Prospective comparison of TTE and TOE, using non-echocardiographic pathological data from the subsequent clinical course as the reference standard, blinded comparison in consecutive patients
	Study design level in hierarchy[57]	2 (blinded comparison in consecutive patients)
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	Yes (all included in analysis, poorer than average TTE image 18% tricuspid valve, 11% mitral valve, 32% aortic valve)

NR, not reported.

Study	**Author**	Shrestha[95]
	Date	1983
	Pathology(ies) (for which accuracy measured)	LA thrombus (in rheumatic heart disease)
	Population AF	NR for whole population, for those with thrombus 45/51 = 88%
Study design	**Study design details**	Retrospective comparison of 2D echocardiography and surgical findings of LA thrombi, surgery within 1 week of TTE
	Study design level in hierarchy[57]	3b
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes (video recordings reviewed by blinded observer)
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unknown
	Were uninterpretable or indeterminate test results reported?	None reported

NR, not reported.

Study	**Author**	Shub[96]
	Date	1983
	Pathology(ies) (for which accuracy measured)	Atrial septal defect
	Population AF	NR
Study design	**Study design details**	Retrospective comparison of 2D echocardiography against surgery/ catheterisation from 171 patients, 154 entered study (nine excluded for poor TTE, eight patients had incomplete examination)
	Study design level in hierarchy[57]	3b comparison with reference standard
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	No
	Were the reference standard results interpreted without knowledge of the results of the index test?	No
	Were uninterpretable or indeterminate test results reported?	Yes (9 of 171 patients excluded for poor image quality)

NR, not reported.

Study	**Author**	Shyu[97]
	Date	1992
	Pathology(ies) (for which accuracy measured)	Ruptured chordae tendineae
	Population AF	Some AF
Study design	**Study design details**	Diagnostic case–control study, blinded Cases = ruptured chordae tendineae Control subjects = MR due to other causes, most catheterisations within 1 week of echocardiography studies 37/40 cases and 18/20 control subjects had catheterisations
	Study design level in hierarchy[57]	3c
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	None reported (all used in analysis)

Study	**Author**	Smith[98]
	Date	1985
	Pathology(ies) (for which accuracy measured)	Ventricular septal rupture (in patients with AMI)
	Population AF	NR
Study design	**Study design details**	Comparison with reference standard, 13 patients excluded for not having reference standard
	Study design level in hierarchy[57]	3b comparison with reference standard
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	No
	Were the reference standard results interpreted without knowledge of the results of the index test?	No
	Were uninterpretable or indeterminate test results reported?	None reported, all used

NR, not reported.

Study	**Author**	Sparrow[99]
	Date	2003
	Pathology(ies) (for which accuracy measured)	LV systolic dysfunction
	Population AF	NR
Study design	**Study design details**	Prospective comparison of accuracy, cross-section not consecutive, blinded
	Study design level in hierarchy[57]	3a
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	TTE as reference standard
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	Yes (13% excluded from study owing to inadequate TTE images)

NR, not reported.

Study	**Author**	Stratton[100]
	Date	1982
	Pathology(ies) (for which accuracy measured)	LV thrombus
	Population AF	Percentage NR but some patients had AF
Study design	**Study design details**	Retrospective comparison of 2D echocardiography and indium-111 platelet imaging and surgical findings. Assessors blinded
	Study design level in hierarchy[57]	3b comparison with reference standard
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	Yes (excluded from analysis)

NR, not reported.

Study	**Author**	Veyrat[101]
	Date	1983
	Pathology(ies) (for which accuracy measured)	AR
	Population AF	38/95 = 40% overall
Study design	**Study design details**	Retrospective comparison of echocardiography against aortic root angiography (some surgical findings)
	Study design level in hierarchy[57]	3b comparison with reference standard
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Unknown
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unknown
	Were uninterpretable or indeterminate test results reported?	None reported, all used

Study	**Author**	Vigna[102]
	Date	1993
	Pathology(ies) (for which accuracy measured)	LA thrombus
	Population AF	59% in AF at time of study
Study design	**Study design details**	Comparison of TTE and TOE, consecutive patients, blinded ('two observers who were unaware of TTE findings') TTE and TOE within 24 hours of each other
	Study design level in hierarchy[57]	2
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	None reported, all used

Study	**Author**	Wong[103]
	Date	1983
	Pathology(ies) (for which accuracy measured)	Mitral and aortic valve stenosis, valvular calcification
	Population AF	NR
Study design	**Study design details**	Prospective comparison of 2D echocardiography and cinefluorography for detection of valvular calcification, blinding, non-consecutive
	Study design level in hierarchy[57]	3a comparison with reference standard
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Were uninterpretable or indeterminate test results reported?	None reported, all used

NR, not reported.

Study	**Author**	Zanolla[104]
	Date	1982
	Pathology(ies) (for which accuracy measured)	Mitral stenosis, mitral valve calcification
	Population AF	NR
Study design	**Study design details**	Retrospective comparison of 2D echocardiography and surgical findings, non-consecutive
	Study design level in hierarchy[57]	3b comparison with reference standard
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	Unknown
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unknown
	Were uninterpretable or indeterminate test results reported?	None reported, all used

NR, not reported.

Study	**Author**	Zotz[105]
	Date	1993
	Pathology(ies) (for which accuracy measured)	Ventricular septal rupture (in patients with AMI)
	Population AF	NR
Study design	**Study design details**	comparison with reference standard, not blinded, investigated consecutively
	Study design level in hierarchy[57]	3b comparison with reference standard
Items from QUADAS[59]	**Were selection criteria clearly described?**	Yes
	Is the reference standard likely to correctly classify the target condition?	Yes
	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes
	Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis?	Yes
	Did patients receive the same reference standard regardless of the index test result?	Yes
	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes
	Were the index test results interpreted without knowledge of the results of the reference standard?	No
	Were the reference standard results interpreted without knowledge of the results of the index test?	No
	Were uninterpretable or indeterminate test results reported?	None reported (all images used in analysis)

NR, not reported.

Prognostic studies: quality assessment

Level in hierarchy of evidence based on Merlin *et al.*:[57]

1. Systematic review of level 2 studies.

2. Prospective cohort study.

3a. All or none study.

3b. Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial (RCT).

3c. Retrospective cohort study.

4. Case series or cohort study of persons at different stages of disease.

Study	**Author**	Atrial Fibrillation Investigators[106]
	Date	1998
	Pathology(ies) (for which accuracy measured)	LV dysfunction, LAD, MVP, MR
	Population AF	All participants non-valvular AF
Study design	**Study design details**	Review of 3 (prospective) RCTs, using data from single arm of each (placebo/control), with outcome of subsequent stroke, also looked at clinical criteria for risk of stroke
	Study design level in hierarchy[57]	3b (review of level 3b)

Study	**Author**	Klem[107]
	Date	2003
	Pathology(ies) (for which accuracy measured)	Reduced LV function, LAD valvular abnormality
	Population AF	A total of 336 patients with non-rheumatic AF and 73 patients with non-rheumatic AF and also diabetes (for both groups, selected from 409 eligible of 474 consecutive patients)
Study design	**Study design details**	Prospective cohort study
	Study design level in hierarchy[57]	2

Study	**Author**	Miyaska[108]
	Date	2000
	Pathology(ies) (for which accuracy measured)	MR
	Population AF	All participants non-rheumatic AF
Study design	**Study design details**	Retrospective database study
	Study design level in hierarchy[57]	3c retrospective cohort study

Study	**Author**	Nakagami[109]
	Date	1998
	Pathology(ies) (for which accuracy measured)	Degree of MR and LAD
	Population AF	A total of 290 patients with non-rheumatic AF
Study design	**Study design details**	Retrospective cohort
	Study design level in hierarchy[57]	3c

Study	**Author**	The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators[110]
	Date	1992
	Pathology(ies) (for which accuracy measured)	Mitral annular calcification, severe MR, LV dysfunction and LAD
	Population AF	A total of 568 non-rheumatic AF, inpatient or outpatient, placebo arm of RCT (SPAF study)
Study design	**Study design details**	Cohort study of placebo arm of RCT
	Study design level in hierarchy[57]	3b analysis of prognostic factors amongst persons in a single arm of a RCT

Appendix 6 Data abstraction tables: prevalence review

Study	**Author**	Agmon *et al.*[111]
	Date	2001
	Location	USA (part of study of random sample of patients in Minnesota, encompassing several health-care providers)
	Study design	Case–control, subjects from another study (SPARC – a cohort study of a random selection of a geographical population)
Population	**Population, eligibility criteria**	Part of SPARC study: cases AF; controls without AF
	Sample size	AF $n = 42$, control subjects $n = 539$
	Male/female	AF male $n = 23$ (54.8%); control subjects male $n = 266$ (49.4%)
	Mean age (years)	AF mean 82 (SD 10), median 84 (range 50–98). Control subjects mean 66 (SD 13), median 63 (range 46–95)
	Diagnosis of AF	Electrocardiography and TOE at time of study recruitment or diagnosed prior to study recruitment
	Mean duration of AF	NR
	Underlying cardiac conditions	Hypertension AF 66.7%, control subjects 53.4% Hyperlipidaemia AF 55.6%, control subjects 45.5% Coronary artery disease AF 35.7%, control subjects 11.7% Previous MI AF 19.1%, control subjects 6.1% Angina AF 23.8%, control subjects 10.2% Cerebrovascular disease AF 23.8%, control subjects 4.8% Carotid artery stenosis of 50% or more AF 12.5%, control subjects 8.9% Mitral stenosis AF 2.4%, control subjects 0.4% MR AF 4.8%, control subjects 0.4% Aortic stenosis AF 2.4%, control subjects 1.3% AR AF 0, control subjects 0.4% History of CHF AF 21.4%, control subjects 2.6%
	Comorbidities (non-cardiac diseases)	DM AF 14.3%, control subjects 8.9%
	Treatment	Insulin for DM AF 4.8%, control subjects 1.9% CABG AF 14.3%, control subjects 3.2% PTCA AF 4.8%, control subjects 2.4% Previous mitral valve surgery AF 7.1%, control subjects 0
Methods	**Diagnostic instrument(s) for pathology**	TOE
	Diagnostic criteria for pathology	Home interview and medical records, TOE 'atherosclerosis defined as irregular intimal thickening with increased echogenicity. Complex atherosclerosis defined as the presence of protruding atheroma greater than 4 mm thick, mobile atherosclerotic debris, or plaque ulceration'
	Description of assessor(s)	NR (cardiology department, presume assessors qualified)
Results	**Pathology (no. of subjects)**	Aortic atherosclerosis AF $n = 31$, control subjects $n = 267$ Complex atherosclerosis AF $n = 7$, control subjects $n = 37$
	Pathology prevalence	Aortic atherosclerosis AF $n = 31/42 = 73.8\%$, control subjects $n = 267/539 = 49.5\%$ Complex atherosclerosis AF $n = 7/42 = 16.7\%$, control subjects $n = 37/539 = 6.9\%$

AR, aeortic regurgitation; CABG, coronary artery bypass graft; NR, not reported; PTCA, percutaneous transluminal coronary angioplasty; SD, standard deviation; SPARC, Stroke Prevention Assessment of Risk in a Community.

