National Institute for Health and Care Excellence

Draft

Heart valve disease presenting in adults: investigation and management

[A] Evidence reviews for symptoms and signs indicating need for echocardiography or direct referral to a specialist

NICE guideline <number>

Evidence reviews underpinning recommendations 1.1.1 to 1.1.5 and 1.1.8 to 1.1.11 in the NICE guideline

March 2021

Draft for Consultation

These evidence reviews were developed by the National Guideline Centre

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ISBN:

Contents

1 Introduction

The assessment of patients with suspected heart valve disease begins with a comprehensive clinical assessment, comprising history taking and systematic physical examination including cardiac auscultation to detect murmurs and associated changes in the normal heart sounds. This initial clinical assessment can be performed in primary care, in hospital settings outside cardiology or within cardiology, it can increase or decrease the suspicion of existence of heart valve disease and it can provide indications of heart valve disease severity. However, the firm diagnosis of existence and of severity of heart valve disease is made with cardiac imaging, primarily with echocardiography.

There is access to echocardiography as a result of a referral from primary care or from hospital settings outside or within cardiology. However, if cardiac auscultation is reassuring, echocardiography may be unnecessary. The capacity for echocardiography is not unlimited and unnecessary assessments would both inconvenience the individual assessed and delay the essential assessment of another individual. Consequently, it is important to identify the symptoms and signs that indicate referral for echocardiography.

The clinical pathway comprising referral for echocardiography and subsequent assessment of the result to decide if referral to a specialist is needed, may introduce delay in the care of patients with severe symptoms due to potentially severe heart valve disease. Consequently, it is important to identify the symptoms and signs that indicate direct referral to a specialist to avoid delay. Specialist clinics offer one stop echocardiography or echocardiography prior to the clinic appointment, as such shortening the clinical pathway.

2 Signs and symptoms indicating echocardiography referral

2.1 In adults with suspected heart valve disease what symptoms and signs indicate referral (for example from primary care) for echocardiography?

2.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Adults aged 18 years and over with suspected heart valve disease in any setting (for example, in primary care) Exclusion: Adults presenting with acute heart failure Children aged less than 18 years. Adults with congenital heart disease (excluding bicuspid aortic valves). Tricuspid stenosis and pulmonary valve disease.
Target condition	Heart valve disease: aortic (including bicuspid) stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation or tricuspid regurgitation

Symptoms and signs	Clinical observations:
	
	Cardiac auscultation (standard or electronic):
	• Presence of new murmur
	• Character of heart sounds:
	  ○ no/soft 2nd heart sound (as in severe AS)
	  ○ added 3rd sound; gallop rhythm (as in severe MR)
	
	Mild or atypical (non-exertional) symptoms or signs:
	• Fatigue
	• Palpitations
	• Shortness of breath (NYHA class I-II)
	• Peripheral oedema (swelling of ankles and legs)
	• Chest pain (Canadian score class 1-2)
	• Exertional dizziness or pre-syncope
	• Abnormal ECG: for example signs of left ventricular hypertrophy or atrial fibrillation
	
	Include the following combinations:
	• murmur alone,
	• murmur + heart sounds,
	• murmur + symptoms,
	• murmur + heart sounds + symptoms
	(not symptoms alone nor heart sounds alone)

Reference standards	• Confirmed diagnosis of HVD by transthoracic or transoesophageal echocardiography

	• Confirmed diagnosis of HVD by invasive cardiac catheterisation will be considered as indirect evidence to avoid excluding older studies
Statistical measures	Diagnostic accuracy of symptoms and signs for a confirmed diagnosis of HVD of any severity. Measured by: **Primary measures** <u>Accuracy data</u> • Sensitivity • Specificity • Raw data to calculate 2x2 tables to calculate sensitivity and specificity (number of true positives, true negatives, false positives and false negatives). **Secondary measures** • Likelihood ratios • Positive Predictive Value (PPV) • Negative Predictive Value (NPV) If insufficient accuracy data are found, diagnostic association of signs and symptoms with a confirmed diagnosis of HVD will be included. Measured by: <u>Association data</u> • Adjusted RR or OR For decision-making, it was agreed that sensitivity should be the primary measure taken into account as avoiding false negatives was considered to be the priority over avoiding false positives to avoid sending many people away early without further testing. Agreed a threshold of ≥60% to represent suitable sensitivity to consider recommending a test, with emphasis on importance of follow-up on those with continuing symptoms or concerns.

Study design	• Single-gate diagnostic studies (these may be called cohort studies or cross-sectional studies) will be included preferentially
	
	• If no/insufficient diagnostic accuracy studies are identified prospective and retrospective cohort studies with multivariate analysis of the association between signs and symptoms and a confirmed diagnosis of heart valve disease will be included.
	
	Confounding factors (if diagnostic association studies are included):
	• Age (<65 years or ≥65 years)
	• Type of murmur:
	  ○ Innocent murmur
	  ○ Ejection systolic murmur
	  ○ Regurgitant systolic murmur
	  ○ Diastolic murmur
	• Presence/absence of anaemia
	• Presence/absence of pregnancy
	• Presence/absence of atrial fibrillation

2.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

2.1.4 Diagnostic evidence

2.1.4.1 Included studies

A search was conducted for cross-sectional and prospective and retrospective cohort studies assessing the diagnostic test accuracy of murmur with or without other signs or symptoms (heart sounds and/or symptoms) to identify whether the condition is present (as indicated by the reference standard) in people under investigation for condition heart valve disease.

Diagnostic association studies that report data on the association between murmur with or without other signs or symptoms (heart sounds and/or symptoms) and diagnosis of heart valve disease were also considered if limited diagnostic studies were available.

Thirty studies with diagnostic accuracy data or data that could be used to calculate diagnostic accuracy data were included in the review; [5, 11, 16-19, 21-23, 27, 29, 34, 51, 72, 86, 97, 103, 109, 113, 117, 121, 132, 137, 139, 143, 163, 171, 174, 175, 230] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below in Tables 3-16.

Most of the studies investigated the accuracy of murmur alone for the diagnosis of heart valve disease, with the definition of the murmur and person conducting auscultation differing between studies. However, two studies[23, 174] looked at murmur plus symptoms, three studies[174,19,132] assessed murmur plus an absent or reduced second heart sound, and one study[174] looked at murmur plus abnormal ECG.

The assessment of the evidence quality was conducted with emphasis on test sensitivity, as this was identified by the committee as the primary measure in guiding decision-making as the priority would be to avoid missing cases (false negatives) and not sending them for further testing as a result. The committee set clinical decision thresholds as sensitivity = 0.60.

Reference standards

Of the 30 studies included in the review, 25 used the preferred reference standard of echocardiography. However, a further 5 studies were included that used cardiac catheterisation as the method of confirming valve disease, as this was the preferred method confirming valve disease before echocardiography was available. This more invasive procedure was used in older studies.

Populations

Studies that involved screening for heart valve disease and murmurs in presumably healthy populations where there could be no reason for a suspicion of heart valve disease were excluded, for example, where screening was performed for everyone who experienced a hip fracture or in populations that were said to be healthy. However, studies where there was not necessarily a suspicion of heart valve disease but had some indication for either attendance at hospital or primary care, echocardiography or were experiencing cardiac symptoms were included, as there was limited evidence where the populations were defined as specifically being suspected of having heart valve disease.

Studies where the presence of a murmur was required for a participant to be included in a study were also included, despite the fact that this would mean all were already known to be index test positive before enrolment. Limited diagnostic accuracy data can be obtained from

these studies, but it was agreed to include these given that murmur would be one of the main reasons for suspicion of heart valve disease and these studies could still provide information on the proportion of those with the murmur that actually had reference standard confirmed valve disease, in the form of the positive predictive ratio. The limitations of these studies were highlighted.

