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**Technology Assessment Report commissioned by the NIHR HTA Programme**

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

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**Rider on responsibility for report**

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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**1. DEFINITION OF TERMS AND LIST OF ABBREVIATIONS**

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

**Definition of technical terms**

|  |  |
| --- | --- |
| Anti-arrhythmic drugs | Pharmacological treatment to correct irregular heartbeats and slow rapid heartbeats |
| Anti-coagulant drugs | Pharmacological treatment to reduce risk of blood clotting |
| Arrhythmia | Abnormality of the normal heart rhythm |
| Atrial fibrillation (AF) | 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 AF | AF that spontaneously terminates within 7 days, usually within 48 hours |
| Permanent AF | Established AF that has not terminated, has terminated but recurred, or for which cardioversion has not been attempted |
| Persistent AF | AF that does not self-terminate, or lasts longer than 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 |

**Abbreviations**

|  |  |
| --- | --- |
| AF | Atrial fibrillation |
| AMI | Acute myocardial infarction |
| AV | Atrioventricular |
| BSE | British Society of Echocardiography |
| CABG | Coronary artery bypass graft |
| CAF | Chronic atrial fibrillation |
| CARAF | Canadian Registry of Atrial Fibrillation |
| CEAC | Cost-Effectiveness Acceptability Curves |
| CEAF | Cost-Effectiveness Acceptability Frontiers |
| CHADS2 | Cardiac Failure, Hypertension, Age, Diabetes, Stroke Doubled |
| CHA2DS2-VASc | Congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and sex category (female) |
| CHF | Congestive heart failure |
| CI | Confidence interval |
| CrI | Credible interval |
| CT | Computer tomography |
| DES | Discrete Event Simulation |
| DM | Diabetes mellitus |
| ECG | Electrocardiogram |
| ESC | European Society of Cardiology |
| FN | False Negative |
| FP | False Positive |
| GOS | Glasgow Outcome Scale |
| GP | General practitioner |
| HR | Hazard ratio |
| HRQoL | Health related quality of life |
| ICER | Incremental cost-effectiveness ratio |
| LAA | Left atrial appendage |
| LA ABN | left atrial abnormality |
| LV | Left ventricular |
| MAICERs | Maximum Acceptable Incremental Cost Effectiveness Ratios |
| MI | Myocardial infarction |
| MRI | Magnetic resonance imaging |
| mRS | Modified Rankin Scale |
| NICE | National Institute for Health and Clinical Excellence |
| NC | Not calculable |
| NCC-CC | National Collaborating Centre for Chronic Conditions |
| NR | Not reported |
| NSF | National Service Framework |
| OAC | Oral Anticoagulant |
| OXVASC | Oxford Vascular Study |
| PE | Pulmonary embolism |
| PSA | Probabilistic Sensitivity Analysis |
| PTCA | Percutaneous transluminal |
| QUADAS | Quality assessment of studies of diagnostic accuracy included in systematic reviews |
| QALY | Quality adjusted life year |
| RAA | Right atrial appendage |
| RCT | Randomised controlled trial |
| RE-LY | Randomized Evaluation of Long-Term Anticoagulation Therapy |
| RHC | Right heart catheterisation |
| RR | Relative risk |
| SD | Standard deviation |
| SF-36 | Short Form questionnaire-36 items |
| SPAF study | Stroke Prevention in Atrial Fibrillation study |
| SPARC study | Stroke Prevention Assessment of Risk in a Community study |
| SPINAF study | Stroke Prevention In Non-rheumatic Atrial Fibrillation study |
| STROBE | Strengthening the reporting of observational studies in epidemiology |
| TIA | Transient ischaemic attack |
| TOE | Transoesophageal echocardiography |
| TN | True Negative |
| TP | True Positive |
| TTE | Transthoracic echocardiography |
| USA | United States of America |
| UK | United Kingdom |

**2 EXECUTIVE SUMMARY**

**2.1 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. By undergoing echocardiography, cardiac abnormalities can be diagnosed earlier than would be possible if symptoms were left to develop. Currently, only selected patients with AF are recommended for TTE, those that have clinically suspected heart disease, or for whom further information is needed for treatment planning.

**2.2 Objectives**

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

**2.3 Methods**

Literature reviews were conducted on the diagnostic accuracy of TTE for clinically important pathologies in AF, and their prevalence in AF patients. MEDLINE searches, and eleven other databases for the prevalence review, were conducted from March to August 2010, and reference lists of relevant articles 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 only be of benefit where patient management was changed. It was assumed that if a left atrial abnormality (LA ABN) 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 LA ABN was incorporated in the model.

A total of 14 separate paired comparisons, comparing a baseline strategy not using TTE with a comparator strategy which 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.

**2.4 Results**

The literature reviews identified forty-four diagnostic accuracy studies, five prognostic studies and sixteen 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 or higher, with the exceptions of atrial thrombi, atrial septal defect and pulmonary embolism, for which sensitivity was lower. Prognostic studies indicated that TTE-diagnosed left ventricular (LV) dysfunction or increased left atrial (LA) diameter 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 and prognosis, however there were reported a significantly increased risk of thromboembolism with mild mitral regurgitation, in contrast with a significantly protective effect of severe mitral regurgitation 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 AF patients 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 CHADS2 score of one point, or whether to prescribe rivaroxaban to patients aged 65 years or above with a CHADS2 score of zero.

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.

**2.5 Discussion**

Diagnostic accuracy of TTE and prevalence of pathologies in AF patients, indicate that routine TTE following AF diagnosis would identify pathologies in many patients, particularly in 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 pulmonary embolism by lung scan and atrial thrombi and atrial septal hypertrophy by TOE, 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 CHADS2 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.

**2.6 Conclusion**

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

Where the CHADS2 tool is used the addition of TTE in identifying patients with LA ABN appears to be cost effective for informing some OAC 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.

**3 BACKGROUND**

**3.1 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. AF is characterised by uncoordinated atrial activation with consequent deterioration of atrial mechanical function.2

AF 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

AF is sometimes associated with other arrhythmias, most commonly atrial flutter or atrial tachycardias, but may occur by itself.3

AF is more common in older people, and at age 80–89 years, almost 9% of people have AF.1 With the aging population and increasing prevalence of chronic heart disease, AF has increased in frequency over the past few years. 2

**Types of AF**

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 thirty 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 recurrenton 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 they 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 AF**

AF 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 disease3 and with normal echocardiogram.2 This term is usually applied to younger patients with AF, that is under 60 years old.2 AF may be triggered by atrial flutter or by other atrial tachycardias.3

AF can be caused by other medical conditions, such as cardiovascular disease, diabetes mellitus, 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

AF occurring in the context of acute myocardial infarction (MI), cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism, 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.3,2 Examples of these causes include acute myocardial infarction, 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

AF is associated with atrial fibrosis and loss of atrial muscle mass.2 A co-existence of normal and fibrosed atrial fibres may explain non-homogeneity of conduction within the condition.2

On the electrocardiogram (ECG), AF is described by the absence of consistent P waves.1,3 Replacing consistent P waves on the electrocardiogram 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. A study of the Canadian Registry of Atrial Fibrillation (CARAF) found the probability of progression to chronic (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, left atrial enlargement, 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 which 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

AF 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 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 of Health and clinical Excellence (NICE) on AF define risk of stroke in AF patients as follows. High risk: previous ischaemic stroke or TIA or thromboembolic event, age≥75 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 with no high risk factors, or age<75 with hypertension, diabetes or vascular disease. Low risk: age <65 with no moderate or high risk factors.1

Several sets of clinical criteria have been proposed for stratifying risk of stroke in AF patients, including Atrial Fibrillation Investigators (AFI) criteria, Stroke Prevention in atrial fibrillation (SPAF) study criteria, and the CHADS2 score (Cardiac Failure, Hypertension, Age, Diabetes, Stroke, Doubled) which is a clinical prediction rule for estimating the risk of stroke in patients with non-rheumatic atrial fibrillation.2

European Society of Cardiology (ESC) 2010 guidelines recommend a risk factor-based approach for assessing stroke risk in patients with non-valvular AF based on CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and sex category (female).6 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, though not all, studies.2,7

Echocardiography may be useful in predicting the prognosis of AF. A retrospective study of pulmonary embolism (PE) in CAF identified TTE variables that were associated with acute PE or chronic thromboembolic pulmonary hypertension in AF as increased right ventricular dimension, higher tricuspid pressure gradient and shorter pulmonary artery acceleration time.8 CAF was also associated with PE in participants with significantly decreased left ventricular dimension and better left ventricular performance.8 A study of the Canadian Registry of Atrial Fibrillation (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 atrial fibrillation, in terms of overall survival, cardiac death and congestive heart failure.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

TOE has also been used to predict prognosis in AF patients.11,12,12

Providencia et al 201113 investigated TTE and TOE in combination with the CHADS2 and CHA2DS2-VASc scores as means of improving risk stratification for thromboembolic events in a cohort of AF patients. They found that TTE diagnosed LV systolic function and LA area measurement may provide a valuable addition to CHADS2 and CHA2DS2-VASc scores.13

**Measurement of AF**

NICE published guidelines on the management of atrial fibrillation 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 less than 24 hours apart, or by an event recorder ECG where symptomatic episodes are more than 24 hours apart.1

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

Regular 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

AF 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 AF**

AF is a common cardiac arrhythmia associated with a substantial degree of morbidity and mortality.14 On average, atrial fibrillation is present in 1-2% of the population.15,16 Epidemiological data has often been 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 atrial fibrillation diagnosis.15 However, two large studies with lengthy follow-up periods, the Framingham Heart Study in the U.S19 and the Renfrew Paisley study16 in the west of Scotland have been notable sources of incidence data. Data from the Framingham Heart Study, showed that two-yearly incidence rates were estimated at 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 were 0.44 per 1000 person-years and 1.31 per 1000 person-years for women and men aged 55 to 64 years.16 Data from the Framingham study showed that men were 1.5 times more likely to develop AF than women.

AF affects approximately 6 million people in Europe and 2.3 million of the U.S. 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 to 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 have demonstrated that atrial fibrillation is more common in those aged 50 years and over: reported rates in 50- to 59- year olds and those aged between 80-89 years were 0.5% and 8.8% respectively.23 Atrial fibrillation 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 to 90 years of age is close to 9%.20 and this trend is often reported15,20,25 Factors influencing this include the increasingly ageing population and the greater proportion of patients with 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 AF**

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

AF 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 4- to 5-fold rise in the risk of stroke in patients with AF.14 The observed increase in risk has been attributed to the presence of left ventricular hypertrophy which is often associated with long-standing AF. 27The 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, AF patients with underlying coronary heart disease and chronic lung disease are more likely to suffer from myocardial infarction and acute respiratory failure.29 Evidence from a longitudinal cohort study has also suggested an increased risk of dementia in patients with AF.30

AF is also associated with an increase in mortality rate. In the Framingham study, 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 U.K.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 atrial fibrillation in 1995 showed that an estimated 244 million pounds which accounted for 0.62% of the total National Health Service (NHS) budget was spent on AFpatients.35 Of this, half of the cost covered the hospitalisation of patients whilst 20% of the total expenditure was for the cost of drug prescriptions. An extra 46.4 million pounds 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 will be approximately 459 million pounds in the year 2000.35

**3.2 Current service provision**

The setting for management may vary depending on the nature and the severity of the condition1,36 (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 AF**

Key guidance documents for the care of patients with atrial fibrillation have been developed by the European Society of Cardiology6, American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA)2,37, the National Institute for Health and Clinical Excellence1 and the National Service Framework committee36 Recommendations within these guidelines emphasize 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 An ECG is also recommended in patients with documented AF.2 The number and duration of ECG monitoring 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 anti-arrhythmic 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 anti-arrhythmic and anti-thrombotic 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, while rate-control treatment is the choice of the 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. (Fuster 20112) 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) (Van Gelder 201038). 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. (Van Gelder 201038). Rate control involves drug therapy with a beta-blocker (e.g. metoprolol), a calcium channel blocker (e.g. verapamil) or a cardiac glycoside (e.g. digoxin). 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 congestive heart failure, patients with AF secondary to a treated or corrected precipitant, or younger patients.1 For persistent AF patients, 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 co-existing underlying structural cardiac abnormalities.1 Antiarrythmic drug therapy usually includes a standard beta-blocker, unless this ineffective or contraindicated. In this case, alternatives such as flecainide, propafenone or sotalol or amiodarone 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, left ventricular dysfunction, valvular or ischaemic heart disease, a systolic blood pressure >100 mmHg and a resting heart rate above 70 beats per minute.1 A rhythm control strategy may also be used for post-operative 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 hour-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 cardiversion.1

Ablation strategies are indicated for AF patients who remain symptomatic following anti-arrhythmic medication or those for whom pharmacological treatment is contraindicated because of intolerance or existing co-morbidity.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 atrioventriclar (AV) node, left atrium, right atrium or the focal pulmonary vein. Various energy sources including ultrasound, microwave, radiofrequency, microwave, 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. While a number of pacing algorithms and techniques exist, the role of permanent pacing in AF patients is still uncertain (AHA, 200544).

Antithrombotic therapy may additionally be given to patients with AF in accordance with risk of stroke. The 2006 recommendations from the National Collaborating Centre for Chronic Conditions 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 anti-platelet 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 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 with no high risk factors, or age<75 with hypertension, diabetes or vascular disease.
* Low risk: age <65 with no moderate or high risk factors

The 2006 NICE guidelines recommend use of warfarin for patients at high risk, and some patients at moderate risk, of stroke.1,2 NICE have recently approved both dabigatran etexilate and rivaroxaban as alternatives for the prevention of stroke in people with atrial fibrillation45,46 last accessed January 2012.47)

ESC 2010 guidelines recommend a risk factor-based approach for patients with non-valvular

AF based on CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and sex category (female).6 Valvular AF is considered high risk for stroke.6

CHA2DS2-VASc uses a point system in which two points are allocated where a patients has a history of stroke or TIA, or age ≥75. One point is allocated for each of the following, age 65–74 years, a history of hypertension, diabetes, recent cardiac failure, vascular disease comprising myocardial infarction, complex aortic plaque, or peripheral arterial disease (PAD), and female sex. ESC 2010 guidelines recommend oral anti-coagulant for AF patients with a CHA2DS2-VASc score of 2 or more, oral-anticoagulant or aspirin for those with a score of 1, and either no antithrombotic therapy or aspirin for those with a score of zero. 6 Where oral anti-coagulation is prescribed, this is generally a vitamin K agonist adjusted for INR range 2.0 to 3.0 (target 2.5).6

Alternative new oral anti-coagulants, the oral direct thrombin inhibitors (e.g. dabigatran etexilate and AZD0837) and the oral factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, betrixaban, YM150, are described in the 2010 ESC guidelines 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 under15 mL/min) or advanced liver disease (impaired baseline clotting function).48

**Current service cost and anticipated costs associated with intervention**

The 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 (include Congenital, Transoesophageal and Foetal 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.

**3.3 Description of TTE**

**Summary of Intervention**

***Aim of transthoracic echocardiography (TTE)***

Transthoracic echocardiography (TTE) 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 (TTE)***

The standard adult transthoracic echocardiogram measures structure and function of the heart. It should reliably describe and quantitative left ventricular systolic and diastolic function, assess all valves including minor abnormalities that may progress or need follow up, basic prosthetic valve function, common congenital abnormalities and cardiomyopathies, and detect 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. Left ventricular (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 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 estimating 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

TTE 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 2-D 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 provides 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. (2005).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 for Echocardiography,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, pre-operative echocardiography for elective and semi-urgent surgery.

Various guidelines for the use of TTE for all indications have been reported in recent years. The British Society of Echocardiography50, provide details of the clinical indications for echocardiography. The Bedfordshire and Hertfordshire Cardiac Network49 describe the effective use of transthoracic Echocardiography (TTE) in adults for indications including heart murmur and palpitations, and the National Imaging Board52 provide 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***

TTE is a non-invasive imaging technique performed with the use of an ultrasound machine. It provides real-time images, is portable and 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, British Society of Echocardiography (BSE) accredited echocardiographer or general practitioner with special interests.1

**Current usage in the NHS**

A prospective survey of the management of atrial fibrillation in the European Society of Cardiology member countries conducted in 2005, showed that 78% (n=757) of patients with first detected atrial fibrillation 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 left ventricular dysfunction or valve disease.

NICE guidelines 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.

**3.4 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 and false negatives. 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

**4 DEFINITION OF THE DECISION PROBLEM**

**4.1 Decision problem**

The purpose of the assessment was to 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?”

The population was newly diagnosed AF patients.

Potential subgroups identified prior to the review were 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; or patients receiving diagnoses of paroxysmal, persistent or permanent AF. Lack of data made analyses of these subgroups impractical.

The technology investigated was transthoracic echocardiography (TTE).

Conventional transthoracic echocardiography (TTE) was the intervention. Included modes were M-mode, two-dimensional/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, intra-operative echocardiography. These would not form the routine TTE. Invasive modes, such as contrast TTE requiring application of dobutamine or adenosine, and would have 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 AF patients. 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 AF patients 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 CHADS2 or CHA2DS2-VASC score of zero). In such a group the use of TTE could detect underlying conditions that are associated with a high risk of stroke and in whom the use of anticoagulant treatment would be recommended.

Outcomes sought related to selected pathologies in AF patients identifiable by TTE. Clinical outcome measures were diagnostic accuracy of TTE in identifying pathologies as measured in terms of sensitivity (proportion of true positives) and specificity (proportion of true negatives) and prognosis of AF populations based on diagnosis of pathology by TTE, and prevalence of these pathologies in AF.

**4.2 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;

to investigate, by systematic review, the prevalence of these pathologies;

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.

**5 ASSESSMENT OF CLINICAL EFFECTIVENESS**

**5.1 Methods for reviewing clinical effectiveness**

The purpose of the assessment report was to assess the effectiveness of performing a routine echocardiogram in all newly diagnosed atrial fibrillation (AF) patients in enabling appropriate treated for patients based on diagnoses of pathologies from TTE. As no clinical studies screening AF patients 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 newly diagnosed AF patients. These were reviews of:

1) diagnostic accuracy of TTE for clinically relevant pathologies in AF patients (section 5.1.2);

2) prevalence of clinically relevant pathologies within the AF population (section 5.1.3).

*5.1.1 Clinically relevant pathologies*

In order for routine TTE screening of newly diagnosed AF patients 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 section 3.4.

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

Inclusion:

1) the pathology could occur in AF patients;

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 the defects 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 pulmonary embolism 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 left ventricular non-compaction.

7) Heart failure

This category comprised congestive heart failure, left ventricular dysfunction or impairment, left atrial enlargement and right ventricular 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.

*5.1.2 Methods for diagnostic accuracy review*

5.1.2.1 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 in section 5.1.1.

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

5.1.2.2 Inclusion and exclusion criteria

**Inclusion**

Population

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

Intervention

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

Comparators

Included comparators were diagnostic techniques appropriate for the selected pathology and included were autopsy, surgery, cardiac catheterisation, transoesophageal echocardiography (TOE), computer tomography (CT), magnetic resonance imaging (MRI).

Outcomes

Included outcomes were the diagnostic accuracy of TTE for each pathology in terms of sensitivity (proportion of true positives), or specificity (proportion of true negatives). 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 true positives divided by the sum of true positives and false negatives. Specificity is calculated as the number of true negatives divided by the sum of true negatives and false positives.

Prognostic accuracy was also included, that is, 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 section 5.1.1) were sought.

For each pathology, we initially sought studies of diagnostic accuracy with a population of atrial fibrillation patients. Where sensitivity or specificity data were lacking from studies of atrial fibrillation 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 which do not compare with a reference standard. For studies of atrial fibrillation patients, study types of any of the four levels were included.

Prognostic accuracy studies were sought. For these, studies with a population of atrial fibrillation 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 were sought.57 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, where 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, intra-operative 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), 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, opinion pieces.

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

5.1.2.3 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 true positives divided by the sum of the number of true positives and the number of false negatives. Specificity was calculated as the number of true negatives divided by the sum of the number of true negatives and the number of false positives. Where possible, confidence intervals were calculated based on the Gaussian formula from Newcombe58, p ± 1.96 × √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 section 5.1.2.2).

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.

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

5.1.3.1 Identification of studies

A comprehensive search was undertaken to systematically identify clinical effectiveness literature concerning the prevalence of clinically important pathologies in AF patients. 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; 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 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. 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.

5.1.3.2 Inclusion and exclusion criteria

**Inclusion**

Population

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

Study types

Epidemiological studies of prevalence of selected pathologies (see section 5.1.1 for pathologies) were sought.

Outcome

Prevalence of selected pathologies (see section 5.1.1 for selected pathologies).

**Exclusion**

The following publication types were excluded: animal studies, editorials, opinion pieces, studies only published in languages other than English, 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.

5.1.3.3 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 in Appendix 6. Quality assessment forms are in Appendix 7.

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

**5.2 Results**

*5.2.1 Diagnostic accuracy of TTE for clinically relevant pathologies*

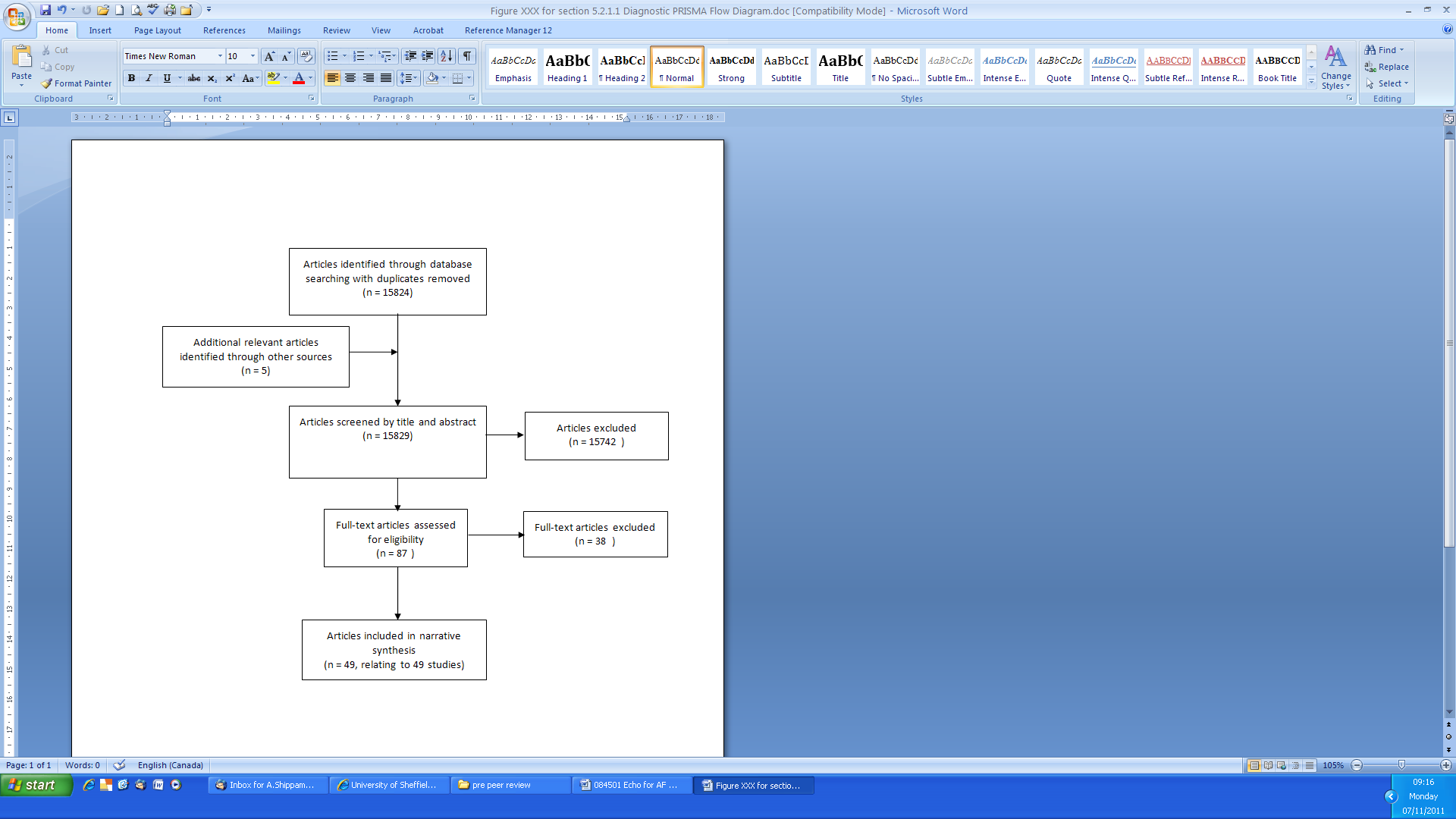
5.2.1.1 Quantity and quality of research available

The literature search yielded 15824 article citations when duplicates had been removed. Figure 1 shows study selection, in a modified version of the PRISMA 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 and 5 prognostic studies 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.

**Figure 1: Study selection for diagnostic review**



**Table 1: Summary of diagnostic accuracy studies**

| Study | Category of pathology | Number of participants enrolled in study | Population AF | Type of TTE | Percentage usable TTE images |
| --- | --- | --- | --- | --- | --- |
| Acar et al 199162 | Ischaemia/thrombosis | 581 | 44.9% AF | 2D TTE | 100 |
| Arques et al 200563 | Heart failure | 40 | 0% | TTE colour M-mode Doppler | 98 |
| Attenhofer Jost et al 200064 | Structural defect and Valvular heart disease | 100 | NR (all had heart murmur) | TTE 2D and continuous wave Doppler | 100 |
| Barron 1988 et al65 | Valvular heart disease | 140 | NR | 2D and Doppler TTE | 100 |
| Bova et al 200366 | Pulmonary disease | 162 | NR | TTE continuous wave Doppler | 97 |
| Casella et al 200967 | Endocarditis | 75 | NR | harmonic imaging TTE | 100 (81.5% good image quality) |
| Cassidy et al 199268 | 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 198970 | Disease of arteries | 555 | NR | TTE | 100 |
| Erbel et al 198471 | Heart failure | 110 | 0% | 2d echocardiography | 100 |
| Grossmann 200272 | Valvular heart disease | 68 | 25% AF | colour Doppler TTE | 100 |
| Groves et al 200473 | Valvular heart disease | 61 | NR | TTE | 100 (selected for having usable data) |
| Guyer et al 198474 | Valvular heart disease | 38 | 82% AF | 2D TTE | 100 (selected for having usable data) |
| Helmcke et al 198775 | Valvular heart disease | 160 | 21% AF | colour Doppler echo | 92 |
| Jassal et al 200776 | Endocarditis | 36 | NR | Harmonic imaging TTE | 100 (17% indeterminate diagnosis but included in analysis) |
| Kaymaz et al 200177 | Ischaemia/thrombosis | 474 | 56.3% AF at time of study | TTE | 100 |
| Kishon et al 199378 | 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 199779 | Ischaemia/thrombosis | 70 | 100% chronic AF | TTE M-mode, 2D and pulsed and colour Doppler | 100 (10% technically inadequate but included in analysis) |
| Lanzarini et al 200580 | Pulmonary disease | 86 | 13% controlled AF | TTE Standard M-mode, 2-dimensional and pulsed and continuous wave Doppler | 100 |
| Maestre et al 200981 | Heart failure | 216 | NR | mode M 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 199383 | Disease of arteries | 110 | NR | colour, Doppler TTE | 100 |
| Nienaber et al 199484 | Disease of arteries | 35 | NR | M-mode, 2D, Doppler TTE | 100 |
| Okura et al 200685 | Cardiomyopathy | 52 | NR | TTE (2D and Doppler) | 85 |
| Pochis et al 199286 | Structural defect | 116 | 53% atrial fibrillation or flutter, or paroxysmal atrial tachycardia | TTE | 92 |
| Reichek et al 198187 | Heart failure | 34 | NR | m-mode echocardiography | 100 |
| Reichlin et al 200488 | Valvular heart disease | 203 | NR (all had heart murmur) | 2-colour Doppler TTE (gold standard comparator) | 100 |
| Roudat et al 198889 | Disease of arteries | 673 | NR | TTE 2D, M-mode | 98 |
| Saraste et al 200590 | Ischaemia/thrombosis | 84 | 4% chronic AF | Doppler TTE, colour and 2D. | 100 |
| Sharifi et al 200391 | Ischaemia/thrombosis | 112 | 100% AF (24% chronic AF) | TTE | 100 (patients selected from group with usable TTE) |
| Sharma et al 199292 | Structural defect | 53 | NR | TTE M-mode (pulsed and continuous wave Doppler and colour flow only available for some patients) | 85 |
| Sheiban et al 198793 | Cardiac masses | 77 | NR | 2D TTE | 100 |
| Shively et al 199194 | Endocarditis | 62 | NR | TTE 2D, M-mode and Doppler colour | 100 (at least 68% good quality) |
| Shrestha et al 198395 | Ischaemia/thrombosis | 293 | 88% patients with thrombus A,F NR whole population | 2D TTE | 100 |
| Shub et al 198396 | Structural defect | 171 | NR | TTE 2D, pulsed Doppler | 95 |
| Shyu et al 199297 | Structural defect | 60 | 77% AF | 2D and colour TTE | 100 |
| Smith et al 198598 | Structural defect | 12 | NR (all post AMI) | cross-sectional Doppler echo | 100 |
| Sparrow et al 200399 | Heart failure | 737 | NR | TTE | 87 |
| Stratton et al 1982100 | Ischaemia/thrombosis | 88 | some AF, percent NR | 2D TTE | 89 |
| Veyrat et al 1983101 | Valvular heart disease | 95 | 40% AF | pulsed Doppler echo | 100 |
| Vigna et al 1993102 | Ischaemia/thrombosis | 59 | 59% in AF at time of study | TTE colour Doppler | 100 |
| Wong et al 1983103 | Valvular heart disease | 113 | NR | 2D echocardiography | 100 |
| Zanolla et al 1982104 | Valvular heart disease | 43 | NR | 2D echocardiography | 100 |
| Zotz et al 1993105 | Structural defect | 17 (16 for colour Doppler) | NR (all post AMI) | Colour Doppler TTE | 100 |

Of the 44 included studies, there were 17 studies that included atrial fibrillation patients in the population, Acar et al 199162, Dittmann et al 198769, Grossmann et al 200272, Guyer et al 198474, Helmcke et al 198775, Kaymaz et al 200177, Kitayama et al 199779, Lanzarini et al 200580, Mugge et al 199582, Pochis et al 199286, Saraste et al 200590, Sharifi et al 200391, Shrestha et al 198395, Shyu et al 199297, Stratton et al 1982100, Veyrat et al 1983101, Vigna et al 1993.102 Of these, for two studies all participants had AF, Kitayama et al 199779 and Sharifi et al 2003.91 While two studies stated that there were no AF patients in the population, Arques et al 200563 and Erbel et al 198471, 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.

TTE methods 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.

**Table 2: Summary of prognostic studies**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study | Category of pathology | Number of participants | Population AF | Prospective or retrospective | Follow-up | Type of TTE |
| Atrial Fibrillation Investigators 1998106 | Heart failure and Valvular heart disease | 1010 | non-valvular AF | Prospective | mean 1.6 years | TTE 2D, M-mode |
| Klem et al 2003107 | Heart failure and Valvular heart disease | 409 | non-rheumatic AF | Prospective | mean 9.6 years | TTE |
| Miyaska et al 2000108 | Valvular heart disease | 173 | non-rheumatic AF | Retrospective | NA | TTE 2D, M-mode |
| Nakagami et al 1998109 | 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 1992110 | Heart failure and Valvular heart disease | 568 | non-rheumatic AF | Prospective | mean 1.3 years | M-mode and 2D and Doppler |

All five included prognostic accuracy studies 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, Atrial Fibrillation Investigators 1998106, Klem et al 2003107, The Stroke Prevention in Atrial Fibrillation Investigators 1992110, with follow-up ranging from mean 1.3 to 9.6 years. Two of the studies, Miyaska et al 2000108, Nakagami et al 1998109, were retrospective. 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 al57, studies ranged from level 2 (higher quality) to level 3c (lower quality). Twelve studies were of level 2, a study of test accuracy with an independent, blinded comparison with a reference standard among consecutive patients, and these were the studies Attenhofer Jost,64 Barron et al.,65 Bova,66 Casella,67 Jassal,76 Lanzarini,80 Maestre,81 Nienaber,83 Reichlin,88 Sharifi,91 Shively94 and Vigna.102 Six of the studies were level 3a, that is they differed from level 2 only in being among non-consecutive patients, Cassidy,68 Groves,73 Guyer,74 Nienaber,84 Sparrow,99 and Wong.103 Twenty-two of the studies were level 3b, comparisons with a reference standard that didn’t meet criteria for higher levels of evidence, Acar J et al.,62 Dittmann,69 Erbel,71 Grossmann,72 Kaymaz,77 Kishon,78 Kitayama,79 Mugge,82 Okura,85 Pochis,86 Reichek,87 Roudaut,89 Saraste,90 Sharma,92 Sheiban,93 Shrestha,95 Shub,96 Smith,98 Stratton,100 Veyrat,101 Zanolla104 and Zotz.105 There were four diagnostic case-control studies, level 3c, Arques,63 Enia75 and Shyu.97

Considering only diagnostic accuracy studies with AF populations there were three level 2 studies Lanzarini,80 Sharifi,91 Vigna,102 one level 3a study Guyer;74 eleven level 3b studies Acar J et al,62 Dittmann,69 Grossmann,72 Kaymaz,77 Kitayama,79 Mugge,82 Pochis,86 Saraste,90 Shrestha,95 Stratton,100 Veyrat;101 and two level 3c studies Helmcke,75 Shyu.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, a prospective cohort study, Klem.107 Two studies were level 3b, analyses of prognostic factors in patients from a single arm of a randomised trial, Atrial Fibrillation Investigators106 and The Stroke Prevention in Atrial Fibrillation Investigators.110 Two studies were level 3c, retrospective cohort studies, Miyaska108 and Nakagami.109

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 AF patients, and so an AF population, while 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 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 poorer images in analysis, Dittmann,69 Jassal,76 Kishon,78 Kitayama,79 Shively,94 or provide separate analyses by the inclusion or exclusion of poor image quality TTE, Casella.67

5.2.1.2 Diagnostic accuracy results

Eight studies 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 hypertrophy86 to 1 for ostium primum atrial septal defect96 or ventricular septal rupture.98 Two studies reported specificity which ranged from 0.9 for rupture of chordae tendineae97 to 0.909 for atrial septal hypertrophy.86 Six of the eight studies used catheterisation, surgery or autopsy as the comparator diagnostic test, while one used clinical cardiac exam, and one used TOE, Table 3.