Study	**Author**	Archer[112]
	Date	1995
	Location	Multicentre, USA
	Study design	Retrospective observational study
Population	**Population, eligibility criteria**	Patients who had completed a larger study ($n = 525$) (SPINAF) comparing placebo and warfarin in the prevention of stroke. Patients were eligible for the 'Transoesophageal Echocardiography substudy' if they had completed SPINAF without an event
	Sample size	Patients with AF = 55 (warfarin $n = 32$, placebo $n = 23$)
	Male/female	Male $n = 55$ (100%)
	Mean age (years)	70.8 ± 6.6
	Diagnosis of AF	NR (reported in prior publication)
	Mean duration of AF	6.2 ± 4.3 years
	Underlying cardiac conditions	NR
	Comorbidities (non-cardiac diseases)	NR
	Treatment	Not described
Methods	**Diagnostic instrument(s) for pathology**	TOE
	Diagnostic criteria for pathology	An echodense mass seen on multiple views in which no flow could be demonstrated by pulsed or colour Doppler
	Description of assessor(s)	NR
Results	**Pathology (no. of subjects)**	LA thrombus $n = 5$; LV thrombus – 2 patent foramen ovale $n = 22$; atrial septal aneurysm $n = 4$
	Pathology prevalence	LA thrombus = 9.1%; LV thrombus – 3.6% patent foramen ovale = 40%; atrial septal aneurysm = 7.3%

NR, not reported; SPINAF, Stroke Prevention In Non-rheumatic Atrial Fibrillation.

Study	**Author**	Blackshear *et al.*[113] (additional details in other references[127,169])
	Date	1999
	Location	USA (multicentre, cardiovascular department)
	Study design	Cross-section study, prospectively sought aortic plaque in patients with AF who were part of a RCT of high-risk (SPAF III study, warfarin vs. warfarin + aspirin) looking at stroke in AF or were part of a prospective cohort study of low-risk patients. Assessed within 3 months of enrolment to RCT
Population	**Population, eligibility criteria**	From two studies: high-risk patients with AF who were part of a RCT (SPAF III study, warfarin vs. warfarin + aspirin) looking at stroke in AF, or were part of a prospective cohort study of low-risk patients
	Sample size	A total of 770 people with AF (786 had TOE but 770 of these had images sufficient to assess or exclude atherosclerotic plaque)
	Male/female	76% male, 24% female
	Mean age (years)	Mean age 69 years, SD 9 (of 786 patients; of 770 patients, mean between 66 and 71 years)
	Diagnosis of AF	Details not in this publication, but patients part of a RCT (SPAF III study, warfarin vs. warfarin + aspirin) looking at stroke in AF; other publications on this trial give details[127]
	Mean duration of AF	Overall, 73% (of 786) had duration of >1 year (19% intermittent AF). Of 7896 patients who had TOE, 404 were considered low risk for stroke, and 382 were considered at high risk for stroke (defined in the study as having at least one of 'prior thromboembolism, systolic blood pressure >160 mmHg, recent heart failure or fractional shortening at least 25%, or female sex and aged >75 years'
	Underlying cardiac conditions	19% (of 786) prior thromboembolism; 25% history of CHF; 13% recent CHF; 26% ischaemic heart disease
	Comorbidities (non-cardiac diseases)	15% DM (of 786); 54% history of hypertension; 14% systolic blood pressure >160 mmHg at entry
	Treatment	High-risk patients, as part of RCT, randomised to adjusted-dose warfarin vs. low, fixed doses of warfarin plus aspirin in combination. Low-risk patients treated with aspirin alone
Methods	**Diagnostic instrument(s) for pathology**	Diagnosis of atherosclerotic plaque by TOE
	Diagnostic criteria for pathology	Atherosclerotic plaque in the thoracic aorta was defined in terms of location and morphology. The aorta was divided into ascending, transverse and descending segments, and plaque was classified as simple (sessile) or complex on the basis of thickness at least 4 mm, ulceration, pedunculation or mobile elements. More information in other publication of the study[169]
	Description of assessor(s)	(In other publication of study, includes interobserver reliability.[169])
Results	**Pathology (no. of subjects)**	Presence of aortic plaque $n = 334$ (of whom simple plaque only $n = 243$) Complex plaque ($n = 193$)
	Pathology prevalence	Aortic plaque 436/770 = 56.6% Complex plaque 193/770 = 25.1%

SD, standard deviation; SPAF, Stroke Prevention in Atrial Fibrillation.

Study	**Author**	Corrado *et al.*[114]
	Date	2004
	Location	Italy, cardiology department, single centre
	Study design	Cross-section, retrospective, patients selected prior to treatment
Population	**Population, eligibility criteria**	AF or atrial flutter, subtherapeutic INR anticoagulation therapy, TOE before cardioversion
	Sample size	41
	Male/female	Male patients without thrombi $n = 23$ (62%) Male patients with thrombi $n = 2$ (50%)
	Mean age (years)	Patients without thrombi 64.35 (SD 10.28) Patients with thrombi 66.25 (SD 0.96)
	Diagnosis of AF	NR
	Mean duration of AF	NR
	Underlying cardiac conditions	Hypertension patients without thrombi $n = 20$ (54%) Hypertension patients with thrombi $n = 2$ (50%) Structural heart disease patients without thrombi $n = 20$ (54%) Structural heart disease patients with thrombi $n = 3$ (75%)
	Comorbidities (non-cardiac diseases)	NR
	Treatment	All anticoagulated
Methods	**Diagnostic instrument(s) for pathology**	TOE
	Diagnostic criteria for pathology	'An atrial thrombus was defined as circumscribed and uniformly consistent echoreflective mass of different texture than atrial wall'
	Description of assessor(s)	Three experienced echocardiographers
Results	**Pathology (no. of subjects)**	LAA thrombus $n = 4$
	Pathology prevalence	9.80%

NR, not reported; SD, standard deviation.

Study	**Author**	Dang *et al.*[115]
	Date	2004
	Location	USA
	Study design	Retrospective review of ECGs ($n = 3935$), which were then matched to patients' discharge records to identify patients with AF
Population	**Population, eligibility criteria**	Patients with AF during the year 1999
	Sample size	Patients with matched ECG and discharge notes of hospital admission ($n = 737$)
	Male/female	Male $n = 413$ (56%)
	Mean age (years)	62.3
	Diagnosis of AF	('Index') ECG – first ECG of any particular patient with a diagnosis of AF Note: One patient could have multiple ECGs
	Mean duration of AF	NR
	Underlying cardiac conditions	Hypertension 45.6%; heart failure 31.1%; AMI 8.1%; cardiomyopathy 4.5%
	Comorbidities (non-cardiac diseases)	Diabetes 22.9%; cerebrovascular disease 6.6%
	Treatment	NR
Methods	**Diagnostic instrument(s) for pathology**	Echocardiography not described further in terms of position of probe (i.e. transoesophageal or transthoracic)
	Diagnostic criteria for pathology	Not described
	Description of assessor(s)	NR
Results	**Pathology (no. of subjects)**	CAD 136/737, mitral valve disease 77/737, all valve diseases 98/737, cardiomyopathy 33/737
	Pathology prevalence	CAD 18.5%, mitral valve disease 10.4%, all valve diseases 13.4%, cardiomyopathy 4.5%

CAD, coronary artery disease; NR, not reported.

Study	**Author**	de Devitiis[28]
	Date	1999
	Location	Germany, single centre, cardiology department
	Study design	Cohort, consecutive patients, prospective
Population	**Population, eligibility criteria**	AF, referred for TOE
	Sample size	Ninety with AF [from 102 studied, 90 (88%) had visualised RAA and LAA]
	Male/female	Patients with AF male $n = 69$, female $n = 21$ out of 90 Control subjects male $n = 15$, female $n = 7$ out of 22
	Mean age (years)	AF mean 60 (SD 13) Controls mean 58 (SD 17)
	Diagnosis of AF	Clinical criteria and 12-lead ECG
	Mean duration of AF	For those with RA thrombi, mean duration 1670 days (SD 1596); for those without RA thrombi, mean 480 days (SD 924)
	Underlying cardiac conditions	Coronary heart disease AF $n = 20$ (out of 90), arterial hypertension AF $n = 19$ [control subjects $n = 1$ (out of 22)], mitral stenosis AF $n = 8$, MR AF $n = 6$, aortic stenosis AF $n = 4$, AR AF $n = 3$, dilated cardiomyopathy AF $n = 10$, myocarditis AF $n = 5$
	Comorbidities (non-cardiac diseases)	Neurological deficit AF $n = 10$, control subjects $n = 18$ Acute peripheral ischaemia AF $n = 4$ PE AF $n = 2$
	Treatment	Anticoagulation therapy AF $n = 50$ Control subjects $n = 7$
Methods	**Diagnostic instrument(s) for pathology**	TTE and TOE
	Diagnostic criteria for pathology	Visualised by echocardiography (TOE)
	Description of assessor(s)	NR (cardiology department, presume assessors qualified)
Results	**Pathology (no. of subjects)**	Twelve patients with left or right or both (included five with both), incorporate 6 RAA thrombosis, 11 LAA thrombosis
	Pathology prevalence	Either or both 13% (RAA 6.7%, LAA 12.2%)

NR, not reported; SD, standard deviation.

Study	**Author**	Heppell[116]
	Date	1997
	Location	Hospital setting, two hospitals in Leeds, UK
	Study design	Prospective observational study
Population	**Population, eligibility criteria**	Patients with evidence of AF from presenting ECG tracings reporting at the inpatients or outpatients departments. AF was confirmed at the time of venous blood sampling and echocardiography
	Sample size	109
	Male/female	Male $n = 69$ (64%); female $n = 38$ (36%)
	Mean age (years)	69.4
	Diagnosis of AF	Diagnosis of AF was obtained from presenting ECG tracing. Diagnosis was subsequently confirmed at the time of venous sampling and echocardiography. Patients who were in sinus rhythm at either of these sessions were reported as having paroxysmal AF
	Mean duration of AF	NR
	Underlying cardiac conditions	Hypertension ($n = 47$) 44%; ischaemic heart disease ($n = 40$) 37%; paroxysmal AF ($n = 14$) 13%; previous stroke ($n = 23$) 21%
	Comorbidities (non-cardiac diseases)	NR
	Treatment	Aspirin use ($n = 54$) 50%
Methods	**Diagnostic instrument(s) for pathology**	TOE. Examination by means of a 5-MHz single-plane probe or 5-MHz multiplane probe
	Diagnostic criteria for pathology	Atrial thrombus was defined as a discrete echodense mass of >5 mm diameter and acoustically distinct from the underlying endocardium
	Description of assessor(s)	Images were analysed online by two observers (authors)
Results	**Pathology (no. of subjects)**	LA thrombi 19/107
	Pathology prevalence	LA thrombi 18%

NR, not reported.

Study	**Author**	Kleemann[117]
	Date	2009
	Location	Hospital, single centre, Germany
	Study design	Prospective observational study
Population	**Population, eligibility criteria**	(Data source: ANTIKoagulation Registry). Patients with short AF (<48 hours in duration) admitted for planned cardioversion between 1994 and 2000
	Sample size	Patients in TOE group = 207
	Male/female	Male *n* = 152 (73%); female *n* = 55 (27%)
	Mean age (years)	Median 63 (range 57–72)
	Diagnosis of AF	From admission notes
	Mean duration of AF	NR
	Underlying cardiac conditions	Hypertensive heart disease (46%); coronary artery disease (53%); hypertrophic valvular disease (7%); dilated cardiomyopathy (17%)
	Comorbidities (non-cardiac diseases)	NR
	Treatment	Prior anticoagulation 63%
Methods	**Diagnostic instrument(s) for pathology**	TOE
	Diagnostic criteria for pathology	Mass present in more than one plane, in the body of the atrium or appendage which is distinct from the underlying endocardium
	Description of assessor(s)	NR
Results	**Pathology (no. of subjects)**	LA thrombus 1.4% (*n* = 3). None of these patients had prior anticoagulation
	Pathology prevalence	LA thrombus 1%; aortic plaques 12%

NR, not reported.