See also the study selection flow chart in Appendix C, and sensitivity and specificity forest plots in Appendix E, and study evidence tables in Appendix D.

2.1.4.2 Excluded studies

See the excluded studies list in Appendix I.

2.1.5 Summary of studies included in the diagnostic evidence

Table 2: Summary of studies included in the evidence review

Study	Population	Target condition	Index test	Reference standard	Comments
Aggarwal 2014[5] n=100 India	Outpatients presenting for echocardiography at Cardiology centre	Heart valve disease: any valve disease	Detection of murmur using stethoscope and specific software Systolic or diastolic murmurs	Echocardiography confirmed heart valve disease	Patients known to have pre-existing heart murmurs excluded ZargisCardioscan™ software used
Amano 1986[11] n=55 Japan	People presenting with early or mid-systolic murmurs	Heart valve disease: mitral regurgitation	Presence of murmur (all had one to be included in study) Apical early or mid-systolic murmurs	Echocardiography confirmed mitral regurgitation	
Aronow 1989[16] n=450 USA	Unselected elderly patients in a long-term health care facility with echocardiography of aortic valve performed	Heart valve disease: aortic regurgitation	Murmur of aortic regurgitation High frequency diastolic decrescendo murmur beginning with A2	Echocardiography confirmed aortic regurgitation	Potentially indirect population: unselected elderly patients in a long-term health care facility – not necessarily suspected HVD
Aronow 1987[17] n=75 USA	Unselected elderly patients in a long-term health care facility with echocardiography of aortic valve performed and	Heart valve disease: aortic stenosis	Aortic systolic ejection murmurs (all had one to be included in the study)	Echocardiography confirmed aortic stenosis	

Study	Population	Target condition	Index test	Reference standard	Comments
	aortic systolic ejection murmurs				
Aronow 1991[18] n=781 USA	Unselected elderly patients in long term health care facility	Heart valve disease: aortic stenosis	Aortic systolic ejection murmur	Echocardiography confirmed AS	Note: only sufficient information to be able to calculate sensitivity (no details of number of true negatives/false positives
Attenhofer Jost 2000[19] n=100 Switzerland	Those referred for echocardiography due to systolic murmur of unknown cause - no prior echo examination	Heart valve disease: aortic stenosis or valvular regurgitation (AR, MR, TR)	Systolic murmur (all had one) Systolic murmur +diminished aortic closure sound (AS and MR only)	Echocardiography confirmed AS or valvular regurgitation (AR, TR, MR)	Reports different types of HVD separately and not possible to report as single group
Barron 1988[21] n=140 USA	People with suspected mitral valve prolapse referred for echocardiography	Heart valve disease: mitral regurgitation or tricuspid regurgitation	Systolic murmur on auscultation	Echocardiography confirmed mitral regurgitation or tricuspid regurgitation	
Barzilai 1988[22] n=59 USA	Hospitalised patients with documented acute myocardial infarction	Heart valve disease: mitral regurgitation	Systolic murmur on auscultation	Echocardiography confirmed mitral regurgitation	
Baur 2006[23] n=198 The Netherlands	Suspected heart failure or valve disease (restricted to: dyspnoea, cardiac murmur or peripheral oedema of unexplained origin)	Heart valve disease: aortic or mitral valve disease (including stenosis and regurgitation)	Cardiac murmur Cardiac murmur + other indication (e.g. dyspnoea, peripheral oedema or other)	Echocardiography confirmed aortic or mitral valve disease	
Breisblatt 1988[27] n=150 USA	Referred for cardiac catheterisation with known ischaemic heart disease and no previous	Heart valve disease: mitral regurgitation	Systolic murmur on physical examination	Radionuclide angiography confirmed mitral regurgitation	Reference standard indirectness: invasive cardiac catheterisation rather than

Study	Population	Target condition	Index test	Reference standard	Comments
	history of valvular disease				echocardiography
Cantley 1995[29] n=32 UK	Those with systolic murmur on clinical examination at acute assessment and rehabilitation unit of hospital	Heart valve disease: aortic stenosis, aortic regurgitation and mitral regurgitation	Systolic murmur on clinical examination (all had one to be included in the study)	Echocardiography confirmed aortic stenosis, aortic regurgitation or mitral regurgitation	Study reports data separately for each type of valve disease and not possible to combine into a single 'HVD' category
Chin 1992[34] n=42 The Netherlands	Those with diagnosed mitral valve prolapse based on echocardiography	Heart valve disease: mitral regurgitation	Late systolic murmur on auscultation	Echocardiography confirmed mitral regurgitation	Selected population that is more likely to have higher incidence of mitral regurgitation as they already have echo-confirmed mitral valve abnormality?
Decoodt 1990[51] n=100 Belgium	Those with mitral valve prolapse confirmed by echocardiography	Heart valve disease: mitral regurgitation	Systolic murmur on auscultation (early systolic, late systolic or holosystolic)	Echocardiography confirmed mitral regurgitation	Selected population that is more likely to have higher incidence of mitral regurgitation as they already have echo-confirmed mitral valve abnormality?
Gardezi 2018[72] n=251 UK	Those undergoing echocardiography at two primary care sites participating in OxVALVE study	Heart valve disease: mild or significant valve disease	Murmur (systolic or diastolic)	Echocardiography confirmed valve disease	Potential population indirectness: screening type study – part of the OxVALVE study where echocardiography performed in asymptomatic people in primary care

Study	Population	Target condition	Index test	Reference standard	Comments
					May not represent current practice and how suspected HVD patients would usually be identified Separates them into mild (aortic sclerosis or any mild regurgitation) and significant (at least moderate regurgitation of any valve or at least mild stenosis of any valve) Taken murmurs as measured by GPs rather than cardiologists, as our review is set before they have been referred to a specialist
Hoffman n 1983[86] n=58 Switzerla nd	Those undergoing right or left heart catheterisation for valvular or coronary heart disease, or both, due to an ill-defined systolic murmur	Heart valve disease: aortic stenosis or mitral regurgitation	Systolic murmur – all had one to be included in the subgroup	Cardiac catheterisation confirmed aortic stenosis or mitral regurgitation	Potential population indirectness: some already with confirmed valve disease (19%) Reference standard indirectness: invasive cardiac catheterisatio n rather than echocardiogra phy

Study	Population	Target condition	Index test	Reference standard	Comments
					Study reports separately for the two types of valve disease and not possible to combine
Kalinauskiene 2019[97] n=30 Lithuania	Obese patients referred for echocardiography due to symptoms or abnormal findings	Heart valve disease: aortic stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation or tricuspid regurgitation	Murmur on electronic or acoustic stethoscope	Echocardiography confirmed valve disease	Provides data separately for stenosis and regurgitation, and also separately for electronic and acoustic stethoscopes. Data was extracted for residents rather than cardiologists as more relevant to the setting of this review.
Kinney 1988[103] n=294 USA	Patients referred for echocardiography at hospital	Heart valve disease: aortic regurgitation, mitral regurgitation or tricuspid regurgitation	Murmur on auscultation (systolic or diastolic)	Echocardiography confirmed aortic regurgitation, mitral regurgitation or tricuspid regurgitation	Gives separately for each type of regurgitation and also for different types of examiners assessing the murmur: student, internet, junior assistant residents, cardiology fellows – selected 'resident' as closest to the area we are interested in.
Labovitz 1985[109] n=51 USA	Patients with mitral annular calcium detected on echocardiography	Heart valve disease: mitral stenosis or mitral regurgitation	Apical systolic murmur	Echocardiography confirmed mitral stenosis or mitral regurgitation (sufficient data to combine as 'any mitral valve disease'	Potential population indirectness: selected population with likely increased incidence of disease as already had