**Table 3: Structural defect**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Pathology | Number of patients analysed | Population AF | Intervention | Comparator diagnostic test | Sensitivity of TTE | Specificity of TTE |
| Attenhofer Jost et al 200064 | Ventricular septal defect | 100 | NR (heart murmur 100%) | TTE | Clinical cardiac exam | TTE as gold standard (presumed sensitivity=1) | TTE as gold standard (presumed specificity=1) |
| Kishon et al 199378 | Ventricular septal defect | 40 | NR (new systolic murmur in 68%) | TTE | Surgery or autopsy | 0.68 (95%CI 0.53-0.82) (if include suspected by TTE then 0.775) | NC |
| Kishon et al 199378 | Rupture of papillary muscle | 22 | NR (new systolic murmur in 100%) | TTE | Surgery or autopsy | 0.46 (95%CI 0.25-0.66) (0.727 if include suspected by TTE) | NC |
| Pochis et al 199286 | Atrial septal hypertrophy | 107 | 53% atrial fibrillation or flutter, or paroxysmal atrial tachycardia | TTE | TOE | 0.25 (95%CI 0.17-0.33) | 0.91 (95%CI 0.85-0.96) |
| Sharma et al 199292 | Atrial septal defect, sinus venosus defect | 45 | NR | TTE | Catheterisation | 0.62 (95%CI 0.48-0.76) | NC |
| Shub et al 198396 | Atrial septal defect, ostium secundum | 105 | NR | TTE | Catheterisation or surgery | 0.89 (95%CI 0.82-0.95) | NC |
| Shub et al 198396 | Atrial septal defect, ostium primum | 32 | NR | TTE | Catheterisation or surgery | 1 | NC |
| Shub et al 198396 | Atrial septal defect, sinus venosus | 16 | NR | TTE | Catheterisation or surgery | 0.434 (95%CI 0.19-0.68) | NC |
| Shyu et al 199297 | Rupture of chordae tendineae | 60 | 77% AF | TTE | Catheterisation or (valve repair) surgery | 0.65 (95%CI 0.53-0.77) | 0.9 (95%CI 0.82-0.98) |
| Smith et al 198598 | Ventricular septal rupture | 12 | NR (all post AMI) | TTE | Catheterisation or autopsy | 1 | NC |
| Zotz et al 1993105 | Ventricular septal rupture | 17 (16 for colour Doppler) | NR (all post AMI) | TTE | Surgery or autopsy | 0.71 (95%CI 0.49-0.92) (if TTE using only conventional view 0.235); by colour Doppler 0.938 | NC |

NC = not calculable, NR=not reported

Nine studies reported diagnostic accuracy of TTE in ischaemic heart disease, Table 4. Sensitivity ranged from 0 for right atrial (RA)79 or left atrial appendage (LAA)102 thrombus to 0.955 for thrombosis of ventricle.100 Specificity ranged from 0.857 for thrombosis of ventricle100 to 1 for left atrial (LA)79 or RA79 thrombus. Five of the studies used surgery or angiography, three used TOE and one used CT as comparators, Table 4.

**Table 4: Ischaemia/thrombosis**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Pathology | Number of patients analysed | Population AF | Intervention | Comparator diagnostic test | Sensitivity of TTE | Specificity of TTE |
| Acar et al 199162 | Left atrial thrombus | 581 | 44.9% AF | TTE | Surgery | 0.28 (95%CI 0.24-0.32) (LA body 0.65, LAA 0.04) | 0.99 ((95%CI 0.99-1.0) |
| Kaymaz et al 200177 | Left atrial thrombus | 474 | 56.3% AF at time of study | TTE | Surgery | 0.32 (95%CI 0.28-0.37) | 0.94 (95%CI 0.91-0.96) |
| Kitayama et al 199779 | Left atrial thrombus | 70 | 100% chronic AF | TTE | CT | 0.67 (95%CI 0.55-0.78) | 1 |
| Kitayama et al 199779 | Right atrial thrombus | 70 | 100% chronic AF | TTE | CT | 0 | 1 |
| Mugge et al 199582 | Atrial septal aneurysm | 195 | 14.4% in AF | TTE | TOE | 0.47 (95%CI 0.41-0.53) | NC |
| Saraste et al 200590 | Coronary artery stenosis (significant stenosis/occlusion in any coronary artery) | 84 | 4% chronic AF | TTE | Angiography | 0.82 (95%CI 0.74-0.90) | 0.92 (95%CI 0.86-0.98) |
| Sharifi et al 200391 | Atrial thrombi | 112 | 100% AF (24% CAF) | TTE | TOE | 0.17 (95%CI 0.09-0.24) (if include SEC as well as thrombus 0.714) | 1 (if include SEC as well as thrombus 1) |
| Shrestha et al 198395 | Left atrial thrombus | 293 | NR whole population, 88% patients with thrombus | TTE | Surgery | 0.59 (95%CI 0.53-0. 64) (LA body 0.750, LAA 0.000) | 0.99 (95%CI 0.97-1.0) |
| Stratton et al 1982100 | Thrombosis of ventricle | 78 | some AF, percent NR | TTE | Surgery or indium-111platelet imaging | 0.86 (95%CI 0.79-0.94) (0.955 if include equivocal diagnoses) | 0.95 (95%CI 0.90-0.99) (0.857 if include equivocal diagnoses) |
| Vigna et al 1993102 | Left atrial thrombus | 59 | 59% in AF at time of study | TTE | TOE | 0.33 (95%CI 0.21-0.45) (LA body 0.44, LAA 0.00) | 1 |

NR=not reported, LAA=left atrial appendage

Two studies reported diagnostic accuracy of TTE in pulmonary disease, Table 5. Sensitivity ranged from 0.523 for pulmonary embolism66 to 1 for pulmonary hypertension.80 Specificity ranged from 0.6 to 1 for pulmonary hypertension.80 The study of pulmonary embolism used perfusion lung scan with radiography or pulmonary angiography as a comparator, whereas the study of pulmonary hypertension used catheterisation, Table 5.

**Table 5: Pulmonary disease**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Pathology | Number of patients analysed | Population AF | Intervention | Comparator diagnostic test | Sensitivity of TTE | Specificity of TTE |
| Bova et al 200366 | Pulmonary embolism | 152 | NR | TTE | Perfusion lung scan with radiography, or pulmonary angiography | 0.52 (95%CI 0.44-0.60) | 0.87 (95%CI 0.82-0.93) |
| Lanzarini et al 200580 | Pulmonary hypertension | 86 | 13% controlled AF | TTE | Catheterisation | 1 using PAPd/TR; 0.88 using PAPs | 0.6 using PAPd/TR; 1 using PAPs |

Three studies reported diagnostic accuracy of TTE in endocarditis, Table 6. Sensitivity ranged from 0.4494 to 0.871.67 Specificity ranged from 0.61567 to 0.98.94 Two of the studies used TOE as a comparator, whereas the other study used information obtained from clinical follow-up, Table 6.

**Table 6: Endocarditis**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Pathology | Number of patients analysed | Population AF | Intervention | Comparator diagnostic test | Sensitivity of TTE | Specificity of TTE |
| Casella et al 200967 | Native valve infective endocarditis | 75 | NR | TTE | TOE | 0.82(95%CI 0.65-0.93). If indeterminate images excluded (n=61) 0.871 (0.702-0.964) | 0.62 (95%CI 0.445-0.77). If indeterminate images excluded 0.857 (0.673-0.960) |
| Jassal et al 200776 | Native valve infective endocarditis | 36 | NR | TTE | TOE | 0.84 (95%CI 0.72-0.96) | 0.88 (95%CI 0.77-0.98) |
| Shively et al 199194 | Endocarditis | 66 episodes in 62 patients (4 patients referred twice) | NR | TTE | non-echocardiographic pathologic data from the subsequent clinical course | 0.44 (95%CI 0.32-0.56) | 0.98 (95%CI 0.95-1.0) |

Twelve studies reported diagnostic accuracy of TTE in valvular heart disease, Table 7. TTE was presumed gold standard for four studies of mitral regurgitation,64,68 aortic stenosis,64,68 mitral valve prolapse,64 valvular heart disease,64,88 aortic regurgitation,64,68 and tricuspid regurgitation.73 Sensitivity ranged from 0.222 for mitral stenosis leaflet calcification103 to 1 for mitral stenosis104 or mitral regurgitation75 or severe aortic regurgitation.69 Specificity ranged from 0.655 for mitral stenosis to 1 for aortic regurgitation or mitral regurgitation. Six of the studies used catheterisation/aortography or radiography/cinefluorograms as comparators, four of the studies used clinical exam, one used TOE and one used CT, Table 7.

**Table 7: Valvular heart disease**

| Study | Pathology | Number of patients analysed | Population AF | Intervention | Comparator diagnostic test | Sensitivity of TTE | Specificity of TTE |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Attenhofer Jost et al 200064 | Mitral regurgitation | 100 | NR (all had heart murmur) | TTE | Clinical cardiac exam | TTE as gold standard (presumed sensitivity = 1) | TTE as gold standard (presumed specificity = 1) |
| Attenhofer Jost et al 200064 | Aortic stenosis | 100 | NR (all had heart murmur) | TTE | Clinical cardiac exam | TTE as gold standard (presumed sensitivity = 1) | TTE as gold standard (presumed specificity=1) |
| Attenhofer Jost et al 200064 | Mitral valve prolapse | 100 | NR (all had heart murmur) | TTE | Clinical cardiac exam | TTE as gold standard (presumed sensitivity = 1) | TTE as gold standard (presumed specificity=1) |
| Attenhofer Jost et al 200064 | Valvular heart disease, aortic and mitral valve | 100 | NR (all had heart murmur) | TTE | Clinical cardiac exam | TTE as gold standard (presumed sensitivity = 1) | TTE as gold standard (presumed specificity=1) |
| Attenhofer Jost 200064 | Aortic regurgitation | 100 | NR (all had heart murmur) | TTE | Clinical cardiac exam | TTE as gold standard (presumed sensitivity = 1) | TTE as gold standard (presumed specificity=1) |
| Barron 1988 et al 65 | Mitral valve prolapse | 140 | NR | TTE | Auscultation | 0.47 (95%CI 0.39-0.55) | 0.90 (95%CI 0.85-0.95) |
| Cassidy et al 1992 68 | Mitral regurgitation | 37 | NR (all had systolic murmur) | TTE | Clinical cardiac exam | TTE as gold standard (presumed sensitivity = 1) | TTE as gold standard (presumed specificity=1) |
| Cassidy et al 1992 68 | Aortic regurgitation | 37 | NR (all had systolic murmur) | TTE | Clinical cardiac exam | TTE as gold standard (presumed sensitivity = 1) | TTE as gold standard (presumed specificity=1) |
| Cassidy 1992 68 | Aortic stenosis | 37 | NR (all had systolic murmur) | TTE | Clinical cardiac exam | TTE as gold standard (presumed sensitivity = 1) | TTE as gold standard (presumed specificity=1) |
| Dittmann et al 198769 | Aortic regurgitation | 55 | 38% AF | TTE | Aortography | pulsed Doppler 0.93 (95%CI 0.86-0.99) (0.87 mild or moderate; 1 severe AR), M-mode 0.62 | pulsed Doppler 1, M-mode 1 |
| Grossmann et al 200272 | Mitral regurgitation | 68 | 25% AF | TTE | TOE | 0.79 (95%CI 0.69-0.89) | 1 |
| Groves et al 200473 | Tricuspid regurgitation | 61 | NR | TTE | CT | TTE as gold standard (presumed sensitivity = 1) | TTE as gold standard (presumed specificity=1) |
| Guyer et al 198474 | Tricuspid stenosis | 38 | 82% AF | TTE | Catheterisation | 0.69 (95%CI 0.55-0.84) | 0.96 (95%CI 0.90-1.0) |
| Helmcke et al 198775 | Mitral regurgitation | 147 | 21% AF | TTE | Catheterisation | 1 | 1 |
| Reichlin et al 200488 | Valvular heart disease | 203 | NR (all had heart murmur) | TTE | Clinical cardiac exam (including auscultation) | TTE as gold standard (presumed sensitivity = 1) | TTE as gold standard (presumed specificity=1) |
| Veyrat et al 1983101 | Aortic regurgitation | 95 | 40% AF | TTE | Aortography | 0.95 (95%CI 0.89-1.0) | 1 |
| Wong et al 1983 103 | Aortic stenosis, calcification | 113 | NR | TTE | Cinefluorograms | 0.76 (95%CI 0.68-0.84) | 0.89 (95%CI 0.83-0.95) |
| Wong et al 1983 103 | Mitral stenosis, annulus calcification | 113 | NR | TTE | Cinefluorograms | 0.77 (95%CI 0.69-0.84) | 0.94 (95%CI 0.89-0.98) |
| Wong et al 1983 103 | Mitral stenosis, leaflet calcification | 113 | NR | TTE | Cineflourograms | 0.22 (95%CI 0.15-0.30) | 0.93 (95%CI 0.88-0.97) |
| Zanolla et al 1982 104 | Mitral stenosis | 43 | NR | TTE | Radiography | 1 | 0.66 (95%CI 0.51-0.80) |

One study reported the accuracy of TTE in differentiating between ischaemic and non-ischaemic cardiomyopathy, Table 8. This study reported a sensitivity of 0.77 and specificity of 0.77 for differentiating between ischaemic and non-ischaemic cardiomyopathy with a comparator of angiography.

**Table 8: Cardiomyopathy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Pathology | Number of patients analysed | Population AF | Intervention | Comparator diagnostic test | Sensitivity of TTE | Specificity of TTE |
| Okura et al 200685 | Cardiomyopathy, differentiating between ischaemic and non-ischaemic | 44 | NR | TTE | Angiography | 0.77 (95%CI 0.64-0.89) | 0.77 (95%CI 0.65-0.90) |

Five studies reported accuracy of TTE in the diagnosis of heart failure, Table 9. TTE was presumed the gold standard for two studies of congestive heart failure81 and left ventricular dysfunction.99 Sensitivity ranged from 0.737 for congestive heart failure63 to 0.93 for left ventricular hypertrophy.87 Specificity ranged from 0.75 for congestive heart failure63 to 1 for left ventricular dysfunction.71 Two of the studies used clinical diagnosis as comparators, two studies used radiography or catheterisation, and one used autopsy results, Table 9.

**Table 9: Heart failure**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Pathology | Number of patients analysed | Population AF | Intervention | Comparator diagnostic test | Sensitivity of TTE | Specificity of TTE |
| Arques et al 200563 | Congestive heart failure | 39 | 0% | TTE | Radiography and clinical signs | 0.74(95%CI 0.60-0.88) | 0.75 (95%CI 0.61-0.89 |
| Erbel et al 198471 | Left ventricular dysfunction, ejection fraction | 110 | 0% | TTE | Catheterisation - cineventriculograms | 0.81 (95%CI 0.73-0.88) | 1 |
| Maestre et al 2009 81 | Congestive heart failure | 216 | NR | TTE | Clinical criteria | TTE as gold standard (presumed sensitivity=1) | TTE as gold standard (presumed specificity=1) |
| Reichek et al 198187 | Left ventricular hypertrophy | 34 | NR | TTE | Autopsy | 0.93 (95%CI 0.84-1) | 0.95 (0.88-1) |
| Sparrow et al 200399 | Left ventricular dysfunction | 621 | NR | TTE | Clinical diagnosis | TTE as gold standard (presumed sensitivity=1) | TTE as gold standard (presumed specificity=1) |

Four studies reported diagnostic accuracy of TTE in aortic dissection, Table 10. Sensitivity ranged from 0.59383 to 0.953.89 Specificity ranged from 0.50889 to 0.977.89 Three studies included surgery or autopsy or angiography as comparators, the other study used aortography, Table 10.

**Table 10: Diseases of arteries**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Pathology | Number of patients analysed | Population AF | Intervention | Comparator diagnostic test | Sensitivity of TTE | Specificity of TTE |
| Enia et al 198970 | Aortic dissection | 555 | NR | TTE | Aortography | 0.92 (95%CI 0.89-0.94) | 0.71 (95%CI 0.68-0.75) |
| Nienaber et al 199484 | Aortic dissection | 35 | NR | TTE | Surgery, autopsy or angiography | 0.77 (95%CI 0.63-0.91) | 0.67 (95%CI 0.51-0.82) |
| Nienaber et al 199383 | Aortic dissection, thoracic | 110 | NR | TTE | Surgery, autopsy or angiography | 0.59 (95%CI 0.51-0.69) | 0.83 (95%CI 0.76-0.90) |
| Roudat et al 198889 | Aortic dissection | 660 | NR | TTE | Surgery, autopsy or angiography or CT | 0.95 (95%CI 0.94-0.97) using dilatation of segment of aorta(0.758 using abnormal linear image in lumen) | 0.51 (95%CI 0.47-0.55) using dilatation of segment of aorta( 0.977 using abnormal linear image in lumen) |

One study reported the diagnostic accuracy of TTE for intra-cardiac masses, Table 11. This study reported sensitivity 0.882 and specificity 0.953, with a comparator of surgery.93

**Table 11: Tumours or cardiac masses**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Pathology | Number of patients analysed | Population AF | Intervention | Comparator diagnostic test | Sensitivity of TTE | Specificity of TTE |
| Sheiban et al 198793 | Intracardiac masses | 77 | NR | TTE | Surgery | 0.88 (95%CI 0.81-0.95) | 0.95 (95%CI 0.91-1.0) |

5.2.1.3 Prognostic study results

Five studies reported prognosis based on TTE diagnosed pathologies in AF populations.

The pathologies were left atrial diameter; mitral annular calcification; mitral valve prolapse; global, moderate to severe or reduced left ventricular systolic dysfunction; any or severe mitral regurgitation; valvular abnormality, Table 12.

Prognosis was investigated by studies for the types of valvular heart disease, mitral annular calcification, mitral valve prolapse, mitral regurgitation and valvular abnormality. Mitral annular calcification was non-significantly associated with thromboembolism by age adjusted analysis relative risk (RR) 0.6 (95%CI 0.2-1.5) p>0.2.110 Mitral valve prolapse had a non-significant association with risk of stroke unadjusted RR 0.29 p = 0.22.106 For mitral regurgitation, grade 1 mitral regurgitation (compared with no MR) OR (odds ratio) 2.689 (95%CI 1.039–7.189) p=0.0434 significantly associated with history of thromboembolic events.108 Severe mitral regurgitation had a non-significant association with risk of stroke (relative to none or mild MR) unadjusted RR 1.7 p = 0.59106, 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, age) 109, and was non-significantly associated with thromboembolism by age adjusted analysis RR 0.4 (95%CI 0.1-3.0) p>0.2.110 For mitral regurgitation, the retrospective studies108 109 found significant associations with prognosis, whereas the prospective studies had non-significant results. Any detected valvular abnormalities had a reported HR for mortality, diabetics 2.05 (95%CI 1.10–3.82) p=0.0229, non-diabetics HR 1.88 (95%CI 1.30–2.70) p=0.0007.107 For this study, diabetics and non-diabetic groups differed in that diabetics were older and had higher co-morbidity 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 1.02/mm (95%CI 0.99-1.06) p = 0.10106, and was reported to have 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).109 Left atrial diameter (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, diabetics 1.01 (95%CI 0.97–1.05) p=0.6445, HR non-diabetics 1.06 (95%CI 1.03–1.08) p<0.0001.107 Moderate to severe left ventricular 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, diabetics 1.52 (95%CI 0.85–2.70) p=0.1598, HR non-diabetics 2.28 (95%CI 1.58-3.29) p<0.0001.107

**Table 12: Prognosis based on TTE diagnosed pathologies in AF**

| Study | Pathology | Number of participants | Population AF | Follow-up | Results |
| --- | --- | --- | --- | --- | --- |
| Atrial Fibrillation Investigators 1998 106 | Moderate to severe left ventricular 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 3.04 p<0.001, multivariate analysis RR 2.5 (95%CI 1.5-4.4) p<0.001 (multivariate analysis includes age, previous stroke/TIA, history of diabetes, history of heart failure, history of hypertension) |
| Atrial Fibrillation Investigators 1998 106 | Left atrial diameter | 1003 | non-valvular AF | mean 1.6 years | non-significant association with risk of stroke unadjusted RR 1.02/mm (95%CI 0.99-1.06 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) |
| Atrial Fibrillation Investigators 1998 106 | Mitral valve prolapse | 991 (of whom 50 MVP) | non-valvular AF | mean 1.6 years | non-significant association with risk of stroke unadjusted RR 0.29 p = 0.22 |
| Atrial Fibrillation Investigators 1998 106 | Severe mitral regurgitation | 863 (of whom 86 severe MR) | non-valvular AF | mean 1.6 years | non-significant association with risk of stroke (relative to none or mild MR) unadjusted RR 1.7 p = 0.59 |
| Klem et al 2003 107 | Reduced left ventricular function | 409 (of whom reduced LV function in 31 of 73 diabetic, and 98 of 336 non-diabetic) | non-rheumatic AF | mean 9.6 years | HR for mortality, diabetics 1.52 (95%CI 0.85-2.70) p=0.1598, non-diabetics HR 2.28 (95%CI 1.58–3.29) p<0.0001 |
| Klem et al 2003 107 | Left atrial diameter | 409 (of whom 73 diabetic, 336 non-diabetic) | non-rheumatic AF | mean 9.6 years | HR for mortality, diabetics 1.01 (95%CI 0.97–1.05) p=0.6445, HR non-diabetics 1.06 (95%CI 1.03–1.08) p<0.0001 |
| Klem et al 2003 107 | Valvular abnormality | 409 (of whom valvular abnormality in 41 of 73 diabetic, and 136 of 336 non-diabetic) | non-rheumatic AF | mean 9.6 years | HR for mortality, diabetics 2.05 (95%CI 1.10–3.82) p=0.0229, non-diabetics HR 1.88 (95%CI 1.30–2.70) p=0.0007 |
| Miyaska et al 2000 108 | Mitral regurgitation | 173 (of whom 104 no MR, 69 grade 1 MR) | non-rheumatic AF | NA (patient records' study) | Grade 1 mitral regurgitation (compared with no MR) OR (odds ratio) 2.689 (95%CI 1.039–7.189) p=0.0434 significantly associated with history of thromboembolic events |
| Nakagami et al 1998 109 | Severe mitral regurgitation | 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) |
| Nakagami et al 1998 109 | Left atrial diameter | 290 | non-rheumatic AF | mean 7.4 years | 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 1992110 | Left atrial diameter | 539 | non-rheumatic AF | mean 1.3 years | Left atrial diameter (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 LVD) |
| The Stroke Prevention in Atrial Fibrillation Investigators 1992 110 | Mitral annular calcification | 568 (of whom 91 MAC) | non-rheumatic AF | mean 1.3 years | non-significantly associated with thromboembolism by age adjusted analysis RR 0.6 (95%CI 0.2-1.5) p>0.2 |
| The Stroke Prevention in Atrial Fibrillation Investigators 1992 110 | Severe mitral regurgitation | 568 (of whom 37 severe MR) | non-rheumatic AF | mean 1.3 years | non-significantly associated with thromboembolism by age adjusted analysis RR 0.4 (95%CI 0.1-3.0) p>0.2 |
| The Stroke Prevention in Atrial Fibrillation Investigators 1992 110 | Left ventricular dysfunction (global) | 568 (of whom 132 LVD) | non-rheumatic AF | mean 1.3 years | by univariate analysis was significantly associated with thromboembolism RR 2.9 (95%CI 1.6-5.3) p<0.001, By multivariate analysis 2.6 (95%CI 1.4-4.9) p=0.003 (multivariate analysis LAD and global LVD) |

*5.2.2 Results of prevalence review*

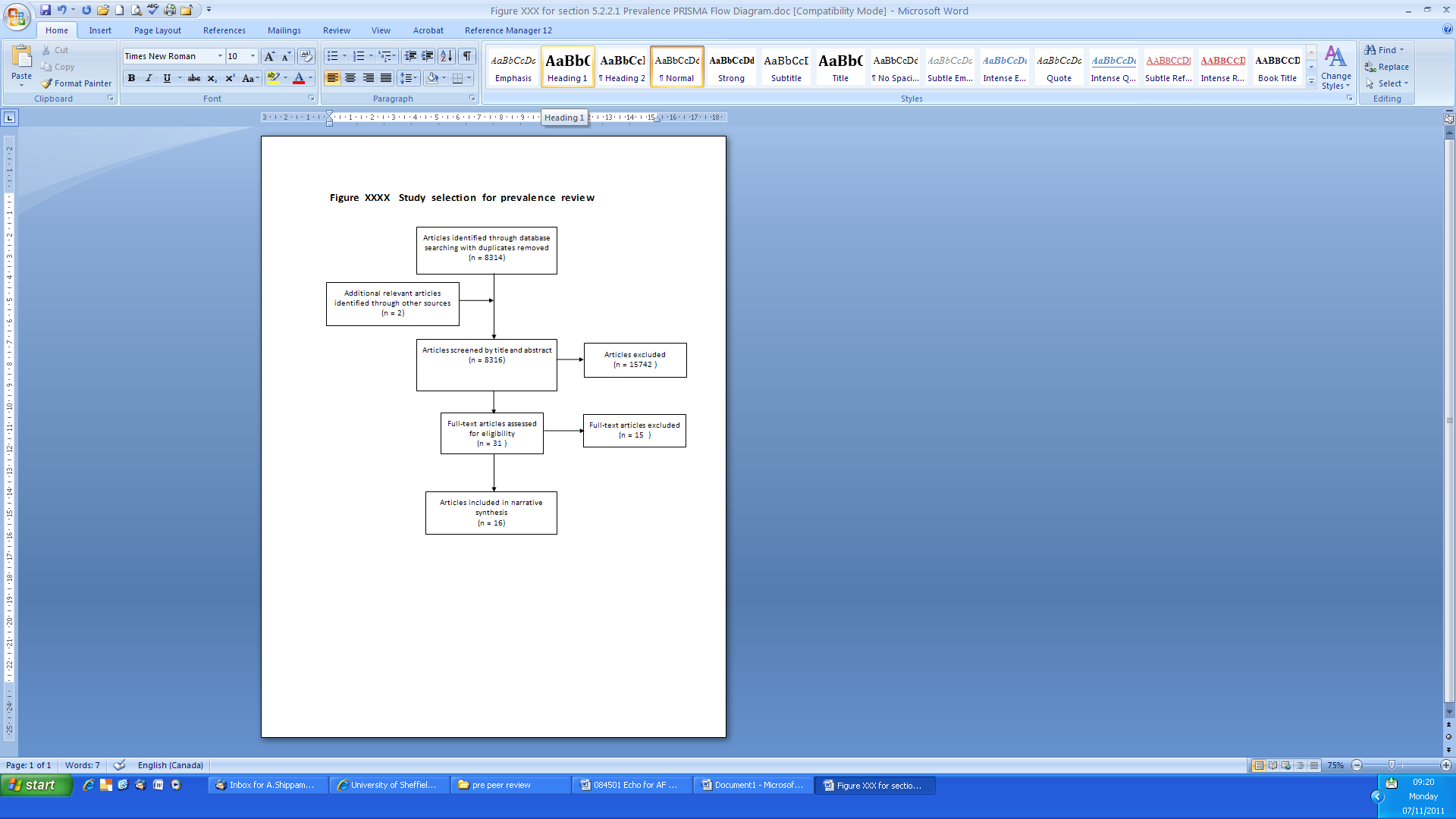
5.2.2.1 Quantity and quality of research available

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.

There were 16 prevalence studies 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.

**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 2001111 | Ischaemia/thrombosis | 42 | AF |
| Archer et al 1995112 | Ischaemia/thrombosis | 55 | non-rheumatic AF |
| Blackshear et al 1999113 | Ischaemia/thrombosis | 770 | AF |
| Corrado et al 2004114 | Ischaemia/thrombosis | 41 | AF or atrial flutter |
| Dang et al 2004115 | Valvular heart disease | 737 | first hospitalisation associated with AF |
| de Divitiis et al 199928 | Ischaemia/thrombosis | 90 | AF |
| Heppell et al 1997116 | Ischaemia/thrombosis | 109 | AF |
| Kleeman et al 2009117 | Ischaemia/thrombosis | 295 | non-valvular AF |
| Levy et al 1999118 | Ischaemia/thrombosis and Valvular heart disease and Cardiomyopathy and Heart failure | 756 | chronic, paroxysmal or recent-onset AF |
| Lip et al 1997119 | Structural defect and Ischaemia/thrombosis and Valvular heart disease and Cardiomyopathy | 111 | AF |
| Maltagliati et al 2006120 | Ischaemia/thrombosis | 757 | AF or atrial flutter |
| Narumiya et al 2003121 | Ischaemia/thrombosis | 50 | Lone AF (28%) or non-lone AF (72%) |
| Santiago et al 1994122 | Ischaemia/thrombosis and Valvular heart disease | 30 | AF |
| Scherr et al 2009123 | Ischaemia/thrombosis | 732 catheter ablations for AF in 585 patients | AF (catheter ablations) |
| Shen et al 2002124 | Ischaemia/thrombosis | 182 | AF and sub-therapeutic INR |
| Tsai et al 1997125 | Ischaemia/thrombosis | 219 | chronic non-rheumatic AF |

Prevalence studies were found for the 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 strengthening the reporting of observational studies in epidemiology (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 studies28,112,114,115,119,121,124 were retrospective in design, eight113,116-118,120,122,123,125 were prospective studies while one111 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. Four studies did not report the methods used to verify the presence or history of AF in eligible patients112,114,120,124,125although one study gave details in a prior publication98 and the others used candidates for cardioversion giving confidence in accuracy of diagnosis. While two retrospective studies28,121 used TOE and TTE in diagnosing the presence of ischaemic heart disease, the methods used to diagnose the presence of co-existing clinically significant cardiac pathologies was not detailed in 3 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 studies113,114,116,123; 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 6 studies.111,113,117,122,123,125 At least one criteria was not satisfied in 3 studies,28,114,116 partially met in 1 study (Dang or had unclear information in one study.112 In the remaining studies118,119,121,124 two or more criteria were not fulfilled.

5.2.2.2 Prevalence results

One prevalence study was identified that sought to identify prevalence of atrial septal defect, as presented in Table 14. This study, Lip et al 1997119, found a prevalence of 0.9% for atrial septal defect. This study looked at a cross-section of patient records in UK primary care.

**Table 14: Prevalence study Structural defect**

|  |  |  |  |
| --- | --- | --- | --- |
| Study | Pathology | Population (n, type of AF) | Prevalence (%) |
| Lip et al 1997119 | Atrial septal defect | 111 AF | 0.9 |

Fifteen studies investigated the prevalence of pathologies within the category Ischaemia/thrombosis, as shown in Table 15. One study, Lip et al 1997,119 found a 28.8% prevalence of ischaemic heart disease.

The six studies reporting prevalence of left atrial thrombus gave differing prevalences ranging from 3%, Kleeman et al 2009,117 to 18%, Heppell et al 1997.116 Both of these studies used TOE to diagnose thrombi. These six studies differed in terms of sample size and population, with Maltagliati et al 2006120 including atrial flutter, Shen et al 2002124 restricting the population to patients with sub-therapeutic INR, Kleeman et al 2009117 used a population admitted for cardioversion.

Six studies investigated prevalence of LAA thrombi, the lowest reported prevalence was for patients undergoing catheter ablations 1.6% Scherr et al 2009123, and the highest was 40% although this study had a small sample size (n=30) Santiago et al 1994.122 Two studies looked at right atrial appendage thrombus, reporting prevalences of 0.5% Maltagliati et al 2006120 and 6.7% de Divitiis et al 1999 28. Both of these studies used TOE to diagnose thrombi.

**Table 15: Prevalence studies Ischaemia/thrombosis**

|  |  |  |  |
| --- | --- | --- | --- |
| Study | Pathology | Population (n, type of AF) | Prevalence (%) |
| Agmon et al 2001111 | Aortic atherosclerosis | 42 AF | 73.8 |
| Agmon et al 2001111 | Complex aortic atherosclerosis | 42 AF | 16.7 |
| Archer et al 1995112 | Left atrial thrombus | 55 non-rheumatic AF | 9.1 |
| Archer et al 1995112 | Left ventricular thrombus | 55 non-rheumatic AF | 3.6 |
| Archer et al 1995112 | Atrial septal aneurysm | 55 non-rheumatic AF | 7.3 |
| Blackshear et al 1999113 | Aortic atherosclerotic plaque | 770 AF | 56.6 |
| Blackshear et al 1999113 | Complex aortic atherosclerotic plaque | 770 AF | 25.1 |
| Corrado et al 2004114 | Left atrial appendage thrombus | 41 AF or flutter | 9.8 |
| de Divitiis et al 199928 | Left atrial appendage thrombus | 90 AF | 12.2 |
| de Divitiis et al 199928 | Right atrial appendage thrombus | 90 AF | 6.7 |
| de Divitiis et al 199928 | Left and/or right atrial appendage thrombus | 90 AF | 13 |
| Heppell et al 1997116 | Left atrial thrombus | 109 AF | 18 |
| Kleeman et al 2009117 | Left atrial thrombus | 295 non-valvular AF or flutter | 3 |
| Levy et al 1999118 | Coronary artery disease | 756 chronic, paroxysmal or recent-onset AF | 16.6 |
| Lip et al 1997119 | Ischaemic heart disease | 111 AF | 28.8 |
| Maltagliati et al 2006120 | Left atrial thrombus | 757 AF or atrial flutter | 6.3 (if exclude left atrial appendage (LAA) 0.3) |
| Maltagliati et al 2006120 | Left atrial appendage thrombus | 757 AF or atrial flutter | 5.5 |
| Maltagliati et al 2006120 | Right atrial appendage thrombus | 757 AF or atrial flutter | 0.5 |
| Narumiya et al 2003121 | Left atrial appendage thrombus | 50, of which 14 lone AF, 36 non-lone AF | 12 (16.7% non-lone AF; 0% lone AF) |
| Santiago et al 1994122 | Left atrial appendage thrombus | 30 AF | 40 |
| Scherr et al 2009123 | Left atrial appendage thrombus | 732 catheter ablations for AF in 585 patients | 1.6 |
| Shen et al 2002124 | Left atrial thrombus | 182 AF and sub-therapeutic INR | 9.9 |
| Tsai et al 1997125 | Left atrial thrombus | 219 chronic non-rheumatic AF | 6.8 |

Four studies investigated the prevalence of valvular pathologies, Table 16. Two of these studies, Dang et al 2004115 and Lip et al 1997119, 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 1999118 would give 18.8% prevalence. Mitral valve disease had a reported prevalence of 10.4%,115 and Santiago et al 1994122 reported prevalence of 30% for mitral regurgitation.