Study	**Author**	Levy *et al.*[118]
	Date	1999
	Location	General practice, multicentre, France
	Study design	Prospective observational study
Population	**Population, eligibility criteria**	Patients presenting in AF or with a history of AF, with at least one episode documented in an ECG report. Study involved 206 cardiologists. Each agreed to enrol and follow up six patients
	Sample size	756
	Male/female	Male $n = 436$ (58%); female $n = 320$ (42%)
	Mean age (years)	68.6 ± 11.4
	Diagnosis of AF	Electrocardiographic diagnosis of AF was made according to Bellet's definition. AF was subdivided into three types: • paroxysmal (history of recurrent episodes of AF lasting >2 minutes and <7 days *or* first episode of AF lasting <7 days or cardioverted within 7 days were also classified in this group) ($n = 167$) • chronic (AF present for >1 month) ($n = 389$), or • recent onset (persistent non-self-terminating AF lasting ≥7 days and <1 month *or* a first symptomatic attack of AF lasting ≥7 days and <1 month *or* an asymptomatic/mildly symptomatic AF of recent discovery *or* an AF episode for which the onset could not be determined were classified in this group) Should the physician opt for cardioversion (either pharmacological or electrical) of AF lasting >7 days but <1 month, the patient was classified in the recent-onset AF group ($n = 200$)
	Mean duration of AF	Patients with CAF 54 ± 77 months
	Underlying cardiac conditions	
	Comorbidities (non-cardiac diseases)	Diabetes ($n = 81$) 10.7%; bronchopulmonary disease ($n = 85$) 11.2%
	Treatment	Antiarrhythmic treatment ($n = 550$) 72.7%; warfarin or similar agent ($n = 276$) 36%; aspirin ($n = 177$) 23.4%; heparin ($n = 18$) 2.4%
Methods	**Diagnostic instrument(s) for pathology**	M-mode and 2D echocardiography (type unspecified)
	Diagnostic criteria for pathology	NR
	Description of assessor(s)	NR
Results	**Pathology (no. of subjects)**	CAD $n = 126$; hypertensive heart disease $n = 162$; valvular (rheumatic) disease $n = 115$; cardiomyopathy includes those with dilated/hypertrophic/other forms of cardiomyopathy $n = 116$; CHF $n = 226$; hypertension $n = 298$
	Pathology prevalence	CAD 16.6%; hypertensive heart disease 21.4%; valvular (rheumatic) disease 15.2%; cardiomyopathy includes those with dilated/hypertrophic/other forms of cardiomyopathy 15%; CHF 29.8%; hypertension 39.4%

CAD, coronary artery disease; NR, not reported.

Study	**Author**	Lip *et al.*[119]
	Date	1997
	Location	UK, primary care
	Study design	Cross-section of patient records (retrospective), looking at prevalence and management of AF in primary care
Population	**Population, eligibility criteria**	AF (in primary care), aged ≥50 years
	Sample size	111
	Male/female	42/111 male (38%)
	Mean age (years)	Mean 72.7 (SD 9.9)
	Diagnosis of AF	ECG
	Mean duration of AF	73% of AF population had CAF, i.e. >6 months
	Underlying cardiac conditions	
	Comorbidities (non-cardiac diseases)	Previous hyperthyroidism 15.3%; alcohol excess 5.4%
	Treatment	NR
Methods	**Diagnostic instrument(s) for pathology**	Investigations by GP or hospital
	Diagnostic criteria for pathology	From patient records
	Description of assessor(s)	NR
Results	**Pathology (no. of subjects)**	Ischaemic heart disease $n = 32$ (including $n = 20$ MI); valvular heart disease $n = 29$; cardiomyopathy $n = 6$; atrial septal defect $n = 1$
	Pathology prevalence	Ischaemic heart disease 28.8%; valvular heart disease 26.1%; cardiomyopathy 5.4%; atrial septal defect 0.9%

NR, not recorded; SD, standard deviation.

Study	**Author**	Maltagliati[120]
	Date	2006
	Location	Hospital setting, Italy
	Study design	Observational study
Population	**Population, eligibility criteria**	Eligible AF (83.6%) or flutter (16.4%) patients on different anticoagulation regimens undergoing cardioversion by TOE
	Sample size	Patients categorised into four groups according to anticoagulant regimen: (1) oral anticoagulation (warfarin) INR>2 ($n = 744$); (2) short-term anticoagulation with unfractionated heparin or with unfractionated heparin plus warfarin for <4 days ($n = 235$); (3) ineffective oral anticoagulation (warfarin) >3 weeks ($n = 43$); and (4) effective oral anticoagulation (warfarin) <3 weeks ($n = 82$). Total = 1104
	Male/female	Male $n = 368$ (67%); female $n = 368$ (33%)
	Mean age (years)	66.3 ± 9.8
	Diagnosis of AF	Not described
	Mean duration of AF	Group 1, 104 ± 121 days; group 4, 35 ± 124 days
	Underlying cardiac conditions	Hypertension (42%), coronary artery disease (20.1%), dilative cardiomyopathy (11.7%), mitral prosthetic valve (5.6%), aortic prosthetic valve (2.3%), history of ictus (2%), history of transient ischaemic attack (2.4%), recent embolic episodes (0.7%), mitral valve disease (11%), dilated cardiomyopathy (10%) and coronary artery disease (7%)
	Comorbidities (non-cardiac diseases)	NR
	Treatment	Anticoagulation
Methods	**Diagnostic instrument(s) for pathology**	TOE
	Diagnostic criteria for pathology	Thrombi identified as presence of echodense masses, mobile or immobile connected to the LA or LAA wall. Images were obtained in different planes from 0º–180º
	Description of assessor(s)	NR
Results	**Pathology (no. of subjects)**	65; LA thrombi $n = 2$; LAA thrombi $n = 59$; RAA thrombi $n = 4$
	Pathology prevalence	6.3%; LA 5.5%; LAA thrombi 0.3%; RAA thrombi 0.5%

NR, not reported.

Study	**Author**	Narumiya[121]
	Date	2003
	Location	Japan, cardiology department single centre
	Study design	Retrospective cross-sectional
Population	**Population, eligibility criteria**	Non-valvular CAF or atrial flutter, had undergone TOE. Excluded left ventricular ejection fraction <0.5
	Sample size	AF $n = 50$ (of which 14 lone AF, 36 non-lone AF); atrial flutter $n = 12$
	Male/female	53 male, 9 female
	Mean age (years)	60 (SD 9.7)
	Diagnosis of AF	Non-valvular CAF was defined by conventional ECG on two occasions separated by at least 1 month, and absence of rheumatic heart disease as determined by echocardiography. Lone AF was defined by excluding coronary artery disease (clinical or laboratory criteria), hyperthyroidism, valvular heart diseases, CHF, cardiomyopathy, chronic obstructive pulmonary disease, cardiomegaly, history of hypertension, age >60 years, insulin-dependent DM, AF only during trauma/surgery, acute medical illness
	Mean duration of AF	NR
	Underlying cardiac conditions	NR
	Comorbidities (non-cardiac diseases)	NR
	Treatment	NR
Methods	**Diagnostic instrument(s) for pathology**	TTE and TOE
	Diagnostic criteria for pathology	Presence of LA or LAA thrombus was defined in TOE views as (1) masses adhering to wall of LA or appendage; (2) motion independent of LAA wall; (3) different echogenic density from LAA wall; and (4) evidence in more than one imaging plane
	Description of assessor(s)	NR
Results	**Pathology (no. of subjects)**	$n = 6$ (all had non-lone AF)
	Pathology prevalence	6/36 non-lone AF = 16.7% (if take all AF/flutter as denominator then 6/62 = 9.7%; if take all AF then 6/50 = 12%)

NR, not reported.

Study	**Author**	Santiago[122]
	Date	1994
	Location	USA, cardiology department, single centre
	Study design	Cross-sectional, prospective
Population	**Population, eligibility criteria**	Group 1, atrial 'fibrillation-flutter'; group 2, AF; group 3, atrial flutter
	Sample size	A total of 61 (out of 63 – two excluded because of mitral regurgitant jet that disallowed adequate echocardiogram) of which 14 'fibrillation-flutter', 30 AF, 17 flutter
	Male/female	AF group: 16 male, 14 female
	Mean age (years)	AF group: 69 (SD 10)
	Diagnosis of AF	ECG
	Mean duration of AF	New arrhythmia (<7 days) 13% of AF group ($n = 4$)
	Underlying cardiac conditions	AF group hypertension 53%, coronary artery disease 13%, neurovascular event 23%, rheumatic heart disease 27%
	Comorbidities (non-cardiac diseases)	NR
	Treatment	AF group anticoagulant (≥21 days) 57%
Methods	**Diagnostic instrument(s) for pathology**	TOE
	Diagnostic criteria for pathology	Thrombi defined as masses adherent to wall of LAA. MR assessed qualitatively on the basis of maximal area of the regurgitant jet
	Description of assessor(s)	NR
Results	**Pathology (no. of subjects)**	AF group LAA thrombus $n = 12$, MR $n = 9$
	Pathology prevalence	AF group LAA thrombus 40%, MR 30%

NR, not reported.

Study	**Author**	Scherr[123]
	Date	2009
	Location	USA
	Study design	Prospective observational study
Population	**Population, eligibility criteria**	Patients with AF referred for catheter ablation of AF
	Sample size	A total of 585 patients undergoing 732 catheter ablations (from 590 patients referred for 737 catheter ablations, of which two procedures were terminated owing to technical difficulties, whereas three cases demonstrating unexpected findings were excluded, giving a total of five cases excluded from the final analysis)
	Male/female	Male $n = 564$ (77%); female $n = 168$ (23%)
	Mean age (years)	57 ± 11 (5% of cases were >75 years old)
	Diagnosis of AF	Diagnosis of AF not clearly stated. However, patient history was examined before the procedure. Paroxysmal AF defined as two or more recurrent AF terminating spontaneously within 7 days. Persistent AF was defined as recurrent AF lasting >7 days or sustained for <7 days owing to pharmacological or electrical cardioversion [$n = 353$ (48%)]
	Mean duration of AF	75.6 ± 69.6 months (calculated using 6.3 ± 5.8 years from the paper)
	Underlying cardiac conditions	Hypertension ($n = 298$) 41%; CHF ($n = 88$) 12%; previous stroke or transient ischaemic attack ($n = 39$) 5%
	Comorbidities (non-cardiac diseases)	DM ($n = 49$) 7%
	Treatment	Unsuccessful class I and III antiarrhythmic treatment, ($n = 1.4 \pm 1.0$); preprocedural anticoagulation ($n = 689$) 94%. At least 4 weeks before ablation patients received warfarin to maintain an INR of between 2 and 3. Warfarin was stopped 5 days before catheter ablation. A bridging treatment with enoxaparin, 0.5–1 mg/kg every 12 hours, was started from the fifth day before procedure. Patients for whom warfarin was contraindicated received antiplatelet agents at the discretion of attending doctor
Methods	**Diagnostic instrument(s) for pathology**	TOE
	Diagnostic criteria for pathology	Patients underwent TOE 24 hours before ablation. The LA cavity and LAA were examined for the presence of thrombi. Atrial thrombus was present if there was a well-circumscribed echodense mass seen in more than one imaging plane that was distinct from the surrounding endocardium and pectinate muscles
	Description of assessor(s)	The presence or absence of LA thrombus was determined by the attending echocardiographer at the time that the TOE was performed. All attending echocardiographers performing and interpreting the TOEs were more than 3 years post training and highly experienced (>50 TOEs per year per physician)
Results	**Pathology (no. of subjects)**	LA thrombus 12/732
	Pathology prevalence	1.60%

Study	**Author**	Shen[124]
	Date	2002
	Location	USA
	Study design	Retrospective (subjects were identified from chart review of consecutive patients who underwent TOE to rule out intra-atrial thrombi before cardioversion of AF – January 1996 and June 2001)
Population	**Population, eligibility criteria**	Patients with subtherapeutic INRs after receiving adequate doses of anticoagulation for ≥3 weeks. Eligibility: AF >48 hours; warfarin treatment ≥3 weeks; completion of full warfarin loading dose (defined as achievement of INR >2 after starting treatment); INR <2 at one or more measurements in the last 3 weeks preceding TOE, with at least one measurement within 7 days of scheduled TOE
	Sample size	182
	Male/female	NR
	Mean age (years)	NR
	Diagnosis of AF	NR
	Mean duration of AF	7.3 ± 16.9 months (reported as duration of AF onset to TOE)
	Underlying cardiac conditions	Hypertension ($n = 48$) 26%; valvular heart disease ($n = 46$) 25%; dilated cardiomyopathy ($n = 2$) 1%; hypertrophic cardiomyopathy ($n = 2$) 1%; congenital atrial septal defect ($n = 1$) 1%; coronary artery disease ($n = 50$) 28%
	Comorbidities (non-cardiac diseases)	DM ($n = 2$) 1%
	Treatment	NR
Methods	**Diagnostic instrument(s) for pathology**	TOE
	Diagnostic criteria for pathology	Atrial thrombus was defined as a uniformly consistent echo-reflective and circumscribed mass, which was distinct in texture from the surrounding wall of the atrium
	Description of assessor(s)	NR
Results	**Pathology (no. of subjects)**	18/182
	Pathology prevalence	9.90%

NR, not reported.