Study	Population	Target condition	Index test	Reference standard	Comments
					echocardiography performed?
Lehmann 1992[113] n=206 USA	Patients with acute myocardial infarction	Heart valve disease: mitral regurgitation	Any murmur	Cardiac catheterisation/ ventriculography confirmed mitral regurgitation	
Limacher 1985[117] n=81 USA	Pregnant women referred for evaluation of murmurs	Heart valve disease: tricuspid regurgitation	Cardiac murmur (all had one to be included in the study)	Echocardiography confirmed tricuspid regurgitation	
Loperfido 1986[121] n=72 Italy	Patients diagnosed with myocardial infarction 1-3 months prior to the study at the coronary care unit based on chest pain, ECG and increase and decrease of creatine kinase-MB fraction	Heart valve disease: mitral regurgitation	Systolic murmur	Echocardiography confirmed mitral regurgitation	Potential population indirectness: not necessarily suspected HVD but all have had MI with cardiac symptoms
McGee 2010[132] n=376 USA	Non-intensive care unit patients undergoing echocardiography - around 16% already known to have valve disease	Heart valve disease: aortic stenosis	Systolic heart murmur Broad apical-based systolic murmur + absence second heart sound	Echocardiography confirmed aortic stenosis	Potential population indirectness: some already known to have valve disease Study reports details separately for different types of valve disease and not possible to combine
Meyers 1982[139] n=75 USA	Patients with suspected aortic regurgitation undergoing aortograms (angiography)	Heart valve disease: aortic regurgitation	Early diastolic murmur of aortic regurgitation	Angiography confirmed aortic regurgitation	Reference standard indirectness: invasive cardiac catheterisation rather than

Study	Population	Target condition	Index test	Reference standard	Comments
					echocardiography
Meyers 1986[137] n=35 USA	Those evaluated by Doppler echocardiography, cardiac auscultation and let ventriculography – 20% with already documented valve disease	Heart valve disease: mitral regurgitation	Systolic murmur	Left ventriculography confirmed mitral regurgitation	Potential population indirectness: some with already diagnosed valve disease. Reference standard indirectness: invasive cardiac catheterisation rather than echocardiography
Mishra, 1992[143] n=103 UK	Pregnant women referred for cardiac opinion	Heart valve disease: any type of echo abnormality – can obtain information for those relevant to our protocol	Pathological or possibly pathological murmur detected	Echocardiography confirmed valve disease	
Panidis 1986[163] n=80 USA	Those with mitral valve prolapse confirmed on echocardiography and signs and symptoms	Heart valve disease: mitral regurgitation	Systolic murmur	Echocardiography confirmed mitral regurgitation	Potential population indirectness: selected population that is more likely to have higher incidence of mitral regurgitation as they already have echo-confirmed mitral valve abnormality?
Rahko 1989[171] n=408 USA	Patients presenting to echocardiography laboratory	Heart valve disease: aortic regurgitation, mitral regurgitation or tricuspid regurgitation	Regurgitant murmur on auscultation	Echocardiography confirmed aortic regurgitation, mitral regurgitation or tricuspid regurgitation	Potential population indirectness: not necessarily suspected HVD but some indication for echocardiography

Study	Population	Target condition	Index test	Reference standard	Comments
					Study reports data for each type of regurgitation separately and not possible to combine as single 'regurgitation' group
Reardon 1996[174] n=148 UK	Acute medical patients aged >65 years admitted to geriatric ward of hospital – data reported only for those with systolic murmurs	Heart valve disease: aortic stenosis	Systolic murmur (all had one to be included in the analysis) Systolic murmur + reduced second heart sound Systolic murmur + symptoms (angina) Systolic murmur + symptoms (dyspnoea) Systolic murmur + abnormal ECG (left ventricular hypertrophy) Systolic murmur + abnormal ECG (atrial fibrillation)	Echocardiography confirmed aortic stenosis	Potential population indirectness: not necessarily suspected HVD but some indications to be admitted to hospital
Reichlin 2004[175] n=203 Switzerland	Adults presenting to medical ED with confirmed systolic murmur present	Heart valve disease: aortic stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation, tricuspid regurgitation and other types of valve disease	Pathological systolic murmur	Echocardiography confirmed valve disease	Note: all had systolic murmurs to be enrolled, but physicians distinguished between innocent and pathological murmurs

Study	Population	Target condition	Index test	Reference standard	Comments
Yamashita 2020[230] n=74 Japan	Inpatients diagnosed with infective endocarditis at a single hospital in Japan between September 2007 and August 2017	Heart valve disease: aortic regurgitation, mitral regurgitation and tricuspid regurgitation (results reported separately for each of these)	Audible cardiac murmur	Echocardiography confirmed valve disease	Note: population includes 14.9% with acute heart failure as a complication of the infective endocarditis

See Appendix D for full evidence.

2.1.6 Summary of the diagnostic evidence

The assessment of the evidence quality was conducted with emphasis on test sensitivity and specificity as this was identified by the committee as the primary measure in guiding decision-making. The committee set a clinical decision threshold of 0.6 for sensitivity.

The populations, target conditions and index tests used across the included studies were considered to be very broad and wide-ranging, and therefore no studies were pooled into a diagnostic meta-analysis. Sensitivity and specificity for each individual study is given below, separated into broad categories based on the population and also by whether the reference standard was echocardiography or cardiac catheterisation.

For studies where all of those included had to be positive for murmur with/without another characteristic (which was used as an index test in our review), sensitivity and specificity, as well as other measures, could not be calculated, and positive predictive values are instead presented.

Note that although all included studies detected heart valve disease as the target condition, the type of heart valve disease that was included in the studies varied. For example, some studies aimed to diagnose and report any type of valve disease (including aortic stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation and tricuspid regurgitation), while others focused specifically on one or two types of valve disease, such as aortic stenosis or mitral stenosis and mitral regurgitation, or any type of regurgitation but not stenosis (i.e. aortic regurgitation, mitral regurgitation and tricuspid regurgitation). Where possible, results have been calculated for ‘any valve disease’; however, in many cases results are reported separately for each type of valve disease as it was not possible to determine how many may have had more than one time of valve disease at the same time to calculate diagnostic accuracy results for overall heart valve disease in each study.

Reference standard – echocardiography

Table 3: Clinical evidence summary: murmur for heart valve disease in various settings in populations with various indications for assessment

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Systolic or diastolic murmur detected with stethoscope and specific software for the diagnosis of any valve disease – **community medicine physician**								PPV: 0.68

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Outpatients presenting for echocardiography	100	Serious[1]	NA	Serious[2]	Serious[3]	Sensitivity= 0.41 (0.28 to 0.56)	VERY LOW	NPV: 0.57 PLR: 2.02 NLR: 0.74 Prevalence on reference standard: 0.51
		Serious[1]	NA	Serious[2]	Serious[3]	Specificity= 0.80 (0.66 to 0.90)	VERY LOW	
Murmur of AR (high frequency diastolic decrescendo murmur beginning with A2) for the diagnosis of AR – **experienced cardiologist**								PPV: 0.93 NPV: 0.92 PLR: 31.96 NLR: 0.20 Prevalence on reference standard: 0.29
Unselected elderly patients in a long-term health care facility	450	Very serious[1]	NA	Serious[2]	None	Sensitivity=0.80 (0.72 to 0.87)	VERY LOW	
		Very serious[1]	NA	Serious[2]	None	Specificity= 0.97 (0.95 to 0.99)	VERY LOW	
Aortic systolic ejection murmur for the diagnosis of AS – **experienced cardiologist**								Prevalence on reference standard: 0.18 Other measures could not be calculated due to insufficient data
Unselected elderly patients in a long-term health care facility	781	Very serious[1]	NA	Serious[2]	None	Sensitivity=0.97 (0.93 to 0.99)	VERY LOW	
		NA	NA	NA	NA	Specificity could not be calculated due to insufficient data provided	NA	
Systolic murmur on auscultation for the diagnosis of MR or TR – **cardiologist**								PPV: 0.51 NPV: 0.74 PLR: 1.93 NLR: 0.65 Prevalence on reference standard: 0.35
People with suspected mitral valve prolapse referred for echocardiography	140	Serious[1]	NA	None	Serious[3]	Sensitivity=0.53 (0.38 to 0.67)	LOW	
		Serious[1]	NA	None	None	Specificity= 0.73 (0.62 to 0.81)	MODERATE	
Systolic murmur on auscultation for the diagnosis of MR – **attending physician**								PPV: 0.63 NPV: 0.70 PLR: 2.61 NLR: 0.68 Prevalence on reference
Hospitalised patients with documented	59	Very serious[1]	NA	Serious[2]	Very serious[3]	Sensitivity=0.43 (0.23 to 0.66)	VERY LOW	
		Very serious[1]	NA	Serious[2]	Very serious[3]	Specificity= 0.83 (0.67 to 0.94)	VERY LOW	