**Table 16: Prevalence studies Valvular heart disease**

|  |  |  |  |
| --- | --- | --- | --- |
| Study | Pathology | Population (n, type of AF) | Prevalence (%) |
| Dang et al 2004115 | Mitral valve disease | 737 first hospitalisation associated with AF | 10.4 |
| Dang et al 2004115 | All valve diseases | 737 first hospitalisation associated with AF | 13.4 |
| Levy et al 1999118 | 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) |
| Levy et al 1999118 | Valvular heart disease non-rheumatic (including mitral valve prolapse) | 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 1997119 | Valvular heart disease | 111 AF | 26.1 |
| Santiago et al 1994122 | Mitral regurgitation | 30AF | 30 |

Three studies investigated the prevalence of pathologies within the category cardiomyopathy, as presented in Table 17. Dang et al 2004115 and Lip et al 1997119 reported prevalence of 4.5%115 to 5.4%119. Levy et al 1999118 reported prevalence of 4.5% for hypertrophic cardiomyopathy, and 9.2% for dilated cardiomyopathy.

**Table 17: Prevalence studies Cardiomyopathy**

|  |  |  |  |
| --- | --- | --- | --- |
| Study | Pathology | Population (n, type of AF) | Prevalence (%) |
| Dang et al 2004115 | Cardiomyopathy | 737 first hospitalisation associated with AF | 4.5 |
| Levy et al 1999118 | 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) |
| Levy et al 1999118 | 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) |
| Levy et al 1999118 | Cardiomyopathy (other) | 756 chronic, paroxysmal or recent-onset AF | 1.2 |
| Lip et al 1997119 | Cardiomyopathy | 111 AF | 5.4 |

Two studies investigated the prevalence of heart failure, as shown in Table 18. Dang et al 2004115 reported prevalence of 31.1%.115 and Levy et al 1999118 reported prevalence of congestive heart failure as 29.8%.118

**Table 18: Heart failure**

|  |  |  |  |
| --- | --- | --- | --- |
| Study | Pathology | Population (n, type of AF) | Prevalence (%) |
| Dang et al 2004115 | Heart failure | 737 first hospitalisation associated with AF | 31.1 |
| Levy et al 1999118 | Congestive heart failure | 756 AF (167 paroxysmal, 389 chronic, 200 recent-onset ) | 29.8 (14% paroxysmal, 43% chronic, 18% recent onset) |

*5.2.3 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 mitral regurgitation, and tricuspid stenosis. Diagnostic accuracy studies without reported AF populations were available for other pathologies including endocarditis, cardiomyopathy, heart failure, left ventricular 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.

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. For most pathologies there was also quite high sensitivity, with the majority having sensitivity of 0.6 or higher, with the exceptions of atrial thrombi, atrial septal defect and pulmonary embolism. Thus screening may result in considerable false negatives for atrial thrombi, atrial septal hypertrophy/ defect and pulmonary embolism. In general, sensitivity was lower for atrial thrombi, atrial septal defect and pulmonary embolism 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 pulmonary embolism 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 where less experienced staff are employed, there is lower accuracy. Even with skilled echocardiographers, there may be inter-observer 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 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 left atrial diameter 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 10mm increments. Valvular abnormality carried a significantly increased risk of mortality. Mitral regurgitation was not significantly associated with stroke or thromboembolism in two studies, however two other studies suggested a significantly increased risk of thromboembolism with mild mitral regurgitation, in contrast with a significantly protective effect of severe mitral regurgitation against stroke. There was no significant association found between mitral annular calcification and thromboembolism, or between mitral valve prolapse and stroke. These findings are consistent with the report of Providencia et al 2011 13, published after the literature search was conducted, that found that TTE diagnosed LV systolic function and LA area measurement may provide a valuable addition to CHADS2 and CHA2DS2-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 (for example as assessed by CHADS2 scores). While 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 AF patients in the included prevalence studies. Cardiomyopathy prevalence was around 5%, and atrial septal defect had a prevalence under 1%.

Studies of AF have reported characteristics of AF patients, including prevalences of cardiac pathologies. This review only found a prevalence study for atrial septal defect, whereas prevalence of structural heart disease, of any type thus encompassing many difference pathologies, has been reported in 46% (Miyasaka 2000 108) or 54% (Corrado 2004 114) of AF patients 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% (Blackshear 1999 113) or 12% (Frykman 2001 134), and coronary disease in 22% (de Divitiis 1999 28), 56% of 188 patients with short-term (<48 hours) AF (Kleeman 2009 117), or 32% of first-detected AF (Nieuwlaat 2005 54), 34% paroxysmal AF (Nieuwlaat 2005 54), 29% (Nieuwlaat 2005 54) persistent AF, 36% (Nieuwlaat 2005 54) permanent AF. Atrial thrombus has been found in 3% AF (Rozenberg 2000 135) or 12-20% in post-mortem studies of valvular AF (DiPasquale 1995 136), LA thrombus in 14% of new onset AF (Rubin 1996 137), and LAA thrombus in 12% non-valvular AF or atrial flutter (Black 1993 138). Results of thrombus prevalence studies within this review fell within these estimates. In the Scherr study123, all patients with atrial flutter had a larger LA diameter (> 4.5 cm) compared to those patients without LA thrombi. It was also noted that the prevalence of LAA thrombi increased with increasing CHADS2 score. While the prevalence of LAA thrombi range between 0.3% to 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 or more. Atrial septal aneurysm has been reported in 2% (Rostagno 1998 139) and left ventricular aneurysm as 1% (SPAF investigators 1992 110) of AF patients. This review did not find studies that set out to assess prevalence of pulmonary disease in AF patients, however pulmonary disease has been reported in 6% of AF patients (Frykman 2001 134). According to the Framingham heart study, approximately a third of women with AF and a fifth of men with AF have valvular heart disease (Kannel 199819). Results of valvular heart disease prevalence studies within this review were broadly in line with other reported estimates. Valvular heart disease has been reported as 10% of asymptomatic AF patients and 26% of symptomatic AF patients (Frykman 2001 134), 23% AF (Levy 1998), 21% of first-detected AF (Nieuwlaat 2005 54), 19% paroxysmal AF 24% persistent AF(Nieuwlaat 200554) , 40% permanent AF (Nieuwlaat 2005 54), with a review estimate of up to 40% AF (Tops 2010140). Cardiomyopathy has been reported in 8% of first-detected AF (Nieuwlaat 200554), 7% paroxysmal AF (Nieuwlaat 200554), 13% persistent AF (Nieuwlaat 200554), and 16% permanent AF (Nieuwlaat 200554). Dilated cardiomyopathy has been found in 11% AF (de Divitiis 1999) and 17% patients with short-term (<48 hours) AF (Kleeman 2009117). Heart failure has been reported in 26% of first-detected AF (Nieuwlaat 2005 54), 23% paroxysmal AF (Nieuwlaat 2005 54), 35% persistent AF (Nieuwlaat 2005), and 49% permanent AF (Nieuwlaat 200554). According to the Framingham heart study, approximately a quarter of men and women with AF have heart failure (Kannel 199819), with up to 42% AF patients developing congestive heart failure during their lifetime (Tsang 2005141). Congestive heart failure in AF study participants has been reported as 28% (Blackshear 1999113) or 40% (Santiago 1994122), 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 AF patients, however aortic dissection has been reported in 7% AF patients (Santiago 1994122).

Overall, diagnostic accuracy of TTE and prevalence of pathologies in AF patients, indicate that routine TTE following AF diagnosis would identify pathologies in many patients, particularly in 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 pulmonary embolism by lung scan and atrial thrombi and atrial septal hypertrophy by TOE, 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. 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 the minimise impact of false positives, although false positives may lead to some unnecessary diagnostic tests.

**6 SIMULATING CLINICAL EVENTS AND ESTIMATING COST EFFECTIVENESS RATIOS**

**6.1 Introduction**

*6.1.1 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)

*6.1.2 The Relationship between information provided by a TTE 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 to 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.

*6.1.3 The decision to prescribe anticoagulants*

Introduction

The specific focus of the model is the clinical decision whether or not to prescribe an oral anticoagulant (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 as an adverse effect increase the risk of major bleeding events, which in some cases can lead to clinical outcomes as, or more, severe than the strokes 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 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 AF patients 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.

*6.1.4 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 (‘true positives’ and ‘true negatives’) and not appropriate in others (‘false positives’ and ‘false negatives’), as indicated in Table 19. This table focuses purely on the clinical issues, whether additional benefits are worth any additional costs will be detailed in later sections of the report.

**Table 19: The conceptual accuracy associated with TTE**

|  |  |  |
| --- | --- | --- |
|  | In reality | |
|  | 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** |
| Diagnostic Strategy indicates additional benefit outweighs additional risk.  **Patient Prescribed drug** | Correct decision to prescribe.  **True Positive (TP)** | Incorrect decision to prescribe.  **False Positive (FP)** |
| Diagnostic Strategy indicates additional benefit does not outweigh additional risk.  **Do not prescribe drug** | Incorrect decision not to prescribe.  **False negative (FN)** | Correct decision not to prescribe.  **True Negative (TN)** |

*6.1.5 The CHADS*2diagnostic tool for assessing the *risk of stroke in AF patients*

The main diagnostic tool currently used to make the decision about whether to prescribe anticoagulants in newly diagnosed AF patients is the CHADS2 insrument

6.1.5.1 CHADS2

The CHADS2 instrument produces a risk score for each patient ranging from zero to six points inclusive according to the criteria shown in Table 20:

**Table 20: The criteria used in performing a CHADS2 assessment**

|  |  |  |
| --- | --- | --- |
| **Code** | **Condition** | **Points** |
| **C** | Congestive heart failure | 1 |
| **H** | Hypertension | 1 |
| **A** | Age ≥ 75 years | 1 |
| **D** | Diabetes mellitus | 1 |
| **S­­­2** | Prior stroke or TIA | 2 |

CHADS2 decision rule and choice of OACs

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 rivaraoxaban states:

Rivaroxaban is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, people with nonvalvular atrial fibrillation with one or more risk factors such as

* Congestive heart failure
* Hypertension
* Age 75 or older
* Diabetes mellitus
* Prior stroke or transient ishaemic attack47

It is noted that this guidance is equivalent to stating that rivaroxaban is recommended for atrial fibrillation patients with a CHADS2 score of one point or more.

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, that is, in people with nonvalvular atrial fibrillation with one or more of the following risk factors:

* Previous stroke, transient ischaemic attach or systemic embolism
* Left ventricular ejection fraction below 40%
* Symptomatic heart failure of Ney York Heart Association (NYHA) class 2 or above
* Age 75 year or older
* Age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension142

It is noted that an implication of the guidance is that dabigatran is indicated in patients who have a CHADS2 score of one point or more if they are aged 65 years or older. In people aged under 65 years, the correspondence between CHADS2 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 CHADS2 score, the mathematical model will only be run in patients aged 65 years or over when considering dabigatran as the OAC of choice.

Based on the above NICE recommendations, recent ESC guidance47 and broad recognition that warfarin carries a higher risk of major bleeding events for most patient groups than either dabigatran or rivaroxaban6 difference CHADS2 thresholds were used for each OAC, as shown in Table 21 below.

**Table 21: The assumed level of CHADS2 at which specific OAC would be performed**

|  |  |  |  |
| --- | --- | --- | --- |
| CHADS2 score | Prescribe Dabigatran | Prescribe Warfarin | Prescribe Rivaroxaban |
| 0 | No | No | No |
| 1 | Yes (age 65 or over) | No | Yes |
| 2 or more | Yes | Yes | Yes |

Comparator strategy CHADS2 + TTE

In our comparator strategy, ‘CHADS2 + TTE’, the decision to coagulate can also be made as a result of TTE identifying a structural feature of left atrial abnormality (LA ABN) that predisposes an individual to a high risk of stroke.143 For the purposes of this report we define LA ABN as a patient having one or more of the following conditions

* left atrial appendage thrombi;
* dense spontaneous echo contrast;
* left atrial appendage low flow velocities

These conditions have been chosen as they are the ones used in a recent publication by Provedencia et al.,144 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 CHADS2 score at or above the threshold required to recommend OACs.
* A TTE indicating the presence of LA ABN.

In effect, this means that some individuals that would not have received OAC with CHADS2 alone will receive OAC following CHADS2+TTE due to detection of LA ABN. It is noted that in no instance would patients who would have received OAC using CHADS2 alone have treatment withheld. As such, it has been assumed that TTE will only provide information that can alter patient management where the CHADS2 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 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 CHADS2 risk factor. Because of this, a number of different scenarios were considered incorporating different combinations of OAC, age, gender, and initial CHADS2 score. A total of 14 scenarios are presented, as described in Table 22 below:

**Table 22: Summary of the 14 comparisons modelled using the mathematical mode**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Scenario | OAC | Age | Initial CHADS2 score | Gender |
| W\_50\_0\_M | warfarin | 50 | 0 | male |
| W\_50\_0\_F | warfarin | 50 | 0 | female |
| W\_50\_1\_M | warfarin | 50 | 1 | male |
| W\_50\_1\_F | warfarin | 50 | 1 | female |
| W\_65\_0\_M | warfarin | 65 | 0 | male |
| W\_65\_0\_F | warfarin | 65 | 0 | female |
| W\_65\_1\_M | warfarin | 65 | 1 | male |
| W\_65\_1\_F | warfarin | 65 | 1 | female |
| R\_50\_0\_M | rivaroxaban | 50 | 0 | male |
| R\_50\_0\_F | rivaroxaban | 50 | 0 | female |
| R\_65\_0\_M | rivaroxaban | 65 | 0 | male |
| R\_65\_0\_F | rivaroxaban | 65 | 0 | female |
| D\_65\_0\_M | dabigatran | 65 | 0 | male |
| D\_65\_0\_F | dabigatran | 65 | 0 | female |

OAC: Oral anticoagulant

6.1.5.2 CHA2DS2-VASc

An alternative variation of the CHADS2 instrument exists, which uses additional information such as gender to make the decision. It was decided not to produce an additional 14 scenarios using CHA2DS2-VASc rather than CHADS2 as the baseline strategy for a number of reasons. These include: the already large number of scenarios considered; the fact the recent NICE guidance on rivaroxaban and dabigatran relate more clearly to CHADS2 than CHA2DS2-VASc scores, and the fact that CHADS2 is the more established of the two instruments.

**6.2 Detailing the mathematical model**

*6.2.1 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 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, that follow from the patient’s clinical characteristics and the decision whether or not to prescribe 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

1. patients who have a major clinical bleed whilst on OAC, have treatment with OACs stopped
2. patients who have a stroke receive OAC, unless they have had a major clinical prior bleed.

In populating the model we elected to use data reported by Providencia et al.144 as this was a recent, internally consistent study which used the CHADS2 tool and had also conducted TOE. Whilst the study was not large (n=405) it was deemed to outweigh the limitations associated with using data from heterogeneous studies which would have required numerous assumptions.

**Figure 3: Graphical Representation of the mathematical model**



*6.2.2 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 of 65 years old with newly diagnosed AF but with none of the following conditions: congestive heart failure; hypertension; diabetes mellitus; prior stroke or TIA; or vascular disease: This patient group has been selected as they would have a CHADS2 score of 0, and thus would not be currently recommended treatment with an OAC. Additionally, otherwise identical cohorts of individuals with a CHADS2 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 ABN 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 lifetable data. These were converted into probabilities of males and females dying in each forthcoming year assuming initial ages of 50 and 65. 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 TTE of diagnosing LA ABN

Table 2 in the paper by Providencia et al.,144 provides sufficient information to calculate an estimate of sensitivity and specificity of TTE in diagnosing LA ABN. This data was used this to derive Tables 23 and 24. Patients were assessed using both TTE and TOE, and for TTE were assigned an echocardiographic risk score ranging depending on how many structural features that are constituents of LA ABN were identified through TTE. It was assumed that TOE was the gold standard and identified all patients with LA ABN.

**Table 23: The data used to estimate sensitivity and specificity of TTE in diagnosing LA ABN**

|  |  |  |
| --- | --- | --- |
| Echocardiographic parameters: Score | Number of patients | Number of patients with LA ABN |
| 0 | 88 | 5 |
| 1 or more | 246 | 87 |
| Total | 334 | 92 |

**Table 24: The estimated accuracy of TTE in diagnosing LA ABN**

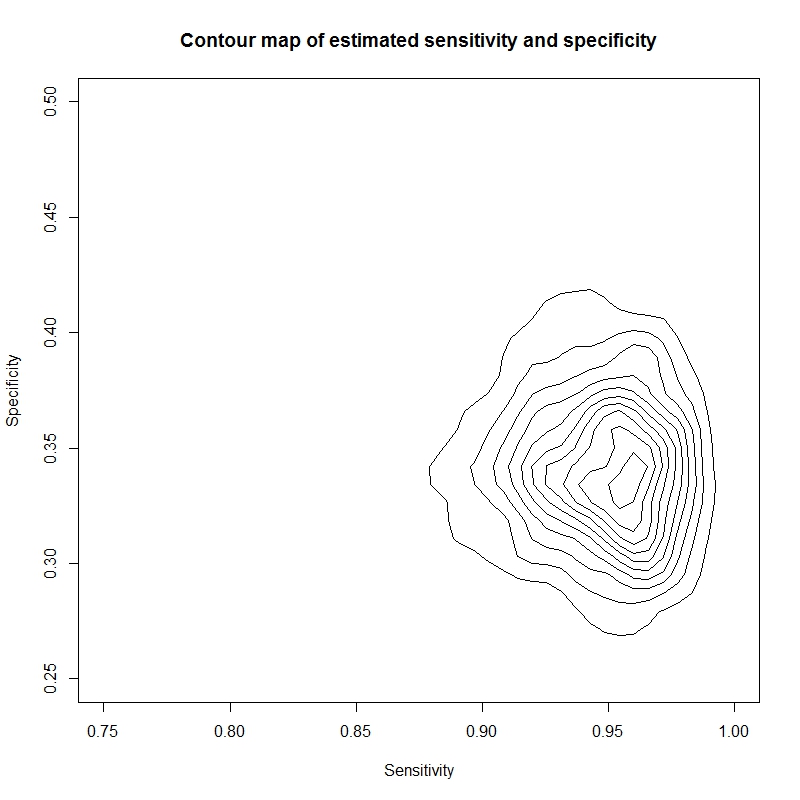
|  |  |  |
| --- | --- | --- |
|  | **Patients with high risk feature** | **Patients without high risk feature** |
| **No high risk feature identified by TTE** | **FN**: 5 | **TN**: 88 – 5 = 83 |
| **High risk feature identified by TTE** | **TP**: 87 | **FP**: 246 – 87 = 159 |

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

* Sensitivity = TP / (TP + FN) = 87 / (87 + 5) = 0.946 (to 3 d.p.)
* Specificity = TN / (TN + FP) = 83 / (83 + 159) = 0.343 (to 3 d.p.)

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 scatter plot as the relative density would have been relatively difficult to ascertain in a scatter plot containing 1,000 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.

**Figure 4: Joint distribution of sensitivity and specificity based on 1000 draws from a Dirichlet distribution**



It was assumed that the derived distributions of sensitivity and specificity was applicable to all patients and was thus assumed applicable to patients who had a CHADS2 score of 0.

Data reported in Table 2 of Provedencia et al.,144 indicate that of 24 patients with a CHADS2 score of 0, 2 had a LA ABN. Given the small data available (the number in the LA ABN group being less than 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 ABN amongst those with CHADS2 score of 0. These values were used to populate beta distributions to allow for uncertainty in the true proportion of patients with LA ABN within the CHADS2 equal 0.

For patients with a CHADS2 score of 0 there were 17 patients out of 79 with a LA ABN.

6.2.3 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.

CHADS2-related stroke risk

We assumed that higher CHADS2 scores were associated with a higher risk of stroke. Our estimates were based on unadjusted stroke risk estimates presented in Friberg et al.145 These estimates are presented in Table 25. 95% CIs were estimated from Beta distributions.

**Table 25: The assumed risk of stroke associated with CHADS2 score**

|  |  |
| --- | --- |
| CHADS2 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) |

Patients with LAA were assumed to have a risk of stroke independent of CHADS2 score. The risk was set as 8.0% (95% CI 7.26 - 8:31) per annum, as reported in Connelly et al.146 For simplicity the risk of stroke was assumed to apply throughout the lifetime of the patient.

Estimating uncertainty in CHADS2-related stroke risk

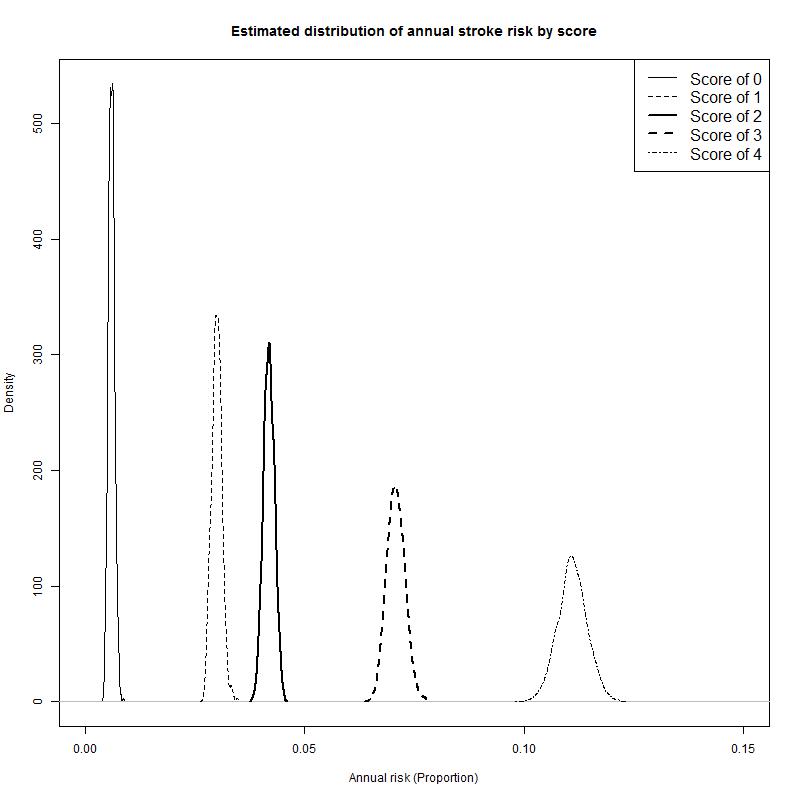
Using CHADS2 score

Introduction

Simulating values

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

**Figure 5: The estimated distribution of annual stroke risk by CHADS2 score**



*6.2.4 The estimated efficacy of each OAC in preventing strokes.*

Effect of dabigatran on stroke risk

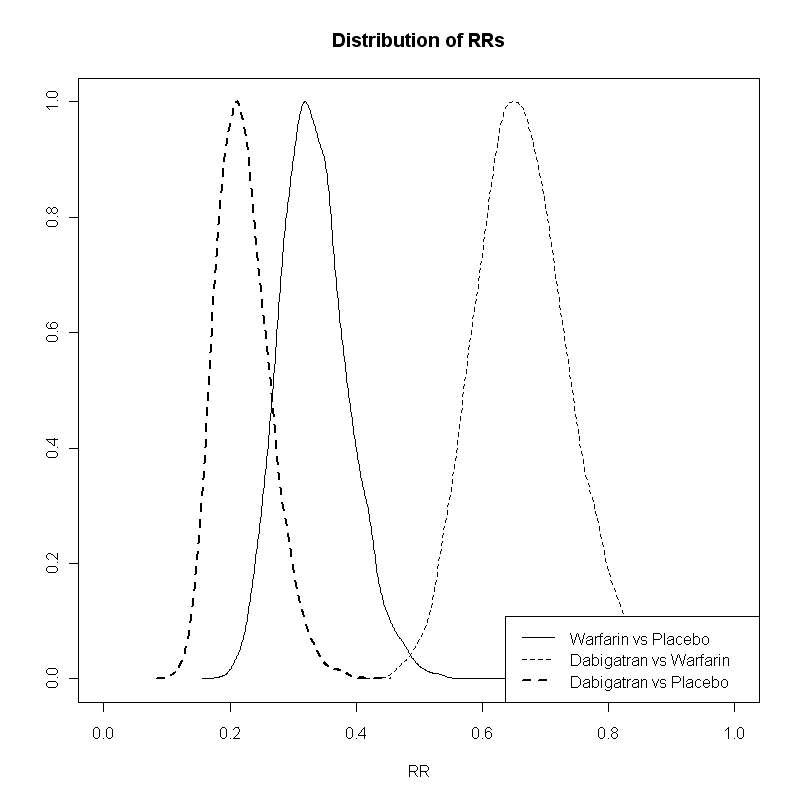
The effect of warfarin at preventing strokes was taken from a 2006 meta-analysis.147 The effects of dabigatran and rivaroxaban compared to placebo (i.e. no treatment) was estimated using an indirect comparison approach. Estimates for the annual risk ratio (RR) of a stroke for patients given 150mg dabigatran twice daily compared with warfarin taken from a paper based on the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study.146 Data on the effect of rivaroxaban were taken from Patel et al.148

One thousand simulated values were sampled from each distribution, with derived values for dabigatran vs. placebo estimated from multiply the relative risks (RR) of the sampled warfarin vs. placebo value and the dabigatran vs. warfarin value, to produce a distribution of estimates of the RR of dabigatran compared with placebo. 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. Table 27 shows the density functions of the three distributions.

**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) | Lognormal | Lip & Edwards 2006146 |
| RR: dabigatran vs. warfarin | 0.66 (0.53 to 0.82) | Lognormal | Connolly et al 2009146 |
| RR: dabigatran vs. placebo | 0.22 (0.15 to 0.32) | Lognormal | Derived from above |
| RR: Rivaroxaban vs. warfarin | 0.88 (0.74 to 1.03) | Lognormal | Patel et al 2011148 |
| RR: Rivaroxaban vs. placebo | 0.30 (0.20 to 0.41) | Lognormal | Derived from above |

**Figure 6: The assumed distributions of each OAC versus placebo**

*6.2.5 The estimated risk of bleed associated with each OAC*

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.

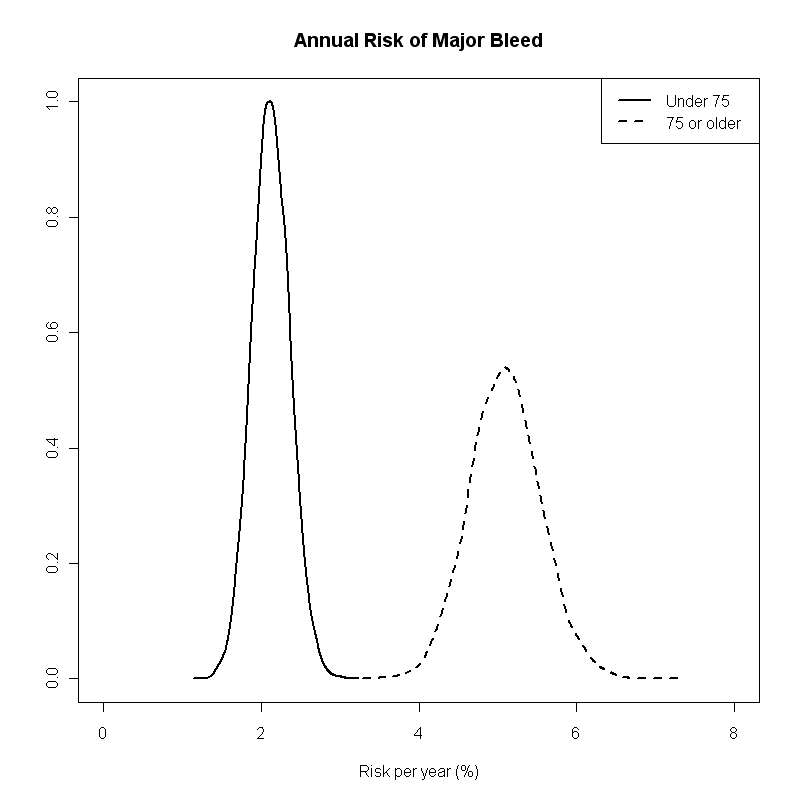
The estimated risk of bleeding associated with dabigatran

The risk of major bleeding events in patients receiving dabigatran was based on results published using data from the RE-LY trial.149 This reported that major bleeding events occurred at a rate of 2.12% per year in patients given dabigatran and under 75 years of age, and at a rate of 5.10% in patients aged 75 years or older. 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 PSA. Table 27 presents credible intervals for these two age groups, and Figure 7 shows these results graphically. Credible intervals were calculated using an presumed sample size: the paper reports 10,855 participants under the age of 75 years and 7258 participants aged over 75 years and that there was an equal probability of assignment between the three trial arms.

**Table 27: Simulated Credible Intervals (CrI) for the annual risk of bleed on dabigatran**

|  |  |  |  |
| --- | --- | --- | --- |
| **Age group** | **Central estimate** | **Presumed Sample size** | **95% CrIs** |
| Under 75 years | 2.12% | 3618150 | 1.66% to 2.60% |
| 75 years or above | 5.10 % | 2419151 | 4.22% to 5.99% |

**Figure 7: Distribution of simulated estimates for the annual risk of bleed on dabigatran**



The estimated risk of bleeding associated with warfarin

Results from the RE-LY study149 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.

**Table 28: The assumed risk of bleeding associated with warfarin treatment**

|  |  |  |
| --- | --- | --- |
| **Age group** | **Central estimate** | **95% CrIs** |
| Under 75 years | 3.04% | 2.49% to 3.62% |
| 75 years or above | 4.38 % | 3.60% to 5.21% |

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 placebo147 with estimates of the risk of bleed given rivaroxiban compared with warfarin.148 The central estimates and credible intervals 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.

**Table 29: The assumed risk of bleeding associated with rivaroxaban treatment**

|  |  |  |
| --- | --- | --- |
| **Age group** | **Central estimate** | **95% CrIs** |
| Under 75 years | 3.15% | 2.46% to 3.96% |
| 75 years or above | 4.55 % | 3.57% to 5.70% |

*6.2.6 The assumed costs associated with each OAC and with TTE*

Cost of dabigatran

This is assumed to cost £920.43 per year, assuming two 150mg tablets daily at a cost of £2.52 per day.152 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 20mg per day.153 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 to 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.152 The annual cost of the drug was taken from the British National Formulary 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.154

Including monitoring costs, this suggests 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 and £258.87.

Cost of TTE

A TTE has been estimated to cost £66 using HRG code RA60Z Simple Echocardiogram.155 A second more expensive estimate of £425 was listed for HRG code EA45Z Complex Echocardiogram (include 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 a 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.

*6.2.7 Simulating the patient experience.*

6.2.7.1 Introduction

The long-term part of the model uses an individual level discrete event simulation (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 AF patients, 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 lifetables. This produces a time to event against which other competing risks are compared. For example, for a patient aged 60 and assigned a life expectancy of 75 years, this baseline next event is assigned a value of 15 years (75-60).

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 OAC.

Only if a patient is receiving OAC do they experience a risk of major bleeds due to 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 five years (1 / 0.2). An event with a 50% risk of occurring per year, however, has an expected time to occurrence of just two 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 below 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** | **Candidate Event selected** |
| Death, not bleed or stroke related | NA (using lifetable data) | 15 years | No |
| Stroke | 0.050 | 18 years | No |
| Bleed | 0.100 | 12 years | Yes |

Out of the three candidate next events, the event with shortest time to occurrence, is that of a bleed. This means 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: Hypothetical second 'next event' candidates for the above patient, now aged 72**

|  |  |  |  |
| --- | --- | --- | --- |
| **Candidate Event name** | **Annual probability** | **Sampled Time to occurrence** | **Candidate Event selected** |
| Death, not bleed or stroke related | NA (using lifetable data) | 3 years | Yes |
| Stroke | 0.125 | 6 years | No |
| Bleed | 0.000 | Infinite | No |

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 three years after the previous event, at the age of 75.

Over the course of the 15 years from age 60 to age 75 that 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 CHADS2 alone diagnostic strategy, or the CHADS2+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.

6.2.7.2 Dynamic features of the model

Dynamic features of the model include:

* Updating the CHADS2 score when a patient reaches the age of 75. This is because being aged 75 or above is a risk factor within CHADS2, and increases the CHADS2 score by one point. This means the annual risk of stroke increases at the age of 75.
* Updating both the CHADS2 score by 2 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 are 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.
* The risk of a major bleeding event when taking Dabigatran (150mg twice daily) was also assumed to change at the age of 75.
* The life expectancy given a GOS 2 state was reduced to a maximum of 3.4 years.

*6.2.8 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

6.2.8.1 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.