Study	**Author**	Tsai[125]
	Date	1996
	Location	China
	Study design	Prospective observational study (consecutive patients with chronic non-rheumatic AF undergoing TOE)
Population	**Population, eligibility criteria**	Patients with chronic non-rheumatic AF (i.e. AF persisting for >30 days) admitted as inpatients or seen as outpatients, undergoing TOE. (Patients were excluded if they had oesophageal disease or could not tolerate TOE)
	Sample size	A total of 219 (of 222 patients included in the study, three had 'non-diagnostic images' on TOE)
	Male/female	Male $n = 161$ (74%); female $n = 58$ (26%)
	Mean age (years)	65 (range 28–82)
	Diagnosis of AF	Serial ECG
	Mean duration of AF	NR
	Underlying cardiac conditions	Hypertension ($n = 97$) 44%; coronary artery disease ($n = 20$) 9%; idiopathic dilated cardiomyopathy ($n = 27$) 12%; non-rheumatic valvular disease ($n = 16$) 7%; hypertrophic cardiomyopathy ($n = 3$) 1%; sick sinus syndrome ($n = 1$) 0.4%; previous thromboembolism ($n = 77$) 35.1%
	Comorbidities (non-cardiac diseases)	Hyperthyroidism ($n = 9$) 4%
	Treatment	Anticoagulation treatment ($n = 15$) 7%; anti-platelet agents ($n = 38$) 17%
Methods	**Diagnostic instrument(s) for pathology**	TOE
	Diagnostic criteria for pathology	Atrial thrombus was defined as a well-circumscribed echogenic mass in the LA cavity or appendage which was distinct from the surrounding pectinate muscles
	Description of assessor(s)	NR
Results	**Pathology (no. of subjects)**	15/219
	Pathology prevalence	6.80%

NR, not reported.

Appendix 7 Quality assessment: prevalence review

Responses may be 'Yes', 'No', 'Unclear', 'NA' (not applicable) or 'partial data provided'.

Study: Agmon 2001[111]		Response
Study background	Background information given	Yes
	Study objectives stated	
Methods	Appropriate study design explained	Yes
	Description of recruitment	
	Eligibility criteria described	
	Methods of assessment or measurement described	
Results	Data on all participants provided	Yes
	Reasons for non-participation outlined	
	Statistical methods described and appropriate	
	Potential sources of biases identified	
	Variables described or identified	

Study: Archer 1995[112]		Response
Study background	Background information given	Yes
	Study objectives stated	
Methods	Appropriate study design explained	Yes
	Description of recruitment	
	Eligibility criteria described	
	Methods of assessment or measurement described	
Results	Data on all participants provided	Yes
	Reasons for non-participation outlined	
	Statistical methods described and appropriate	
	Potential sources of biases identified	Unclear
	Variables described or identified	Yes

Study: Blackshear 1999[113]		Response
Study background	Background information given	Yes
	Study objectives stated	
Methods	Appropriate study design explained	Yes
	Description of recruitment	
	Eligibility criteria described	Yes[a]
	Methods of assessment or measurement described	
Results	Data on all participants provided	Yes
	Reasons for non-participation outlined	
	Statistical methods described and appropriate	
	Potential sources of biases identified	
	Variables described or identified	

a Partial data reported in this reference but full details available in previous publications.

Study: Corrado 2004[114]		Response
Study background	Background information given	Yes
	Study objectives stated	
Methods	Appropriate study design explained	Yes
	Description of recruitment	
	Eligibility criteria described	
	Methods of assessment or measurement described	
Results	Data on all participants provided	Yes
	Reasons for non-participation outlined	
	Statistical methods described and appropriate	
	Potential sources of biases identified	No
	Variables described or identified	Yes

Study: Dang 2004[115]		Response
Study background	Background information given	Yes
	Study objectives stated	
Methods	Appropriate study design explained	Yes
	Description of recruitment	
	Eligibility criteria described	
	Methods of assessment or measurement described	
Results	Data on all participants provided	Yes
	Reasons for non-participation outlined	
	Statistical methods described and appropriate	
	Potential sources of biases identified	Partial data provided
	Variables described or identified	Yes

Study: de Divitiis 1999[28]		Response
Study background	Background information given	Yes
	Study objectives stated	
Methods	Appropriate study design explained	Yes
	Description of recruitment	
	Eligibility criteria described	
	Methods of assessment or measurement described	
Results	Data on all participants provided	Yes
	Reasons for non-participation outlined	
	Statistical methods described and appropriate	
	Potential sources of biases identified	No
	Variables described or identified	Yes

Study: Heppell 1997[116]		Response
Study background	Background information given	Yes
	Study objectives stated	
Methods	Appropriate study design explained	Yes
	Description of recruitment	
	Eligibility criteria described	
	Methods of assessment or measurement described	
Results	Data on all participants provided	No
	Reasons for non-participation outlined	Yes
	Statistical methods described and appropriate	
	Potential sources of biases identified	
	Variables described or identified	

Study: Kleeman 2009[117]		Response
Study background	Background information given	Yes
	Study objectives stated	
Methods	Appropriate study design explained	Yes
	Description of recruitment	
	Eligibility criteria described	
	Methods of assessment or measurement described	
Results	Data on all participants provided	Yes
	Reasons for non-participation outlined	
	Statistical methods described and appropriate	
	Potential sources of biases identified	
	Variables described or identified	

Study: Levy 1999[118]		Response
Study background	Background information given	Yes
	Study objectives stated	
Methods	Appropriate study design explained	Yes
	Description of recruitment	
	Eligibility criteria described	
	Methods of assessment or measurement described	No
Results	Data on all participants provided	Yes
	Reasons for non-participation outlined	
	Statistical methods described and appropriate	
	Potential sources of biases identified	Unclear
	Variables described or identified	

Study: Lip 1997[119]		Response
Study background	Background information given	Yes
	Study objectives stated	
Methods	Appropriate study design explained	Yes
	Description of recruitment	
	Eligibility criteria described	
	Methods of assessment or measurement described	
Results	Data on all participants provided	NA
	Reasons for non-participation outlined	
	Statistical methods described and appropriate	Yes
	Potential sources of biases identified	
	Variables described or identified	

Study: Maltagliati 2006[120]		Response
Study background	Background information given	Yes
	Study objectives stated	
Methods	Appropriate study design explained	Yes
	Description of recruitment	
	Eligibility criteria described	
	Methods of assessment or measurement described	
Results	Data on all participants provided	Yes
	Reasons for non-participation outlined	
	Statistical methods described and appropriate	
	Potential sources of biases identified	Unclear
	Variables described or identified	Yes

Study: Narumiya 2003[121]		Response
Study background	Background information given	Yes
	Study objectives stated	
Methods	Appropriate study design explained	Yes
	Description of recruitment	
	Eligibility criteria described	
	Methods of assessment or measurement described	
Results	Data on all participants provided	NA
	Reasons for non-participation outlined	
	Statistical methods described and appropriate	Yes
	Potential sources of biases identified	No
	Variables described or identified	Partial data provided

Study: Santiago 1994[122]		Response
Study background	Background information given	Yes
	Study objectives stated	
Methods	Appropriate study design explained	Yes
	Description of recruitment	
	Eligibility criteria described	
	Methods of assessment or measurement described	
Results	Data on all participants provided	Yes
	Reasons for non-participation outlined	
	Statistical methods described and appropriate	
	Potential sources of biases identified	
	Variables described or identified	

Study: Scherr 2009[123]		Response
Study background	Background information given	Yes
	Study objectives stated	
Methods	Appropriate study design explained	Yes
	Description of recruitment	
	Eligibility criteria described	
	Methods of assessment or measurement described	
Results	Data on all participants provided	Yes
	Reasons for non-participation outlined	
	Statistical methods described and appropriate	
	Potential sources of biases identified	
	Variables described or identified	

Study: Shen 2002[124]		Response
Study background	Background information given	Yes
	Study objectives stated	
Methods	Appropriate study design explained	Yes
	Description of recruitment	
	Eligibility criteria described	
	Methods of assessment or measurement described	
Results	Data on all participants provided	Yes
	Reasons for non-participation outlined	NA
	Statistical methods described and appropriate	Yes
	Potential sources of biases identified	No
	Variables described or identified	Unclear

Study: Tsai 1997[125]		Response
Study background	Background information given	Yes
	Study objectives stated	
Methods	Appropriate study design explained	Yes
	Description of recruitment	
	Eligibility criteria described	
	Methods of assessment or measurement described	
Results	Data on all participants provided	Yes
	Reasons for non-participation outlined	
	Statistical methods described and appropriate	
	Potential sources of biases identified	
	Variables described or identified	