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
acute myocardial infarction								standard: 0.39
Cardiac murmur for the diagnosis of any aortic or mitral valve disease – **GPs**								PPV: 0.19 NPV: 0.99 PLR: 2.06 NLR: 0.09 Prevalence on reference standard: 0.10
Suspected heart failure or valve disease (restricted to: dyspnoea, cardiac murmur or peripheral oedema of unexplained origin)	198	Very serious[1]	NA	None	Serious[3]	Sensitivity=0.95 (0.75 to 1.00)	VERY LOW	
		Very serious[1]	NA	None	None	Specificity= 0.54 (0.46 to 0.61)	LOW	
Systolic or diastolic murmur for the diagnosis of any valve disease								
Those undergoing echocardiography at two primary care sites participating in OxVALVE study	251	Mild valve disease (aortic sclerosis or mild regurgitation) – **GPs**						PPV: 0.67 NPV: 0.32 PLR: 0.97 NLR: 1.01 Prevalence on reference standard: 0.68
		Serious[1]	NA	Serious[2]	None	Sensitivity=0.32 (0.25 to 0.40)	LOW	
		Serious[1]	NA	Serious[2]	Serious[3]	Specificity= 0.67 (0.55 to 0.77)	VERY LOW	
		Significant valve disease (at least moderate regurgitation or at least mild stenosis of any valve) – **GPs**						PPV: 0.20 NPV: 0.88 PLR: 1.45 NLR: 0.80 Prevalence on reference standard: 0.14
		Serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=0.44 (0.28 to 0.62)	VERY LOW	
		Serious[1]	NA	Serious[2]	None	Specificity= 0.69 (0.63 to 0.75)	LOW	
Murmur on electronic or acoustic stethoscope for the diagnosis of any valve disease – **3rd year medical resident doctor**								
Obese patients referred for echocardiography	30	Aortic stenosis – resident using acoustic stethoscope						PPV:0.25 NPV:0.92 PLR:3.00 NLR:0.75 Prevalence on reference
		Serious[1]	NA	Serious[2]	Very serious[3]	Sensitivity=0.33 (0.01 to 0.91)	VERY LOW	
		Serious[1]	NA	Serious[2]	Serious[3]	Specificity= 0.89 (0.71 to 0.98)	VERY LOW	

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
due to symptoms or abnormal findings								standard:0.10
		Aortic stenosis – resident using electronic stethoscope						PPV:0.25
		Serious[1]	NA	Serious[2]	Very serious[3]	Sensitivity=0.33 (0.01 to 0.91)	VERY LOW	NPV:0.92 PLR:3.00 NLR:0.75
		Serious[1]	NA	Serious[2]	Serious[3]	Specificity=0.89 (0.71 to 0.98)	VERY LOW	Prevalence on reference standard:0.10
		Aortic regurgitation – resident using acoustic stethoscope						PPV:1.00
		Serious1	NA	Serious[2]	Very serious[3]	Sensitivity=0.26 (0.09 to 0.51)	VERY LOW	NPV:0.44 PLR: Not calculable
		Serious1	NA	Serious[2]	Serious[3]	Specificity=1.00 (0.72 to 1.00)	VERY LOW	NLR:0.74 Prevalence on reference standard:0.63
		Aortic regurgitation – resident using electronic stethoscope						PPV:1.00
		Serious1	NA	Serious[2]	Very serious[3]	Sensitivity=0.37 (0.16 to 0.62)	VERY LOW	NPV:0.48 PLR: Not calculable
		Serious1	NA	Serious[2]	Serious[3]	Specificity=1.00 (0.72 to 1.00)	VERY LOW	NLR:0.63 Prevalence on reference standard:0.63
		Mitral stenosis – resident using acoustic stethoscope						NPV: 1.00
		Serious1	NA	NA	NA	Sensitivity could not be calculated due to none being positive for MS	NA	Prevalence on reference standard: 0.00
		Serious1	NA	Serious[2]	None	Specificity=0.97 (0.83 to 1.00)	LOW	Other values not calculable
		Mitral stenosis – resident using electronic stethoscope						NPV: 1.00
		Serious1	NA	Serious[2]	NA	Sensitivity could not be calculated due to none being positive for MS	NA	Prevalence on reference standard: 0.00
		Serious1	NA	Serious[2]	None	Specificity=0.97 (0.83 to 1.00)	LOW	Other values not calculable
		Mitral regurgitation – resident using acoustic stethoscope						

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
		Serious1	NA	Serious[2]	Serious[3]	Sensitivity=0.76 (0.55 to 0.91)	VERY LOW	PPV:0.90 NPV:0.33 PLR:1.90 NLR:0.40 Prevalence on reference standard:0.83
		Serious1	NA	Serious[2]	Very serious[3]	Specificity=0.60 (0.15 to 0.95)	VERY LOW	
		Mitral regurgitation – resident using electronic stethoscope						PPV:0.88 NPV:0.33 PLR:1.40 NLR:0.40 Prevalence on reference standard:0.83
		Serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=0.84 (0.64 to 0.95)	VERY LOW	
		Serious[1]	NA	Serious[2]	Very serious[3]	Specificity=0.40 (0.05 to 0.85)	VERY LOW	
		Tricuspid regurgitation – resident using acoustic stethoscope						PPV:0.91 NPV:0.47 PLR:5.00 NLR:0.56 Prevalence on reference standard:0.67
		Serious[1]	NA	Serious[2]	Very serious[3]	Sensitivity=0.50 (0.27 to 0.73)	VERY LOW	
		Serious[1]	NA	Serious[2]	Very serious[3]	Specificity=0.90 (0.55 to 1.00)	VERY LOW	
		Tricuspid regurgitation – resident using electronic stethoscope						PPV:0.87 NPV:0.53 PLR:3.25 NLR:0.44 Prevalence on reference standard:0.67
		Serious[1]	NA	Serious[2]	Very serious[3]	Sensitivity=0.65 (0.41 to 0.85)	VERY LOW	
		Serious[1]	NA	Serious[2]	Very serious[3]	Specificity=0.80 (0.44 to 0.97)	VERY LOW	
Systolic or diastolic murmur on auscultation for the diagnosis of AR, MR or TR								
Patients referred for echocardiography at hospital	294	Aortic regurgitation – **junior assistant residents**						PPV: 0.27 NPV: 0.79 PLR: 1.33 NLR: 0.99 Prevalence on reference standard: 0.214
		Very serious[1]	NA	Serious[2]	None	Sensitivity=0.05 (0.01 to 0.13)	VERY LOW	
		Very serious[1]	NA	Serious[2]	None	Specificity=0.97 (0.94 to 0.99)	VERY LOW	
		Aortic regurgitation – **senior assistant residents**						NPV: 0.77 NLR: 1.10 Prevalence on
		Very serious[1]	NA	Serious[2]	None	Sensitivity=0.00 (0.00 to 0.06)	VERY LOW	