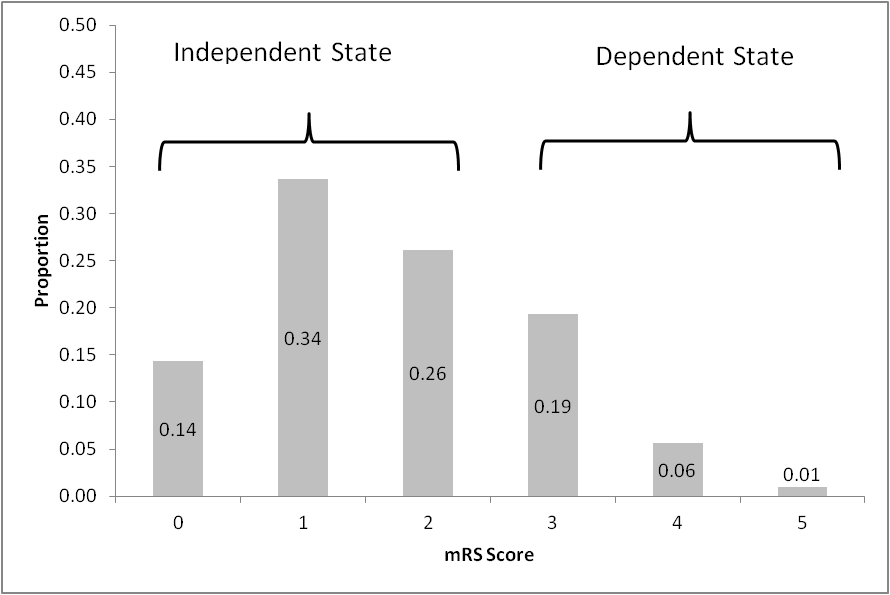
The outcome following a stroke is estimated using a two stage process, using data from Rivero-Arias.156 This paper reported that of 1,283 patients who had a stroke within the Oxford vascular study (OXVASc) cohort, 24.8% (319 / 1,283) were dead within 24 months. Of those who survived, the degree of disability 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 to 5, as shown in Table 32.

**Table 32: The modified Rankin Score (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. |

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.

**Figure 8: Distribution of stroke outcomes at 24 months (survivors at 24 months only)**

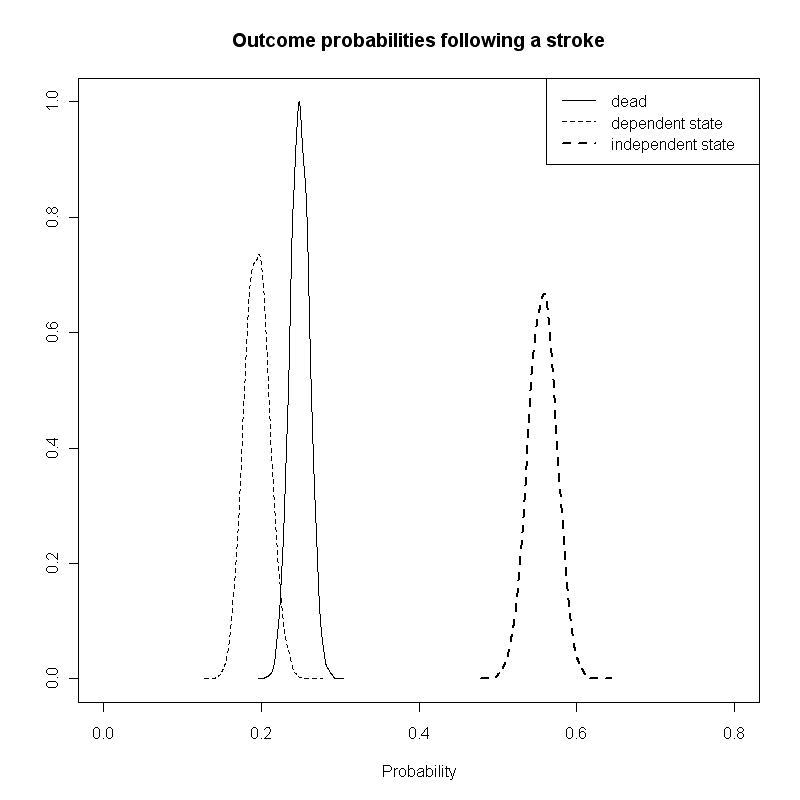


Uncertainty in the proportion of patients who survive a stroke was represented using a Binomial distribution. As it is required for the accurate calculation of utility multipliers associated with dependent and independent states, the proportion of patients in each of the six mRS outcome states was used 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) 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.

**Table 33: Estimated proportions of patient states following a stroke**

|  |  |  |
| --- | --- | --- |
| **State** | **Central Estimate** | **95% intervals** |
| Dead | 0.25 | 0.23 to 0.27 |
| Independent | 0.56 | 0.52 to 0.59 |
| Dependent | 0.19 | 0.16 to 0.23 |

**Figure 9: The estimated distribution of patients 24 months after a stroke**



6.2.8.2 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.156

Utility multipliers following a stroke were estimated from data which presented EQ-5D mapped utility estimates for the utility associated with each of the six modified Rankin Scale (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 proportion of each of the constituent mRS states within the dependent and independent stroke category needs 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 6.2.7.1);
2. Divide the six states into the independent stroke category (mRS 0-2) and dependent stroke category (mRS 3-5);
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. 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.

**Table 34: The estimated utility multipliers following a non-fatal stroke**

|  |  |
| --- | --- |
| **Category** | **Central utility estimate (95% CrIs)** |
| Independent State | 0.822 (0.819 to 0.824) |
| Dependent State | 0.482 (0.477 to 0.487) |

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

Comparison with previous utility multiplier estimates

Our estimated utility multipliers are very similar to those presented in Dorman et al.,157 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 has an estimated EQ-5D score around zero, and around 75% were in the least worst category mRS 3, which has an estimated EQ-5D score over 0.5. The discrepancy may reflect improvements in the prognosis following strokes in the decade that separates the studies used.

6.2.8.3 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.158 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, and the cost per night to follow a lognormal distribution due to the asymmetry of the confidence intervals and the fact a negative cost is implausible.

Ten thousand draws from both distributions were combined in a random order in order to produce a distribution of estimated cost per death. Bootstrapping was used to simulate uncertainty in the mean of this distribution; 1,000 draws from this bootstrapped distribution of means was used within the PSA. Costs were then inflation adjusted.159 The estimated mean costs together with 95% CrIs are presented in Table 35.

**Table 35: Estimated mean cost of death due to stroke**

|  |  |
| --- | --- |
| **Value** | **Central estimate (95% CrIs)** |
| Cost of death due to stroke | £9319( £9259 to £9378) |

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 2009-10 NHS reference costs.155

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,155 with costs inflation adjusted from 2005-6 to 2009-10 values.159 A summary of these costs is presented in Table 36.

**Table 36: Estimated mean cost of dependent state due to stroke**

|  |  |
| --- | --- |
| **Value** | **Central estimate (95% CrIs)** |
| 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) |

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 2009-10 NHS reference costs.155

The ongoing cost of a patient in an independent state due to stroke was estimated using data reported in the National Stroke Strategy Impact Assessment,159 with costs inflation adjusted from 2005-6 to 2009-10 values. A summary of these costs is presented in Table 37.

**Table 37: The estimated mean cost following an independent stroke**

|  |  |
| --- | --- |
| **Value** | **Central estimate (95% CrIs)** |
| 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) |

*6.2.9 The outcome following major clinical bleed*

6.2.9.1 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 haemorrhage
* Non-fatal intracranial haemorrhage

There is a wide variation in the effects of an intracranial haemorrhage. To represent this variation, outcomes following non-fatal intracranial haemorrhage are further subdivided into four distinct states according to the Glasgow Outcome Scale (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 gastrointestinal (GI) haemorrhage
3. Non-fatal intracranial (IC) haemorrhage

The proportions of these three events are estimated from Table 79 of a 2009 HTA monograph,160 which is derived from a 2003 meta-analysis.161 Uncertainty about the relative distribution of these three outcomes was represented using a Dirichlet distribution. These results are shown in Table 38.

**Table 38: Probability of event categories following a major bleeding episode**

|  |  |  |
| --- | --- | --- |
| **Event category** | **Dirichlet distribution value** | **Central estimate (95% CrIs)** |
| Fatal bleed | 22.7 | 0.114 (0.777 to 0.157) |
| Non-fatal gastrointestinal | 28.4 | 0.795 (0.743 to 0.843) |
| Non-fatal intracranial | 198.9 | 0.091 (0.059 to 0.129) |

If a non-fatal intracranial haemorrhage occurs, the effect of this bleed on patient outcome is simulated using data that maps outcomes onto the Glasgow Outcome Scale (GOS), which categorises a patient’s state after a traumatic brain injury.162 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.163

**Table 39: Probability of GOS categories following non-fatal intracranial haemorrhage**

|  |  |  |
| --- | --- | --- |
| **Event category** | **Dirichlet distribution value** | **Central estimate (95% CrIs)** |
| GOS 2 | 115.5 | 0.116 (0.097 to 0.136) |
| GOS 3 | 140 | 0.140 (0.119 to 0.162) |
| GOS 4 | 79.3 | 0.079 (0.063 to 0.097) |
| GOS 5 | 665.1 | 0.665 (0.636 to 0.694) |

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 al163 reducing the life expectancy to 3.4 years, where it was otherwise expected to be greater.163

6.2.9.2 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 gastrointestinal haemorrhage on long-term quality of life are generally considered to be very small. A decision analysis by Goodacre et al.,164 assumed the event resulted in no utility loss. A separate decision analysis model by Meenan et al.,165 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 depend 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 onto each GOS state using data from the same patient group that was used to inform the stroke utilities.156 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 onto is that reported at 24 months within the Rivero-Arias paper.156 The assumed mapping between GOS scores and mRS scores, together with the estimated utility multipliers with 95% CrIs, are presented in Table 40.

**Table 40: Assumed relationship between GOS and mRS, and estimated utility multipliers for each GOS state**

|  |  |  |
| --- | --- | --- |
| **Glasgow Outcome Scale** | **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) |

6.2.9.3 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.

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 gastrointestinal haemorrhage was derived from 2009 Reference costs, currency code FZ38E (‘Gastrointestinal Bleed with length of stay two days or more without major CC’) for non-elective inpatients.155 The central estimate plus 95% CIs are presented in Table 41.

**Table 41: Mean cost estimates for GI bleeds**

|  |  |
| --- | --- |
| **Value** | **Central estimate (95% CIs)** |
| One-off cost of GI bleed | £1,261 ( £1,212 to £1,310) |

Costs of an intracranial haemorrhage

The costs of an intracranial haemorrhage 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 gastrointestinal 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 is presented in Table 42.

**Table 42: Cost components for GOS states**

|  |  |  |
| --- | --- | --- |
| **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 |

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

**Table 43: Details and sources of component costs associated with different GOS states**

|  |  |  |  |
| --- | --- | --- | --- |
| **Cost component name** | **Distribution** | **Details** | **Source** |
| GI equivalent costs | Normal (μ = 1261, σ = 25) | Code FZ38E | DoH155 |
| GOS 2 intensive care costs | Gamma (α = 165, β = 6) |  | Holmes163 |
| GOS 2 rehabilitation costs | Gamma (α = 250, β = 120) |  | Holmes163 |
| Nursing home costs | 52 x Gamma (α = 159, β = 6) |  | Holmes163 |
| Intracranial procedures costs | Normal (μ = 8829, σ = 633) | Code AA17Z | DoH155 |
| GOS 3 annual care cost | Gamma (α = 326, β = 104) |  | Holmes163 |
| GOS 4 rehabilitation costs | Gamma (α = 385, β = 45) |  | Holmes163 |

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

**Table 44: Estimated costs associated with different GOS outcomes**

|  |  |  |
| --- | --- | --- |
| **State** | **Mean One-off Costs (95% CrIs)** | **Mean Ongoing Costs (95% CrIs)** |
| GOS 2 | £46,785 (£40,895 to £53,250) | £50,047 (£49,645 to £50,434) |
| GOS 3 | £10,096 (£8,849 to £11,363) | £33,949 (£33,843 to £33,969) |
| GOS 4 | £27,419 (£22,582 to £32,964) | None |
| GOS 5 | £1,261 (£1,211 to £1,309) | None |

**6.3 Analyses undertaken**

To facilitate the interpretation of results four cohorts of patients were simulated assuming that CHADS2 was the prevalent tool. These four cohorts were:

1. Patients with a CHADS2 score of 0 (or 1 when considering warfarin) who have LA ABN which was detected by TTE
2. Patients with a CHADS2 score of 0 (1 when considering warfarin) who have LA ABN which was not detected by TTE
3. Patients with a CHADS2 score of 0 (1 when considering warfarin) who do not have LA ABN which was not detected by TTE
4. Patients with a CHADS2 score of 0 (1 when considering warfarin) who do not have LA ABN but where a TTE indicated that LA ABN was present.

The first two cohorts represent higher risk patients, the remaining two cohorts represent low-risk patients. Cohort 1 represents a true positive, cohort 2 represents a false negative, cohort 3 represents a true negative and cohort 4 represents a false negative. 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 ABN.

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 CHADS2 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 strategy: a scatterplot of the output of the PSA; **.166** the cost-effectiveness acceptability frontier (CEAF) over willingness to pay thresholds ranging from £0/QALY to £50,000/QALY; **167** and mean costs, QALYs and ICERs estimated from the mathematic models. The CEAF was used is it incorporates information from both expected value of perfect information (EVPI) analyses and cost-effectiveness acceptability curves in a single measure. cur summary statistics of the patient

The expected value of perfect information (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.168. 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 assuming that the incidence of AF was 1 per 1,000 person years (approximately the pooled rate for women and men aged 55 to 64 years reported by the Renfrew Paisley study).16 that there are 6.7 million people aged between 55 and 64 years in England and Wales,169 that 6% of people are in the CHADS2 0 category,144 and that 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 sub-populations 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 which indicates the maximum level of investment to reduce uncertainty in a subset of one or more parameters170 could not be undertaken for computational reasons. This is because each PSA run of 1,000 iterations, for each of the 14 groups considered, took approximately one hour to run, meaning EVPPI would take approximately 14,000 hours to run,, equivalent to over one and a half years of uninterrupted computing time.

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

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 ABN.

**6.4 Results**

6.4.1 Main clinical and cost effectiveness results

Results

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 scatter is in the north-west quadrant, suggested 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.

**Table 45: Summary of patient experience simulation comparing TTE and no TTE strategies in 50 year old males, with an initial CHADS2 score of zero, in informing the decision whether to treat patients with warfarin**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Cause of Death (%) | | | Average Number of Events | | | |
| Strategy | Life Years | 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 ABN treated | 28.928 | 10.8 | 1.8 | 87.4 | 0.111 | 0.223 | 0.014 | 0.112 |
| TTE = Transthoracic Echocardiography; LA ABN = Left Atrial Abnormality; ICH = Intracranial haemorrhage; NICH = Non- intracranial haemorrhage | | | | | | | | |

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| --- | --- |
| X:\EchoAF\R\Figures\W_50_0_M__PSA.jpeg | X:\EchoAF\R\Figures\W_50_0_M__CEAF.jpeg |
| a ) Scatterplot of difference in costs (£) against differences in QALYs | b) Cost-effectiveness Acceptability Frontier |
| |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***W\_50\_0\_M*** | **Mean Cost** | **Mean QALY** |  |  | **Mean** | **Jackknifed 95% Credible Intervals** | | | | | | | *No TTE* | £ 2,459 | 13.60 |  | ***ICER (£/QALY)*** | -£ 26,489 | -£ 26,552 | to | | -£ 26,408 | |  | | *TTE* | £ 4,712 | 13.51 |  | *Interpretation:* | *Dominated* | | |  | |  |  | | |
| c) Mean costs, QALYs and ICERs | |

**Figure 10: PSA scatterplots, CEAFs and mean ICERs in the W\_50\_0\_M comparison**

CEAF: Cost effectiveness acceptability frontier ICER: Incremental cost-effectiveness ratio PSA: Probabilistic scatterplots

Results

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 scatter is in the north-west quadrant, suggested 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.

**Table 46: Summary of patient experience simulation comparing TTE and no TTE strategies in 50 year old females with initial CHADS2 score of zero, treated with Warfarin**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Cause of Death (%) | | | Average Number 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 ABN treated | 31.734 | 12.6 | 2.1 | 85.2 | 0.130 | 0.259 | 0.017 | 0.130 |
| TTE = Transthoracic Echocardiography; LA ABN = Left Atrial Abnormality; ICH = Intracranial haemorrhage; NICH = Non- intracranial haemorrhage | | | | | | | | |

|  |  |
| --- | --- |
| X:\EchoAF\R\Figures\W_50_0_F__PSA.jpeg | X:\EchoAF\R\Figures\W_50_0_F__CEAF.jpeg |
| a ) Scatterplot of difference in costs (£) against differences in QALYs | b) Cost-effectiveness Acceptability Frontier |
| |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***W\_50\_0\_F*** | **Mean Cost** | **Mean QALY** |  |  | **Mean** | **Jackknifed 95% Credible Intervals** | | | | | | | *No TTE* | £ 2,815 | 14.27 |  | ***ICER (£/QALY)*** | -£ 34,078 | -£ 34,175 | to | | -£ 33,952 | |  | | *TTE* | £ 5,405 | 14.19 |  | *Interpretation:* | *Dominated* | | |  | |  |  | | |
| c) Mean costs, QALYs and ICERs | |

**Figure 11: PSA scatterplots, CEAFs and mean ICERs in the W\_50\_0\_F comparison**

CEAF: Cost effectiveness acceptability frontier ICER: Incremental cost-effectiveness ratio PSA: Probabilistic scatterplots

Results

Summary results for this treatment option and patient group are shown in table 47 and figure 12 below. The PSA scatter 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 table c in figure 12, 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 47: Summary of patient experience simulation comparing TTE and no TTE strategies in 65 year old males with initial CHADS2 score of zero, treated with Warfarin**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Cause of Death (%) | | | Average Number 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 ABN treated | 17.204 | 8.0 | 1.3 | 90.7 | 0.078 | 0.172 | 0.010 | 0.079 |
| TTE = Transthoracic Echocardiography; LA ABN = Left Atrial Abnormality; ICH = Intracranial haemorrhage; NICH = Non- intracranial haemorrhage | | | | | | | | |

|  |  |
| --- | --- |
| X:\EchoAF\R\Figures\W_65_0_M__PSA.jpeg | X:\EchoAF\R\Figures\W_65_0_M__CEAF.jpeg |
| a ) Scatterplot of difference in costs (£) against differences in QALYs | b) Cost-effectiveness Acceptability Frontier |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***W\_65\_0\_M*** | **Mean Cost** | **Mean QALY** |  |  | **Mean** | **Jackknifed 95% Credible Intervals** | | | | | | *No TTE* | £ 1,527 | 9.12 |  | ***ICER (£/QALY)*** | £ 66,793 | £ 66,217 | to | £ 67,599 | |  | | *TTE* | £ 2,467 | 9.13 |  | *Interpretation:* | *Neither dominated nor dominating* | | | |  |  | | |
| c) Mean costs, QALYs and ICERs | |

**Figure 12: PSA scatterplots, CEAFs and mean ICERs in the W\_65\_0\_M comparison**

CEAF: Cost effectiveness acceptability frontier ICER: Incremental cost-effectiveness ratio PSA: Probabilistic scatterplots

Results

Summary results for this treatment option and patient group are shown in table 48 and figure 13 below. 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 £1,000 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.

**Table 48: Summary of patient experience simulation comparing TTE and no TTE strategies in 65 year old females with initial CHADS2 score of zero, treated with Warfarin**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Cause of Death (%) | | | Average Number 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 ABN treated | 19.531 | 9.6 | 1.6 | 88.8 | 0.096 | 0.205 | 0.012 | 0.095 |
| TTE = Transthoracic Echocardiography; LA ABN = Left Atrial Abnormality; ICH = Intracranial haemorrhage; NICH = Non- intracranial haemorrhage | | | | | | | | |

|  |  |
| --- | --- |
| X:\EchoAF\R\Figures\W_65_0_F__PSA.jpeg | X:\EchoAF\R\Figures\W_65_0_F__CEAF.jpeg |
| a ) Scatterplot of difference in costs (£) against differences in QALYs | b) Cost-effectiveness Acceptability Frontier |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***W\_65\_0\_F*** | **Mean Cost** | **Mean QALY** |  |  | **Mean** | **Jackknifed 95% Credible Intervals** | | | | | | *No TTE* | £ 1,974 | 9.94 |  | ***ICER (£/QALY)*** | £ 39,485 | £ 39,291 | to | £ 39,754 | |  | | *TTE* | £ 3,106 | 9.97 |  | *Interpretation:* | *Neither dominated nor dominating* | | | |  |  | | |
| c) Mean costs, QALYs and ICERs | |

**Figure 13: PSA scatterplots, CEAFs and mean ICERs in the W\_65\_0\_F comparison**

CEAF: Cost effectiveness acceptability frontier ICER: Incremental cost-effectiveness ratio PSA: Probabilistic scatterplots

Results

In this patient group and treatment option the mathematical model 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 approximately half a QALY difference in means between the two strategies (the table in part c of figure 14) and approximately a £3,000 difference in mean costs. The mean ICER is estimated to be slightly over £6,000/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 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 over 99%.

**Table 49: Summary of patient experience simulation comparing TTE and no TTE strategies in 50 year old males with initial CHADS2 score of one, treated with Warfarin**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Cause of Death (%) | | | Average Number of Events | | | |
| Strategy | Life Years | 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 ABN treated | 26.250 | 20.8 | 3.5 | 75.7 | 0.218 | 0.424 | 0.025 | 0.208 |
| TTE = Transthoracic Echocardiography; LA ABN = Left Atrial Abnormality; ICH = Intracranial haemorrhage; NICH = Non- intracranial haemorrhage | | | | | | | | |

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| --- | --- |
| X:\EchoAF\R\Figures\W_50_1_M__PSA.jpeg | X:\EchoAF\R\Figures\W_50_1_M__CEAF.jpeg |
| a ) Scatterplot of difference in costs (£) against differences in QALYs | b) Cost-effectiveness Acceptability Frontier |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***W\_50\_1\_M*** | **Mean Cost** | **Mean QALY** |  |  | **Mean** | **Jackknifed 95% Credible Intervals** | | | | | | *No TTE* | £ 7,334 | 12.00 |  | ***ICER (£/QALY)*** | £ 6,274 | £ 6,269 | to | £ 6,278 | |  | | *TTE* | £ 10,343 | 12.48 |  | *Interpretation:* | *Neither dominated nor dominating* | | | |  |  | | |
| c) Mean costs, QALYs and ICERs | |

**Figure 14: PSA scatterplots, CEAFs and mean ICERs in the W\_50\_1\_M comparison**

CEAF: Cost effectiveness acceptability frontier ICER: Incremental cost-effectiveness ratio PSA: Probabilistic scatterplots

Results

In this patient group and treatment option the mathematical model 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 approximately half a QALY difference in means between the two strategies (the table in part c of figure 15) and approximately a £3,000 difference in mean costs. The mean ICER is estimated to be slightly over £7,000/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 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 over 99%.

**Table 50: Summary of patient experience simulation comparing TTE and no TTE strategies in 50 year old females with initial CHADS2 score of one, treated with Warfarin**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Cause of Death (%) | | | Average Number of Events | | | |
| Strategy | Life Years | 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 ABN treated | 28.660 | 22.8 | 3.8 | 73.4 | 0.243 | 0.459 | 0.027 | 0.234 |
| TTE = Transthoracic Echocardiography; LA ABN = Left Atrial Abnormality; ICH = Intracranial haemorrhage; NICH = Non- intracranial haemorrhage | | | | | | | | |

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| --- | --- |
| X:\EchoAF\R\Figures\W_50_1_F__PSA.jpeg | X:\EchoAF\R\Figures\W_50_1_F__CEAF.jpeg |
| a ) Scatterplot of difference in costs (£) against differences in QALYs | b) Cost-effectiveness Acceptability Frontier |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***W\_50\_1\_F*** | **Mean Cost** | **Mean QALY** |  |  | **Mean** | **Jackknifed 95% Credible Intervals** | | | | | | *No TTE* | £ 8,308 | 12.54 |  | ***ICER (£/QALY)*** | £ 7,197 | £ 7,192 | to | £ 7,202 | |  | | *TTE* | £ 11,919 | 13.04 |  | *Interpretation:* | *Neither dominated nor dominating* | | | |  |  | | |
| c) Mean costs, QALYs and ICERs | |

**Figure 15: PSA scatterplots, CEAFs and mean ICERs in the W\_50\_1\_F comparison**

CEAF: Cost effectiveness acceptability frontier ICER: Incremental cost-effectiveness ratio PSA: Probabilistic scatterplots

Results

In this patient group and treatment option the mathematical model 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 approximately a fifth of a QALY difference in means between the two strategies (the table in part c of figure 16) and approximately a £2,500 difference in mean costs. 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.

**Table 51: Summary of patient experience simulation comparing TTE and no TTE strategies in 65 year old males with initial CHADS2 score of one, treated with Warfarin**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Cause of Death (%) | | | Average Number of Events | | | |
| Strategy | Life Years | 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 ABN treated | 16.361 | 12.5 | 2.1 | 85.4 | 0.121 | 0.265 | 0.016 | 0.125 |
| TTE = Transthoracic Echocardiography; LA ABN = Left Atrial Abnormality; ICH = Intracranial haemorrhage; NICH = Non- intracranial haemorrhage | | | | | | | | |

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| --- | --- |
| X:\EchoAF\R\Figures\W_65_1_M__PSA.jpeg | X:\EchoAF\R\Figures\W_65_1_M__CEAF.jpeg |
| a ) Scatterplot of difference in costs (£) against differences in QALYs | b) Cost-effectiveness Acceptability Frontier |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***W\_65\_1\_M*** | **Mean Cost** | **Mean QALY** |  |  | **Mean** | **Jackknifed 95% Credible Intervals** | | | | | | *No TTE* | £ 3,242 | 8.41 |  | ***ICER (£/QALY)*** | £ 10,626 | £ 10,612 | to | £ 10,633 | |  | | *TTE* | £ 5,737 | 8.64 |  | *Interpretation:* | *Neither dominated nor dominating* | | | |  |  | | |
| c) Mean costs, QALYs and ICERs | |

**Figure 16: PSA scatterplots, CEAFs and mean ICERs in the W\_65\_1\_M comparison**

CEAF: Cost effectiveness acceptability frontier ICER: Incremental cost-effectiveness ratio PSA: Probabilistic scatterplots

Results

In this patient group and treatment option 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 approximately a fifth ofa QALY difference in means between the two strategies (the table in part c of figure 17) and approximately a £4,000 difference in mean costs. The mean ICER is estimated to be slightly under £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.

**Table 52: Summary of patient experience simulation comparing TTE and no TTE strategies in 65 year old females with initial CHADS2 score of one, treated with Warfarin**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Cause of Death (%) | | | Average Number of Events | | | |
| Strategy | Life Years | 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 ABN treated | 18.544 | 14.2 | 2.5 | 83.3 | 0.141 | 0.300 | 0.018 | 0.149 |
| TTE = Transthoracic Echocardiography; LA ABN = Left Atrial Abnormality; ICH = Intracranial haemorrhage; NICH = Non- intracranial haemorrhage | | | | | | | | |

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| a ) Scatterplot of difference in costs (£) against differences in QALYs | b) Cost-effectiveness Acceptability Frontier |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***W\_65\_1\_F*** | **Mean Cost** | **Mean QALY** |  |  | **Mean** | **Jackknifed 95% Credible Intervals** | | | | | | *No TTE* | £ 3,929 | 9.15 |  | ***ICER (£/QALY)*** | £ 14,953 | £ 14,941 | to | £ 14,964 | |  | | *TTE* | £ 7,248 | 9.38 |  | *Interpretation:* | *Neither dominated nor dominating* | | | |  |  | | |
| c) Mean costs, QALYs and ICERs | |

**Figure 17: PSA scatterplots, CEAFs and mean ICERs in the W\_65\_1\_F comparison**

CEAF: Cost effectiveness acceptability frontier ICER: Incremental cost-effectiveness ratio PSA: Probabilistic scatterplots

Results

In this patient group and treatment option 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 £2,000 more expensive and slightly less effective than the no TTE strategy. The CEAF indicates that the TTE strategy (solid line) does not appear the optimal strategy at all willingness to pay thresholds from £0/QALY to £50,000/QALY compared with the no TTE strategy (dashed line).

**Table 53: Summary of patient experience simulation comparing TTE and no TTE strategies in 50 year old males with initial CHADS2 score of zero, treated with Rivaroxiban**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Cause of Death (%) | | | Average Number of Events | | | |
| Strategy | Life Years | 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 ABN treated | 28.963 | 10.5 | 1.8 | 87.6 | 0.108 | 0.219 | 0.014 | 0.113 |
| TTE = Transthoracic Echocardiography; LA ABN = Left Atrial Abnormality; ICH = Intracranial haemorrhage; NICH = Non- intracranial haemorrhage | | | | | | | | |

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| X:\EchoAF\R\Figures\R_50_0_M__PSA.jpeg | X:\EchoAF\R\Figures\R_50_0_M__CEAF.jpeg |
| a ) Scatterplot of difference in costs (£) against differences in QALYs | b) Cost-effectiveness Acceptability Frontier |
| |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***R\_50\_0\_M*** | **Mean Cost** | **Mean QALY** |  |  | **Mean** | **Jackknifed 95% Credible Intervals** | | | | | | | *No TTE* | £ 2,449 | 13.61 |  | ***ICER (£/QALY)*** | -£ 34,060 | -£ 34,170 | to | | -£ 33,910 | |  | | *TTE* | £ 4,614 | 13.54 |  | *Interpretation:* | *Dominated* | | |  | |  |  | | |
| c) Mean costs, QALYs and ICERs | |

**Figure 18: PSA scatterplots, CEAFs and mean ICERs in the R\_50\_0\_M comparison**

CEAF: Cost effectiveness acceptability frontier ICER: Incremental cost-effectiveness ratio PSA: Probabilistic scatterplots

Results

In this patient group and treatment option 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 £2,500 more expensive and slightly less effective than the no TTE strategy. The CEAF indicates that the TTE strategy (solid line) does not appear the optimal strategy at all willingness to pay thresholds from £0/QALY to £50,000/QALY compared with the no TTE strategy (dashed line).

**Table 54: Summary of patient experience simulation comparing TTE and no TTE strategies in 50 year old females with initial CHADS2 score of zero, treated with Rivaroxiban**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Cause of Death (%) | | | Average Number 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 ABN treated | 31.772 | 12.4 | 2.1 | 85.5 | 0.127 | 0.255 | 0.017 | 0.130 |
| TTE = Transthoracic Echocardiography; LA ABN = Left Atrial Abnormality; ICH = Intracranial haemorrhage; NICH = Non- intracranial haemorrhage | | | | | | | | |

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| --- | --- |
| X:\EchoAF\R\Figures\R_50_0_F__PSA.jpeg | X:\EchoAF\R\Figures\R_50_0_F__CEAF.jpeg |
| a ) Scatterplot of difference in costs (£) against differences in QALYs | b) Cost-effectiveness Acceptability Frontier |
| |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***R\_50\_0\_F*** | **Mean Cost** | **Mean QALY** |  |  | **Mean** | **Jackknifed 95% Credible Intervals** | | | | | | | *No TTE* | £ 2,779 | 14.27 |  | ***ICER (£/QALY)*** | -£ 47,535 | -£ 47,773 | to | | -£ 47,271 | |  | | *TTE* | £ 5,315 | 14.22 |  | *Interpretation:* | *Dominated* | | |  | |  |  | | |
| c) Mean costs, QALYs and ICERs | |

**Figure 19: PSA scatterplots, CEAFs and mean ICERs in the R\_50\_0\_F comparison**

CEAF: Cost effectiveness acceptability frontier ICER: Incremental cost-effectiveness ratio PSA: Probabilistic scatterplots

Results

For this patient group and treatment combination, the majority of the PSA scatter (figure 20a) are either in the north east or north west quadrant. Slightly more of the scatter 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 (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 only estimated to become optimal at around £33,700/QALY.

**Table 55: Summary of patient experience simulation comparing TTE and no TTE strategies in 65 year old males with initial CHADS2 score of zero, treated with Rivaroxiban**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Cause of Death (%) | | | Average Number of Events | | | |
| Strategy | Life Years | 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 ABN treated | 17.221 | 7.8 | 1.3 | 90.9 | 0.076 | 0.169 | 0.010 | 0.080 |
| TTE = Transthoracic Echocardiography; LA ABN = Left Atrial Abnormality; ICH = Intracranial haemorrhage; NICH = Non- intracranial haemorrhage | | | | | | | | |

|  |  |
| --- | --- |
| X:\EchoAF\R\Figures\R_65_0_M__PSA.jpeg | X:\EchoAF\R\Figures\R_65_0_M__CEAF.jpeg |
| a ) Scatterplot of difference in costs (£) against differences in QALYs | b) Cost-effectiveness Acceptability Frontier |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***R\_65\_0\_M*** | **Mean Cost** | **Mean QALY** |  |  | **Mean** | **Jackknifed 95% Credible Intervals** | | | | | | *No TTE* | £ 1,510 | 9.12 |  | ***ICER (£/QALY)*** | £ 30,310 | £ 30,179 | to | £ 30,487 | |  | | *TTE* | £ 2,393 | 9.15 |  | *Interpretation:* | *Neither dominated nor dominating* | | | |  |  | | |
| c) Mean costs, QALYs and ICERs | |

**Figure 20: PSA scatterplots, CEAFs and mean ICERs in the R\_65\_0\_M comparison**

CEAF: Cost effectiveness acceptability frontier ICER: Incremental cost-effectiveness ratio PSA: Probabilistic scatterplots

Results

The mathematical model results suggest that the TTE strategy is more expensive and slightly more clinically effective, on the average, than the no TTE strategy, with the PSA scatter appearing slightly more predominant in the north east than the north west quadrant. The mean ICER estimate is slightly over £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. 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.