Appendix 8 Excluded studies: diagnostic review

Studies excluded at full paper stage for diagnostic review

Study	Reason for exclusion
Abbasi 1980[170]	Population not AF, AF study available for diagnostic accuracy of pathology
Aghassi 2005[171]	Grading severity of diagnosed condition, rather than diagnosing condition
Agricola 2008[172]	Excluded intervention, stress echocardiography
Alkhadi 2007[173]	Grading severity of diagnosed condition, rather than diagnosing condition
Assey 1981[174]	Population not AF, higher-level evidence available for diagnostic accuracy of pathology
Babic 1991[175]	Population not AF, AF study available for diagnostic accuracy of pathology
Badran 2009[176]	Excluded intervention, combination of carotid and thoracic echocardiography
Blanchard 1981[177]	Population not AF, AF study available for diagnostic accuracy of pathology
Blot-Souletie 2007[178]	Grading severity of diagnosed condition, rather than diagnosing condition
Bogren 1980[179]	Review of case reports, cases differed in their use of comparator(s)
Buchner 2008[180]	Grading severity of diagnosed condition, rather than diagnosing condition
Casiglia 2008[181]	Prognostic study, general population, AF excluded
Charron 1997[182]	Excluded comparator, study of familial hypertrophic cardiomyopathy, comparator was genotyping
Chen 1985[183]	Population not AF, AF study available for diagnostic accuracy of pathology
Egeblad 1983[184]	Grading severity of diagnosed condition, rather than diagnosing condition
Fleischmann 1994[185]	Prognostic study, population with chest pain, population not AF
Gonzalez-Torrecilla 2000[186]	Excluded intervention, TOE and TTE combined
Hsiao 2006[187]	Population not AF, higher-level evidence available for diagnostic accuracy of PE
Irani 1996[188]	Population not AF, higher-level evidence available for diagnostic accuracy of pathology
Khanna 2004[189]	Grading severity of diagnosed condition, rather than diagnosing condition
Khumri 2007[190]	TOE, not TTE (prognostic study)
Kruger 2001[191]	Population not AF, AF study available for diagnostic accuracy of pathology
Lembcke 2008[192]	Grading severity of diagnosed condition, rather than diagnosing condition
Meng 2002[193]	Population not AF, higher-level evidence available for diagnostic accuracy of pathology
Miyatake 1986[194]	Population not AF, AF study available for diagnostic accuracy of pathology
Mogelvang 2009[195]	Prognostic study, general population, AF excluded
Nitta 1988[196]	Grading severity of diagnosed condition, rather than diagnosing condition
Pechacek 1984[197]	Population not AF, AF study available for diagnostic accuracy of pathology
Peteiro 2008[198]	Excluded intervention, exercise echocardiography
Roe 2000[199]	Echocardiography combined with clinical criteria, no separate data for TTE alone
Sallach 2009[200]	Excluded intervention, contrast echocardiography
Stafford 1985[201]	Population not AF, higher-level evidence available for diagnostic accuracy of pathology

Study	Reason for exclusion
Steckleberg 1991[202]	Prognostic study, population not AF
Stevens 2009[203]	Prognostic study, population with stable coronary artery disease, population not AF
Takamoto 1985[204]	Population not AF, AF study available for diagnostic accuracy of pathology
Thuny 2005[205]	Prognostic study, population not AF
Visser 1983[206]	Population not AF, AF study available for diagnostic accuracy of pathology
Willens 2006[207]	Prognostic study, population undergoing coronary angiography, population not AF

Appendix 9 Excluded studies: prevalence review

Studies excluded at full paper stage for prevalence review

Study	Reason for exclusion
Black 1993[138]	Did not set out to assess prevalence of selected pathology
Colkesen 2008[208]	
DiPasquale[136]	
Kannel 1998[19]	
Levy 1991[40]	
Miyasaka 2000[108]	
Miyasaka 2007[209]	
Nieuwlaat 2005[54]	
Rozenberg 2000[135]	
Rubin 1996[137]	
Tops 2010[141]	
Tsang 2005[142]	
Frykman 2001[134]	
Rostagno 1998[139]	
SPAF Investigators 1992[110]	

Appendix 10 Parameters used in mathematical models

TABLE 63 Sources of parameters used in model

Parameter	Category	Description	Reference(s)
Risks/ probabilities	Death from other causes	Non-parametric	UK life tables[145]
	Sensitivity and specificity of TTE in detecting LA abnormality	Jointly estimated from Dirichlet distribution (FN, TP, TN, FP) = (5, 87, 83, 159)	Table 2 of Providencia *et al.*[13]
	Proportion of patients with LA abnormality	Beta (2.5, 22.5) for $CHADS_2$ Beta (0.5, 11.5) for CHA_2DS_2-VASc (Both with prior of 0.5 added to both cell counts)	Table 2 of Providencia *et al.*[13]
	Annual stroke risk by $CHADS_2$ score	Simulated from log-normal distribution	Friberg *et al.*[146]
	Annual stroke risk in those with LA abnormality	Simulated from log-normal distribution	Connolly *et al.*[147]
	RR of stroke in patients receiving dabigatran	Indirect comparison simulation approach	Lip and Edwards[148] for RR of warfarin vs. placebo Eikelboom *et al.*[150] for RR of dabigatran vs. warfarin
	Annual major bleeding risk for patients receiving dabigatran	Stratified by age CrI calculated using simulation approach	Eikelboom *et al.*[150]
	Outcome following stroke	Simulation- and mapping-based approach	Method described in report using results published in Rivero-Arias *et al.*[153]
	Outcome following a major bleeding event	Previous estimates	Simpson *et al.* 2010[210]
Utilities	Baseline utilities by age and gender	Regression-based approach	Ara *et al.* 2010[211]
	Utility multiplier following stroke, utility multiplier following major non-fatal intracranial bleed	Simulation- and mapping-based approach	Method described here using results published in Rivero-Arias *et al.*[153]
Costs	Annual cost of dabigatran (£)	821.25	NICE, full guidance, 2012[212]
	Cost of TTE (£)	66	NHS Reference Costs[152]
	Cost of death due to stroke (£)	7019 (95% CrI 6975 to 7064)	Sandercock *et al.*[155]
	Costs in stroke survivors	Various. Differing according to dependent and independent states. Subdivided into ongoing and continuing costs	NHS Reference Costs[152] NHS Stroke Strategy Impact Assessment[213] *Unit Costs of Health and Social Care 2010* (Curtis 2001[156])
	Costs of fatal bleed	Assumed identical to costs of death due to stroke	
	Costs of non-fatal bleed	Various Depends on whether bleed is gastrointestinal or intracranial. If intracranial, depends on severity of resulting disability	NHS Reference Costs[152]

Appendix 11 Influence of assumed sensitivity and specificity of transthoracic echocardiography in identifying left atrial abnormality on incremental cost-effectiveness ratio estimates

TABLE 64 The change in the ICER (in £1000/QALY) when different assumptions are made regarding the sensitivity and specificity of TTE in identifying LA abnormality in each of the 14 mathematical model comparisons

W_50_0_M

		Sensitivity										
W_50_0_M		0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Specificity	**0.0**	D	D	D	D	D	D	D	D	D	D	∞
	0.1	D	D	D	D	D	D	D	D	D	D	8.4
	0.2	D	D	D	D	D	D	D	D	D	D	5.7
	0.3	D	D	D	D	D	D	D	D	D	70.7	4.9
	0.4	D	D	D	D	D	D	D	D	D	26.2	4.4
	0.5	D	D	D	D	D	D	D	D	>99	17.1	4.2
	0.6	D	D	D	D	D	D	D	D	65.6	13.1	4.0
	0.7	D	D	D	D	D	D	D	D	35.0	10.9	3.8
	0.8	D	D	D	D	D	D	D	>99	24.5	9.5	3.8
	0.9	D	D	D	D	D	D	D	63.9	19.2	8.5	3.7
	1.0	D	D	D	D	D	D	>99	40.2	16.0	7.8	3.6

∞, infinity; D, dominated.

W_50_0_F

		Sensitivity										
W_50_0_F		0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Specificity	**0.0**	D	D	D	D	D	D	D	D	D	D	∞
	0.1	D	D	D	D	D	D	D	D	D	D	8.4
	0.2	D	D	D	D	D	D	D	D	D	D	5.9
	0.3	D	D	D	D	D	D	D	D	D	56.8	5.0
	0.4	D	D	D	D	D	D	D	D	D	25.2	4.6
	0.5	D	D	D	D	D	D	D	D	>99	17.1	4.4
	0.6	D	D	D	D	D	D	D	D	53.2	13.4	4.2
	0.7	D	D	D	D	D	D	D	>99	32.3	11.2	4.1
	0.8	D	D	D	D	D	D	D	97.4	23.7	9.9	4.0
	0.9	D	D	D	D	D	D	D	52.0	19.1	8.9	3.9
	1.0	D	D	D	D	D	D	>99	36.2	16.2	8.2	3.9

∞, infinity; D, dominated.

W_65_0_M

		Sensitivity										
W_65_0_M		0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Specificity	**0.0**	D	D	D	D	D	D	D	D	D	D	∞
	0.1	D	D	D	D	D	D	D	D	D	D	8.9
	0.2	D	D	D	D	D	D	D	D	D	29.8	4.9
	0.3	D	D	D	D	D	D	D	D	62.8	13.9	3.6
	0.4	D	D	D	D	D	D	D	>99	25.0	9.3	2.9
	0.5	D	D	D	D	D	D	>99	38.8	15.9	7.1	2.5
	0.6	D	D	D	D	D	>99	56.6	23.4	11.8	5.8	2.3
	0.7	D	D	D	D	D	80.4	32.1	16.9	9.4	5.0	2.1
	0.8	D	D	D	D	>99	42.3	22.6	13.3	7.9	4.4	1.9
	0.9	D	D	D	>99	54.5	28.9	17.5	11.0	6.9	4.0	1.8
	1.0	D	D	>99	69.3	36.1	22.1	14.4	9.5	6.1	3.6	1.7

∞, infinity; D, dominated.

W_65_0_F

		Sensitivity										
W_65_0_F		0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Specificity	**0.0**	D	D	D	D	D	D	D	D	D	D	∞
	0.1	D	D	D	D	D	D	D	D	D	>99	8.1
	0.2	D	D	D	D	D	D	D	D	>99	24.4	4.6
	0.3	D	D	D	D	D	D	D	>99	39.8	12.9	3.4
	0.4	D	D	D	D	D	D	>99	54.5	20.9	9.0	2.8
	0.5	D	D	D	D	D	>99	68.6	28.8	14.4	7.0	2.5
	0.6	D	D	D	D	>99	82.0	36.5	19.8	11.1	5.8	2.3
	0.7	D	D	D	>99	94.7	44.0	25.1	15.2	9.1	5.0	2.1
	0.8	D	D	>99	>99	51.3	30.3	19.2	12.4	7.8	4.5	2.0
	0.9	D	>99	>99	58.4	35.4	23.2	15.7	10.6	6.9	4.1	1.9
	1.0	>99	>99	65.4	40.4	27.1	18.9	13.3	9.2	6.1	3.7	1.8

∞, infinity; D, dominated.

W_50_1_M

		Sensitivity										
W_50_1_M		0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Specificity	**0.0**	9.8	9.8	9.9	9.9	9.9	10.0	10.1	10.3	10.6	11.6	∞
	0.1	9.3	9.3	9.3	9.2	9.1	9.1	9.0	8.8	8.5	7.8	5.6
	0.2	8.9	8.8	8.7	8.6	8.5	8.4	8.1	7.8	7.3	6.4	4.3
	0.3	8.5	8.4	8.3	8.2	8.0	7.8	7.5	7.1	6.5	5.6	3.9
	0.4	8.2	8.1	8.0	7.8	7.6	7.3	7.0	6.6	6.0	5.1	3.7
	0.5	7.9	7.8	7.6	7.4	7.2	7.0	6.6	6.2	5.6	4.8	3.6
	0.6	7.7	7.5	7.4	7.2	6.9	6.7	6.3	5.9	5.3	4.6	3.5
	0.7	7.4	7.3	7.1	6.9	6.7	6.4	6.0	5.6	5.1	4.4	3.4
	0.8	7.2	7.1	6.9	6.7	6.4	6.2	5.8	5.4	4.9	4.3	3.4
	0.9	7.0	6.9	6.7	6.5	6.2	6.0	5.6	5.2	4.7	4.1	3.4
	1.0	6.9	6.7	6.5	6.3	6.1	5.8	5.5	5.1	4.6	4.0	3.3

∞, infinity; D, dominated.