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
		Very serious[1]	NA	Serious[2]	None	Specificity= 0.91 (0.86 to 0.94)	VERY LOW	reference standard: 0.214 Other values not calculable
		Mitral regurgitation – **junior assistant residents**						PPV: 0.48 NPV: 0.71 PLR: 1.87 NLR: 0.85 Prevalence on reference standard: 0.327
		Very serious[1]	NA	Serious[2]	None	Sensitivity=0.28 (0.19 to 0.38)	VERY LOW	
		Very serious[1]	NA	Serious[2]	None	Specificity= 0.85 (0.79 to 0.90)	VERY LOW	
		Mitral regurgitation – **senior assistant residents**						PPV: 0.39 NPV: 0.68 PLR: 1.30 NLR: 0.97 Prevalence on reference standard: 0.327
		Very serious[1]	NA	Serious[2]	None	Sensitivity=0.13 (0.07 to 0.21)	VERY LOW	
		Very serious[1]	NA	Serious[2]	None	Specificity= 0.90 (0.85 to 0.94)	VERY LOW	
		Tricuspid regurgitation – **junior assistant residents**						PPV: 1.00 NPV: 0.87 NLR: 0.73 Prevalence on reference standard: 0.167 PLR not calculable
		Very serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=0.27 (0.15 to 0.41)	VERY LOW	
		Very serious[1]	NA	Serious[2]	None	Specificity= 1.00 (0.99 to 1.00)	VERY LOW	
		Tricuspid regurgitation – **senior assistant residents**						PPV: 1.00 NPV: 0.88 NLR: 0.67 Prevalence on reference standard: 0.167 PLR not calculable
		Very serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=0.33 (0.20 to 0.48)	VERY LOW	
		Very serious[1]	NA	Serious[2]	None	Specificity= 1.00 (0.99 to 1.00)	VERY LOW	
Systolic murmur for the diagnosis of MR – **cardiologist (performed at coronary care unit)**								PPV: 0.81 NPV: 0.52 PLR: 3.47 NLR: 0.74
Patients diagnos	72	Serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=0.33 (0.19 to 0.49)	VERY LOW	

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
ed with myocardial infarction 1-3 months prior to the study at the coronary care unit		Serious[1]	NA	Serious[2]	Serious[3]	Specificity= 0.91 (0.75 to 0.98)	VERY LOW	Prevalence on reference standard: 0.56
Systolic heart murmur for the diagnosis of AS – **physician in primary and specialist medical care department**								PPV: 0.33 NPV: 0.99 PLR: 1.96 NLR: 0.05 Prevalence on reference standard: 0.20
Non-intensive care unit patients undergoing echocardiography	376	Very serious[1]	NA	Serious[2]	None	Sensitivity=0.97 (0.90 to 1.00)	VERY LOW	
		Very serious[1]	NA	Serious[2]	None	Specificity= 0.50 (0.44 to 0.56)	VERY LOW	
Regurgitant murmur on auscultation for the diagnosis of AR, MR or TR – **cardiologist**								
Patients presenting to an echocardiography laboratory	408	Aortic regurgitation						PPV: 0.34 NPV: 0.99 PLR: 5.90 NLR: 0.11 Prevalence on reference standard: 0.08
		Very serious[1]	NA	Serious[2]	None	Sensitivity=0.60 (0.52 to 0.69)	VERY LOW	
		Very serious[1]	NA	Serious[2]	None	Specificity= 0.98 (0.95 to 0.99)	VERY LOW	
		Mitral regurgitation						PPV: 0.28 NPV: 0.98 PLR: 3.49 NLR: 0.20 Prevalence on reference standard: 0.10
		Very serious[1]	NA	Serious[2]	None	Sensitivity=0.56 (0.48 to 0.64)	VERY LOW	
		Very serious[1]	NA	Serious[2]	None	Specificity= 0.89 (0.85 to 0.93)	VERY LOW	
		Tricuspid regurgitation						PPV: 0.42 NPV: 0.97 PLR: 10.15 NLR: 0.41 Prevalence on reference standard: 0.07
		Very serious[1]	NA	Serious[2]	None	Sensitivity=0.23 (0.16 to 0.31)	VERY LOW	
		Very serious[1]	NA	Serious[2]	None	Specificity= 0.98 (0.96 to 1.00)	VERY LOW	

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Pathological systolic murmur (as interpreted by auscultator) for the diagnosis of any valve disease – **emergency department attending physician**								PPV: 0.59 NPV: 0.88 PLR: 2.63 NLR: 0.27 Prevalence on reference standard: 0.35
Adults presenting to medical ED with confirmed systolic murmur present	203	Serious[1]	NA	Serious[2]	None	Sensitivity=0.82 (0.71 to 0.90)	LOW	
		Serious[1]	NA	Serious[2]	None	Specificity=0.69 (0.60 to 0.77)	LOW	
Audible cardiac murmur for the diagnosis of aortic regurgitation – **unclear who assessed murmur**								PPV: 0.47 NPV: 0.76 PLR: 1.44 NLR: 0.52 Prevalence on reference standard: 0.38
Inpatients diagnosed with infective endocarditis at a single hospital in Japan	74	Very serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=0.75 (0.55 to 0.89)	VERY LOW	
		Very serious[1]	NA	Serious[2]	Serious[3]	Specificity=0.48 (0.33 to 0.63)	VERY LOW	
Audible cardiac murmur for the diagnosis of mitral regurgitation – **unclear who assessed murmur**								
Inpatients diagnosed with infective endocarditis at a single hospital in Japan	74	Very serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=0.66 (0.51 to 0.79)	VERY LOW	PPV: 0.69 NPV: 0.45 PLR: 1.27 NLR: 0.71 Prevalence on reference standard: 0.64
		Very serious[1]	NA	Serious[2]	Serious[3]	Specificity=0.48 (0.29 to 0.68)	VERY LOW	
Audible cardiac murmur for the diagnosis of tricuspid regurgitation – **unclear who assessed murmur**								
Inpatients diagnosed with infective endocarditis at a single hospital in Japan	74	Very serious[1]	NA	Serious[2]	Very serious[3]	Sensitivity=0.62 (0.38 to 0.82)	VERY LOW	PPV: 0.29 NPV: 0.72 PLR: 1.03 NLR: 0.96 Prevalence on reference standard: 0.28
		Very serious1[1]	NA	Serious[2]	Serious[3]	Specificity=0.40 (0.26 to 0.54)	VERY LOW	

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[2] *Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were considered to have a high degree of indirectness, and downgraded by 2 increments if the majority of studies were considered to have a very high degree of indirectness.*

[3] *Imprecision was assessed by considering the width of the confidence intervals around the sensitivity and specificity. A variation of 0-20% was considered precise, 20-40% serious imprecision, and >40% very serious imprecision.*

Table 4: Clinical evidence summary: murmur for heart valve disease in populations with MVP that has already been diagnosed by echocardiography