**Table 56: Summary of patient experience simulation comparing TTE and no TTE strategies in 65 year old females with initial CHADS2 score of zero, treated with Rivaroxiban**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Cause of Death (%) | | | Average Number of Events | | | |
| Strategy | Life Years | 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 ABN treated | 19.554 | 9.4 | 1.6 | 89.0 | 0.093 | 0.201 | 0.012 | 0.096 |
| TTE = Transthoracic Echocardiography; LA ABN = Left Atrial Abnormality; ICH = Intracranial haemorrhage; NICH = Non- intracranial haemorrhage | | | | | | | | |

|  |  |
| --- | --- |
| X:\EchoAF\R\Figures\R_65_0_F__PSA.jpeg | X:\EchoAF\R\Figures\R_65_0_F__CEAF.jpeg |
| a ) Scatterplot of difference in costs (£) against differences in QALYs | b) Cost-effectiveness Acceptability Frontier |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***R\_65\_0\_F*** | **Mean Cost** | **Mean QALY** |  |  | **Mean** | **Jackknifed 95% Credible Intervals** | | | | | | *No TTE* | £ 1,955 | 9.95 |  | ***ICER (£/QALY)*** | £ 22,751 | £ 22,681 | to | £ 22,844 | |  | | *TTE* | £ 3,039 | 9.99 |  | *Interpretation:* | *Neither dominated nor dominating* | | | |  | | | |
| c) Mean costs, QALYs and ICERs | |

**Figure 21: PSA scatterplots, CEAFs and mean ICERs in the R\_65\_0\_F comparison**

CEAF: Cost effectiveness acceptability frontier ICER: Incremental cost-effectiveness ratio PSA: Probabilistic scatterplots

Results

The mathematical model results suggest that the TTE strategy is more expensive and slightly more clinically effective, on the average, than the no TTE strategy, with the PSA scatter appearing slightly more predominant in the north east than the north west quadrant. The mean ICER estimate is slightly under £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. 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.

**Table 57: Summary of patient experience simulation comparing TTE and no TTE strategies in 65 year old males with initial CHADS2 score of zero, treated with Dabigatran**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Cause of Death (%) | | | Average Number of Events | | | |
| Strategy | Life Years | 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 ABN treated | 17.251 | 7.5 | 1.3 | 91.2 | 0.072 | 0.163 | 0.010 | 0.081 |
| TTE = Transthoracic Echocardiography; LA ABN = Left Atrial Abnormality; ICH = Intracranial haemorrhage; NICH = Non- intracranial haemorrhage | | | | | | | | |

|  |  |
| --- | --- |
| X:\EchoAF\R\Figures\D_65_0_M__PSA.jpeg | X:\EchoAF\R\Figures\D_65_0_M__CEAF.jpeg |
| a ) Scatterplot of difference in costs (£) against differences in QALYs | b) Cost-effectiveness Acceptability Frontier |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***D\_65\_0\_M*** | **Mean Cost** | **Mean QALY** |  |  | **Mean** | **Jackknifed 95% Credible Intervals** | | | | | | *No TTE* | £ 1,489 | 9.13 |  | ***ICER (£/QALY)*** | £ 14,728 | £ 14,693 | to | £ 14,782 | |  | | *TTE* | £ 2,321 | 9.18 |  | *Interpretation:* | *Neither dominated nor dominating* | | | |  | | | |
| c) Mean costs, QALYs and ICERs | |

**Figure 22: PSA scatterplots, CEAFs and mean ICERs in the D\_65\_0\_M comparison**

CEAF: Cost effectiveness acceptability frontier ICER: Incremental cost-effectiveness ratio PSA: Probabilistic scatterplots

Results

The mathematical model results suggest that the TTE strategy is more expensive and slightly more clinically effective, on the average, than the no TTE strategy, with the PSA scatter appearing slightly more predominant in the north east than the north west quadrant. The mean ICER estimate is slightly over £12,000, and the CEAF 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.

**Table 58: Summary of patient experience simulation comparing TTE and no TTE strategies in 65 year old females with initial CHADS2 score of zero, treated with Dabigatran**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Cause of Death (%) | | | Average Number of Events | | | |
| Strategy | Life Years | 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 ABN treated | 19.598 | 9.0 | 1.6 | 89.4 | 0.089 | 0.195 | 0.012 | 0.097 |
| TTE = Transthoracic Echocardiography; LA ABN = Left Atrial Abnormality; ICH = Intracranial haemorrhage; NICH = Non- intracranial haemorrhage | | | | | | | | |

…

|  |  |
| --- | --- |
| X:\EchoAF\R\Figures\D_65_0_F__PSA.jpeg | X:\EchoAF\R\Figures\D_65_0_F__CEAF.jpeg |
| a ) Scatterplot of difference in costs (£) against differences in QALYs | b) Cost-effectiveness Acceptability Frontier |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***D\_65\_0\_F*** | **Mean Cost** | **Mean QALY** |  |  | **Mean** | **Jackknifed 95% Credible Intervals** | | | | | | *No TTE* | £ 1,942 | 9.95 |  | ***ICER (£/QALY)*** | £ 12,314 | £ 12,290 | to | £ 12,348 | |  | | *TTE* | £ 2,946 | 10.01 |  | *Interpretation:* | *Neither dominated nor dominating* | | | |  |  | | |
| c) Mean costs, QALYs and ICERs | |

**Figure 23: PSA scatterplots, CEAFs and mean ICERs in the D\_65\_0\_F comparison**

CEAF: Cost effectiveness acceptability frontier ICER: Incremental cost-effectiveness ratio PSA: Probabilistic scatterplots

6.4.2 EVPI results

The individual EVPI curves for MAICERs varying from £0/QALY to £50,000/QALY are presented in table 59 below. 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.

**Figure 24: Relationship between individual EVPI and MAICER for all 14 comparisons, together with individual and EVPI at MAICERs of £20,000/QALY and £30,000/QALY**

|  |  |
| --- | --- |
| X:\EchoAF\R\Figures\W_50_0_M__EVPI.jpeg | X:\EchoAF\R\Figures\W_50_0_F__EVPI.jpeg |
| |  |  |  |  |  | | --- | --- | --- | --- | --- | | **MAICER** | **Individual EVPI (£)** | **Population EVPI (£million)** | | | | **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 (£million)** | | | | **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 | |
| 1. **W\_50\_0\_M** | 1. **W\_50\_0\_F** |
| C:\Users\Jon Minton\Google Drive\EchoAF\R\Figures\W_65_0_M__EVPI.jpeg | C:\Users\Jon Minton\Google Drive\EchoAF\R\Figures\W_65_0_F__EVPI.jpeg |
| |  |  |  |  |  | | --- | --- | --- | --- | --- | | **MAICER** | **Individual EVPI (£)** | **Population EVPI (£million)** | | | | **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 | | |  |  |  |  |  | | --- | --- | --- | --- | --- | | **MAICER** | **Individual EVPI (£)** | **Population EVPI (£million)** | | | | **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 | |
| 1. **W\_65\_0\_M** | 1. **W\_65\_0\_F** |
| C:\Users\Jon Minton\Google Drive\EchoAF\R\Figures\W_50_1_M__EVPI.jpeg | C:\Users\Jon Minton\Google Drive\EchoAF\R\Figures\W_50_1_F__EVPI.jpeg |
| |  |  |  |  |  | | --- | --- | --- | --- | --- | | **MAICER** | **Individual EVPI (£)** | **Population EVPI (£million)** | | | | **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 (£million)** | | | | **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 | |
| 1. **W\_50\_1\_M** | 1. **W\_50\_1\_F** |
| C:\Users\Jon Minton\Google Drive\EchoAF\R\Figures\W_65_1_M__EVPI.jpeg | C:\Users\Jon Minton\Google Drive\EchoAF\R\Figures\W_65_1_F__EVPI.jpeg |
| |  |  |  |  |  | | --- | --- | --- | --- | --- | | **MAICER** | **Individual EVPI (£)** | **Population EVPI (£million)** | | | | **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 | | |  |  |  |  |  | | --- | --- | --- | --- | --- | | **MAICER** | **Individual EVPI (£)** | **Population EVPI (£million)** | | | | **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 | |
| 1. **W\_65\_1\_M** | 1. **W\_65\_1\_F** |
| C:\Users\Jon Minton\Google Drive\EchoAF\R\Figures\R_50_0_M__EVPI.jpeg | C:\Users\Jon Minton\Google Drive\EchoAF\R\Figures\R_50_0_F__EVPI.jpeg |
| |  |  |  |  |  | | --- | --- | --- | --- | --- | | **MAICER** | **Individual EVPI (£)** | **Population EVPI (£million)** | | | | **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 (£million)** | | | | **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 | |
| 1. **R\_50\_0\_M** | 1. **R\_50\_0\_F** |
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| |  |  |  |  |  | | --- | --- | --- | --- | --- | | **MAICER** | **Individual EVPI (£)** | **Population EVPI (£million)** | | | | **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 | | |  |  |  |  |  | | --- | --- | --- | --- | --- | | **MAICER** | **Individual EVPI (£)** | **Population EVPI (£million)** | | | | **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 | |
| 1. **R\_65\_0\_M** | 1. **R\_65\_0\_F** |
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| |  |  |  |  |  | | --- | --- | --- | --- | --- | | **MAICER** | **Individual EVPI (£)** | **Population EVPI (£million)** | | | | **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 (£million)** | | | | **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 | |
| 1. **D\_65\_0\_M** | 1. **D\_65\_0\_F** |

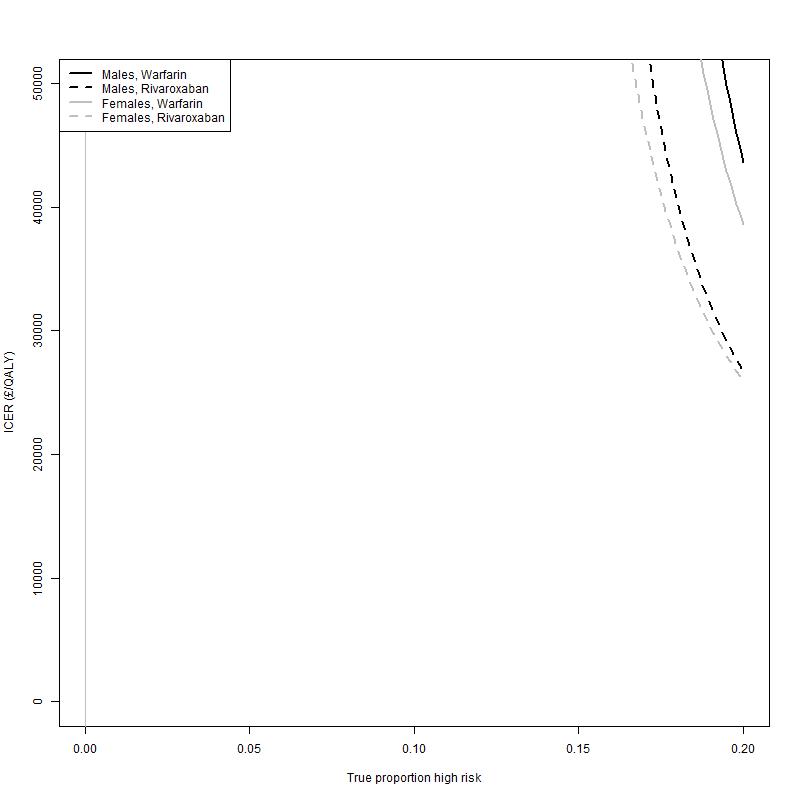
EVPI: Expected value of perfect information MAICER: Maximum acceptable incremental cost effectiveness ratio QALY: Quality adjusted lifeyear

6.4.3 Sensitivity of ICERs to joint sensitivity and specificity of TTE, and true prevalence of LA ABN

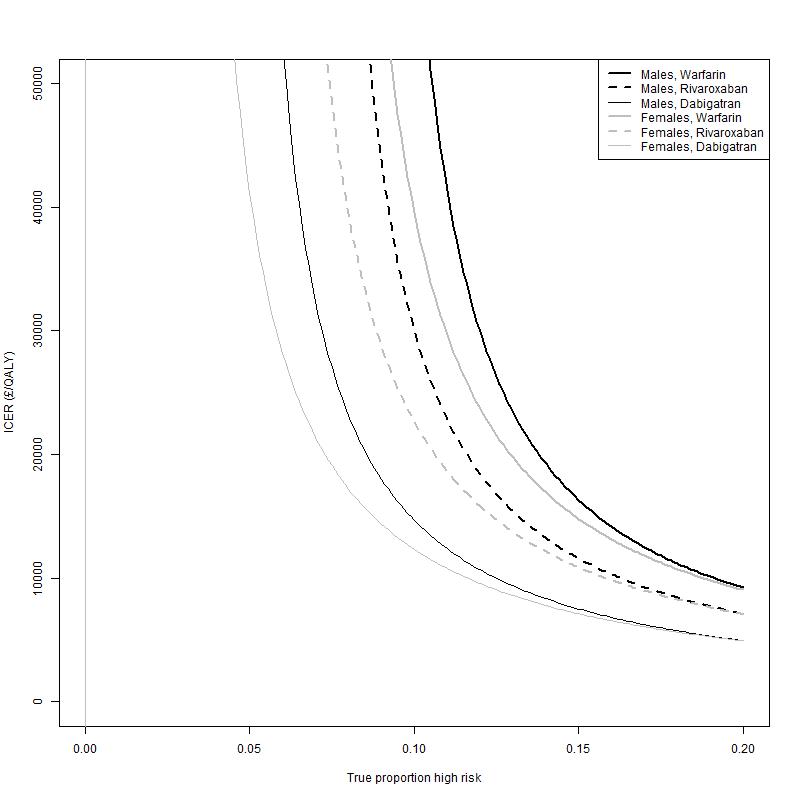
In order to explore the influence of certain parameters on the cost effectiveness estimates, the effect of changing the sensitivity and specificity estimates, holding all other values at their means, were calculated for each of the 14 comparisons. These are presented in appendix 11.

Additionally, the influence of difference assumptions about the true proportion with LA ABN was estimated in a similar way. These are presented in figure 25 for people aged 50 with a CHADS2 score of zero, figure 26 for people aged 65 with a CHADS2 score of zero, and in figure 27 for people with a CHADS2 score of one point.

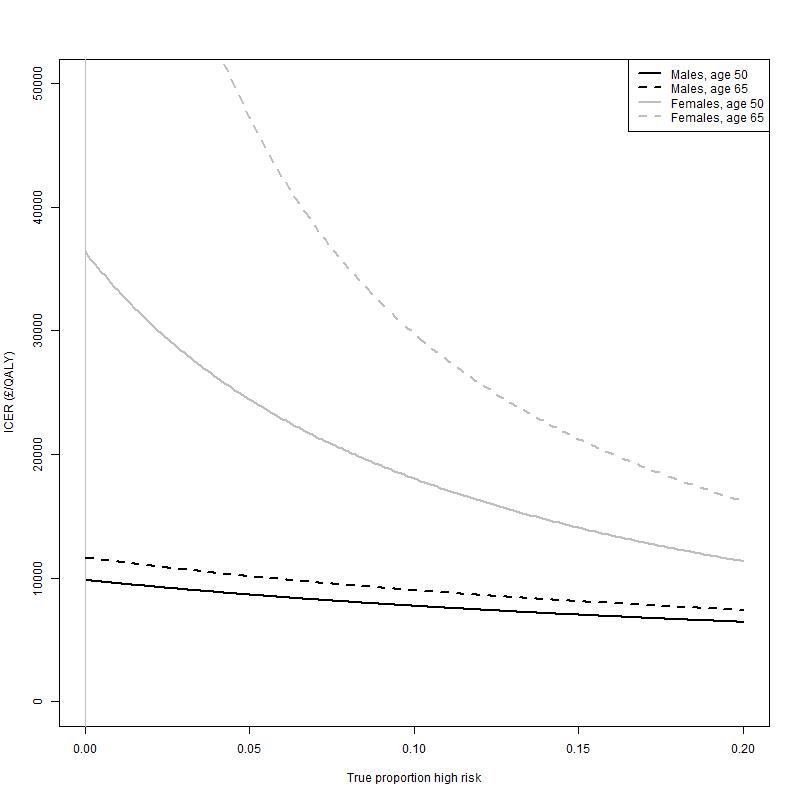
**Figure 25: Effect of true proportion of population with LA ABN on estimated ICER in 50 year olds with a CHADS2 score of zero**



**Figure 26: Effect of true proportion of population with LA ABN on estimated ICER in 65 year olds with a CHADS2 score of zero**



**Figure 27: Effect of true proportion of population with LA ABN on estimated ICER in people aged either 50 or 65 who have a CHADS2 score of one point**



The figures indicate that, over the range of values considered here, the true prevalence of the LA ABN could have a significant influence on the ICER in people aged 65 with a CHADS2 score of zero, suggesting that identifying the true value of this parameter in these patient populations may be more important than in fifty year olds or people with a CHADS2 of one point. Amongst people with a CHADS2 score of one point, it may be more valuable to identify the true value of this parameter in females than in males.

6.4.4. 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 STA 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 below.

**Table 59: Summary of patient populations modelled**

|  |  |
| --- | --- |
| **Patient population** | **OACs considered** |
| Males, age 50, CHADS2 score of zero | Warfarin, rivaroxaban |
| Females, age 50, CHADS2 score of zero | Warfarin, rivaroxaban |
| Male, age 65, CHADS2 score of zero | Warfarin, rivaroxaban, dabigatran |
| Females, age 65, CHADS2 score of zero | Warfarin, rivaroxaban, dabigatran |
| Males, age 50, CHADS2 score of one | Warfarin |
| Females, age 50, CHADS2 score of one | Warfarin |
| Male, age 65, CHADS2 score of one | Warfarin |
| Females, age 65, CHADS2 score of one | Warfarin |

tient populationban, dabigatranzeroidered, as shown in table X below. dered:ng TTE into the decision making process, compare

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 with a CHADS2 score of zero would involve six comparisons. In addition, because rivararoxaban is effectively recommended by NICE at a CHADS2 score of one, and dabigatran effectively recommended at a CHADS2 score of one in people aged 65 or over, 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.

6.4.5 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).

6.4.6 Interpretation of the results

The series of results presented above can be simplistically summarised as shown in table 60 below:

**Table 60: Qualitative summary of main results**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Age | Gender | CHADS2 score of 1 | OAC | Ruled out by simple dominance | Likely to be cost effective at £20,000/QALY |
| 50 | male | no | warfarin | yes | no |
| 50 | female | no | warfarin | yes | no |
| 65 | male | no | warfarin | no | no |
| 65 | female | no | warfarin | no | no (possibly at £30,000/QALY) |
| 50 | male | yes | warfarin | no | yes |
| 50 | female | yes | warfarin | no | yes |
| 65 | male | yes | warfarin | no | yes |
| 65 | female | yes | warfarin | no | yes |
| 50 | male | no | rivaroxaban | yes | no |
| 50 | female | no | rivaroxaban | yes | no |
| 65 | male | no | rivaroxaban | no | no (possibly at £30,000/QALY) |
| 65 | female | no | rivaroxaban | no | maybe |
| 65 | male | no | dabigatran | no | yes |
| 65 | female | no | dabigatran | no | yes |

These results suggest that:

* In newly diagnosed patients with a CHADS2 score of one, who are not already receiving warfarin, rivaroxaban, or dabigatran, then it may be cost effective to use TTE to help inform the decision whether to prescribe warfarin;
* In newly diagnosed patients aged 65 or older, it may be cost effective to use TTE to help inform the decision about whether to prescribe dabigatran.

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 ABN that were gained from the TTE then it is possible that TTE would be perceived as cost effective.

6.4.7 Limitations in the modelling.

Assumptions have been made within the modelling that have simplified the decision problem. Whilst 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 on CHADS2 scores alone. Alternative baseline strategies include the use of CHA2DS2-VASc, andCHADS2 orCHA2DS2-VASc scores in combination with bleed risk scores such as 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 150mg twice daily, rather than allowing some patients to receive a lower dose of 110mg 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 – 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 to base the economic evaluation was a relatively small study, of fewer than 400 patients, and in the group of interest, those patients who would be given a CHADS2 score of 0, fewer than 25 patients, and fewer than 80 patients with a CHADS2 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 lifetables and were not adjusted for the probability of bleeding or stroke mortality. As such, the risk of mortality is likely to be slightly over-estimated.

6) The sensitivity and specificity of TTE in identifying LA ABN 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 ABN. 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 CHADS2 score, and so the mathematical model was only be run in patients aged 65 years or over when considering dabigatran as the OAC of choice.

**6.5 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; CINAHL, Web of Science (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 atrial fibrillation

**Intervention:** Transthoracic echocardiogram

**Comparators:** Conventional therapy

**Setting:** Interventions delivered within any geographical jurisdiction

**Outcomes:** Cost perquality-adjusted life-years (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 atrial fibrillation;
* the intervention was not transthoracic echocardiogram;
* studies that reported only costs or outcomes;
* studies that were not full economic evaluation like cost-minimisation analysis;
* studies that were not published papers such as editorials, commentaries and letters; and
* studies that were not published in English language.

All the potentially relevant citations were imported to Reference Manager Software [version 12] and duplicates were removed. The titles and abstracts of the unique studies were then screened according to the pre-determined 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.

*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*

One thousand and thirty-eight studies were identified through the systematic searches. Following the removal of duplicate citations, eight hundred and eighty-one unique studies were retrieved. Of these, forty-three potentially relevant citations were retrieved for a more detailed inspection. Further, twenty-six studies were excluded and seventeen studies were retrieved for double screening. After double screening, seventeen studies were excluded as they failed to satisfy one or more inclusion criteria.

**7 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES**

The assessment of newly diagnosed patients with AF with a TTE is unlikely to cause a significant impact to either the NHS or other parties. TTEs are relatively easily available as well as both safe and non-invasive for patients, with staff 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 due to the reduction in stroke following appropriate management, although there is likely to be an increase in bleed related admissions.**8 DISCUSSION**

**8.1 Statement of principle findings**

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 or higher, with the exceptions of atrial thrombi, atrial septal defect and pulmonary embolism, for which sensitivity was lower. There was a high prevalence (around 25-30%) of ischaemic heart disease, valvular heart disease and heart failure in AF patients 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 pulmonary embolism by lung scan and atrial thrombi and atrial septal hypertrophy by TOE to avoid false negatives for these pathologies.

The results of the mathematical model indicated that in newly diagnosed patients with a CHADS2 score of one, who are not already receiving warfarin, rivaroxaban, or dabigatran, then it may be cost effective to use TTE to help inform the decision whether to prescribe warfarin. In newly diagnosed patients aged 65 or older, 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.

**8.2 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 due to limiting to studies published in 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 co-morbidities 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 newly diagnosed AF patients could address the impact on patients, which may go beyond simple changes in medical treatment, although any such trial would be costly due 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 AF patients 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 ABN in patients categorised by CHADS2 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 it is probably that TTE is cost effective.

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

**8.3 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.144 as this was recent, internally consistent study, using the CHADS2 tool and 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 ABN was sparse, and additionally that the numbers of patients in the CHADS2 0 or 1 categories was small, all less than 80 patients, with three values less than 25.

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

**8.4 Other relevant factors**

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

**9 CONCLUSIONS**

**9.1 Implications for service provision**

Our conclusions have little implications for service provision. Should TTE be recommended for those patients with CHADS2 scores of 0 or 1, 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 use of existing TTE equipment and extra staff time needed.

**9.2 Suggested research priorities**

Following-up newly diagnosed AF patients 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 a CHADS2 scores 0 or 1 that have LA ABN. 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 ABN should be collected.

Any additional benefit of TTE further to those associated with treatment for stroke prevention also needs to be researched. Even small gains would equate to TTE being perceived as cost effective.**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 | left atrial thrombus (includes left atrial appendage thrombus), right atrial thrombus (includes right atrial appendage thrombus), thrombosis of ventricle, atherosclerotic heart disease (coronary artery atherosclerosis/disease/stenosis), aneurysm of heart |
| 3 | Pulmonary disease | pulmonary embolism, 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, left ventricular non-compaction |
| 7 | Heart failure | Congestive heart failure, left atrial enlargement, left or right ventricular 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, even though ECG may indicate their diagnoses, ECG would not provide a definitive diagnosis. Left atrial 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 http://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 AF diagnosis, or at time of AF diagnosis

Transposition of great arteries, Fallot’s tetralogy, atrioventricular 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 TTE)

Myocardial rupture, cardiac tamponade

**Appendix 2: Diagnosis of pathologies**

Diagnostic tools used for pathologies are reported in the table below

Personal communications (in date order) from

Professor John Chambers, Guy’s & St Thomas’ Hospital, 7.7.11

Dr Rick Steeds, University Hospital (Queen Elizabeth) NHS Foundation Trust, 8.7.11

Dr Guy Lloyd, Eastbourne Hospital, 11.07.11

**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 | left atrial thrombus (includes left atrial appendage thrombus) | TOE primary tool for investigation |
|  |  | right atrial thrombus (includes right atrial appendage 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 | pulmonary embolism | For this, TTE/TOE would not be used for the primary investigation. Pulmonary embolism is diagnosed on the history, serum fibrin degradation products (FDP) 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 (right heart catheterisation) 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 |
| 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 |
|  |  | left ventricular non-compaction | TTE primary tool for investigation, may be used with cardiac MRI |
| 7 | Heart failure | Congestive heart failure | TTE primary tool for investigation, may be used with cardiac MRI |
|  |  | Left ventricular dysfunction or impairment | TTE primary tool for investigation, may be used with cardiac MRI or MUGA (Multi Gated Acquisition Scan) |
|  |  | Left atrial enlargement | TTE primary tool for investigation |
|  |  | Right ventricular dysfunction | TTE primary tool for investigation, may be used with 3DTTE 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 |

**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. (17404)

2 ((aortic or aorta or mitral or pulmonary or triscuspid or valvular) and (regurgitation or stenosis or incompetence or insufficiency)).mp. (83008)

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. (40373)

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. (12797)

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. (17404)

16 valvular defects.mp. (167)

17 valvular heart disease.mp. or Heart Valve Diseases/ (17403)

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. (54399)

24 hypertension, pulmonary/ or primary pulmonary hypertension.mp. (19785)

25 aortic diseases/ or aortic disease.mp. or aorta disease.mp. (11798)

26 aortic aneurysm/ or aortic aneurysm.mp. or aorta aneurysm.mp. (33140)

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. (11825)

33 cardiomyopathy, hypertrophic/ or hypertrophic cardiomyopathy.mp. (11890)

34 Heart failure/ or heart failure.mp. (104920)

35 hypertrophy, left ventricular/ or left ventricular hypertrophy.mp. or left ventricular impairment.mp. (15400)

36 heart left ventricle hypertrophy.mp. (0)

37 congestive heart failure.mp. (27387)

38 endocarditis/ or endocarditis.mp. (26716)

39 pericarditis/ or pericarditis.mp. (11273)

40 myocardial ischemia/ or ischemic heart disease.mp. or heart muslce ischemia.mp. (39971)

41 (angina or angina pectoris or angina pectoris, variant or angina, unstable or ludwig's angina or microvascular angina).mp. (54437)

42 coronary thrombosis/ or coronary thrombosis.mp. (5820)

43 (atherosclerotic heart disease or atherosclerotic cardiovascular disease).mp. (1343)

44 Myocardial Infarction/co (22261)

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. (47650)

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. (40602)

55 (coronary artery anuerysm or aorta anuerysm).mp. (0)

56 heart neoplasms/ or heart masses.mp. or cardiac masses.mp. (11718)

57 heart tumo?r.mp. (91)

58 pulmonary embolism/ or pulmonary embolism.mp. or lung embolism.mp. (32491)

59 lung disease/ or pulmonary disease.mp. (79806)

60 hypertension, pulmonary/ or pulmonary hypertension.mp. (26664)

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 (622101)

64 exp epidemiologic studies/ (1222832)

65 exp epidemiology/ (17055)

66 epidemiology.tw. (73246)

67 exp prevalence/ (135244)

68 prevalence.ti. (60865)

69 exp incidence/ (134727)

70 incidence.ti. (58881)

71 64 or 65 or 66 or 67 or 68 or 69 or 70 (1481934)

72 63 and 71 (102242)

73 atrial fibrillation/ (25007)

74 af.tw. (13864)

75 atrial fibrillation.tw. (26363)

76 73 or 74 or 75 (40470)

77 72 and 76 (3488)

**Diagnostic**

1 heart valve diseases/ or heart valve problems.mp. or valvular heart disease.mp. (17116)

2 ((aortic or aorta or mitral or pulmonary or triscuspid or vavular) and (regurgitation or stenosis or incompetence or insufficiency)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (81348)

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] (39689)

8 congenital heart malformation.mp. (99)

9 heart septal defects, atrial/ or atrial spetal 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. (12594)

13 heart atrium septal defect.mp. (0)

14 aortic coartation/ or coartation 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/ (15539)

17 valvular defects.mp. (165)

18 valvular heart disease.mp. or Heart Valve Diseases/ (17115)

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. (52978)

25 hypertension, pulmonary/ or primary pulmonary hypertension.mp. (19366)

26 aortic diseases/ or aortic disease.mp. or aorta disease.mp. (11598)

27 aortic aneurysm/ or aortic aneurysm.mp. or aorta aneurysm.mp. (32524)

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] (11481)

34 cardiomyopathy, hypertrophic/ or hypertrophic cardiomyopathy.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (11642)

35 Heart failure/ or heart failure.mp. (101953)

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] (14894)

37 heart left ventricle hypertrophy.mp. (0)

38 congestive heart failure.mp. (26691)

39 endocarditis/ or endocarditis.mp. (26285)

40 pericarditis/ or pericarditis.mp. (11130)

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] (38960)

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] (53232)

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] (21843)

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. (46892)

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] (39871)

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] (11574)

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] (31929)

60 lung disease/ or pulmonary disease.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (78271)

61 hypertension, pulmonary/ or pulmonary hypertension.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (25991)

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 (609155)

65 Echocardiography/ (54742)

66 echocardiography.mp. (98874)

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 (99048)

71 prognosis.sh. (281258)

72 diagnosed.tw. (240154)

73 cohort:.mp. (196722)

74 predictor:.tw. (132468)

75 death.tw. (335379)

76 exp models, statistical/ (168145)

77 71 or 72 or 73 or 74 or 75 or 76 (1175870)

78 exp "Sensitivity and Specificity"/ (299564)

79 sensitivity.tw. (389280)

80 specificity.tw. (245482)

81 ((pre-test or pretest) adj probability).tw. (833)

82 post-test probability.tw. (237)

83 predictive value$.tw. (47609)

84 likelihood ratio$.tw. (5527)

85 78 or 79 or 80 or 81 or 82 or 83 or 84 (764660)

86 77 or 85 (1827791)

87 64 and 70 and 86 (17997)

88 limit 87 to (humans and "all adult (19 plus year s)") (12787)

**Appendix 4: Data abstraction tables Diagnostic review**

**Diagnostic studies data extraction**

|  |  |  |
| --- | --- | --- |
| Study | Author | Acar J et al62 |
|  | Date | 1991 |
|  | Pathology(ies) for which accuracy measured | thrombosis, left atrial thrombi |
| Population | Population AF | 44.9% AF |
|  | Population details | 581 patients who subsequently underwent mitral valve surgery, for mitral stenosis. |
| Methods | TTE details | 2-D TTE, ALOKA echocardiograph used for first 276 patients, and a Hewlett-Packard 77020A for the last 305 with a 2.5 MHz transducer. |
|  | Was TTE the reference/gold standard | N |
|  | Diagnostic comparator(s) details | Surgery |
| Results | Usable TTE (as % of those having TTE) | 100 |
|  | Study results | Transthoracic 2D echo 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. |

|  |  |  |
| --- | --- | --- |
| Study | Author | Arques63 |
|  | Date | 2005 |
|  | Pathology(ies) for which accuracy measured | congestive heart failure |
| Population | Population AF | no history of arrhythmia |
|  | Population details | 20 chronic hypertensive patients normal with left ventricular ejection fractions who met Vasan’s criteria for definite diastolic HF, 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 indexes) tissue Doppler (E/Ea). 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 over 15 mm Hg. |
| Results | Usable TTE (as % of those having TTE) | 19/20 95percent |
|  | Study results | The colour M-mode Doppler E/Vp (Ratio of peak E mitral velocity to Vp velocity) index in diagnosing congestive heart failure 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% confidence interval 0.69 to 0.95, p 0.001; sensitivity 73.7%, specificity 75%, accuracy 74.3%). |

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| Study | Author | Attenhofer Jost64 |
|  | Date | 2000 |
|  | Pathology(ies) for which accuracy measured | aortic stenosis, mitral valve prolapse, combined aortic and mitral valve disease, ventricular septal defect (also mitral regurgitation and aortic regurgitation, for which there is higher level evidence available) |
| Population | Population AF | NR (all had heart murmur) |
|  | Population details | 100 consecutive patients referred for systolic murmur |
| Methods | TTE details | TTE 2D and continuous wave Doppler performed using a Hewlett Packard 2500 (Andover, Massachusetts) or Vingmed CFM 800 (Horten, Norway) system. |
|  | Was TTE the reference/gold standard | Yes |
|  | Diagnostic comparator(s) details | clinical cardiac exam |
| Results | Usable TTE (as % of those having TTE) | 100 |
|  | Study results | TTE as gold standard |

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| Study | Author | Barron et al65 |
|  | Date | 1988 |
|  | Pathology(ies) for which accuracy measured | Mitral Valve Prolapse |
| Population | Population AF | NR |
|  | Population details | 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 echo is assumed standard |
|  | Diagnostic comparator(s) details | Auscultation |
| Results | Usable TTE (as % of those having TTE) | 100 |
|  | Study results | With auscultation as the reference standard for MVP, 2D echo has a sensitivity of 47 % and a specificity of 89 % |