W_50_1_F

		Sensitivity										
W_50_1_F		0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Specificity	**0.0**	11.6	11.6	11.7	11.7	11.8	11.8	11.9	12.1	12.4	13.3	∞
	0.1	11.0	11.0	10.9	10.8	10.8	10.6	10.5	10.2	9.8	8.9	5.7
	0.2	10.5	10.4	10.3	10.1	10.0	9.7	9.4	9.0	8.3	7.2	4.5
	0.3	10.0	9.9	9.7	9.6	9.3	9.0	8.7	8.2	7.4	6.3	4.2
	0.4	9.6	9.4	9.3	9.1	8.8	8.5	8.1	7.5	6.8	5.7	4.0
	0.5	9.2	9.1	8.9	8.6	8.4	8.0	7.6	7.1	6.3	5.3	3.8
	0.6	8.9	8.7	8.5	8.3	8.0	7.6	7.2	6.7	6.0	5.1	3.8
	0.7	8.6	8.4	8.2	8.0	7.7	7.3	6.9	6.4	5.7	4.9	3.7
	0.8	8.4	8.2	7.9	7.7	7.4	7.0	6.6	6.1	5.5	4.7	3.7
	0.9	8.1	7.9	7.7	7.4	7.1	6.8	6.4	5.9	5.3	4.6	3.6
	1.0	7.9	7.7	7.5	7.2	6.9	6.6	6.2	5.7	5.2	4.5	3.6

∞, infinity; D, dominated.

W_65_1_M

		Sensitivity										
W_65_1_M		0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Specificity	**0.0**	36.3	36.3	36.4	36.6	36.7	37.0	37.3	37.9	39.0	42.4	∞
	0.1	30.8	30.3	29.8	29.1	28.3	27.2	25.8	23.8	20.7	15.5	4.6
	0.2	26.7	26.0	25.2	24.3	23.1	21.6	19.8	17.5	14.3	9.8	2.8
	0.3	23.7	22.9	21.9	20.8	19.5	18.0	16.2	13.9	11.0	7.3	2.2
	0.4	21.3	20.4	19.4	18.3	17.0	15.5	13.7	11.6	9.0	5.9	1.9
	0.5	19.3	18.4	17.4	16.3	15.0	13.6	11.9	10.0	7.7	5.0	1.7
	0.6	17.7	16.8	15.8	14.7	13.5	12.1	10.6	8.8	6.8	4.4	1.6
	0.7	16.3	15.5	14.5	13.5	12.3	11.0	9.5	7.9	6.0	3.9	1.5
	0.8	15.2	14.3	13.4	12.4	11.3	10.0	8.7	7.2	5.5	3.6	1.4
	0.9	14.2	13.4	12.5	11.5	10.4	9.3	8.0	6.6	5.0	3.3	1.4
	1.0	13.3	12.5	11.7	10.7	9.7	8.6	7.4	6.1	4.7	3.1	1.3

∞, infinity; D, dominated.

W_65_1_F

		Sensitivity										
W_65_1_F		0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Specificity	**0.0**	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	∞
	0.1	71.9	69.7	67.1	64.1	60.4	56.1	50.6	43.8	34.7	22.3	4.4
	0.2	55.3	52.7	49.8	46.5	42.8	38.5	33.6	27.8	21.0	12.8	2.7
	0.3	45.0	42.5	39.7	36.6	33.2	29.5	25.3	20.6	15.2	9.2	2.2
	0.4	38.0	35.6	33.0	30.2	27.2	23.9	20.3	16.4	12.1	7.3	1.9
	0.5	32.9	30.7	28.3	25.8	23.1	20.2	17.1	13.7	10.0	6.1	1.7
	0.6	29.1	27.0	24.8	22.6	20.1	17.5	14.8	11.8	8.7	5.3	1.6
	0.7	26.0	24.1	22.2	20.1	17.8	15.5	13.0	10.4	7.6	4.7	1.6
	0.8	23.6	21.8	20.0	18.1	16.0	13.9	11.7	9.3	6.9	4.3	1.5
	0.9	21.6	20.0	18.3	16.5	14.6	12.7	10.6	8.5	6.3	3.9	1.4
	1.0	19.9	18.4	16.8	15.1	13.4	11.6	9.7	7.8	5.8	3.6	1.4

∞, infinity; D, dominated.

R_50_0_M

		Sensitivity										
R_50_0_M		0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Specificity	**0.0**	D	D	D	D	D	D	D	D	D	D	∞
	0.1	D	D	D	D	D	D	D	D	D	D	7.5
	0.2	D	D	D	D	D	D	D	D	D	D	5.1
	0.3	D	D	D	D	D	D	D	D	D	38.2	4.3
	0.4	D	D	D	D	D	D	D	D	D	19.0	3.9
	0.5	D	D	D	D	D	D	D	D	82.0	13.3	3.6
	0.6	D	D	D	D	D	D	D	D	35.4	10.5	3.5
	0.7	D	D	D	D	D	D	D	>99	23.2	8.9	3.3
	0.8	D	D	D	D	D	D	D	54.8	17.7	7.8	3.2
	0.9	D	D	D	D	D	D	>99	34.4	14.5	7.1	3.2
	1.0	D	D	D	D	D	D	78.5	25.5	12.4	6.5	3.1

∞, infinity; D, dominated.

R_50_0_F

		Sensitivity										
R_50_0_F		0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Specificity	**0.0**	D	D	D	D	D	D	D	D	D	D	∞
	0.1	D	D	D	D	D	D	D	D	D	D	7.5
	0.2	D	D	D	D	D	D	D	D	D	D	5.2
	0.3	D	D	D	D	D	D	D	D	D	35.2	4.4
	0.4	D	D	D	D	D	D	D	D	D	19.1	4.0
	0.5	D	D	D	D	D	D	D	D	63.0	13.7	3.8
	0.6	D	D	D	D	D	D	D	D	32.9	11.0	3.7
	0.7	D	D	D	D	D	D	D	90.7	22.9	9.4	3.6
	0.8	D	D	D	D	D	D	D	46.8	17.9	8.3	3.5
	0.9	D	D	D	D	D	D	>99	32.2	14.9	7.5	3.4
	1.0	D	D	D	D	D	D	60.7	24.8	12.9	6.9	3.4

∞, infinity; D, dominated.

R_65_0_M

		Sensitivity										
R_65_0_M		0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Specificity	**0.0**	D	D	D	D	D	D	D	D	D	D	∞
	0.1	D	D	D	D	D	D	D	D	D	>99	8.0
	0.2	D	D	D	D	D	D	D	D	>99	20.4	4.4
	0.3	D	D	D	D	D	D	D	>99	31.5	10.8	3.1
	0.4	D	D	D	D	D	D	>99	41.5	16.9	7.5	2.5
	0.5	D	D	D	D	D	>99	50.7	22.7	11.7	5.8	2.2
	0.6	D	D	D	D	>99	59.1	28.2	15.7	9.0	4.8	1.9
	0.7	D	D	D	>99	66.7	33.4	19.6	12.1	7.4	4.1	1.7
	0.8	D	D	>99	73.8	38.4	23.4	15.2	9.9	6.3	3.6	1.6
	0.9	D	>99	80.3	43.2	27.1	18.1	12.4	8.4	5.5	3.3	1.5
	1.0	>99	86.3	47.7	30.6	21.0	14.8	10.5	7.3	4.9	3.0	1.4

∞, infinity; D, dominated.

R_65_0_F

		Sensitivity										
R_65_0_F		0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Specificity	**0.0**	D	D	D	D	D	D	D	D	D	D	∞
	0.1	D	D	D	D	D	D	D	D	D	77.0	7.3
	0.2	D	D	D	D	D	D	D	D	65.3	17.4	4.1
	0.3	D	D	D	D	D	D	>99	61.4	23.9	10.1	3.0
	0.4	D	D	D	D	D	>99	59.5	28.4	14.8	7.3	2.4
	0.5	D	D	D	D	>99	58.3	31.7	18.6	10.9	5.8	2.1
	0.6	D	D	>99	>99	57.5	34.2	21.8	14.0	8.7	4.8	1.9
	0.7	D	>99	>99	57.0	36.3	24.4	16.7	11.3	7.3	4.2	1.7
	0.8	>99	93.2	56.6	37.9	26.6	19.0	13.6	9.5	6.3	3.7	1.6
	0.9	87.0	56.2	39.3	28.5	21.1	15.6	11.5	8.2	5.6	3.4	1.5
	1.0	56.0	40.4	30.1	22.9	17.5	13.3	10.0	7.3	5.0	3.1	1.5

∞, infinity; D, dominated.

D_65_0_M

		Sensitivity										
D_65_0_M		0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Specificity	**0.0**	D	D	D	D	D	D	D	D	D	D	∞
	0.1	D	D	D	D	D	D	D	D	D	44.1	6.8
	0.2	D	D	D	D	D	D	D	>99	36.0	12.8	3.6
	0.3	D	D	D	D	D	>99	84.7	33.4	16.2	7.6	2.5
	0.4	D	D	D	D	>99	62.0	32.0	18.3	10.5	5.5	1.9
	0.5	D	D	>99	>99	52.3	31.2	19.8	12.7	7.9	4.3	1.6
	0.6	>99	>99	79.3	46.9	30.7	20.9	14.4	9.8	6.3	3.6	1.4
	0.7	>99	66.5	43.5	30.3	21.8	15.8	11.4	8.0	5.3	3.1	1.2
	0.8	58.8	41.1	30.0	22.4	16.9	12.7	9.4	6.7	4.5	2.7	1.1
	0.9	39.3	29.8	22.9	17.8	13.8	10.6	8.0	5.8	4.0	2.4	1.0
	1.0	29.6	23.4	18.6	14.8	11.7	9.2	7.0	5.2	3.6	2.2	1.0

∞, infinity; D, dominated.

D_65_0_F

		Sensitivity										
D_65_0_F		0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Specificity	**0.0**	D	D	D	D	D	D	D	D	D	D	∞
	0.1	D	D	D	D	D	D	D	D	>99	28.3	6.2
	0.2	D	D	D	D	D	>99	>99	46.8	23.8	11.2	3.3
	0.3	D	D	>99	>99	99.6	57.0	35.4	22.2	13.4	7.1	2.4
	0.4	>99	>99	97.7	63.5	43.6	30.6	21.5	14.7	9.5	5.3	1.9
	0.5	96.6	67.9	49.8	37.2	28.0	21.0	15.5	11.0	7.4	4.3	1.6
	0.6	54.5	42.5	33.5	26.4	20.7	16.1	12.2	8.9	6.1	3.6	1.4
	0.7	38.1	31.0	25.3	20.5	16.5	13.0	10.1	7.5	5.2	3.1	1.3
	0.8	29.3	24.5	20.4	16.8	13.7	11.0	8.6	6.4	4.5	2.8	1.2
	0.9	23.9	20.2	17.1	14.3	11.8	9.5	7.5	5.7	4.0	2.5	1.1
	1.0	20.1	17.3	14.7	12.4	10.3	8.4	6.7	5.1	3.6	2.3	1.1

∞, infinity; D, dominated.

Appendix 12 Search strategy for economic evaluations of transthoracic echocardiography in atrial fibrillation

Database

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1948 to present>.