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Late systolic murmur on auscultation for the diagnosis of MR – **unclear who did examination**								PPV: 0.82 NPV: 0.80 PLR: 6.23 NLR: 0.35 Prevalence on reference standard: 0.42
Those with diagnosed mitral valve prolapse based on echocardiography	42	Very serious[1]	NA	Serious[2]	Very serious[3]	Sensitivity=0.69 (0.39 to 0.91)	VERY LOW	
		Very serious[1]	NA	Serious[2]	Very serious[3]	Specificity=0.89 (0.65 to 0.99)	VERY LOW	
Systolic murmur on auscultation (early, late or holosystolic included) for the diagnosis of MR – **unclear who did examination**								PPV: 0.90 NPV: 0.85 PLR: 8.01 NLR: 0.15 Prevalence on reference standard: 0.54
Those with mitral valve prolapse confirmed by echocardiography	100	Very serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=0.87 (0.75 to 0.95)	VERY LOW	
		Very serious[1]	NA	Serious[2]	Serious[3]	Specificity=0.89 (0.76 to 0.96)	VERY LOW	
Systolic murmur for the diagnosis of MR – **unclear who did examination**								PPV: 0.81 NPV: 0.46 PLR: 1.99 NLR: 0.53 Prevalence on reference standard: 0.69
Those with mitral valve prolapse confirmed on echocardiography and signs and symptoms	80	Serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=0.64 (0.50 to 0.76)	VERY LOW	
		Serious[1]	NA	Serious[2]	Serious[3]	Specificity=0.68 (0.46 to 0.85)	VERY LOW	

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[2] *Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were considered to have a high degree of indirectness, and downgraded by 2 increments if the majority of studies were considered to have a very high degree of indirectness.*

[3] *Imprecision was assessed by considering the width of the confidence intervals around the sensitivity and specificity. A variation of 0-20% was considered precise, 20-40% serious imprecision, and >40% very serious imprecision.*

Table 5: Clinical evidence summary: murmur for heart valve disease in a population with mitral annular calcium observed by echocardiography

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Apical systolic murmur for the diagnosis of mitral stenosis or regurgitation – **unclear who did examination**								PPV: 0.39 NPV: 0.74 PLR: 1.29 NLR: 0.71 Prevalence on reference standard: 0.33
Patients with mitral annular calcium detected on echocardiography	51	Very serious [1]	NA	Serious [2]	Serious [3]	Sensitivity=0.59 (0.41 to 0.76)	VERY LOW	
		Very serious [1]	NA	Serious [2]	Very serious [3]	Specificity=0.53 (0.29 to 0.76)	VERY LOW	

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[2] *Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were considered to have a high degree of indirectness, and downgraded by 2 increments if the majority of studies were considered to have a very high degree of indirectness.*

[3] *Imprecision was assessed by considering the width of the confidence intervals around the sensitivity and specificity. A variation of 0-20% was considered precise, 20-40% serious imprecision, and >40% very serious imprecision.*

Table 6: Clinical evidence summary: murmur for heart valve disease (all with murmur to be included)

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size [1]	Quality
Apical early or mid-systolic murmur for the diagnosis of MR – prevalence 0.53 – **unclear who did examination**							
People presenting with early or mid-systolic murmurs	55	Very serious[2]	NA	Serious[3]	Could not be assessed	PPV=0.53	VERY LOW
Aortic systolic ejection murmur for the diagnosis of AS – prevalence 0.56 – **experienced cardiologist**							

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size [1]	Quality
Unselected elderly patients in a long-term health care facility with aortic systolic ejection murmurs	75	Serious[2]	NA	Serious[3]	Could not be assessed	PPV=0.56	VERY LOW
Systolic murmur for the diagnosis of AS, AR, MR or TR – **cardiologists**							
Referred for echocardiography due to systolic murmur of unknown cause - no prior echo examination	100	<u>Aortic stenosis</u> - prevalence 0.29					
		Serious[2]	NA	Serious[3]	Could not be assessed	PPV=0.29	VERY LOW
		<u>Aortic regurgitation</u>- prevalence 0.28					
		Serious[2]	NA	Serious[3]	Could not be assessed	PPV=0.28	VERY LOW
		<u>Mitral regurgitation</u> - prevalence 0.30					
		Serious[2]	NA	Serious[3]	Could not be assessed	PPV=0.30	VERY LOW
		<u>Tricuspid regurgitation</u> - prevalence 0.24					
		Serious[2]	NA	Serious[3]	Could not be assessed	PPV=0.24	VERY LOW
Systolic murmur on clinical examination for the diagnosis of AS, AR or MR – **unclear who did examination**							
Those with systolic murmur on clinical examination at acute assessment and rehabilitation unit of hospital	32	<u>Aortic stenosis</u> – prevalence 0.38					
		Very serious[2]	NA	Serious[3]	Could not be assessed	PPV=0.38	VERY LOW
		<u>Aortic regurgitation</u> – prevalence 0.45					
		Very serious[2]	NA	Serious[3]	Could not be assessed	PPV=0.45	VERY LOW
		<u>Mitral regurgitation</u> – prevalence 0.55					
		Very serious[2]	NA	Serious[3]	Could not be assessed	PPV=0.55	VERY LOW

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size [1]	Quality
Systolic murmur for the diagnosis of AS – prevalence 0.81 – **junior hospital doctor and one of authors**							
Acute medical patients aged >65 years admitted to geriatric ward of hospital with confirmed systolic murmur present	148	Very serious [2]	NA	Serious[3]	Could not be assessed	PPV=0.81	VERY LOW

[1] *In these studies, all patients had to have a murmur to be included in the study. Therefore, sensitivity and specificity could not be calculated, and positive predictive values are instead presented for each study.95% confidence intervals could not be calculated for this effect measure.*

[2] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[3] *Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were considered to have a high degree of indirectness, and downgraded by 2 increments if the majority of studies were considered to have a very high degree of indirectness.*

Table 7: Clinical evidence summary: murmur + dyspnoea for heart valve disease in acute medical patients admitted to geriatric ward of hospital

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Systolic murmur + symptoms (dyspnoea) for the diagnosis of AS – **junior hospital doctor and one of authors**								PPV: 1.00 NPV: 0.24 PLR: could not be calculated as there were no false positives reported NLR: 0.73 Prevalence on reference standard: 0.81
Acute medical patients aged >65 years admitted to geriatric ward of hospital with confirmed systolic murmur present	148	Very serious[1]	NA	None	Serious[2]	Sensitivity=0.27 (0.17 to 0.40)	VERY LOW	
		Very serious[1]	NA	None	Serious[2]	Specificity=1.00 (0.78 to 1.00)	VERY LOW	

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[2] *Imprecision was assessed by considering the width of the confidence intervals around the sensitivity and specificity. A variation of 0-20% was considered precise, 20-40% serious imprecision, and >40% very serious imprecision.*

Table 8: Clinical evidence summary: murmur + angina for heart valve disease in acute medical patients admitted to geriatric ward of hospital

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Systolic murmur + symptoms (angina) for the diagnosis of AS – **junior hospital doctor and one of authors**								PPV: 1.00
Acute medical patients aged >65 years admitted to geriatric ward of hospital with confirmed systolic murmur present	148	Very serious[1]	NA	None	None	Sensitivity=0.03 (0.00 to 0.11)	LOW	NPV: 0.19 PLR: could not be calculated as there were no false positives reported NLR: 0.97 Prevalence on reference standard: 0.81
		Very serious[1]	NA	None	Serious[2]	Specificity=1.00 (0.78 to 1.00)	VERY LOW	

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[2] *Imprecision was assessed by considering the width of the confidence intervals around the sensitivity and specificity. A variation of 0-20% was considered precise, 20-40% serious imprecision, and >40% very serious imprecision.*

Table 9: Clinical evidence summary: murmur + other indication (dyspnoea, peripheral oedema or other) for heart valve disease in patients with suspected heart failure of heart valve disease)

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Cardiac murmur + other indication (e.g. dyspnoea, peripheral oedema or other) for the diagnosis of any aortic or mitral valve disease – **GPs**								PPV: 0.35
Suspected heart failure	198	Very serious[1]	NA	None	Very serious[2]	Sensitivity=0.60 (0.36 to 0.81)	VERY LOW	NPV: 0.95

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
or valve disease (restricted to: dyspnoea, cardiac murmur or peripheral oedema of unexplained origin)		Very serious[1]	NA	None	None	Specificity=0.88 (0.82 to 0.92)	LOW	PLR: 4.85 NLR: 0.46 Prevalence on reference standard: 0.10