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| Study | Author | Bova66 |
|  | Date | 2003 |
|  | Pathology(ies) for which accuracy measured | pulmonary embolism |
| 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 (Andover, MA) 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 % of those having TTE) | 97 |
|  | Study results | Using right ventricular dilatation provided a very low sensitivity for PE (31%; 95% confidence interval [CI] 21-41%) and high specificity (94%; 95% CI: 89-99%). Twenty of 68(29%) cases of PE were correctly diagnosed. Maximal tricuspid regurgitant velocity had sensitivity and specificity values of 51% (95% CI: 38-64%) and 88% (95% CI: 81-95%), 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: 19-39%) sensitivity and a 96% (95% CI: 92-100%) specificity; 135 patients had diagnostic results and 16 of 68 patients (23%) with PE were correctly identified. Utilizing either criterion yielded a 52% (95% CI: 40-64%) sensitivity and 87% (95% CI: 80-95%) specificity. One hundred and fifty-two patients had diagnostic results and 34 of the 68 (50%) patients with PE were identified |

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| Study | Author | Casella67 |
|  | Date | 2009 |
|  | Pathology(ies) for which accuracy measured | native valve infective endocarditis |
| Population | Population AF | no AF |
|  | Population details | 75 patients referred to echo centre, suspected endocarditis |
| Methods | TTE details | Harmonic TTE was performed using a Philips (Andover, MA, USA) Sonos 2400, 5500, 7500 or iE33 cardiac ultrasound system, with a 1.3-1.5 MHz transducer. |
|  | Was TTE the reference/gold standard | no (TOE as reference) |
|  | Diagnostic comparator(s) details | TOE |
| Results | Usable TTE (as % 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, 64.5–93.0%) and TNR was 61.5% (95% CI, 44.6–76.6%) 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%) while TNR was 85.7% (95% CI, 67.3–96.0%). TPR was different according to native valve involved (86.6% for mitral valve, 71.4% for aortic valve). |

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| Study | Author | Cassidy68 |
|  | Date | 1992 |
|  | Pathology(ies) for which accuracy measured | aortic stenosis (also mitral regurgitation and aortic regurgitation, 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 echo (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 % of those having TTE) | 91 |
|  | Study results | 41 patients were studied in two 6-month periods. Overall, clinical and echo 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 |

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| Study | Author | Dittmann69 |
|  | Date | 1987 |
|  | Pathology(ies) for which accuracy measured | aortic regurgitation in mitral valve disease |
| Population | Population AF | 38percent (n=21) |
|  | Population details | 55 consecutive patients with aortic and/or mitral valve disease |
| Methods | TTE details | M mode echocardiograph and pulsed Doppler echocardiographs were performed using the Toshiba SSH-40 A, and the Toshiba SDS-21 A, with an ultrasound frequency of 2.4MHz. The pulse repetition frequency of the range gated Doppler signal was 4 KHz 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 % of those having TTE) | 100 |
|  | Study results | In 13 of 55 patients (3 with mitral stenosis, 3 with mitral incompetence, 3 with combined mitral lesions, 3 with aortic stenosis, one with aortic and mitral stenosis) neither angiography nor pulsed Doppler echo (PDE) showed AR (specificity 100%). Apart from 3 patients with poor echo 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. Mitral valve disease did not affect quantification of AR (n = 20 patients). |

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| Study | Author | Enia70 |
|  | Date | 1989 |
|  | Pathology(ies) for which accuracy measured | aortic dissection involving the ascending aorta |
| Population | Population AF | NR |
|  | Population details | 46 consecutive patients clinically suspected of having aortic dissection. Control group of 509 consecutive unselected patients who underwent both aortography and echo during same period. (included valve disease, CAD, congenital heart disease, cardiomyopathy) |
| Methods | TTE details | Echocardiography performed using a Picker 80 CI and Aloka SSD-800 echo systems. |
|  | Was TTE the reference/gold standard | No |
|  | Diagnostic comparator(s) details | aortography and clinical signs in group of clinically suspected of having aortic dissection. |
| Results | Usable TTE (as % of those having TTE) | 100 |
|  | Study results | The TTE diagnosis of aortic dissection (using 3 echo signs) had a sensitivity of 48%, and a specificity 100%. For echo 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 61 percent, respectively. |

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| Study | Author | Erbel71 |
|  | Date | 1984 |
|  | Pathology(ies) for which accuracy measured | left ventricular function |
| Population | Population AF | no AF |
|  | Population details | 110 patients with suspected coronary artery disease, congestive cardiomyopathy and valvular heart disease |
| Methods | TTE details | 2D echocardiography was performed using a Diasonics 3400 R real-time, phased array sector scanner, with a 2.25MHz transducer. |
|  | Was TTE the reference/gold standard | No |
|  | Diagnostic comparator(s) details | catheterisation – cineventriculograms |
| Results | Usable TTE (as % of those having TTE) | 100 |
|  | Study results | Left ventricular ejection fraction had a sensitivity 81%, and a specificity 100%. EDV (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 ESV (end systolic volume) sensitivity was 94%, and specificity 85%. For stroke volume sensitivity was 30%, and specificity 98%. |

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| Study | Author | Grossmann72 |
|  | Date | 2002 |
|  | Pathology(ies) for which accuracy measured | mitral regurgitation |
| Population | Population AF | 25percent AF |
|  | Population details | 68 consecutive patients. 57 with mitral regurgitation 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 3.75MHz transducer. |
|  | Was TTE the reference/gold standard | N |
|  | Diagnostic comparator(s) details | TOE, cardiac catheterisation |
| Results | Usable TTE (as % of those having TTE) | 100 |
|  | Study results | In the 11 patients without mitral regurgitation, no flow convergence region was present during TTE and TOE. Among the 57 patients with mitral regurgitation, a proximal flow convergence region could be imaged in 45 (79%) by TTE versus 50 (88%) by TOE (p = nonsig). |

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| Study | Author | Groves73 |
|  | Date | 2004 |
|  | Pathology(ies) for which accuracy measured | Tricuspid Regurgitation |
| Population | Population AF | NR |
|  | Population details | 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 | y for diagnosis (RH catheterisation for grading severity) |
|  | Diagnostic comparator(s) details | multidetector CT, right heart catheterisation (RHC) |
| Results | Usable TTE (as % of those having TTE) | 100 |
|  | Study results | With respect to RHC data, the correlation between severity assessment of TR between CT and echocardiography using the Kappa weighted coefficient was 0.56 (moderately good agreement), and the correlation between mean pulmonary pressure and TR grading on echocardiography was r=0:685 p<0.001. When using TTE as gold standard, CT assessment of TR had a sensitivity of 90.4% and a specificity of 100% in detecting echocardiographic TR. For TR graded as more than trivial by echocardiography, sensitivity of CT was 100%. |

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| Study | Author | Guyer74 |
|  | Date | 1984 |
|  | Pathology(ies) for which accuracy measured | rheumatic tricuspid stenosis |
| Population | Population AF | 31/38 82percent |
|  | Population details | 38 patients with rheumatic valvular disease who had undergone cardiac catheterisation and echo |
| Methods | TTE details | 2D TTE performed using etiher a Smith-Kline Instruments Ekosector 10 or an Advanced Technology Laboratories Mark III scanner. |
|  | Was TTE the reference/gold standard | No |
|  | Diagnostic comparator(s) details | right and left heart catheterisation |
| Results | Usable TTE (as % 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 hemodynamic evaluations. However, when the smaller group of 17 patients who had simultaneous right atrial and right ventricular pressure recordings were considered separately, there was complete agreement between the echocardiographic and hemodynamic data. |

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| Study | Author | Helmcke75 |
|  | Date | 1987 |
|  | Pathology(ies) for which accuracy measured | mitral regurgitation |
| Population | Population AF | 31/82 study group 38percent. None of control group (overall 21%) |
|  | Population details | 82 patients with angiographically proven MR. Control group of 65 with normal mitral valvular function |
| Methods | TTE details | Colour Doppler echocardiograph 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 velcotiies up to 60cm/sec. |
|  | Was TTE the reference/gold standard | No |
|  | Diagnostic comparator(s) details | cardiac catheterisation / angiography |
| Results | Usable TTE (as % of those having TTE) | 152/160 = 95percent |
|  | Study results | Sixty-five patients had no mitral regurgitation by both colour Doppler and angiography and 82 patients had mitral regurgitation by both techniques. Thus the sensitivity and specificity of colour Doppler for the detection of mitral regurgitation was 100%. |

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| Study | Author | Jassal76 |
|  | Date | 2007 |
|  | Pathology(ies) for which accuracy measured | Endocarditis |
| Population | Population AF | NR |
|  | Population details | 36 consecutive inpatients with an intermediate likelihood of endocarditis |
| Methods | TTE details | Harmonic imaging TTE performed using a Vivid 7, GE Medical System (Milwaukee, WI) and a 1.5 MHz to 1.7 MHz transducer. |
|  | Was TTE the reference/gold standard | No |
|  | Diagnostic comparator(s) details | TOE |
| Results | Usable TTE (as % 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. 6 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 16/19 positive (84%), and the specificity of TTE with reference to TOE was 14/16 (88%). |

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| Study | Author | Kaymaz77 |
|  | Date | 2001 |
|  | Pathology(ies) for which accuracy measured | thrombosis, left atrial thrombi |
| Population | Population AF | 56.3% AF at time of study |
|  | Population details | 474 consecutive patients with rheumatic mitral valve disease. |
| Methods | TTE details | TTE was performed by a Vingmed CFM 800 echocardiography system (Horten, Norway) with a 3.25 MHz transducer. |
|  | Was TTE the reference/gold standard | N |
|  | Diagnostic comparator(s) details | TOE |
| Results | Usable TTE (as % of those having TTE) | 100 |
|  | Study results | Preoperative transthoracic echocardiography diagnosed thrombi in the left atrium in 34 (32%) of the patients in whom thrombi in the left atrium or in both left atrium and left atrial appendage were detected intra-operatively. None of thrombi confined to left atrium appendage were visualized by preoperative transthoracic echocardiography. Of the 418 transthoracic echocardiographic examinations considered as negative for thrombi, 347 were true negative and 71 were false-negative. Preoperative transthoracic echocardiographic assessment was false-positive for thrombi in 22 patients. According to these results, the sensitivity, specificity, positive predictive value, negative predictive value, and the diagnostic accuracy of transthoracic echocardiography were 32%, 94%, 61%, 83%,and 80%, respectively. |

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| Study | Author | Kishon78 |
|  | Date | 1993 |
|  | Pathology(ies) for which accuracy measured | ventricular septal defect (VSD) and papillary muscle rupture (PR), postmyocardial infarction |
| 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 2-D echo, and 26 were studied by Doppler technique, 9 were studied by TOE |
| Methods | TTE details | All patients examined by 2-D TTE with wide-angled scanners (mechanical or phased array)with 2.25MHz or 3.5MHz 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 % 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 4 more), and 10 of 22 papillary rupture patients. Colour Doppler TTE was not available for all participants. Doppler/colour TTE detected 19/20 VSD and 0/6 PR. |

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| Study | Author | Kitayama79 |
|  | Date | 1997 |
|  | Pathology(ies) for which accuracy measured | right atrial thrombi and left atrial thrombi |
| Population | Population AF | 100% chronic atrial fibrillation |
|  | Population details | 70 consecutive, chronic AF |
| Methods | TTE details | TTE M-mode, 2D and pulsed and colour Doppler were performed using a Toshiba Sonolayer SSH-140A Toshiba Inc., Tokyo, Japan) with a 2.5- or 3.75MHz transducer. |
|  | Was TTE the reference/gold standard | no (study says no gold standard) |
|  | Diagnostic comparator(s) details | cardiac ultrafast computed tomography (unclear time between TTE and CT) |
| Results | Usable TTE (as % of those having TTE) | 90 |
|  | Study results | TTE detected 4/6 LA thrombi and 0/5 RA thrombi detected by CT. |

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| Study | Author | Lanzarini80 |
|  | Date | 2005 |
|  | Pathology(ies) for which accuracy measured | pulmonary hypertension |
| Population | Population AF | 13% controlled AF |
|  | Population details | 86 consecutive patients with chronic heart failure |
| Methods | TTE details | TTE Standard M-mode, 2-dimensional and pulsed and continuous wave Doppler performed using a System Five (GE-Vingmend, 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 % 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 utilizing 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 negative predictive values (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 odds ratio (OR) indicative of strong association. ACT and PAPd/TR, the 2 parameters with the highest feasibility, allowed us to identify 46 of 49 (94%) hypertensive cases. |

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| Study | Author | Maestre81 |
|  | Date | 2009 |
|  | Pathology(ies) for which accuracy measured | left ventricular dysfunction, heart failure |
| Population | Population AF | NR |
|  | Population details | 216 consecutive patients with a suspected diagnosis of heart failure (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 | Y |
|  | Diagnostic comparator(s) details | clinical criteria. |
| Results | Usable TTE (as % of those having TTE) | 100 |
|  | Study results | With TTE as gold standard the Framingham clinical criteria are very sensitive (92%) and moderately specific (79%). |

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| Study | Author | Mugge82 |
|  | Date | 1995 |
|  | Pathology(ies) for which accuracy measured | atrial septal aneurysm |
| Population | Population AF | 14.4% in AF |
|  | Population details | 195 patients with ASA diagnosis confirmed by TOE |
| Methods | TTE details | Colour Doppler TTE (manufacturer details not reported). |
|  | Was TTE the reference/gold standard | N |
|  | Diagnostic comparator(s) details | TOE (colour or contrast TOE) within 24 hours of TTE |
| Results | Usable TTE (as % 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%). |

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| Study | Author | Nienaber83 |
|  | Date | 1993 |
|  | Pathology(ies) for which accuracy measured | aortic dissection, thoracic |
| Population | Population AF | NR |
|  | Population details | 110 patients with clinically suspected aortic dissection. |
| Methods | TTE details | Colour, Doppler TTE performed using sector scanners (V3400 R CV60, Diasonics, Palo Alto, Calif.; or HP 77065 or HP Sonos 1000, Hewlett-Packard, Andover, Mass.) with 2.25-3.5 MHz transducers. |
|  | Was TTE the reference/gold standard | N |
|  | Diagnostic comparator(s) details | TOE, CT, MRI, Interoperative findings, autopsy, or contrast angiography. |
| Results | Usable TTE (as % of those having TTE) | 100 |
|  | Study results | TTE had a sensitivity of 59.3%. The specificity of TTE was 83%. |

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| Study | Author | Nienaber84 |
|  | Date | 1994 |
|  | Pathology(ies) for which accuracy measured | aortic dissection |
| Population | Population AF | NR |
|  | Population details | 35 consecutive patients with suspected dissection of the thoracic aorta |
| Methods | TTE details | M-mode, 2-D, and Doppler TTE performed using sector scanners (V3400 R CV60 Diasonics Inc., Palo Alto, CA, a Hewlett Packard 77065 equipped with a 77570 Mitsubishi video copy processor and a HP Sonos 1000, Hewlett Packard Inc., Andover Division, Andover, M) with 2.25 and 3.5 MHz transducers. |
|  | Was TTE the reference/gold standard | N |
|  | 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 % of those having TTE) | 100 |
|  | Study results | TTE evaluation identified 20 of 26 patients with confirmed evidence of thoracic aortic dissection and was false negative in 6 patients (2 type A and 4 type B dissections). Moreover, there were three false positive 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. |

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| Study | Author | Okura85 |
|  | Date | 2006 |
|  | Pathology(ies) for which accuracy measured | Cardiomyopathy |
| Population | Population AF | NR |
|  | Population details | 52 consecutive patients (44 with usable data) who presented LV dilation and diffuse LV systolic dysfunction. Group 1 = 13 patients given the diagnosis of ICM by coronary angiogram. Group 2 = 31 non-ICM. |
| Methods | TTE details | TTE 2D and Doppler, with patients in the left lateral decubitus position, using Vivid7, GE Medical Systems, Milwaukee WI, with M3s (1.5-4 MHz) and M7 (12MHz) phased-array transducer) |
|  | Was TTE the reference/gold standard | echo markers |
|  | Diagnostic comparator(s) details | coronary angiogram |
| Results | Usable TTE (as % of those having TTE) | 85 |
|  | Study results | Differentiating between ischaemic cardiomyopathy (ICM) from non ICM, 2DTTE echo markers peak diastolic systolic velocity ration (DSVR) less than 1.8 or mean DSVR less than 1.8 had sensitivity = 77%, and specificity 77% |

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| Study | Author | Pochis86 |
|  | Date | 1992 |
|  | Pathology(ies) for which accuracy measured | atrial septal hypertrophy |
| Population | Population AF | 53% atrial fibrillation or flutter, or paroxysmal atrial tachycardia |
|  | Population details | 158 consecutive patients referred for TOE, TTE available for 116. |
| Methods | TTE details | TTE and TOE used ultrasound systems Acuson 128XP/10 with a single-plane probe, Mountainview, California and General Electric RT6800 with a bi-plane probe, Milwaukee, Wisconsin. |
|  | Was TTE the reference/gold standard | N |
|  | Diagnostic comparator(s) details | TOE |
| Results | Usable TTE (as % of those having TTE) | 116-9/116= 92percent |
|  | Study results | 107 patients had both TTE and TOE. TTE sensitivity25%, specificity 91%, positive predictive value 18%, negative predictive value 94% |

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| Study | Author | Reichek87 |
|  | Date | 1981 |
|  | Pathology(ies) for which accuracy measured | left ventricular hypertrophy |
| Population | Population AF | NR |
|  | Population details | 34 patients with TTE and ECGs compared with postmortem 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 % 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. |
| Study | Author | Reichlin88 |
|  | 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-color Doppler TTE (gold standard comparator) performed using a Toshiba Sonolayer SSH 140 A. |
|  | Was TTE the reference/gold standard | Y |
|  | Diagnostic comparator(s) details | initial clinical evaluation including auscultation. |
| Results | Usable TTE (as % 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. |

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| Study | Author | Roudaut89 | |
|  | 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 % of those having TTE) | 90percent 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 dilation of at least one segment of the aorta (sensitivity 95 % , specificity 51 ) and a typical abnormal linear intraluminal echo 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 111 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. | |
| Study | Author | | Saraste90 |
|  | Date | | 2005 |
|  | Pathology(ies) for which accuracy measured | | coronary artery stenosis |
| Population | Population AF | | 4percent chronic AF |
|  | Population details | | 84 consecutive patients referred for diagnostic coronary angiography because of suggested significant CAD |
| Methods | TTE details | | Ultrasound apparatus Sequoia C 256, Acuson Inc, Mountain view, Calif; and standard 3.5MHz transducer. Doppler colour mapping with data postprocessing 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 | | N (angiography as reference) |
|  | Diagnostic comparator(s) details | | coronary angiography |
| Results | Usable TTE (as % 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 a specificity of 90%. For left anterior descending coronary artery stenosis the sensitivity was 73%, and a specificity of 92%. For left circumflex coronary artery stenosis the sensitivity was 38%, and the specificity of 99%. For right coronary artery stenosis the sensitivity was 63%, and the specificity was 96%. |

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| Study | Author | Sharifi91 |
|  | 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 CAF (24%) |
| Methods | TTE details | TTE performed using a Sonos 5500 (Philips, Bothel, WA) system. |
|  | Was TTE the reference/gold standard | No |
|  | Diagnostic comparator(s) details | TOE (within 2months after TTE) |
| Results | Usable TTE (as % 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 echo 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 transoesophageal echocardiography, only one had thrombus found by transthoracic echocardiography, whereas of all 14 patients who had spontaneous echo contrast on Transoesophageal echocardiography, 10 had spontaneous echo contrast on their transthoracic echocardiogram. |

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| Study | Author | Sharma92 |
|  | Date | 1992 |
|  | Pathology(ies) for which accuracy measured | atrial septal defect (sinus venosus defect) |
| Population | Population AF | NR |
|  | Population details | 53 patients, but 8 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 for later part of study. |
|  | Was TTE the reference/gold standard | No |
|  | Diagnostic comparator(s) details | TOE, cineangiography (cardiac catheterisation) |
| Results | Usable TTE (as % 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 |

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| Study | Author | Sheiban93 |
|  | 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 3.5mHz transducer. |
|  | Was TTE the reference/gold standard | No |
|  | Diagnostic comparator(s) details | Surgery |
| Results | Usable TTE (as % of those having TTE) | 100 |
|  | Study results | 2DE detected intracardiac masses with a sensitivity of 88.2% and a specificity of 95.3% |

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| Study | Author | Shively 199194 |
|  | 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 perfomed using a 77020A system (Hewlett-Packard) with 2.5 MHz and 5 MHz transducers. |
|  | Was TTE the reference/gold standard | No |
|  | Diagnostic comparator(s) details | Surgery |
| Results | Usable TTE (as % 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%) |

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| Study | Author | Shrestha95 |
|  | Date | 1983 |
|  | Pathology(ies) for which accuracy measured | left atrial thrombus (in rheumatic heart disease) |
| Population | Population AF | NR for whole population, for those with thrombus 45/51=88% |
|  | Population details | 293 patients with rheumatic heart disease with left atrial 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). 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 % of those having TTE) | 100 |
|  | Study results | Of the 293 patients, 33 had left atrial thrombi by two-dimensional echocardiographic criteria. This diagnosis was confirmed at surgery and histopathologic study in 30 patients (specificity 98.8%). A thrombus was not found in three patients. In 21 other patients, left atrial thrombi were present but were not detected by two-dimensional echocardiography (sensitivity 58.8%). Ten of these 21 had thrombi in the left atrial cavity. In 11 patients, thrombi were located in the left atrial appendage, all of which were missed by two-dimensional echocardiography. Excluding these 11 left atrial appendage thrombi, the sensitivity of two-dimensional echocardiography for detecting left atrial cavity thrombi was 75.0%. |

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| Study | Author | Shub96 |
|  | Date | 1983 |
|  | Pathology(ies) for which accuracy measured | atrial septal defect |
| Population | Population AF | NR |
|  | Population details | 154 patients with documented atrial septal defect (by catheter or surgery) with satisfactory echo |
| Methods | TTE details | TTE 2D, subcostal, was performed using 80 degree phased-array scanning systems (Varian-Diasonics) with 2.25 and 3.5 MHz transducers and a mechanical sector scanner (Advanced Technology Laboratories) with 3 and 5 MHz transducers. |
|  | Was TTE the reference/gold standard | No |
|  | Diagnostic comparator(s) details | catheterisation or surgery, contrast echo (only for 71 patients) |
| Results | Usable TTE (as % of those having TTE) | 154-9/154= 94percent |
|  | 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 visualized (false negative response) in 12 patients (11%) with an ostium secundum defect and in 9 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. |

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| Study | Author | Shyu97 |
|  | 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 TEE before surgery, who went on to undergo surgery. Group 2 = 20 control patients with moderate or severe mitral regurgitation and negligible mitral stenosis due to other causes who underwent TTE, TEE and subsequent mitral valve surgery. |
| Methods | TTE details | 2-D Doppler TTE, Toshiba SSH65A Aloka 870 ultrasound system with 2.5MHz or 3.75MHz precordial transducer, in standard parasternal and apical transducer positions. Colour Doppler TTE assessed MR by criteria of Spain et al |
|  | Was TTE the reference/gold standard | No |
|  | Diagnostic comparator(s) details | TOE (within 2 days of TTE), cardiac catheterisation (most within one weeks of TTE) |
| Results | Usable TTE (as % of those having TTE) | 100 |
|  | Study results | With reference to cardiac catheterisation, TTE had a sensitivity of 65% and specificity of 90% and negative predictive value of 56% for diagnosis of ruptured chordae tendineae |

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| Study | Author | Smith98 |
|  | Date | 1985 |
|  | Pathology(ies) for which accuracy measured | ventricular septal rupture (in patients with acute myocardial infarction) |
| Population | Population AF | NR |
|  | Population details | 13 patients with ventricular septal rupture |
| Methods | TTE details | cross-sectional Doppler echo performed using an IREX system IIIB 2-dimensional phased array sector scanner with a 2.5 MHz transducer (Ramsey, New Jersey, USA). |
|  | Was TTE the reference/gold standard | No |
|  | Diagnostic comparator(s) details | catheterisation or autopsy |
| Results | Usable TTE (as % 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, six of the thirteen cases could be visualised |

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| Study | Author | Sparrow99 |
|  | Date | 2003 |
|  | Pathology(ies) for which accuracy measured | left ventricular systolic dysfunction |
| Population | Population AF | NR |
|  | Population details | 621 patients prescribed loop diuretics in general practices |
| Methods | TTE details | TTE using a phased array sector scanner (Vingmed CFM 700). |
|  | Was TTE the reference/gold standard | Yes |
|  | Diagnostic comparator(s) details | clinical diagnosis made in primary care |
| Results | Usable TTE (as % of those having TTE) | 100 |
|  | Study results | TTE as gold standard. General practice/clinical diagnoses showed high false positive rates. Individual or combinations of clinical features did not accurately predict left ventricular systolic dysfunction |

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| Study | Author | Stratton100 |
|  | Date | 1982 |
|  | Pathology(ies) for which accuracy measured | left ventricular thrombus |
| Population | Population AF | percent NR but some patients had AF |
|  | Population details | 78 patients with suspected left ventricular thrombus |
| Methods | TTE details | 2d echocardiography performed using either a wide-angle, phased-array sector scanner (Toshiba, 45 patients) or a wide-angle, mechanical sector scanner (A.T.L Laboratories, 33 patients). |
|  | Was TTE the reference/gold standard | No |
|  | Diagnostic comparator(s) details | surgical findings/ indium-111platelet imaging |
| Results | Usable TTE (as % of those having TTE) | 78/88=89percent |
|  | 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), while that of an equivocal study was only 29% (two of seven). |

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| Study | Author | Veyrat101 |
|  | Date | 1983 |
|  | Pathology(ies) for which accuracy measured | aortic regurgitation |
| Population | Population AF | 38/95 40percent overall |
|  | Population details | 83 patients with suspected aortic regurgitation. Control group of 12 normal subjects |
| Methods | TTE details | Pulsed Doppler echo performed using an ATL 851 (ALT, Bellevue, WA) with a pulsed Doppler 3 MHz velocimeter and a two-dimensional 90 degree 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 % of those having TTE) | 100 |
|  | Study results | A group of 12 normal subjects and 83 patients, including 40 patients with aortic regurgitation proven by aortography, were investigated. 38 patients with aortic regurgitation were diagnosed by Doppler echocardiography (diagnostic sensitivity 95%, specificity 100%) |

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| Study | Author | Vigna102 |
|  | Date | 1993 |
|  | Pathology(ies) for which accuracy measured | left atrial thrombus |
| Population | Population AF | 59% in AF at time of study |
|  | Population details | 59 consecutive nonanticoagulated mitral stenosis patients (35 AF, 24 SR) |
| Methods | TTE details | TTE colour Doppler performed using an ALOKA 879SDS system and a 2.5 or 3.5 MHz transducer. |
|  | Was TTE the reference/gold standard | no |
|  | Diagnostic comparator(s) details | TOE within 24hours of TTE |
| Results | Usable TTE (as % of those having TTE) | 100 |
|  | Study results | Left atrial thrombus was found by TTE in 4 patients (6.7 percent) and by TOE in 12 (20.3 percent)(p<0.01). Of the 12 patients with LA thrombus at TOE, 11 were in atrial fibrillation. Thrombus was found in LA body by TTE in four patients (6.7 percent) and by TOE in nine (15.2 percent) (p = NS). Left atrial appendage thrombus was found by TOE in 4 patients(6.7 percent) (Fig 1) and by TTE in none (p<0.01). One patient had two thrombi, one in the LA body and the other in the LA appendage. |

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| Study | Author | Wong103 |
|  | Date | 1983 |
|  | Pathology(ies) for which accuracy measured | mitral and aortic valve stenosis valvular calcification |
| Population | Population AF | NR |
|  | Population details | 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 | 35mm cineflourograms (radiologic) |
| Results | Usable TTE (as % of those having TTE) | 100 |
|  | Study results | Echocardiographic sensitivity for detecting calcium in both the mitral anulus and aortic valve was 76 percent; specificity was 89 to 94 percent. 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 percent. |

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| Study | Author | Zanolla104 |
|  | Date | 1982 |
|  | Pathology(ies) for which accuracy measured | mitral stenosis, mitral valve calcification |
| Population | Population AF | NR |
|  | Population details | 43 patients with rheumatic disease of the mitral valve by surgery |
| Methods | TTE details | 2d echocardiography was performed using a commercially available 300 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 % of those having TTE) | 100 |
|  | Study results | There were 14 true positives, 19 true negatives, 10 false positives and no false negatives, for two-dimensional echocardiography, there was a sensitivity of 100% and a specificity of 65%. It is concluded that two-dimensional echocardiography is an extremely sensitive method for assessing mitral valve calcification, and is prospectively useful also in planning reconstruction versus replacement in mitral valve surgery. Nevertheless, the consistent number of false positives affecting two-dimensional echocardiography represents a definite limit to the specificity. |

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| Study | Author | Zotz105 |
|  | Date | 1993 |
|  | Pathology(ies) for which accuracy measured | ventricular septal rupture (in patients with acute myocardial infarction) |
| Population | Population AF | NR |
|  | Population details | 17 consecutive patients presenting a new systolic murmur after the onset of acute MI, 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 2.5MHz transducer, standard and unconventional views |
|  | Was TTE the reference/gold standard | N |
|  | Diagnostic comparator(s) details | surgery or autopsy, also contrast echo and TOE |
| Results | Usable TTE (as % of those having TTE) | 100 |
|  | Study results | Conventional TTE identified VSR in 4/17, using unconventional views 12/17; and colour Doppler 15/16. |

**Prognostic studies data extraction**

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| Study | Author | Atrial Fibrillation Investigators106 |
|  | Date | 1998 |
|  | Pathology(ies) for which prognosis measured | left ventricular dysfunction, Left atrial diameter, mitral valve prolapse, mitral regurgitation |
| 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 ischemic strokes occurred (annual rate, 4.7%). Moderate to severe left ventricular systolic dysfunction shown via 2-dimensional echocardiography was a strong independent predictor of stroke (relative risk, 2.5; P,.001) in the 1010 patients in whom echocardiographic values for left ventricular function were available. Left atrial diameter by Mmode echocardiography did not predict stroke (relative risk, 1.02/mm; P = .10). Mitral regurgitation or mitral valve prolapse or left ventricular mass were not significantly associated with stroke. |

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| Study | Author | Klem107 |
|  | Date | 2003 |
|  | Pathology(ies) for which prognosis measured | reduced LV function, left atrial diameter, valvular abnormality |
| Population | Population details | 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 (9.6years) Reduced left ventricular function diabetic HR 1.52 (0.85–2.70) p=0.1598, nondiabetic HR 2.28 (1.58–3.29) p<0.0001; Left atrial diameter diabetic HR 1.01 (0.97–1.05) p= 0.6445, nondiabetic HR 1.06 (1.03–1.08) p<0.0001;  Valvular abnormality diabetic HR 2.05 (1.10–3.82) p=0.0229, nondiabetic HR 1.88 (1.30–2.70)p= 0.0007 |

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| Study | Author | Miyaska108 |
|  | Date | 2000 |
|  | Pathology(ies) for which prognosis measured | mitral regurgitation |
| Population | Population details | all participants non-rheumatic AF |
| Methods | TTE details | TTE 2D, M-mode performed by Aloka 870SSD wtih a 3.5 MHz transducer. |
| Results | Results | of 69 patients (30%) with grade 1 mitral regurgitation, and 104 patients (45%) with no mitral regurgitation. Patients with grade 1 mitral regurgitation had significantly higher prevalence of thromboembolic events (28%) than those with mitral regurgitation grade 2 or higher (8%, P 0.006) or those with no mitral regurgitation (11%, P 0.007). A history of previous thromboembolic events were compared between 173 patients with grade 1 mitral regurgitation and those with no mitral regurgitation using the logistic regression analysis adjusted for age, sex, administration of warfarin, and presence of hypertension, diabetes mellitus, structural heart disease, enlarged left atrium (over40 mm), chronic atrial fibrillation, and grade 1 mitral regurgitation. Grade 1 mitral regurgitation (odds ratio 2.689, 95% confidence interval 1.039–7.189, P 0.0434) and no warfarin administration (odds ratio 0.045, 95% confidence interval 0.002–0.242, P 0.0036) were significantly associated with the history of thromboembolic events. The presence of mild mitral regurgitation in nonrheumatic atrial fibrillation was associated with higher prevalence of thromboembolic events. |

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| Study | Author | Nakagami109 |
|  | Date | 1998 |
|  | Pathology(ies) for which prognosis measured | degree of mitral regurgitation and left atrial diameter |
| Population | Population details | 290 patients with non-rheumatic AF |
| Methods | TTE details | TTE M-mode, 2D and colour Doppler performed using a Toshiba 160A system 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 greater than 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-square = 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. (MR protective against stroke if LAD large) within 7.4 years follow-up, In 95 patients with LAD of greater than or equal to 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-square = 3.95, p = 0.047) . In other groups with LAD of less than 47 mm, the incidence of stroke had no association with the degree of MR. |

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| Study | Author | The Stroke Prevention in Atrial Fibrillation Investigators110 |
|  | Date | 1992 |
|  | Pathology(ies) for which prognosis measured | mitral annular calcification, severe mitral regurgitation, LV dysfunction and LA diameter |
| Population | Population details | 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 Center) |
| Results | Results | mean 1.3years follow-up, risk of ischaemic stroke or thromboembolism, global left ventricular dysfunction RR 2.6 p=0.003; left atrial size p=0.02 LA 2.4cm/msquared RR=1.6, LA 2.9cm/msquared RR=2.7 |

**Appendix 5: Quality assessment Diagnostic review**

Level in hierarchy of evidence based on Merlin et al57

1) Systematic review of level 2 studies;

2) Study of test accuracy, 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 J et al62 |
| --- | --- | --- |
|  | Date | 1991 |
|  | Pathology(ies) (for which accuracy measured) | thrombosis, left atrial thrombi |
|  | Population AF | 44.9% AF |
| Study design | Study design details | Comparison of TTE against surgery for the diagnosis of left atrial thrombi in mitral stenosis (also some cases TOE and angiography) in patients who subsequently underwent mitral valve surgery. |
|  | Study design level in hierarchy57 | 3b comparison with reference standard |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | N |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | N |
|  | Were un-interpretable or indeterminate test results reported? | none reported, all cases used in analysis |