Search strategy

1. Economics/ (26,174)
2. 'costs and cost analysis'/ (39,208)
3. Cost-benefit analysis/ (52,318)
4. Cost control/ (18,902)
5. Cost savings/ (7217)
6. Cost of illness/ (14,510)
7. Cost sharing/ (1697)
8. 'deductibles and coinsurance'/ (1308)
9. Medical savings accounts/ (450)
10. Health care costs/ (22,054)
11. Direct service costs/ (958)
12. Drug costs/ (10,541)
13. Employer health costs/ (1041)
14. Hospital costs/ (6577)
15. Health expenditures/ (11,915)
16. Capital expenditures/ (1908)
17. Value of life/ (5196)
18. exp economics, hospital/ (17,442)
19. exp economics, medical/ (13,323)
20. Economics, nursing/ (3854)
21. Economics, pharmaceutical/ (2279)
22. exp 'fees and charges'/ (25,506)
23. exp budgets/ (11,098)
24. (low adj cost).mp. (17,558)
25. (high adj cost).mp. (6674)
26. (health?care adj cost$).mp. (2986)
27. (fiscal or funding or financial or finance).tw. (65,465)
28. (cost adj estimate$).mp. (1188)
29. (cost adj variable).mp. (28)
30. (unit adj cost$).mp. (1263)
31. (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (141,645)
32. or/1-31 (397,254)
33. tte.mp. (1269)
34. tte.tw. (1268)
35. transthoracic echocardiography.mp. (4415)
36. (transthorac$ or trans-thorac$ or (trans$ and thorac$)).mp. (45,938)
37. (echocardiog$ adj (transthorac$ or trans-thorac$ or (trans$ and thorac$))).mp. (448)
38. 33 or 34 or 35 or 36 or 37 (46,183)
39. 32 and 38 (346)

40. heart valve diseases/ or heart valve problems.mp. or valvular heart disease.mp. (18,610)
41. ((aortic or aorta or mitral or pulmonary or triscuspid or valvular) and (regurgitation or stenosis or incompetence or insufficiency)).mp. (89,068)
42. heart valve regurgitation.mp. (11)
43. heart valve stenosis.mp. (9)
44. mitral valve disease.mp. (2005)
45. heart defects, congenital/ or congenital heart disease.mp. (43,519)
46. congenital heart malformation.mp. (116)
47. heart septal defects, atrial/ or atrial septal defect.mp. (9900)
48. heart septum defect.mp. (2)
49. heart ventricle septum defect.mp. (0)
50. heart septal defects, ventricular/ or ventricular septal defect.mp. (13,692)
51. heart atrium septal defect.mp. (0)
52. aortic coarctation/ or coarctation of the aorta.mp. (9)
53. aorta coarctation.mp. (80)
54. heart valve diseases/ or heart valve problems.mp. or valvular heart disease.mp. (18,610)
55. valvular defects.mp. (174)
56. valvular heart disease.mp. or Heart Valve Diseases/ (18,609)
57. aortic valve disease.mp. (1598)
58. aorta valve disease.mp. (1)
59. mitral valve disease.mp. (2005)
60. pulmonary valve disease.mp. (26)
61. ductus ateriosus, pulmonary/ or patent ductus arteriosus.mp. (5453)
62. cardiomyopathies/ or cardiomyopath$.mp. (59,553)
63. hypertension, pulmonary/ or primary pulmonary hypertension.mp. (21,843)
64. aortic diseases/ or aortic disease.mp. or aorta disease.mp. (12,643)
65. aortic aneurysm/ or aortic aneurysm.mp. or aorta aneurysm.mp. (36,522)
66. (aortic dissection or aorta dissection).mp. (6630)
67. intramural haematoma.mp. (168)
68. aortic rupture/ or aortic rupture.mp. or aorta rupture.mp. (7750)
69. aortic dilation.mp. (162)
70. aortic pathology.mp. (393)
71. cardiomyopathy, dilated/ or dilated cardiomyopthy.mp. or congestive cardiomyopathy.mp. (12,727)
72. cardiomyopathy, hypertrophic/ or hypertrophic cardiomyopathy.mp. (12,875)
73. Heart failure/ or heart failure.mp. (117,623)
74. heart left ventricle hypertrophy.mp. (0)
75. congestive heart failure.mp. (29,007)
76. endocarditis/ or endocarditis.mp. (28,538)
77. pericarditis/ or pericarditis.mp. (11,917)
78. myocardial ischemia/ or ischemic heart disease.mp. or heart muslce ischemia.mp. (42,783)
79. (angina or angina pectoris or angina pectoris, variant or angina, unstable or ludwig's angina or microvascular angina).mp. (56,678)
80. coronary thrombosis/ or coronary thrombosis.mp. (6319)
81. (atherosclerotic heart disease or atherosclerotic cardiovascular disease).mp. (1502)
82. Myocardial Infarction/co (23,244)
83. (chordae tenineae adj rupture).mp. (0)
84. (papillary muscle$ adj rupture).mp. (338)
85. heart papillary muscle rupture.mp. (0)
86. (thrombosis adj atrium).mp. (0)
87. heart atrium thrombosis.mp. (0)
88. (thrombosis adj auricular appendage).mp. (0)
89. (thrombosis adj ventricle).mp. (0)
90. Thrombosis/ or heart ventricle thrombosis.mp. (50,804)

91. left ventricular aneurysm/ or heart aneurysm/ or left ventricular aneurysm.mp. or heart left ventricle anuerysm.mp. (6502)
92. (aneurysm/ or aneurysm.mp.) and (ventricular mural or coronary artery or coronary vessels or aortic).mp. (44,698)
93. (coronary artery anuerysm or aorta anuerysm).mp. (0)
94. heart neoplasms/ or heart masses.mp. or cardiac masses.mp. (12,581)
95. heart tumo?r.mp. (100)
96. pulmonary embolism/ or pulmonary embolism.mp. or lung embolism.mp. (34,879)
97. lung disease/ or pulmonary disease.mp. (86,405)
98. hypertension, pulmonary/ or pulmonary hypertension.mp. (29,346)
99. cor pulmonale.mp. (3519)
100. heart murmurs/ or heart murmur$.mp. (3499)
101. or/40-100 (662,970)
102. 32 and 38 and 101 (95)

Appendix 13 Study protocol

NHS
National Institute for
Health Research

Protocol HTA Technology Assessment Report

October 2009

08/45/01 HTA TAR

1. Title of the project

Echocardiography in newly diagnosed atrial fibrillation patients

2. Name of TAR team and project 'lead'

TAR team: School of Health and Related Research (ScHARR) Technology Assessment Group, The University of Sheffield.

Project lead: Emma Simpson, Research Fellow, Health Economics and Decision Science, ScHARR, University of Sheffield, Regents Court, 30 Regent Street, Sheffield S1 4DA.
Tel: 0114 222 0708, Fax: 0114 272 4095, Email: e.l.simpson@sheffield.ac.uk

Address for correspondence
All correspondence should be sent to the project lead (e.l.simpson@sheffield.ac.uk), the project administrator (Andrea Shippam, a.shippam@sheffield.ac.uk) and the managing director of ScHARR-TAG (Eva Kaltenthaler, e.kaltenthaler@sheffield.ac.uk).

3. Plain English Summary

Cardiac arrhythmias affect the heart, causing an irregular heartbeat. Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia.[1] AF is more common in older people. At age 80–89 years, almost 9% of people have AF.[1] It can occur in both men and women, but is more common in men. AF does not always cause symptoms, but may cause palpitations, chest pain, dizziness, or fainting.[1] An irregular heartbeat makes the heart less efficient at circulating blood around the body. This can increase the risk of blood clots developing within the circulatory system. If left untreated, AF is a significant risk factor for stroke and other morbidities.[1] AF can be caused by other medical conditions, such as heart disease or hypertension, or may occur following surgery.[1]

Transthoracic echocardiography (TTE) is a procedure that allows imaging of the heart and blood flow.[2] By undergoing echocardiography, cardiac abnormalities can be diagnosed earlier than would be possible if symptoms were left to develop.[1] Currently, only selected patients with AF have TTE. These patients are selected because their clinical symptoms mean that heart disease is suspected, or because treatment planning requires the further information that TTE can provide.[1]

The aim of this report is to evaluate whether all newly diagnosed AF patients should have TTE, rather than just the selected AF patients for whom TTE is currently recommended.

4. Decision problem

4.1 Purpose of assessment

The assessment will address the question "What is the clinical and cost effectiveness of performing a routine echocardiogram in all newly diagnosed atrial fibrillation (AF) patients in preventing complications arising from AF, in comparison with current practice of selective testing?"

4.2 Clear definition of the intervention (e.g. licensed indications, dosages being considered)

Echocardiography is an ultrasound imaging procedure used to examine the heart. Transthoracic echocardiography (TTE) is non-invasive echocardiography, performed by placing the ultrasound device across the chest.[1] TTE images cardiac structures including all four cardiac valves, cardiac walls and the velocity of blood flow in the heart by using beams of sound at frequencies of 2.5-5MHz.[2]

TTE may be used to refine clinical risk stratification for antithrombotic therapy.[1] It can also be used to assess the risk of recurrent AF following cardioversion, or to assess the risk of developing postoperative AF.[1]

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

The assessment will investigate the effects of performing routine TTE in all newly diagnosed AF patients. In this case, the intervention would be performed soon after diagnosis of AF, without requiring symptoms of further pathology to be present. If data are available the cost effectiveness of targeting TTE in sub-populations of newly diagnosed AF patients will be undertaken.

4.4 Relevant comparators

The comparator for all intervention strategies will be current practice. Treatment for AF depends on the type of AF diagnosed, as well as comorbidities, drug contraindications and patient preference.[1] Pharmacological treatments include antithrombotic therapy, antiarrhythmic agents, beta-blockers or rate-limiting calcium antagonists. Other treatments may include electrical cardioversion or surgical procedures (such as pacemaker therapy, arrhythmia surgery, catheter ablation or use of atrial defibrillators).[1]

4.5 Population and relevant sub-groups

The main focus of the assessment will be newly diagnosed AF patients for whom TTE is not currently recommended. This will include patients with AF for whom the need to initiate anticoagulation therapy has already been decided on clinical criteria, as NICE guidelines for AF[1] state that TTE should not be routinely performed in this circumstance. As stated in section 4.3, if data are available the cost effectiveness of targeting TTE in sub-populations of newly diagnosed AF patients will be undertaken. This could allow some sub-groups to receive TTE whilst others do not.

The assessment will also evaluate not using TTE in any newly diagnosed AF patients. This will allow an analysis of the cost effectiveness of TTE in patients currently meeting the criteria for recommended TTE in the NICE guidelines for AF.[1] These comprise:

Younger patients for whom a baseline echocardiogram is important for long-term management;

Patients for whom cardioversion (electrical or pharmacological) is being considered;

Patients in whom there is a high risk or a suspicion of underlying structural/functional heart disease (such as heart failure or heart murmur) that influences their subsequent management;

Patients in need of clinical risk stratification for antithrombotic therapy.

Sub groups
Where data are available, the assessment will consider separately patients with AF for whom the need to initiate anticoagulation therapy has already been decided on clinical criteria.

Where data are available, the assessment will consider separately those patients for whom AF was diagnosed when they presented with associated medical conditions (heart failure, stroke or thromboembolism), as opposed to patients with AF as primary diagnosis whether asymptomatic, or based on symptoms not requiring hospital visit.

Where data are available, the assessment will consider separately patients with paroxysmal, persistent or permanent diagnoses of AF.

4.6 Key factors to be addressed (e.g. clinical and cost outcomes, further considerations, problematic factors)

The objectives of the review are:
to investigate (by systematic review) the prevalence of clinically important pathology in AF;
to investigate (by systematic review) the diagnostic accuracy of TTE for these abnormalities;
to estimate the potential benefits and harms due to altered treatment based on results of TTE;
to estimate the incremental cost effectiveness of routine TTE for newly diagnosed compared with current practice of TTE in selected AF patients;
to estimate the incremental cost effectiveness of providing routine TTE to subgroups within the newly diagnosed AF patient population (where data are available).