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[2] *Imprecision was assessed by considering the width of the confidence intervals around the sensitivity and specificity. A variation of 0-20% was considered precise, 20-40% serious imprecision, and >40% very serious imprecision.*

Table 10: Clinical evidence summary: systolic murmur + absent/reduced second heart sound for heart valve disease

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Systolic murmur + diminished aortic closure sound for the diagnosis of AS or MR - **cardiologists**								
Those referred for echocardiography due to systolic murmur of unknown cause - no prior echo examination	100	Aortic stenosis						Prevalence on reference standard 0.29 Other values could not be calculated
		Serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=0.29 (0.13 to 0.49)	VERY LOW	
		NA	NA	NA	NA	Could not calculate specificity as insufficient information provided	NA	
		Mitral regurgitation						Prevalence on reference standard 0.30 Other values could not be calculated
		Serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=0.10 (0.02 to 0.27)	VERY LOW	
		NA	NA	NA	NA	Could not calculate specificity as insufficient information provided	NA	

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Broad apical-based systolic murmur + absent second heart sound for the diagnosis of AS – **physician in primary and specialist medical care department**								Prevalence on reference standard 0.20 Other values could not be calculated
Non-intensive care unit patients undergoing echocardiography	376	Very serious[1]	NA	Serious[2]	Serious[4]	PLR[5]= 15.7 (1.0 to 251.0) (reported in the study)	VERY LOW	
Systolic murmur + reduced second heart sound for the diagnosis of AS – **junior hospital doctor and one of authors**								PPV: 1.00 NPV: 0.27 PLR: could not be calculated as there were no false positives reported NLR: 0.61 Prevalence on reference standard: 0.81
Acute medical patients aged >65 years admitted to geriatric ward of hospital with confirmed systolic murmur present	148	Very serious[1]	NA	None	Serious[3]	Sensitivity=0.39 (0.28 to 0.52)	VERY LOW	
		Very serious[1]	NA	None	Serious[3]	Specificity=1.00 (0.78 to 1.00)	VERY LOW	

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[2] *Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were considered to have a high degree of indirectness, and downgraded by 2 increments if the majority of studies were considered to have a very high degree of indirectness.*

[3] *Imprecision was assessed by considering the width of the confidence intervals around the sensitivity and specificity. A variation of 0-20% was considered precise, 20-40% serious imprecision, and >40% very serious imprecision.*

[4] *For the PLR reported in the study, serious imprecision was considered to be present as the confidence intervals crossed 1 and are very wide.*

[5] *PLR was reported in this study and it was not possible to calculate sensitivity and specificity; PLR as reported in the study is therefore presented.*

Table 11: Clinical evidence summary: non-flow murmur for heart valve disease in pregnant women

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Pathological or possibly pathological murmur (as interpreted by auscultator) for the diagnosis of any valve disease – **senior cardiologist**								PPV: 0.18 NPV: 1.00 PLR: 5.50 NLR: 0.00 Prevalence on reference standard: 0.04
Pregnant women referred for cardiac opinion	103	Serious[1]	NA	Serious[2]	Very serious[3]	Sensitivity=1.00 (0.40 to 1.00)	VERY LOW	
		Serious[1]	NA	Serious[2]	None	Specificity=0.82 (0.73 to 0.89)	LOW	

[1] Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

[2] Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were considered to have a high degree of indirectness, and downgraded by 2 increments if the majority of studies were considered to have a very high degree of indirectness.

[3] Imprecision was assessed by considering the width of the confidence intervals around the sensitivity and specificity. A variation of 0-20% was considered precise, 20-40% serious imprecision, and >40% very serious imprecision.

Table 12: Clinical evidence summary: murmur in pregnant women for heart valve disease (all with murmur to be included)

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size [1]	Quality
Cardiac murmur for the diagnosis of TR – prevalence 0.43 – **referring physician**							
Pregnant women referred for evaluation of murmurs	81	Very serious[2]	NA	Serious[3]	Could not be assessed	PPV=0.43	VERY LOW

[1] In these studies, all patients had to have a murmur to be included in the study. Therefore, sensitivity and specificity could not be calculated, and positive predictive values are instead presented for each study.95% confidence intervals could not be calculated for this effect measure.

[2] Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

[3] Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were considered to have a high degree of indirectness, and downgraded by 2 increments if the majority of studies were considered to have a very high degree of indirectness.

Table 13: Clinical evidence summary: murmur + abnormal ECG (left ventricular hypertrophy) for heart valve disease in acute medical patients admitted to geriatric ward of hospital

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Systolic murmur + abnormal ECG (left ventricular hypertrophy) for the diagnosis of AS – **junior hospital doctor and one of authors**								PPV: 0.94 NPV: 0.22 PLR: 3.41 NLR: 0.83 Prevalence on reference standard: 0.81
Acute medical patients aged >65 years admitted to geriatric ward of hospital with confirmed systolic murmur present	148	Very serious[1]	NA	None	Serious[2]	Sensitivity=0.23 (0.13 to 0.35)	VERY LOW	
		Very serious[1]	NA	None	Very serious[2]	Specificity=0.93 (0.68 to 1.00)	VERY LOW	

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[2] *Imprecision was assessed by considering the width of the confidence intervals around the sensitivity and specificity. A variation of 0-20% was considered precise, 20-40% serious imprecision, and >40% very serious imprecision.*

Table 14: Clinical evidence summary: murmur + abnormal ECG (atrial fibrillation) for heart valve disease in acute medical patients admitted to geriatric ward of hospital

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Systolic murmur + abnormal ECG (atrial fibrillation) for the diagnosis of AS – **junior hospital doctor and one of authors**								PPV: 0.71 NPV: 0.16 PLR: 0.51 NLR: 1.16 Prevalence on reference standard: 0.81
Acute medical patients aged >65 years admitted to geriatric ward of hospital with confirmed systolic murmur present	148	Very serious[1]	NA	None	None	Sensitivity=0.15 (0.08 to 0.26)	LOW	
		Very serious[1]	NA	None	Very serious[2]	Specificity=0.73 (0.45 to 0.92)	VERY LOW	

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[2] *Imprecision was assessed by considering the width of the confidence intervals around the sensitivity and specificity. A variation of 0-20% was considered precise, 20-40% serious imprecision, and >40% very serious imprecision.*

Reference standard – cardiac catheterisation

Table 15: Clinical evidence summary: murmur for heart valve disease in various settings in populations with various indications for assessment

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Systolic murmur on physical examination for the diagnosis of MR – **cardiologists**								PPV: 0.42 NPV: 0.97 PLR: 3.01 NLR: 0.15 Prevalence on reference standard: 0.19
Referred for cardiac catheterisation with known ischaemic heart disease and no previous history of valvular disease	150	Serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=0.90 (0.73 to 0.98)	VERY LOW	
		Serious[1]	NA	Serious[2]	None	Specificity=0.70 (0.61 to 0.78)	LOW	
Any murmur for the diagnosis of MR – **cardiology attending physician or fellow**								PPV: 0.21 NPV: 0.88 PLR: 1.74 NLR: 0.91 Prevalence on reference standard: 0.13
Patients with acute myocardial infarction	206	Very serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=0.19 (0.06 to 0.38)	VERY LOW	
		Very serious[1]	NA	Serious[2]	None	Specificity=0.89 (0.84 to 0.93)	VERY LOW	
Early diastolic murmur of AR for the diagnosis of AR – **attending cardiologist**								PPV: 0.96 NPV: 0.28 PLR: 3.27 NLR: 0.35 Prevalence on reference standard: 0.88
Patients with suspected aortic regurgitation undergoing aortograms	75	Very serious[1]	NA	None	Serious[3]	Sensitivity=0.73 (0.60 to 0.83)	VERY LOW	
		Very serious[1]	NA	None	Very serious[3]	Specificity=0.78 (0.40 to 0.97)	VERY LOW	