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| --- | --- | --- |
| Study | Author | Arques63 |
|  | Date | 2005 |
|  | Pathology(ies) (for which accuracy measured) | congestive heart failure |
|  | 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 hierarchy57 | 3c |
| Items from QUADAS 59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | Y |

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| --- | --- | --- |
| Study | Author | Attenhofer Jost64 |
|  | Date | 2000 |
|  | Pathology(ies) (for which accuracy measured) | aortic stenosis, mitral valve prolapse, combined aortic and mitral valve disease, ventricular septal defect (also mitral regurgitation and aortic regurgitation, 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 exam immediately before TTE, TTE as reference standard |
|  | Study design level in hierarchy 57 | 2 |
| Items from QUADAS 59 | Were selection criteria clearly described? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | none reported, all cases used |

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| Study | Author | Barron et al.65 |
|  | Date | 1988 |
|  | Pathology(ies) (for which accuracy measured) | Mitral Valve Prolapse |
|  | 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? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | U |
|  | Were un-interpretable or indeterminate test results reported? | none reported, all cases used |

|  |  |  |
| --- | --- | --- |
| Study | Author | Bova66 |
|  | Date | 2003 |
|  | Pathology(ies) (for which accuracy measured) | pulmonary embolism |
|  | 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? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | Y |

|  |  |  |
| --- | --- | --- |
| Study | Author | Casella67 |
|  | 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? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | Y (all used in analysis, separate analysis excluding poor image quality) |

|  |  |  |
| --- | --- | --- |
| Study | Author | Cassidy68 |
|  | Date | 1992 |
|  | Pathology(ies) (for which accuracy measured) | aortic stenosis (also mitral regurgitation and aortic regurgitation, 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? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | Y |

|  |  |  |
| --- | --- | --- |
| Study | Author | Dittmann69 |
|  | Date | 1987 |
|  | Pathology(ies) (for which accuracy measured) | aortic regurgitation in mitral valve disease |
|  | Population AF | 38percent (n=21) |
| Study design | Study design details | comparison of pulsed Doppler echo, m-mode echo, clinical signs and cardiac catheterisation, consecutive patients, TTE one day before catheterisation |
|  | Study design level in hierarchy 57 | 3b comparison with reference standard |
| Items from QUADAS 59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | U |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | U |
|  | Were un-interpretable or indeterminate test results reported? | Y (states no exclusions for inadequate exams) |

|  |  |  |
| --- | --- | --- |
| Study | Author | Enia70 |
|  | 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? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | N |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | N |
|  | Were un-interpretable or indeterminate test results reported? | none reported, all tests used |

|  |  |  |
| --- | --- | --- |
| Study | Author | Erbel71 |
|  | Date | 1984 |
|  | Pathology(ies) (for which accuracy measured) | left ventricular function |
|  | Population AF | no AF |
| Study design | Study design details | retrospective Comparison of diagnostic accuracy of 4 echo markers by catheterisation and echocardiography , TTE the day before catheterisation |
|  | Study design level in hierarchy 57 | 3b comparison with reference standard |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | U |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | U |
|  | Were un-interpretable or indeterminate test results reported? | none reported, all used |

|  |  |  |
| --- | --- | --- |
| Study | Author | Grossmann72 |
|  | Date | 2002 |
|  | Pathology(ies) (for which accuracy measured) | mitral regurgitation |
|  | Population AF | 25percent AF |
| Study design | Study design details | Comparison of TTE and TOE with the some patients having catheterisation for the detection and quantification of mitral regurgitation using the proximal flow convergence method. consecutive patients, TTE and TOE performed during same exam |
|  | Study design level in hierarchy 57 | 3b comparison with reference standard |
| Items from QUADAS 59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y (if TOE reference standard, rather than catheterisation) |
|  | Did patients receive the same reference standard regardless of the index test result? | Y (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)? | N |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | N |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | N |
|  | Were un-interpretable or indeterminate test results reported? | none reported |

|  |  |  |
| --- | --- | --- |
| Study | Author | Groves73 |
|  | 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 (TR). 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? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | NA (selected for having usable exams) |

|  |  |  |
| --- | --- | --- |
| Study | Author | Guyer74 |
|  | Date | 1984 |
|  | Pathology(ies) (for which accuracy measured) | rheumatic tricuspid stenosis |
|  | Population AF | 31/38 82percent |
| Study design | Study design details | retrospective comparison of echocardiography and cardiac catheterisation in selected patients with both exams, catheterisation with one year of TTE |
|  | Study design level in hierarchy 57 | 3a |
| Items from QUADAS 59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | NA [selected for having both exams] |

|  |  |  |
| --- | --- | --- |
| Study | Author | Helmcke75 |
|  | Date | 1987 |
|  | Pathology(ies) (for which accuracy measured) | mitral regurgitation |
|  | Population AF | 31/82 with MR 38percent. None without MR (overall 21%) |
| Study design | Study design details | comparison of colour Doppler echo and cardiac catheterisation angiograph in those with and without MR |
|  | Study design level in hierarchy57 | 3c |
| Items from QUADAS59 | Were selection criteria clearly described? | N |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | Y |

|  |  |  |
| --- | --- | --- |
| Study | Author | Jassal76 |
|  | 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 24hours of TOE |
|  | Study design level in hierarchy57 | 2 |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | Y (indeterminate TTE included in analysis) |

|  |  |  |
| --- | --- | --- |
| Study | Author | Kaymaz77 |
|  | Date | 2001 |
|  | Pathology(ies) (for which accuracy measured) | thrombosis, left atrial thrombi |
|  | Population AF | 56.3% AF at time of study |
| Study design | Study design details | Comparison of TTE and TOE measurements of left atrial thrombi (before surgery) against intraoperative findings. consecutive patients, TTE and TOE within 1-5 days prior to surgery |
|  | Study design level in hierarchy57 | 3b comparison with reference standard |
| Items from QUADAS59 | Were selection criteria clearly described? | y |
|  | Is the reference standard likely to correctly classify the target condition? | y |
|  | 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? | y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | y |
|  | Did patients receive the same reference standard regardless of the index test result? | y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | N |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | N |
|  | Were un-interpretable or indeterminate test results reported? | none reported all included in analysis |

|  |  |  |
| --- | --- | --- |
| Study | Author | Kishon78 |
|  | Date | 1993 |
|  | Pathology(ies) (for which accuracy measured) | ventricular septal defect and papillary muscle rupture, postmyocardial infarction |
|  | 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 hierarchy57 | 3b |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | N |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | N |
|  | Were un-interpretable or indeterminate test results reported? | Y (included in analysis) |

|  |  |  |
| --- | --- | --- |
| Study | Author | Kitayama79 |
|  | Date | 1997 |
|  | Pathology(ies) (for which accuracy measured) | right atrial thrombi and left atrial thrombi |
|  | Population AF | 100% chronic atrial fibrillation |
| Study design | Study design details | comparison of TTE and CT, consecutive patients, (unclear if blinded) |
|  | Study design level in hierarchy57 | 3b |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | N (according to Kitayama et al) |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | U |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | U |
|  | Were un-interpretable or indeterminate test results reported? | Y (included in analysis) |

|  |  |  |
| --- | --- | --- |
| Study | Author | Lanzarini80 |
|  | 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 24hours, consecutive patients, blinded |
|  | Study design level in hierarchy57 | 2 |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | none reported, all cases used |

|  |  |  |
| --- | --- | --- |
| Study | Author | Maestre81 |
|  | Date | 2009 |
|  | Pathology(ies) (for which accuracy measured) | left ventricular 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 hierarchy57 | 2 |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | none reported, all used |

|  |  |  |
| --- | --- | --- |
| Study | Author | Mugge82 |
|  | Date | 1995 |
|  | Pathology(ies) (for which accuracy measured) | atrial septal aneurysm |
|  | 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 24hours of each other. |
|  | Study design level in hierarchy57 | 3b comparison with reference standard. |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | N |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | N |
|  | Were un-interpretable or indeterminate test results reported? | NA [selection for having both exams] |

|  |  |  |
| --- | --- | --- |
| Study | Author | Nienaber83 |
|  | Date | 1993 |
|  | Pathology(ies) (for which accuracy measured) | aortic dissection, thoracic |
|  | 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 2 imaging procedures, all patients validated by angiography, surgery or autopsy) |
|  | Study design level in hierarchy57 | 2 |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | none reported all used |

|  |  |  |
| --- | --- | --- |
| Study | Author | Nienaber84 |
|  | 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 morphologic evaluation and anatomical mapping of the thoracic aorta, blinded |
|  | Study design level in hierarchy57 | 3a |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | none reported all used |

|  |  |  |
| --- | --- | --- |
| Study | Author | Okura85 |
|  | 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 1week of each other |
|  | Study design level in hierarchy57 | 3b |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | N |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | N |
|  | Were un-interpretable or indeterminate test results reported? | Y |

|  |  |  |
| --- | --- | --- |
| Study | Author | Pochis86 |
|  | Date | 1992 |
|  | Pathology(ies) (for which accuracy measured) | atrial septal hypertrophy |
|  | Population AF | 53% atrial fibrillation 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 (LHAS). Assessors blinded to other results. |
|  | Study design level in hierarchy57 | 3b - comparison with reference standard. |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | Y |

|  |  |  |
| --- | --- | --- |
| Study | Author | Reichek87 |
|  | Date | 1981 |
|  | Pathology(ies) (for which accuracy measured) | left ventricular hypertrophy |
|  | Population AF | NR |
| Study design | Study design details | retrospective comparison of various diagnostic measures in patient groups |
|  | Study design level in hierarchy57 | 3b comparison with reference standard |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | U |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | U |
|  | Were un-interpretable or indeterminate test results reported? | none reported |

|  |  |  |
| --- | --- | --- |
| Study | Author | Reichlin88 |
|  | 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 hierarchy57 | 2 |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | NA [TTE as gold standard] |

|  |  |  |
| --- | --- | --- |
| Study | Author | Roudaut89 |
|  | 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 hierarchy57 | 3b comparison with reference standard |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | N |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | N |
|  | Were un-interpretable or indeterminate test results reported? | Y (excluded from analysis n=13 of 673) |

|  |  |  |
| --- | --- | --- |
| Study | Author | Saraste90 |
|  | Date | 2005 |
|  | Pathology(ies) (for which accuracy measured) | coronary artery stenosis |
|  | Population AF | 4percent chronic AF |
| 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 hierarchy57 | 3b - study of test accuracy, includes reference standard |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | None reported, all images used in calculation of sensitivity/specificity |

|  |  |  |
| --- | --- | --- |
| Study | Author | Sharifi91 |
|  | 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 hierarchy57 | 2 |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | NA (selected for usable data) |

|  |  |  |
| --- | --- | --- |
| Study | Author | Sharma92 |
|  | 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 hierarchy57 | 3b |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | N |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | N |
|  | Were un-interpretable or indeterminate test results reported? | Y ( 8 cases with inadequate TTE or angiography were excluded from analysis) |

|  |  |  |
| --- | --- | --- |
| Study | Author | Sheiban93 |
|  | Date | 1987 |
|  | Pathology(ies) (for which accuracy measured) | intracardiac masses |
|  | Population AF | NR |
| Study design | Study design details | prospective comparison of 2d echo and surgery |
|  | Study design level in hierarchy57 | 3b comparison with reference standard |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | U |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | U |
|  | Were un-interpretable or indeterminate test results reported? | none reported all used |

|  |  |  |
| --- | --- | --- |
| Study | Author | Shively94 |
|  | 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 pathologic data from the subsequent clinical course as the reference standard, blinded comparison in consecutive patients |
|  | Study design level in hierarchy57 | 2 (blinded comparison in consecutive patients) |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | Y (all included in analysis, poorer than average TTE image 18% tricuspid valve, 11% mitral valve, 32% aortic valve) |

|  |  |  |
| --- | --- | --- |
| Study | Author | Shrestha95 |
|  | Date | 1983 |
|  | Pathology(ies) (for which accuracy measured) | left atrial 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 echo and surgical findings of left atrial thrombi, surgery within 1week of TTE |
|  | Study design level in hierarchy57 | 3b |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y (video recordings reviewed by blinded observer) |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | U |
|  | Were un-interpretable or indeterminate test results reported? | none reported |

|  |  |  |
| --- | --- | --- |
| Study | Author | Shub96 |
|  | Date | 1983 |
|  | Pathology(ies) (for which accuracy measured) | atrial septal defect |
|  | Population AF | NR |
| Study design | Study design details | retrospective comparison of 2d echo against surgery/cath. from 171 patients, 154 entered study (9 excluded for poor TTE, 8 patients incomplete exam) |
|  | Study design level in hierarchy57 | 3b comparison with reference standard |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | N |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | N |
|  | Were un-interpretable or indeterminate test results reported? | Y (9 of 171 patients excluded for poor image quality) |

|  |  |  |
| --- | --- | --- |
| Study | Author | Shyu97 |
|  | 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, controls=mitral regurgitation due to other causes, most catheterisations within 1week of echo studies, 37/40 cases and 18/20 controls had catheterisations |
|  | Study design level in hierarchy57 | 3c |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | none reported (all used in analysis) |

|  |  |  |
| --- | --- | --- |
| Study | Author | Smith98 |
|  | Date | 1985 |
|  | Pathology(ies) (for which accuracy measured) | ventricular septal rupture (in patients with acute myocardial infarction) |
|  | Population AF | NR |
| Study design | Study design details | comparison with reference standard, of 13 patients 1 excluded for not having reference standard |
|  | Study design level in hierarchy57 | 3b comparison with reference standard |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | N |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | N |
|  | Were un-interpretable or indeterminate test results reported? | none reported all used |

|  |  |  |
| --- | --- | --- |
| Study | Author | Sparrow99 |
|  | Date | 2003 |
|  | Pathology(ies) (for which accuracy measured) | left ventricular systolic dysfunction |
|  | Population AF | NR |
| Study design | Study design details | prospective comparison of accuracy, cross-section not consecutive, blinded |
|  | Study design level in hierarchy57 | 3a |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | Y (13% excluded from study due to inadequate TTE images) |

|  |  |  |
| --- | --- | --- |
| Study | Author | Stratton100 |
|  | Date | 1982 |
|  | Pathology(ies) (for which accuracy measured) | left ventricular thrombus |
|  | Population AF | percent NR but some patients had AF |
| Study design | Study design details | retrospective comparison of 2d echo and indium 111 platelet imaging and surgical findings. Assessors blinded |
|  | Study design level in hierarchy57 | 3b comparison with reference standard |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | Y (excluded from analysis) |

|  |  |  |
| --- | --- | --- |
| Study | Author | Veyrat101 |
|  | Date | 1983 |
|  | Pathology(ies) (for which accuracy measured) | aortic regurgitation |
|  | Population AF | 38/95 40percent overall |
| Study design | Study design details | retrospective comparison of echo against aortic root angiography (some surgical findings). |
|  | Study design level in hierarchy57 | 3b comparison with reference standard |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | U |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | U |
|  | Were un-interpretable or indeterminate test results reported? | none reported all used |

|  |  |  |
| --- | --- | --- |
| Study | Author | Vigna102 |
|  | Date | 1993 |
|  | Pathology(ies) (for which accuracy measured) | left atrial 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 24hours of each other |
|  | Study design level in hierarchy57 | 2 |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | none reported all used |

|  |  |  |
| --- | --- | --- |
| Study | Author | Wong103 |
|  | 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 echo and cinefluorograms for detection of valvular calcification, blinding , non-consecutive |
|  | Study design level in hierarchy57 | 3a comparison with reference standard |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | Y |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | Y |
|  | Were un-interpretable or indeterminate test results reported? | non reported all used |

|  |  |  |
| --- | --- | --- |
| Study | Author | Zanolla104 |
|  | 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 echo and surgical findings, non-consecutive |
|  | Study design level in hierarchy57 | 3b comparison with reference standard |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | U |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | U |
|  | Were un-interpretable or indeterminate test results reported? | none reported all used |

|  |  |  |
| --- | --- | --- |
| Study | Author | Zotz105 |
|  | Date | 1993 |
|  | Pathology(ies) (for which accuracy measured) | ventricular septal rupture (in patients with acute myocardial infarction) |
|  | Population AF | NR |
| Study design | Study design details | comparison with reference standard, not blinded, investigated consecutively |
|  | Study design level in hierarchy57 | 3b comparison with reference standard |
| Items from QUADAS59 | Were selection criteria clearly described? | Y |
|  | Is the reference standard likely to correctly classify the target condition? | Y |
|  | 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? | Y |
|  | Did the whole sample (rather than a random selection of the sample) receive verification using a reference standard of diagnosis? | Y |
|  | Did patients receive the same reference standard regardless of the index test result? | Y |
|  | Was the reference standard independent of the index test (i.e. the index test did not form part of  the reference standard)? | Y |
|  | Were the index test results interpreted without knowledge of the results of the reference  standard? | N |
|  | Were the reference standard results interpreted without knowledge of the results of the index  test? | N |
|  | Were un-interpretable or indeterminate test results reported? | none reported (all images used in analysis) |

**Prognostic studies Quality assessment**

Level in hierarchy of evidence based on Merlin et al57

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;

3c) Retrospective cohort study;

4) Case series, or cohort study of persons at different stages of disease.

|  |  |  |
| --- | --- | --- |
| Study | Author | Atrial Fibrillation Investigators106 |
|  | Date | 1998 |
|  | Pathology(ies) (for which accuracy measured) | left ventricular dysfunction, Left atrial diameter, mitral valve prolapse, mitral regurgitation |
|  | 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 hierarchy57 | 3b (review of level 3b) |

|  |  |  |
| --- | --- | --- |
| Study | Author | Klem107 |
|  | Date | 2003 |
|  | Pathology(ies) (for which accuracy measured) | reduced LV function, left atrial diameter, valvular abnormality |
|  | Population AF | 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 hierarchy57 | 2 |

|  |  |  |
| --- | --- | --- |
| Study | Author | Miyaska108 |
|  | Date | 2000 |
|  | Pathology(ies) (for which accuracy measured) | mitral regurgitation |
|  | Population AF | all participants non-rheumatic AF |
| Study design | Study design details | retrospective database study |
|  | Study design level in hierarchy57 | 3c retrospective cohort study. |

|  |  |  |
| --- | --- | --- |
| Study | Author | Nakagami109 |
|  | Date | 1998 |
|  | Pathology(ies) (for which accuracy measured) | degree of mitral regurgitation and left atrial diameter |
|  | Population AF | 290 patients with non-rheumatic AF |
| Study design | Study design details | retrospective cohort |
|  | Study design level in hierarchy57 | 3c |

|  |  |  |
| --- | --- | --- |
| Study | Author | The Stroke Prevention in Atrial Fibrillation Investigators110 |
|  | Date | 1992 |
|  | Pathology(ies) (for which accuracy measured) | mitral annular calcification, severe mitral regurgitation, LV dysfunction and LA diameter |
|  | Population AF | 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 hierarchy57 | 3b analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial. |

**Appendix 6: Data abstraction tables Prevalence review**

| Study | Author | Agmon et al111 |
| --- | --- | --- |
|  | Date | 2001 |
|  | Location | USA (part of study of random sample of patients in Minnesota, encompassing several healthcare providers) |
|  | Study design | case-control, subjects from another study (SPARC, Stroke Prevention Assessment of Risk in a Community, a cohort study of a random selection of a geographical population) |
| Population | Population, eligibility criteria | part of SPARC study : cases AF; control without AF |
|  | Sample size | AF n=42, controls n=539 |
|  | Male/ Female | AF male n=23 (54.8%); controls male n=266 (49.4%) |
|  | Mean age(yrs) | AF mean 82 (SD10), median 84 (range 50-98). Controls mean 66 (SD13) median 63 (range 46-95) |
|  | Diagnosis of AF | ECG 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%, controls 53.4%; hyperlipidaemia AF 55.6%, controls 45.5%; coronary artery disease AF 35.7%, controls 11.7%, previous MI AF 19.1%, controls 6.1%, angina AF 23.8%, controls 10.2%. Cerebrovascular disease AF 23.8%, controls 4.8% . Carotid artery stenosis of 50% or more AF 12.5%, controls 8.9%. mitral stenosis AF 2.4%, controls 0.4%. Mitral regurgitation AF 4.8%, controls 0.4%. aortic stenosis AF 2.4%, controls 1.3%. AR AF 0, controls 0.4%. history of CHF AF 21.4%, controls 2.6% |
|  | Co-morbidities (non- cardiac diseases) | diabetes mellitus AF 14.3%, controls 8.9%. |
|  | Treatment | insulin for DM AF 4.8%, controls 1.9%. CABG AF 14.3%, controls 3.2%. PTCA AF 4.8%, controls 2.4%. Previous mitral valve surgery AF 7.1%, controls 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 4mm thick, mobile atherosclerotic debris, or plaque ulceration" |
|  | Description of Assessor(s) | NR (cardiology dept, presume assessors qualified) |
| Results | Pathology (number of subjects) | aortic atherosclerosis AF n=31, controls n=267. complex atherosclerosis AF n=7, controls n=37 |
|  | Pathology prevalence (%) | aortic atherosclerosis AF n=31/42 = 73.8% , controls n=267/539 = 49.5%. complex atherosclerosis AF n=7/42 = 16.7%, controls n=37/539 = 6.9% |

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| Study | Author | Archer112 |
|  | Date | 1995 |
|  | Location | Multicentre, USA |
|  | Study design | Retrospective observational study |
| Population | Population, eligibility criteria | Patients who had completed a larger study (n=525) (SPINAF-Stroke Prevention In Nonrheumatic Atrial Fibrillation) 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 | AF patients - 55 (warfarin - 32; placebo - 23) |
|  | Male/ Female | M-55 (100%) |
|  | Mean age(yrs) | 70.8±6.6 |
|  | Diagnosis of AF | Not reported (reported in prior publication) |
|  | Mean Duration of AF | 6.2 + 4.3 years. |
|  | Underlying cardiac conditions | Not reported |
|  | Co-morbidities (non- cardiac diseases) | Not reported |
|  | Treatment | Not described |
| Methods | Diagnostic instrument (s) for pathology | Transoesophageal echocardiography |
|  | 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) | Not reported |
| Results | Pathology (number of subjects) | Left atrial thrombus - 5; left ventricular thrombus - 2 patent foramen ovale - 22; atrial septal aneurysm - 4; |
|  | Pathology prevalence (%) | Left atrial thrombus - 9.1%; left ventricular thrombus - 3.6% patent foramen ovale - 40%; atrial septal aneurysm - 7.3%; |

| Study | Author | Blackshear et al113  [Additional details in other references127,171] |
| --- | --- | --- |
|  | Date | 1999 |
|  | Location | USA (multicentre, cardiovascular dept) |
|  | Study design | cross-section study, Prospectively sought aortic plaque in patients with AF (who were part of an RCT of high-risk (Stroke Prevention in Atrial Fibrillation (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 2 studies: high-risk patients with AF who were part of an RCT (Stroke Prevention in Atrial Fibrillation (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 | 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(yrs) | mean age 69, SD 9 (of 786 patients; of 770 patients mean between 66 and 71) |
|  | Diagnosis of AF | Details not in this publication, but patients part of an RCT (Stroke Prevention in Atrial Fibrillation (SPAF) III study, warfarin vs. warfarin+aspirin) looking at stroke in AF; other publications on this trial give details127 |
|  | Mean Duration of AF | 73% (of 786) had duration of more than 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 1 of "prior thromboembolism, systolic blood pressure >160 mm Hg, 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 congestive heart failure; 13% recent congestive heart failure; 26% ischaemic heart disease |
|  | Co-morbidities (non- cardiac diseases) | 15% diabetes mellitus (of 786); 54% history of hypertension; 14% systolic BP >160mmHG at entry |
|  | Treatment | high risk patients, as part of RCT, randomised to adjusted-dose warfarin versus low, fixed doses of warfarin plus aspirin in combination for high-risk patients. Low risk patient treated with aspirin alone |
| Methods | Diagnostic instrument (s) for pathology | diagnosis of atherosclerotic plaque by transoesophageal echocardiography (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 study171 |
|  | Description of Assessor(s) | [in other publication of study, includes inter-observer reliability171] |
| Results | Pathology (number 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% |

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| Study | Author | Corrado et al114 |
|  | 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, sub-therapeutic INR anticoagulation therapy, TOE before cardioversion |
|  | Sample size | 41 |
|  | Male/ Female | male patients without thrombi n=23 (62%), patients with thrombi n=2 (50%) |
|  | Mean age(yrs) | patients without thrombi 64.35 (SD10.28), patients with thrombi 66.25 (SD0.96) |
|  | Diagnosis of AF | NR |
|  | Mean Duration of AF | NR |
|  | Underlying cardiac conditions | hypertension patients without thrombi n=20 (54%), patients with thrombi n=2 (50%); structural heart disease patients without thrombi n=20 (54%), patients with thrombi n=3 (75%) |
|  | Co-morbidities (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) | 3 experienced echocardiographers |
| Results | Pathology (number of subjects) | LAA thrombus n=4 |
|  | Pathology prevalence (%) | 9.80% |

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| --- | --- | --- |
| Study | Author | Dang et al115 |
|  | 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 | M- 413(56%) |
|  | Mean age(yrs) | 62.3 |
|  | Diagnosis of AF | ('Index') ECG- first ECG of any particular patient with a diagnosis of AF. NB 1 patient could have multiple ECGs. |
|  | Mean Duration of AF | not reported |
|  | Underlying cardiac conditions | #Hypertension-45.6%; Heart failure-31.1%; ; Acute MI-8.1%; Cardiomyopathy-4.5% |
|  | Co-morbidities (non- cardiac diseases) | Diabetes -22.9%; Cerebrovascular disease-6.6% |
|  | Treatment | Not reported |
| 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) | not reported |
| Results | Pathology (number 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% |

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| --- | --- | --- |
| Study | Author | de Devitiis28 |
|  | Date | 1999 |
|  | Location | Germany, single centre, cardiology dept |
|  | Study design | cohort, consecutive patients, prospective |
| Population | Population, eligibility criteria | AF, referred for TOE |
|  | Sample size | 90 with AF (from 102 studied, 90 (88%) had visualised RA and LA appendages) |
|  | Male/ Female | AF patients male n=69, female n=21 out of 90. controls male n=15 female n=7 out of 22 |
|  | Mean age(yrs) | AF mean 60 (SD13). Controls mean 58 (SD17) |
|  | Diagnosis of AF | clinical criteria and 12 lead ECG |
|  | Mean Duration of AF | for those with RA thrombi, mean duration AF in days 1,670 (SD1,596); for those without RA thrombi 480 (SD924) |
|  | Underlying cardiac conditions | coronary heart disease AF n=20 (out of 90), arterial hypertension AF n= 19 (controls n=1 (out of 22)), mitral stenosis AF n=8, mitral regurgitation AF n=6, aortic stenosis AF n=4, aortic regurgitation AF n=3, dilated cardiomyopathy AF n=10, myocarditis AF n=5 |
|  | Co-morbidities (non- cardiac diseases) | neurologic deficit AF n=10, controls n=18. acute peripheral ischaemia AF n=4. pulmonary embolism AF n= 2 |
|  | Treatment | anticoagulation therapy AF n=50, controls n=7 |
| Methods | Diagnostic instrument (s) for pathology | TTE and TOE |
|  | Diagnostic criteria for pathology | visualised by echo (TOE) |
|  | Description of Assessor(s) | NR (cardiology dept, presume assessors qualified) |
| Results | Pathology (number of subjects) | 12 patients with left or right or both (included 5 with both), incorporate 6 right atrial appendage thrombosis, 11 left atrial appendage thrombosis |
|  | Pathology prevalence (%) | either or both 13% (RAA 6.7%, LAA 12.2% ) |

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| Study | Author | Heppell116 |
|  | Date | 1997 |
|  | Location | Hospital setting, two.(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 | M-69(64%);F-38(36%) |
|  | Mean age(yrs) | 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 echography. Patients who were in sinus rhythm at either of these sessions were reported as having paroxysmal AF. |
|  | Mean Duration of AF | Not reported |
|  | Underlying cardiac conditions | Hypertension-(n=47)-44%;Ischaemic heart disease (n=40)-37%;Paroxysmal AF(n=14)-13%; Previous stroke (n=23)-21% |
|  | Co-morbidities (non- cardiac diseases) | Not reported |
|  | Treatment | Aspirin use' - (n=54)-50% |
| Methods | Diagnostic instrument (s) for pathology | Transoesophageal echocardiography. Examination by means of a 5 MHZ single plane probe of 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 on-line by two observers (authors) |
| Results | Pathology (number of subjects) | Left atrial thrombi;19/107 |
|  | Pathology prevalence (%) | Left atrial thrombi-18% |

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| --- | --- | --- |
| Study | Author | Kleemann117 |
|  | Date | 2009 |
|  | Location | Hospital, single centre, Germany |
|  | Study design | Prospective observational study |
| Population | Population, eligibility criteria | (Data source : ANTIKogulation 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 | M-152 (73%); F-55 (27%) |
|  | Mean age(yrs) | median -63 (Range: 57-72) |
|  | Diagnosis of AF | From admission notes |
|  | Mean Duration of AF | Not reported |
|  | Underlying cardiac conditions | hypertensive heart disease(46%); coronary artery disease(53%); hypertrophic valvular disease(7%); dilated cardiomyopathy(17%) |
|  | Co-morbidities (non- cardiac diseases) | Not reported |
|  | Treatment | prior anticoagulation-63% |
| Methods | Diagnostic instrument (s) for pathology | Transoesophageal echocardiography |
|  | Diagnostic criteria for pathology | Mass present in > 1 plane, in the body of the atrium or appendage which is distinct from the underlying endocardium |
|  | Description of Assessor(s) | Not reported |
| Results | Pathology (number of subjects) | LA thrombus- 1.4% \*(n=3). None of these patients had prior anticoagulation |
|  | Pathology prevalence (%) | LA thrombus-1%;aortic plaques-12% |

| Study | Author | Levy et al118 |
| --- | --- | --- |
|  | 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 6 patients |
|  | Sample size | 756 |
|  | Male/ Female | M-436 (58%); F- 320 (42%) |
|  | Mean age(yrs) | 68.6 ±11.4 |
|  | Diagnosis of AF | Electrocardiographic diagnosis of AF was made according to Bellet’s definition. AF was subdivided into 3 types: paroxysmal( history of recurrent episodes of AF lasting > 2 minutes and <7 days OR first episode of AF lasting <7days 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 less than 1 month, the patient was classified in the recent onset AF group.(n=200) |
|  | Mean Duration of AF | Patients with chronic AF - 54 ± 77 months |
|  | Underlying cardiac conditions |  |
|  | Co-morbidities (non- cardiac diseases) | Diabetes (n=81) - 10.7%; Bronchopulmonary disease (n=85) - 11.2% |
|  | Treatment | Anti-arrhythmic 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 2DEchocardiography (type unspecified). |
|  | Diagnostic criteria for pathology | Not reported |
|  | Description of Assessor(s) | Not reported |
| Results | Pathology (number of subjects) | CAD (n=126) -16.6%; Hypertensive heart disease (n=162) - 21.4%; Valvular (rheumatic) disease (n=115) - 15.2%; cardiomyopathy includes those with dilated/ hypertrophic/ other forms of cardiomyopathy (n=116)-15%; Congestive heart failure (n=226) - 29.8%; Hypertension (n = 298) -39.4% |
|  | Pathology prevalence (%) | CAD (n=126) -16.6%; Hypertensive heart disease (n=162) - 21.4%; Valvular (rheumatic) disease (n=115) - 15.2%; cardiomyopathy includes those with dilated/ hypertrophic/ other forms of cardiomyopathy (n=116)-15%; Congestive heart failure (n=226) - 29.8%; Hypertension (n = 298) -39.4% |

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| Study | Author | Lip et al119 |
|  | 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 or over |
|  | Sample size | 111 |
|  | Male/ Female | 42/111 M 38% |
|  | Mean age(yrs) | mean 72.7 (SD 9.9) |
|  | Diagnosis of AF | ECG |
|  | Mean Duration of AF | 73% of AF population had chronic AF, i.e. More than 6 months |
|  | Underlying cardiac conditions |  |
|  | Co-morbidities (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 (number 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% |

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| Study | Author | Maltagliati120 |
|  | 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 4 groups according to anticoagulant regimen-(1): oral anticoagulation (warfarin) INR>2 (n=744)(2) short-term anticoagulation with unfractionated heparin or with unfractionated heparin+warfarin for < 4 days (n=235)(3) ineffective oral anticoagulation(warfarin)> 3 weeks (n=43)(4) effective oral anticoagulation (warfarin) < 3 weeks(n=82). Total =1104 |
|  | Male/ Female | M-368 (67%);F-368 (33%) |
|  | Mean age(yrs) | 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 TIA(2.4%),recent embolic episodes(0.7%) mitral valve disease (11%), dilated cardiomyopathy (10%), and coronary artery disease (7%). |
|  | Co-morbidities (non- cardiac diseases) | Not reported |
|  | Treatment | Anticoagulation |
| Methods | Diagnostic instrument (s) for pathology | Transoesophageal echocardiography |
|  | Diagnostic criteria for pathology | Thrombi-identified as presence of echodense masses, mobile or immobile connected to the left atrium or LAA wall. Images were obtained in different planes from 0º-180º. |
|  | Description of Assessor(s) | Not reported |
| Results | Pathology (number of subjects) | 65; LA thrombi-2; LAA thrombi -59; RAA thrombi -4 |
|  | Pathology prevalence (%) | 6.3% ; LA-5.5%; LAA thrombi-0.3%; RAA thrombi- 0.5% . |

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| Study | Author | Narumiya121 |
|  | Date | 2003 |
|  | Location | Japan, cardiology dept single centre |
|  | Study design | retrospective cross-sectional |
| Population | Population, eligibility criteria | non-valvular chronic AF or atrial flutter, had had TOE. Excluded LVEF<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(yrs) | mean 60 (SD9.7) |
|  | Diagnosis of AF | non-valvular chronic AF was defined by conventional ECG on 2 occasions separated by at least 1month, and absence of rheumatic heart disease as determined by echocardiography. Lone AF was defined by excluding coronary artery disease (clinical or lab criteria), hyperthyroidism, valvular heart diseases, congestive heart failure, cardiomyopathy, chronic obstructive pulmonary disease, cardiomegaly, history of hypertension, age over 60, insulin-dependent diabetes mellitus, AF only during trauma/surgery, acute medical illness |
|  | Mean Duration of AF | NR |
|  | Underlying cardiac conditions | NR |
|  | Co-morbidities (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 (number 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%) |