5. Report methods for synthesis of evidence of clinical effectiveness

Two reviews (1 - prevalence of clinically important pathology in AF; 2 - diagnostic accuracy of TTE for these abnormalities) of the evidence will be undertaken systematically following the general principles recommended in the QUOROM statement.[3]

Population
The population will be the same for both reviews.
Inclusion
Newly diagnosed AF patients. Diagnosis of AF is confirmed by electrocardiogram (ECG), which may be standard ECG, 24-hour ambulatory ECG or event recorder ECG. The population for this review will be those AF patients for whom TTE is not currently recommended. This will include patients with AF for whom the need to initiate anticoagulation therapy has already been decided on clinical criteria,

Sub groups
Where data are available, the assessment will consider separately subgroups of Patients currently meeting the criteria for recommended TTE in the NICE guidelines for AF,[1] as routine TTE would not alter practice for these patients. These comprise: younger patients for whom a baseline echocardiogram is important for long-term management; patients for whom cardioversion (electrical or pharmacological) is being considered; patients in whom there is a high risk or a suspicion of underlying structural/functional heart disease (such as heart failure or heart murmur) that influences their subsequent management; patients in need of clinical risk stratification for antithrombotic therapy.

Where data are available, the assessment will consider separately patients with AF for whom the need to initiate anticoagulation therapy has already been decided on clinical criteria, for whom NICE guidelines for AF[1] state that TTE should not be routinely performed.

Where data are available, the assessment will consider separately those patients for whom AF was diagnosed when they presented with associated medical conditions (heart failure, stroke

or thromboembolism), as opposed to patients with AF as primary diagnosis whether asymptomatic, or based on symptoms not requiring hospital visit.

Where data are available, the assessment will consider separately patients with paroxysmal, persistent or permanent diagnoses of AF.

Study selection and data extraction strategy
For both reviews, study selection will be made by one reviewer. The following publication types will be excluded: animal models, preclinical and biological studies, editorials, opinion pieces, studies only published in languages other than English, reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality. Data will be extracted independently by one reviewer using a standardised data extraction form and checked by another. Discrepancies will be resolved by discussion.

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 and Citation Searching.

Databases:
Electronic databases: including MEDLINE; Medline in Process (for latest publications); EMBASE; The Cochrane Library including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, DARE, NHS EED and HTA databases; NIHR Clinical Research Network Portfolio database; NRR (National Research Register) Archive; Web of Science Proceedings; Current Controlled Trials; Clinical Trials.gov; FDA website; EMEA website and relevant conference proceedings.

The draft search strategy is shown in Appendix 1.

5.1 Review of prevalence of pathology in AF patients

Prevalence of pathology in AF patients will be sought from epidemiological studies.
Pathologies will be restricted to those that could be identified by TTE. These include left ventricular impairment or hypertrophy, weakened heart muscle/cardiomyopathy, heart valve problems, aortic aneurysm, blood clots, tumours, pericarditis, pulmonary hypertension. Quality assessment will depend on types of studies identified, but is likely to be based on the STROBE statement (see Appendix 2).[4] Data will be tabulated and discussed in a narrative review.

5.2 Review of diagnostic accuracy of TTE

Diagnostic accuracy of TTE will be sought from studies comparing detected pathology from TTE or other diagnostic tools. Outcomes of sensitivity (proportion of true positives) and specificity (proportion of true negatives) will be identified. Studies looking at prognostic accuracy will also be sought, that is, TTE results predicting later cardiovascular events. Quality assessment will depend on types of studies identified, but is likely to be based on QUADAS (see Appendix 2).[5] Data will be tabulated and discussed in a narrative review. Where appropriate, meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes.

5.3 Further information needed

Further clinical data needed for economic modelling will be sought from clinical guidelines, advice from clinical experts or systematic reviews.

If studies of prognostic accuracy (i.e. the ability of TTE to predict cardiovascular events) are not available, it will be necessary to find data on the risk of cardiovascular events arising from each clinically important pathology.

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 needed.

6. Report methods for synthesising evidence of cost-effectiveness

A systematic review of the existing literature studying the cost-effectiveness of echocardiography in newly diagnosed AF patients will be undertaken. In addition, a new economic model will be developed to compare a treatment strategy which incorporates early use of echocardiography for all newly diagnosed AF patients, with a strategy that incorporates early use of echocardiography only in patients outlined by the NICE AF guideline (i.e. current practice).

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 echocardiography for newly diagnosed AF patients. An economic search filter will be integrated into the search strategy to identify relevant studies. Identified economic literature will be critically appraised and assessed using the Drummond checklist.[6] 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 will be constructed, it is likely that a Markov model approach will be used, and the primary outcome from the model will be an estimate of the incremental cost per additional quality adjusted life year (QALY) gained associated with use of echocardiography for newly diagnosed AF patient. The time horizon of our analysis will be a patient's lifetime in order to reflect the chronic nature of the disease and potential mortality. The perspective will be that of the National Health Services and Personal Social Services. Both costs and QALYs will be discounted at 3.5%. Modelling assumptions will be taken from the literature, supplemented by clinical expert opinion where necessary. In the absence of direct data, QALYs will have to be selected from those included in publications for studies of treatments for AF in fairly general populations in the UK, such as radio-frequency catheter ablation versus anti-arrhythmic drug therapy.[7]

The model structure will be determined in consultation with clinical experts. The different types of AF (paroxysmal, persistent and permanent), the different treatment strategies (rate control and rhythm control) and the associated treatment pathways will need to be taken into account. The model will include estimates of the difference that echocardiography makes to ensuring appropriate care for the different types of AF patients, as well as costs of the intervention and subsequent downstream costs associated with appropriate and inappropriate care. This will enable an analysis of whether early echocardiography is cost effective for different patient groups.

Ideally, health related quality of life estimates will be available from the reviewed literature. In the absence of such evidence, the economic 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. National sources (e.g. NHS reference costs[8], national unit costs[9], British National Formulary[10]) as well as the reviewed literature 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 parameters that will be included in the economic model. Therefore the uncertainty around the parameter estimates will be modelled to take account of this. The uncertainty in the central value for each required parameter will be represented by a distribution, enabling probabilistic sensitivity analysis to be undertaken on the model results. This will allow an assessment of the uncertainty to be made, and the results will be interpreted accordingly. Through expected value of information analysis and expected value of perfect parameter information analysis we will identify whether further research is valuable, and in which areas further research is likely to be particularly valuable.

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.

8. Competing interests of authors

Nick Latimer previously worked on a project about dronedarone funded by Sanofi-Aventis. To date, dronedarone has not been considered by NICE for use in the NHS.

9. Timetable/milestones

Milestone	Date
Draft protocol	31st July 2009
Final protocol	23rd October 2009
Progress report	August 2010
Assessment report	September 2010

TAR Team

Emma Simpson, Research Fellow, ScHARR: has experience in systematic reviews of health technologies including involvement in Heath Technology Assessment Reports. She will lead the project and undertake the systematic reviewing of clinical effectiveness and has been involved in developing the protocol.

Nick Latimer, Research Fellow, ScHARR: has experience in operational research techniques. He has been involved in developing the protocol.

Patrick Fitzgerald, Research Fellow, ScHARR: has experience in operational research techniques. He will undertake the review of cost effectiveness and development of the cost-effectiveness model.

Matt Stevenson, Operational Research Analyst, ScHARR: will supervise the development of the cost effectiveness model.

Anna Cantrell, Information Officer, ScHARR: has experience of undertaking literature searches for the ScHARR Technology Assessment Group systematic reviews and other external projects. She will develop the search strategy and undertake the electronic literature searches.

Edith Poku, Research Associate, ScHARR: will assist in the systematic reviewing of clinical effectiveness.

Andrea Shippam, Project Administrator: will assist in the retrieval of papers and in preparing and formatting the report.

Dr Navroz Masani, Consultant Cardiologist, Department of Cardiology, University Hospital of Wales, Heath Park, Cardiff CF14 4XW: will act as a clinical advisor.

Professor Gregory YH Lip, Consultant Cardiologist and Professor of Cardiovascular Medicine, University Department of Medicine, City Hospital, Birmingham B18 7QH: will act as a clinical advisor.

10. Appendices

Appendix 1 Draft search strategy

The search strategy below was developed on Medline (OVID), a similar search will be performed on the other databases.

Prevalence of pathology in Atrial Fibrillation patients

1. Atrial Fibrillation/
2. af.tw.
3. atrial fibrillation.tw.
4. or/1-3
5. Ventricular Dysfunction, Left/
6. Hypertrophy, Left Ventricular/
7. left ventricular impairment$.tw.
8. left ventricular hypertrophy.tw.
9. Cardiomyopathies/
10. heart valve problem$.tw.
11. "Heart Valve Diseases"/
12. Aortic Aneurysm/
13. aortic aneurysm.tw.
14. blood clot$.tw.
15. Pericarditis/
16. pericarditi$.tw.
17. Neoplasms/
18. tumour$.tw.
19. or/5-18
20. 4 and 19
21. exp Epidemiologic Studies/
22. exp Epidemiology/
23. epidemiology.tw.
24. exp Prevalence/
25. prevalence.ti.
26. exp Incidence/
27. incidence.ti.
28. or/21-27
29. 20 and 28

The above search combines terms for atrial fibrillation (1-3) with terms for the different pathologies that could occur in atrial fibrillation patients and can be identified by TTE (5-18) with terms to identify epidemiological studies.

Diagnostic Accuracy of Transthoracic Echocardiography

1. Atrial Fibrillation/
2. af.tw.
3. atrial fibrillation.tw.
4. or/1-3
5. Echocardiography/
6. echocardiograp$.tw.
7. transthoracic echocardiography.tw.
8. tte.tw.
9. or/5-8
10. 4 and 9
11. exp "Sensitivity and Specificity"/

12. sensitivity.tw.
13. specificity.tw.
14. ((pre-test or pretest) adj probability).tw.
15. post-test probability.tw.
16. predictive value$.tw.
17. likelihood ratio$.tw.
18. or/11-17
19. 10 and 18

The above search combines terms to describe atrial fibrillation (1-3) and terms to describe transthoracic echocardiography (5-8). The search is e combined with a search filters designed to retrieve diagnostic studies (11-17) to retrieve information on the diagnostic accuracy of transthoracic echocardiography.

Appendix 2 Draft data extraction

Forms to be adapted from the following

QUADAS (quality assessment of studies of diagnostic accuracy)[5]

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)[4]

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

11. References

1. National Collaborating Centre for Chronic Conditions NICE clinical guideline 36. Atrial fibrillation: national clinical guideline for management in primary and secondary care. 2006.

2. Patient UK website Echocardiography. *http://www.patient.co.uk/doctor/Echocardiography.htm* 2009.

3. Moher, David, Cook, Deborah J., Eastwood, Susan, Olkin, Ingram, Rennie, Drummond, and Stroup, Donna F. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. *The Lancet* 27-11-1999; **354** 1896-1900.

4. Elm, Erik von, Altman, Douglas G., Egger, Matthias, Pocock, Stuart J., Gotzsche, Peter C., Vandenbroucke, Jan P., and STROBE, Initiative Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 20-10-2007; **335** 806-808.

5. Whiting, Penny, Rutjes, Anne, Reitsma, Johannes, Bossuyt, Patrick, and Kleijnen, Jos The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology* 2003; **3** 25.

6. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, and Stoddart GL Critical assessment of economic evaluation. In: 'Methods for the economic evaluation of health care programmes'. 3rd edition. 2005.

7. McKenna, C., Palmer, S., Rodgers, M., Chambers, D., Hawkins, N., Golder, S., Van Hout, S., Pepper, C., Todd, D., and Woolacott, N. Cost-effectiveness of radiofrequency catheter ablation for the treatment of atrial fibrillation in the United Kingdom. *Heart* 1-4-2009; **95** 542-549.

8. Department of Health NHS reference costs 2007-08. 2009.

9. Curtis L Unit Costs of Health and Social Care. 2008.

10. BNF British National Formulary 57. 2009.

EME
HS&DR
HTA
PGfAR
PHR

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