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| Study | Author | Santiago122 |
|  | Date | 1994 |
|  | Location | USA, cardiology dept, 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 | 61 (of 63, 2 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(yrs) | AF group mean age 69 (SD10) |
|  | 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% |
|  | Co-morbidities (non- cardiac diseases) | NR |
|  | Treatment | AF group anticoagulant (21 days or more) 57% |
| Methods | Diagnostic instrument (s) for pathology | TOE |
|  | Diagnostic criteria for pathology | thrombi defined as masses adherent to wall of LAA. Mitral regurgitation assessed qualitatively on the basis of maximal area of the regurgitant jet |
|  | Description of Assessor(s) | NR |
| Results | Pathology (number of subjects) | AF group LAA thrombus n=12, MR n=9 |
|  | Pathology prevalence (%) | AF group LAA thrombus 40% , MR 30% |

| Study | Author | Scherr123 |
| --- | --- | --- |
|  | Date | 2009 |
|  | Location | USA |
|  | Study design | Prospective observational study |
| Population | Population, eligibility criteria | AF patients referred for catheter ablation of AF |
|  | Sample size | 585 patients undergoing 732 catheter ablations (from 590 patients referred for 737 catheter ablation, of which two procedures were terminated due to technical difficulties , while three cases demonstrating unexpected findings were excluded, giving a total of five cases were excluded from the final analysis.) |
|  | Male/ Female | M-564(77%); F-168(23%) |
|  | Mean age(yrs) | 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 ≥ 2 recurrent AF terminating spontaneously within 7 days. Persistent AF was defined as recurrent AF lasting > 7 days or sustained for < 7days due to pharmacologic or electrical cardioversion (n=353(48%)) |
|  | Mean Duration of AF | 75.6±69.6(calculated using 6.3 ± 5.8 years from the paper) |
|  | Underlying cardiac conditions | Hypertension(n=298)-41%;Congestive heart failure(88)-12%;previous stroke or TIA(39)-5% |
|  | Co-morbidities (non- cardiac diseases) | Diabetes mellitus(49)-7% |
|  | Treatment | Unsuccessful anti-arrhythmic treatment (class I and III)-1.4±1.0; Preprocedural anticoagulation(n=689)-94% At least four weeks before ablation patients received warfarin to maintain International normalised ratio, INR, 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 5th day before procedure. Patients in whom warfarin was contraindicated received antiplatelet agents at the discretion of attending doctor. |
| Methods | Diagnostic instrument (s) for pathology | Transoesophageal echocardiography |
|  | Diagnostic criteria for pathology | Patients underwent TOE 24 hours before ablation. The LA cavity and LA appendage were examined for the presence of thrombi. Atrial thrombus was present if there was a well-circumscribed echo-dense 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 (number of subjects) | Left atrial thrombus-12/732 |
|  | Pathology prevalence (%) | 1.60% |

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| --- | --- | --- | --- | --- |
| Study | Author | | Shen124 | |
|  | Date | | 2002 | |
|  | Location | | USA | |
|  | Study design | | Retrospective (Subjects were identified from chart review of consecutive patients who underwent transoesophageal echocardiography (TOE) to rule out intra-atrial thrombi before cardioversion of AF – January 1996 and June 2001.) | |
| Population | Population, eligibility criteria | | Patients with sub-therapeutic INRs after receiving adequate doses of anticoagulation for≥ 3 weeks. Eligibility: AF>48hours; Warfarin treatment ≥ 3 weeks; completion of full warfarin loading dose (defined as achievement of INR > 2 after starting treatment; INR < 2 at ≥ 1 measurement in the last 3 weeks preceding TOE with at least one measurement within 7 days of scheduled TOE. | |
|  | Sample size | | 182 | |
|  | Male/ Female | | not reported | |
|  | Mean age(yrs) | | not reported | |
|  | Diagnosis of AF | | not reported | |
|  | Mean Duration of AF | | 7.3±16.9 (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%; | |
|  | Co-morbidities (non- cardiac diseases) | | Diabetes mellitus(n=2)-1% | |
|  | Treatment | | not reported | |
| Methods | Diagnostic instrument (s) for pathology | | Transoesophageal echocardiography | |
|  | 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) | | not reported | |
| Results | Pathology (number of subjects) | | 18/182 | |
|  | Pathology prevalence (%) | | 9.90% | |
| Study | | Author | | Tsai125 |
|  | | 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 > 30days) admitted as in-patients or seen as out-patients, undergoing TOE. (Patients were excluded if they had oesophageal disease or could not tolerate TOE) |
|  | | Sample size | | 219(Of 222 patients included in the study, 3 had 'non-diagnostic images' on TOE) |
|  | | Male/ Female | | M-161 (74%); F-58-(26%) |
|  | | Mean age(yrs) | | 65 (Range 28-82) |
|  | | Diagnosis of AF | | Serial ECG |
|  | | Mean Duration of AF | | not reported |
|  | | 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% |
|  | | Co-morbidities (non- cardiac diseases) | | Hyperthyroidism(n=9)-4% |
|  | | Treatment | | Anti-coagulation treatment(n=15)-7%; Anti-platelet agents(n=38)-17% |
| Methods | | Diagnostic instrument (s) for pathology | | Transoesophageal echocardiography |
|  | | Diagnostic criteria for pathology | | Atrial thrombus was defined as a well-circumscribed echogenic mass in the left atrial cavity or appendage which was distinct from the surrounding pectinate muscles. |
|  | | Description of Assessor(s) | | not reported |
| Results | | Pathology (number of subjects) | | 15/219 |
|  | | Pathology prevalence (%) | | 6.80% |

**Appendix 7: Quality assessment Prevalence review**

Responses may be YES (Y), NO (N), UNCLEAR (U), NA (not applicable), or P (partial data provided)

|  |  |  |
| --- | --- | --- |
| Study | Author date | Agmon 2001111 |
| Study background | Background information given | Y |
|  | Study objectives stated | Y |
| Methods | Appropriate study design explained | Y |
|  | Description of recruitment | Y |
|  | Eligibility criteria described | Y |
|  | Methods of assessment or measurement described | Y |
| Results | Data on all participants provided | Y |
|  | Reasons for non-participation outlined | Y |
|  | Statistical methods described and appropriate | Y |
|  | Potential sources of biases identified | Y |
|  | Variables described or identified | Y |

|  |  |  |
| --- | --- | --- |
| Study | Author date | Archer 1995112 |
| Study background | Background information given | Y |
|  | Study objectives stated | Y |
| Methods | Appropriate study design explained | Y |
|  | Description of recruitment | Y |
|  | Eligibility criteria described | Y |
|  | Methods of assessment or measurement described | Y |
| Results | Data on all participants provided | Y |
|  | Reasons for non-participation outlined | Y |
|  | Statistical methods described and appropriate | Y |
|  | Potential sources of biases identified | U |
|  | Variables described or identified | Y |

|  |  |  |
| --- | --- | --- |
| Study | Author date | Blackshear 1999113 |
| Study background | Background information given | Y |
|  | Study objectives stated | Y |
| Methods | Appropriate study design explained | Y |
|  | Description of recruitment | Y |
|  | Eligibility criteria described | Y\* |
|  | Methods of assessment or measurement described | Y\* |
| Results | Data on all participants provided | Y |
|  | Reasons for non-participation outlined | Y |
|  | Statistical methods described and appropriate | Y |
|  | Potential sources of biases identified | Y |
|  | Variables described or identified | Y |

\* partial data reported in this reference, but full details available in previous publications

|  |  |  |
| --- | --- | --- |
| Study | Author date | Corrado 2004114 |
| Study background | Background information given | Y |
|  | Study objectives stated | Y |
| Methods | Appropriate study design explained | Y |
|  | Description of recruitment | Y |
|  | Eligibility criteria described | Y |
|  | Methods of assessment or measurement described | Y |
| Results | Data on all participants provided | Y |
|  | Reasons for non-participation outlined | Y |
|  | Statistical methods described and appropriate | Y |
|  | Potential sources of biases identified | N |
|  | Variables described or identified | Y |

|  |  |  |
| --- | --- | --- |
| Study | Author date | Dang 2004115 |
| Study background | Background information given | Y |
|  | Study objectives stated | Y |
| Methods | Appropriate study design explained | Y |
|  | Description of recruitment | Y |
|  | Eligibility criteria described | Y |
|  | Methods of assessment or measurement described | Y |
| Results | Data on all participants provided | Y |
|  | Reasons for non-participation outlined | Y |
|  | Statistical methods described and appropriate | Y |
|  | Potential sources of biases identified | P |
|  | Variables described or identified | Y |

|  |  |  |
| --- | --- | --- |
| Study | Author date | de Divitiis 199928 |
| Study background | Background information given | Y |
|  | Study objectives stated | Y |
| Methods | Appropriate study design explained | Y |
|  | Description of recruitment | Y |
|  | Eligibility criteria described | Y |
|  | Methods of assessment or measurement described | Y |
| Results | Data on all participants provided | Y |
|  | Reasons for non-participation outlined | Y |
|  | Statistical methods described and appropriate | Y |
|  | Potential sources of biases identified | N |
|  | Variables described or identified | Y |

|  |  |  |
| --- | --- | --- |
| Study | Author date | Heppell 1997116 |
| Study background | Background information given | Y |
|  | Study objectives stated | Y |
| Methods | Appropriate study design explained | Y |
|  | Description of recruitment | Y |
|  | Eligibility criteria described | Y |
|  | Methods of assessment or measurement described | Y |
| Results | Data on all participants provided | N |
|  | Reasons for non-participation outlined | Y |
|  | Statistical methods described and appropriate | Y |
|  | Potential sources of biases identified | Y |
|  | Variables described or identified | Y |

|  |  |  |
| --- | --- | --- |
| Study | Author date | Kleeman 2009117 |
| Study background | Background information given | Y |
|  | Study objectives stated | Y |
| Methods | Appropriate study design explained | Y |
|  | Description of recruitment | Y |
|  | Eligibility criteria described | Y |
|  | Methods of assessment or measurement described | Y |
| Results | Data on all participants provided | Y |
|  | Reasons for non-participation outlined | Y |
|  | Statistical methods described and appropriate | Y |
|  | Potential sources of biases identified | Y |
|  | Variables described or identified | Y |

|  |  |  |
| --- | --- | --- |
| Study | Author date | Levy 1999118 |
| Study background | Background information given | Y |
|  | Study objectives stated | Y |
| Methods | Appropriate study design explained | Y |
|  | Description of recruitment | Y |
|  | Eligibility criteria described | Y |
|  | Methods of assessment or measurement described | N |
| Results | Data on all participants provided | Y |
|  | Reasons for non-participation outlined | Y |
|  | Statistical methods described and appropriate | Y |
|  | Potential sources of biases identified | U |
|  | Variables described or identified | U |

|  |  |  |
| --- | --- | --- |
| Study | Author date | Lip 1997119 |
| Study background | Background information given | Y |
|  | Study objectives stated | Y |
| Methods | Appropriate study design explained | Y |
|  | Description of recruitment | Y |
|  | Eligibility criteria described | Y |
|  | Methods of assessment or measurement described | Y |
| Results | Data on all participants provided | NA |
|  | Reasons for non-participation outlined | NA |
|  | Statistical methods described and appropriate | Y |
|  | Potential sources of biases identified | Y |
|  | Variables described or identified | Y |

|  |  |  |
| --- | --- | --- |
| Study | Author date | Maltagliati 2006120 |
| Study background | Background information given | Y |
|  | Study objectives stated | Y |
| Methods | Appropriate study design explained | Y |
|  | Description of recruitment | Y |
|  | Eligibility criteria described | Y |
|  | Methods of assessment or measurement described | Y |
| Results | Data on all participants provided | Y |
|  | Reasons for non-participation outlined | Y |
|  | Statistical methods described and appropriate | Y |
|  | Potential sources of biases identified | U |
|  | Variables described or identified | Y |

|  |  |  |
| --- | --- | --- |
| Study | Author date | Narumiya 2003121 |
| Study background | Background information given | Y |
|  | Study objectives stated | Y |
| Methods | Appropriate study design explained | Y |
|  | Description of recruitment | Y |
|  | Eligibility criteria described | Y |
|  | Methods of assessment or measurement described | Y |
| Results | Data on all participants provided | NA |
|  | Reasons for non-participation outlined | NA |
|  | Statistical methods described and appropriate | Y |
|  | Potential sources of biases identified | N |
|  | Variables described or identified | P |

|  |  |  |
| --- | --- | --- |
| Study | Author date | Santiago 1994122 |
| Study background | Background information given | Y |
|  | Study objectives stated | Y |
| Methods | Appropriate study design explained | Y |
|  | Description of recruitment | Y |
|  | Eligibility criteria described | Y |
|  | Methods of assessment or measurement described | Y |
| Results | Data on all participants provided | Y |
|  | Reasons for non-participation outlined | Y |
|  | Statistical methods described and appropriate | Y |
|  | Potential sources of biases identified | Y |
|  | Variables described or identified | Y |

|  |  |  |
| --- | --- | --- |
| Study | Author date | Scherr 2009123 |
| Study background | Background information given | Y |
|  | Study objectives stated | Y |
| Methods | Appropriate study design explained | Y |
|  | Description of recruitment | Y |
|  | Eligibility criteria described | Y |
|  | Methods of assessment or measurement described | Y |
| Results | Data on all participants provided | Y |
|  | Reasons for non-participation outlined | Y |
|  | Statistical methods described and appropriate | Y |
|  | Potential sources of biases identified | Y |
|  | Variables described or identified | Y |

|  |  |  |
| --- | --- | --- |
| Study | Author date | Shen 2002124 |
| Study background | Background information given | Y |
|  | Study objectives stated | Y |
| Methods | Appropriate study design explained | Y |
|  | Description of recruitment | Y |
|  | Eligibility criteria described | Y |
|  | Methods of assessment or measurement described | Y |
| Results | Data on all participants provided | Y |
|  | Reasons for non-participation outlined | N/A |
|  | Statistical methods described and appropriate | Y |
|  | Potential sources of biases identified | N |
|  | Variables described or identified | U |

|  |  |  |
| --- | --- | --- |
| Study | Author date | Tsai 1997125 |
| Study background | Background information given | Y |
|  | Study objectives stated | Y |
| Methods | Appropriate study design explained | Y |
|  | Description of recruitment | Y |
|  | Eligibility criteria described | Y |
|  | Methods of assessment or measurement described | Y |
| Results | Data on all participants provided | Y |
|  | Reasons for non-participation outlined | Y |
|  | Statistical methods described and appropriate | Y |
|  | Potential sources of biases identified | Y |
|  | Variables described or identified | Y |

**Appendix 8: Excluded studies Diagnostic review**

**Studies excluded at full paper stage for diagnostic review**

| Study | Reason for exclusion |
| --- | --- |
| Abbasi 1980172 | Population not AF, AF study available for diagnostic accuracy of pathology |
| Aghassi 2005173 | grading severity of diagnosed condition, rather than diagnosing condition |
| Agricola 2008174 | excluded intervention, stress echocardiography |
| Alkhadi 2007175 | grading severity of diagnosed condition, rather than diagnosing condition |
| Assey 1981176 | Population not AF, higher level evidence available for diagnostic accuracy of pathology |
| Babic 1991177 | Population not AF, AF study available for diagnostic accuracy of pathology |
| Badran 2009178 | excluded intervention, combination of carotid and thoracic echocardiography |
| Blanchard 1981179 | Population not AF, AF study available for diagnostic accuracy of pathology |
| Blot-Souletie 2007180 | grading severity of diagnosed condition, rather than diagnosing condition |
| Bogren 1980181 | review of case reports, cases differed in their use of comparator(s) |
| Buchner 2008182 | grading severity of diagnosed condition, rather than diagnosing condition |
| Casiglia 2008183 | prognostic study, general population, AF excluded |
| Charron 1997184 | excluded comparator, study of familial hypertrophic cardiomyopathy, comparator was genotyping |
| Chen 1985185 | Population not AF, AF study available for diagnostic accuracy of pathology |
| Egeblad 1983186 | grading severity of diagnosed condition, rather than diagnosing condition |
| Fleischmann 1994187 | prognostic study, population with chest pain, population not AF |
| Gonzalez-Torrecilla 2000188 | excluded intervention, TOE and TTE combined |
| Hsiao 2006189 | Population not AF, higher level evidence available for diagnostic accuracy of pulmonary embolism |
| Irani 1996190 | Population not AF, higher level evidence available for diagnostic accuracy of pathology |
| Khanna 2004191 | grading severity of diagnosed condition, rather than diagnosing condition |
| Khumri 2007192 | TOE, not TTE (prognostic study) |
| Kruger 2001193 | Population not AF, AF study available for diagnostic accuracy of pathology |
| Lembcke 2008194 | grading severity of diagnosed condition, rather than diagnosing condition |
| Meng 2002195 | Population not AF, higher level evidence available for diagnostic accuracy of pathology |
| Miyatake 1986196 | Population not AF, AF study available for diagnostic accuracy of pathology |
| Mogelvang 2009197 | prognostic study, general population, AF excluded |
| Nitta 1988198 | grading severity of diagnosed condition, rather than diagnosing condition |
| Pechacek 1984199 | Population not AF, AF study available for diagnostic accuracy of pathology |
| Peteiro 2008200 | excluded intervention, exercise echocardiography |
| Roe 2000201 | echocardiography combined with clinical criteria, no separate data for TTE alone |
| Sallach 2009202 | excluded intervention, contrast echocardiography |
| Stafford 1985203 | Population not AF, higher level evidence available for diagnostic accuracy of pathology |
| Steckleberg 1991204 | prognostic study, population not AF |
| Stevens 2009205 | prognostic study, population with stable coronary artery disease, population not AF |
| Takamoto 1985206 | Population not AF, AF study available for diagnostic accuracy of pathology |
| Thuny 2005207 | prognostic study, population not AF |
| Visser 1983208 | Population not AF, AF study available for diagnostic accuracy of pathology |
| Willens 2006209 | 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 1993138 | did not set out to assess prevalence of selected pathology |
| Colkesen 2008210 | did not set out to assess prevalence of selected pathology |
| DiPasquale136 | did not set out to assess prevalence of selected pathology |
| Kannel 199819 | did not set out to assess prevalence of selected pathology |
| Levy 1998211 | did not set out to assess prevalence of selected pathology |
| Miyasaka 2000108 | did not set out to assess prevalence of selected pathology |
| Miyasaka 2007212 | did not set out to assess prevalence of selected pathology |
| Nieuwlaat 200554 | did not set out to assess prevalence of selected pathology |
| Rozenberg 2000135 | did not set out to assess prevalence of selected pathology |
| Rubin 1996137 | did not set out to assess prevalence of selected pathology |
| Tops 2010140 | did not set out to assess prevalence of selected pathology |
| Tsang 2005141 | did not set out to assess prevalence of selected pathology |
| Frykman 2001134 | did not set out to assess prevalence of selected pathology |
| Rostagno 1998139 | did not set out to assess prevalence of selected pathology |
| SPAF investigators 1992110 | did not set out to assess prevalence of selected pathology |

**Appendix 10: Parameters used in mathematical models**

Table 63: Sources of parameters used in model

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Category** | **Description** | **References** |
| **Risks/Probabilities** | Death from other causes | Nonparametric | UK Lifetables. |
| Sensitivity and Specificity of TTE in detecting LA ABN | Jointly estimated from Dirichlet distribution  (FN, TP, TN, FP) =  (5, 87, 83, 159) | Table 2 of Providencia et al 2012 |
| Proportion of patients with LA ABN | Beta(2.5, 22.5) for CHADS2  Beta(0.5, 11.5) for CHA2DS2-VASc  (Both with prior of 0.5 added to both cell counts.) | Table 2 of Providencia et al 2012 |
| Annual stroke risk by CHADS2 score | Simulated from Lognormal distribution | Friberg 2012 |
| Annual stroke risk in those with LA ABN | Simulated from Lognormal distribution | Connolly et al 2009 |
| Relative risk (RR) of stroke in patients receiving dabigatran | Indirect comparison simulation approach | Lip et al 2006 for RR of warfarin compared with placebo  Eikelboom et al 2011 for RR of dabigatran compared with warfarin |
| Annual major bleeding risk for patients receiving dabigatran | Statified by age. Credible interval calculated using simulation approach | Eikelboom et al 2011 |
| Outcome following stroke | Simulation & mapping based approach | Method described in report using results published in  Rivero-Arias et al 2010 |
| Outcome following a major bleeding event | Previous estimates | Simpson et al 2010 |
| **Utilities** | Baseline utilities by age and gender | Regression based approach | Ara et al 2010 |
| Utility multiplier following stroke, utility multiplier following major non-fatal intracranial bleed | Simulation & mapping based approach | Method described here using results published in  Rivero-Arias et al 2010 |
| **Costs** | Annual cost of dabigatran | £821.25 | NICE FAD, 2011 |
| Cost of TTE | £66 | NHS Reference Costs |
| Cost of death due to stroke | £7,019 (95% CrI £6,975 to £7,064) | Sandercock et al 2002 |
| Costs in stroke survivors | Various. Differing according to dependent and independent states. Subdivided into ongoing and continuing costs | NHS Reference Costs  NHS Stroke Strategy Impact Assessment  Unit Costs of Health and Social Care 2010 |
| Costs of fatal bleed | Assumed identical to costs of death due to stroke | |
| Costs of nonfatal bleed | Various  Depends on whether bleed is gastrointestinal or intracranial. If intracranial, depends on severity of resulting disability | NHS Reference Costs |

**Appendix 11: The influence of assumed sensitivity and specificity of TTE in identifying LA ABN on ICER 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 ABN in each of the 14 mathematical model comparisons**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***W\_50*** | | *Sensitivity* | | | | | | | | | | | | ***0\_M*** | | **0** | **0.1** | **0.2** | **0.3** | **0.4** | **0.5** | **0.6** | **0.7** | **0.8** | **0.9** | **1** | | *Specificity* | **0** | D | D | D | D | D | D | D | D | D | D | Inf | | **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** | D | D | D | D | D | D | >99 | 40.2 | 16.0 | 7.8 | 3.6 | |
| 1. W\_50\_0\_M |
| |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***W\_50*** | | *Sensitivity* | | | | | | | | | | | | ***0\_F*** | | **0** | **0.1** | **0.2** | **0.3** | **0.4** | **0.5** | **0.6** | **0.7** | **0.8** | **0.9** | **1** | | *Specificity* | **0** | D | D | D | D | D | D | D | D | D | D | Inf | | **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** | D | D | D | D | D | D | >99 | 36.2 | 16.2 | 8.2 | 3.9 | |
| 1. W\_50\_0\_F |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***W\_65*** | | *Sensitivity* | | | | | | | | | | | | ***0\_M*** | | **0** | **0.1** | **0.2** | **0.3** | **0.4** | **0.5** | **0.6** | **0.7** | **0.8** | **0.9** | **1** | | *Specificity* | **0** | D | D | D | D | D | D | D | D | D | D | Inf | | **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** | D | D | >99 | 69.3 | 36.1 | 22.1 | 14.4 | 9.5 | 6.1 | 3.6 | 1.7 |  1. W\_65\_0\_M |
| |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***W\_65*** | | Sensitivity | | | | | | | | | | | | ***0\_F*** | | **0** | **0.1** | **0.2** | **0.3** | **0.4** | **0.5** | **0.6** | **0.7** | **0.8** | **0.9** | **1** | | *Specificity* | **0** | D | D | D | D | D | D | D | D | D | D | Inf | | **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** | >99 | >99 | 65.4 | 40.4 | 27.1 | 18.9 | 13.3 | 9.2 | 6.1 | 3.7 | 1.8 | |
| 1. W\_65\_0\_F |
| |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***W\_50*** | | *Sensitivity* | | | | | | | | | | | | ***1\_M*** | | **0** | **0.1** | **0.2** | **0.3** | **0.4** | **0.5** | **0.6** | **0.7** | **0.8** | **0.9** | **1** | | *Specificity* | **0** | 9.8 | 9.8 | 9.9 | 9.9 | 9.9 | 10.0 | 10.1 | 10.3 | 10.6 | 11.6 | Inf | | **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** | 6.9 | 6.7 | 6.5 | 6.3 | 6.1 | 5.8 | 5.5 | 5.1 | 4.6 | 4.0 | 3.3 | |
| 1. W\_50\_1\_M |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***W\_50*** | | *Sensitivity* | | | | | | | | | | | | ***1\_F*** | | **0** | **0.1** | **0.2** | **0.3** | **0.4** | **0.5** | **0.6** | **0.7** | **0.8** | **0.9** | **1** | | *Specificity* | **0** | 11.6 | 11.6 | 11.7 | 11.7 | 11.8 | 11.8 | 11.9 | 12.1 | 12.4 | 13.3 | Inf | | **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** | 7.9 | 7.7 | 7.5 | 7.2 | 6.9 | 6.6 | 6.2 | 5.7 | 5.2 | 4.5 | 3.6 | |
| 1. W\_50\_1\_F |
| |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***W\_65*** | | *Sensitivity* | | | | | | | | | | | | ***1\_M*** | | **0** | **0.1** | **0.2** | **0.3** | **0.4** | **0.5** | **0.6** | **0.7** | **0.8** | **0.9** | **1** | | *Specificity* | **0** | 36.3 | 36.3 | 36.4 | 36.6 | 36.7 | 37.0 | 37.3 | 37.9 | 39.0 | 42.4 | Inf | | **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** | 13.3 | 12.5 | 11.7 | 10.7 | 9.7 | 8.6 | 7.4 | 6.1 | 4.7 | 3.1 | 1.3 | |
| 1. W\_65\_1\_M |
| |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***W\_65*** | | *Sensitivity* | | | | | | | | | | | | ***1\_F*** | | **0** | **0.1** | **0.2** | **0.3** | **0.4** | **0.5** | **0.6** | **0.7** | **0.8** | **0.9** | **1** | | *Specificity* | **0** | >99 | >99 | >99 | >99 | >99 | >99 | >99 | >99 | >99 | >99 | Inf | | **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** | 19.9 | 18.4 | 16.8 | 15.1 | 13.4 | 11.6 | 9.7 | 7.8 | 5.8 | 3.6 | 1.4 | |
| 1. W\_65\_1\_F |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***R\_50*** | | *Sensitivity* | | | | | | | | | | | | ***0\_M*** | | **0** | **0.1** | **0.2** | **0.3** | **0.4** | **0.5** | **0.6** | **0.7** | **0.8** | **0.9** | **1** | | *Specificity* | **0** | D | D | D | D | D | D | D | D | D | D | Inf | | **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** | D | D | D | D | D | D | 78.5 | 25.5 | 12.4 | 6.5 | 3.1 | |
| 1. R\_50\_0\_M |
| |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***R\_50*** | | *Sensitivity* | | | | | | | | | | | | ***0\_F*** | | **0** | **0.1** | **0.2** | **0.3** | **0.4** | **0.5** | **0.6** | **0.7** | **0.8** | **0.9** | **1** | | *Specificity* | **0** | D | D | D | D | D | D | D | D | D | D | Inf | | **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** | D | D | D | D | D | D | 60.7 | 24.8 | 12.9 | 6.9 | 3.4 | | |
| 1. R\_50\_0\_F | |
| |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***R\_65*** | | *Sensitivity* | | | | | | | | | | | | ***0\_M*** | | **0** | **0.1** | **0.2** | **0.3** | **0.4** | **0.5** | **0.6** | **0.7** | **0.8** | **0.9** | **1** | | *Specificity* | **0** | D | D | D | D | D | D | D | D | D | D | Inf | | **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** | >99 | 86.3 | 47.7 | 30.6 | 21.0 | 14.8 | 10.5 | 7.3 | 4.9 | 3.0 | 1.4 | | |
| 1. R\_65\_0\_M | |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***R\_65*** | | *Sensitivity* | | | | | | | | | | | | ***0\_F*** | | **0** | **0.1** | **0.2** | **0.3** | **0.4** | **0.5** | **0.6** | **0.7** | **0.8** | **0.9** | **1** | | *Specificity* | **0** | D | D | D | D | D | D | D | D | D | D | Inf | | **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** | 56.0 | 40.4 | 30.1 | 22.9 | 17.5 | 13.3 | 10.0 | 7.3 | 5.0 | 3.1 | 1.5 | |
| 1. R\_65\_0\_F |
| |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***D\_65*** | | *Sensitivity* | | | | | | | | | | | | ***0\_M*** | | **0** | **0.1** | **0.2** | **0.3** | **0.4** | **0.5** | **0.6** | **0.7** | **0.8** | **0.9** | **1** | | *Specificity* | **0** | D | D | D | D | D | D | D | D | D | D | Inf | | **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** | 29.6 | 23.4 | 18.6 | 14.8 | 11.7 | 9.2 | 7.0 | 5.2 | 3.6 | 2.2 | 1.0 | |
| 1. D\_65\_0\_M |
| |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | ***D\_65*** | | *Sensitivity* | | | | | | | | | | | | ***0\_F*** | | **0** | **0.1** | **0.2** | **0.3** | **0.4** | **0.5** | **0.6** | **0.7** | **0.8** | **0.9** | **1** | | *Specificity* | **0** | D | D | D | D | D | D | D | D | D | D | Inf | | **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** | 20.1 | 17.3 | 14.7 | 12.4 | 10.3 | 8.4 | 6.7 | 5.1 | 3.6 | 2.3 | 1.1 | |
| 1. D\_65\_0\_F |

**D: Dominated Continued overleaf (for 1st four pages)**

**ICER: Incremental cost-effectiveness ratio**

**Appendix 12: Search Strategy for economic evaluations of TTE in AF**

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1948 to Present>

Search Strategy:

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1 Economics/ (26174)

2 "costs and cost analysis"/ (39208)

3 Cost-benefit analysis/ (52318)

4 Cost control/ (18902)

5 Cost savings/ (7217)

6 Cost of illness/ (14510)

7 Cost sharing/ (1697)

8 "deductibles and coinsurance"/ (1308)

9 Medical savings accounts/ (450)

10 Health care costs/ (22054)

11 Direct service costs/ (958)

12 Drug costs/ (10541)

13 Employer health costs/ (1041)

14 Hospital costs/ (6577)

15 Health expenditures/ (11915)

16 Capital expenditures/ (1908)

17 Value of life/ (5196)

18 exp economics, hospital/ (17442)

19 exp economics, medical/ (13323)

20 Economics, nursing/ (3854)

21 Economics, pharmaceutical/ (2279)

22 exp "fees and charges"/ (25506)

23 exp budgets/ (11098)

24 (low adj cost).mp. (17558)

25 (high adj cost).mp. (6674)

26 (health?care adj cost$).mp. (2986)

27 (fiscal or funding or financial or finance).tw. (65465)

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. (141645)

32 or/1-31 (397254)

33 tte.mp. (1269)

34 tte.tw. (1268)

35 transthoracic echocardiography.mp. (4415)

36 (transthorac$ or trans-thorac$ or (trans$ and thorac$)).mp. (45938)

37 (echocardiog$ adj (transthorac$ or trans-thorac$ or (trans$ and thorac$))).mp. (448)

38 33 or 34 or 35 or 36 or 37 (46183)

39 32 and 38 (346)

40 heart valve diseases/ or heart valve problems.mp. or valvular heart disease.mp. (18610)

41 ((aortic or aorta or mitral or pulmonary or triscuspid or vavular) and (regurgitation or stenosis or incompetence or insufficiency)).mp. (89068)

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. (43519)

46 congenital heart malformation.mp. (116)

47 heart septal defects, atrial/ or atrial spetal 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. (13692)

51 heart atrium septal defect.mp. (0)

52 aortic coartation/ or coartation of the aorta.mp. (9)

53 aorta coarctation.mp. (80)

54 heart valve diseases/ or heart valve problems.mp. or valvular heart disease.mp. (18610)

55 valvular defects.mp. (174)

56 valvular heart disease.mp. or Heart Valve Diseases/ (18609)

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. (59553)

63 hypertension, pulmonary/ or primary pulmonary hypertension.mp. (21843)

64 aortic diseases/ or aortic disease.mp. or aorta disease.mp. (12643)

65 aortic aneurysm/ or aortic aneurysm.mp. or aorta aneurysm.mp. (36522)

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. (12727)

72 cardiomyopathy, hypertrophic/ or hypertrophic cardiomyopathy.mp. (12875)

73 Heart failure/ or heart failure.mp. (117623)

74 heart left ventricle hypertrophy.mp. (0)

75 congestive heart failure.mp. (29007)

76 endocarditis/ or endocarditis.mp. (28538)

77 pericarditis/ or pericarditis.mp. (11917)

78 myocardial ischemia/ or ischemic heart disease.mp. or heart muslce ischemia.mp. (42783)

79 (angina or angina pectoris or angina pectoris, variant or angina, unstable or ludwig's angina or microvascular angina).mp. (56678)

80 coronary thrombosis/ or coronary thrombosis.mp. (6319)

81 (atherosclerotic heart disease or atherosclerotic cardiovascular disease).mp. (1502)

82 Myocardial Infarction/co (23244)

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. (50804)

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. (44698)

93 (coronary artery anuerysm or aorta anuerysm).mp. (0)

94 heart neoplasms/ or heart masses.mp. or cardiac masses.mp. (12581)

95 heart tumo?r.mp. (100)

96 pulmonary embolism/ or pulmonary embolism.mp. or lung embolism.mp. (34879)

97 lung disease/ or pulmonary disease.mp. (86405)

98 hypertension, pulmonary/ or pulmonary hypertension.mp. (29346)

99 cor pulmonale.mp. (3519)

100 heart murmurs/ or heart murmur$.mp. (3499)

101 or/40-100 (662970)

102 32 and 38 and 101 (95)

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