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Apical systolic murmur of MR for the diagnosis of MR – **unclear who performed the examination**								PPV: 0.93 NPV: 0.75 PLR: 11.79 NLR: 0.28 Prevalence on reference standard: 0.54
Those evaluated by Doppler echocardiography, cardiac auscultation and left ventriculography	35	Very serious[1]	NA	Serious[2]	Very serious[3]	Sensitivity=0.74 (0.49 to 0.91)	VERY LOW	
		Very serious[1]	NA	Serious[2]	Serious[3]	Specificity=0.94 (0.70 to 1.00)	VERY LOW	

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[2] *Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were considered to have a high degree of indirectness, and downgraded by 2 increments if the majority of studies were considered to have a very high degree of indirectness.*

[3] *Imprecision was assessed by considering the width of the confidence intervals around the sensitivity and specificity. A variation of 0-20% was considered precise, 20-40% serious imprecision, and >40% very serious imprecision.*

Table 16: Clinical evidence summary: systolic murmur for heart valve disease (all with murmur to be included)

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size [1]	Quality
Systolic murmur for the diagnosis of AS or MR – **unclear who performed the examination**							
Those undergoing right or left heart catheterisation for valvular or coronary heart disease, or both, due to an ill-defined systolic murmur	58	<u>Aortic stenosis</u> – prevalence 0.38					
		Very serious [2]	NA	Serious[3]	Could not be assessed	PPV=0.38	VERY LOW
		<u>Mitral regurgitation</u> – prevalence 0.62					
		Very serious [2]	NA	Serious[3]	Could not be assessed	PPV=0.62	VERY LOW

[1] *In these studies, all patients had to have a murmur to be included in the study. Therefore, sensitivity and specificity could not be calculated, and positive predictive values are instead presented for each study.95% confidence intervals could not be calculated for this effect measure.*

[2] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[3] *Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were considered to have a high degree of indirectness, and downgraded by 2 increments if the majority of studies were considered to have a very high degree of indirectness.*

2.1.7 Economic evidence

2.1.7.1 Included studies

No health economic studies were included.

2.1.7.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix F.

2.1.8 Summary of included economic evidence

None

2.1.9 Economic model

This area was not prioritised for new cost-effectiveness analysis.

2.1.10 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 17: UK cost of echocardiogram

Resource	Unit cost	Source
Simple Echocardiogram (a)	£108	NHS reference Costs 2017/18[151]
Complex Echocardiogram (b)	£196	NHS reference Costs 2017/18[151]

(a) Cost code RD51A outpatient
(b) Cost code EY50Y outpatient

3 Signs and symptoms indicating referral to a specialist

3.1 In adults with suspected heart valve disease, what symptoms and signs indicate direct referral (for example from primary care) to a specialist?

3.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 18: PICO characteristics of review question

Population	Adults aged 18 years and over with suspected heart valve disease in any setting (for example, in primary care) Exclusion: Children aged less than 18 years. Adults with congenital heart disease (excluding bicuspid aortic valves). Tricuspid stenosis and pulmonary valve disease. Adults presenting with acute heart failure
Target condition	Severe heart valve disease: aortic (including bicuspid) stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation or tricuspid regurgitation

Symptoms and signs	<u>Clinical observations:</u>
	
	Cardiac auscultation (standard or electronic):
	• Presence of new murmur
	• Character of heart sounds:
	  ○ no/soft 2nd heart sound (as in severe AS)
	  ○ added 3rd sound; gallop rhythm (as in severe MR)
	
	Signs, severe symptoms or simple investigations:
	• Shortness of breath (exertional breathlessness, for example classified as NYHA class ≥2)
	• Shortness of breath + elevated serum natriuretic peptides (B-type natriuretic peptide [BNP] or N-terminal pro-B-type natriuretic peptide [NT-proBNP]; for example NT-proBNP 400-2000 or >2000 ng/litre)
	• Peripheral oedema (ie. swelling of ankles and legs)
	• Peripheral oedema (ie. swelling of ankles and legs) + BNP or NT proBNP (for example NT-proBNP 400-2000 or >2000 ng/litre)
	• Pulmonary oedema
	• Exertional chest pain (Canadian score class 2+)
	• Exertional syncope (fainting)
	• Abnormal ECG: for example signs of LV hypertrophy or AF
	
	<u>Include the following combinations:</u>
	• murmur alone
	• murmur + heart sounds
	• murmur + any of the listed symptoms, signs, or investigative findings

	• murmur + heart sounds + any of the listed symptoms, signs, or investigative findings • murmur + heart failure (not symptoms alone nor heart sounds alone)
Reference standard	Confirmed diagnosis of severe HVD by transthoracic or transoesophageal echocardiography
Statistical measures	Diagnostic accuracy of symptoms and signs for a confirmed diagnosis of **severe** HVD. Measured by: **Primary measures** <u>Accuracy data</u> • Sensitivity • Specificity • Raw data to calculate 2x2 tables to calculate sensitivity and specificity (number of true positives, true negatives, false positives and false negatives). **Secondary measures** • Likelihood ratios • Positive Predictive Value (PPV) • Negative Predictive Value (NPV) • Receiver Operating Characteristic (ROC) curve or area under curve for BNP and NT pro-BNP If insufficient accuracy data are found, diagnostic association of signs and symptoms with a confirmed diagnosis of severe HVD will be included. Measured by: <u>Association data</u> • Adjusted RR or OR For decision-making, it was agreed that sensitivity should be the primary measure taken into account as avoiding false negatives was considered to be the priority over avoiding false positives to avoid sending many people away early without further testing. Agreed a threshold of ≥60% to represent suitable sensitivity to consider recommending a test, with emphasis on importance of follow-up on those with continuing symptoms or concerns.
Study design	• Single-gate diagnostic studies (these may be called cohort studies or cross-sectional studies) will be included preferentially • If no/insufficient diagnostic accuracy studies are identified prospective and retrospective cohort studies with multivariate analysis of the association between signs and symptoms and a confirmed diagnosis of severe heart valve disease will be included. Confounding factors (if diagnostic association studies are included): • Age (<65 years or ≥65 years)

- Type of murmur:
  - Innocent murmur
  - Ejection systolic murmur
  - Regurgitant systolic murmur
  - Diastolic murmur
- Presence/absence of atrial fibrillation

3.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

3.1.4 Diagnostic evidence

3.1.4.1 Included studies

A search was conducted for cross-sectional and prospective and retrospective cohort studies assessing the diagnostic test accuracy of murmur with or without other signs or symptoms (heart sounds and/or symptoms) to identify whether the condition is present (as indicated by the reference standard) in people under investigation for condition **severe** heart valve disease.

Diagnostic association studies that report data on the association between murmur with or without other signs or symptoms (heart sounds and/or symptoms) and diagnosis of severe heart valve disease were also considered if limited diagnostic accuracy studies were available.

Nineteen studies with diagnostic accuracy data or data that could be used to calculate diagnostic accuracy data were included in the review; [3, 5, 16-19, 51, 63, 89, 109, 117, 121, 131, 132, 134, 163, 171, 174, 191] these are summarised in Table 19 below. Most of the studies investigated the accuracy of murmur alone for the diagnosis of severe heart valve disease, with the definition of the murmur and person conducting auscultation differing between studies. However, two studies[174, 191] looked at murmur plus symptoms, three studies[3, 132, 174]assessed murmur plus an absent or reduced second heart sound, and one study[174] looked at murmur plus abnormal ECG.

One of these studies[19] also provided diagnostic association data for a particular index test (murmur + diminished aortic closure sound) for the diagnosis of moderate or severe aortic stenosis.

Evidence from these studies is summarised in the clinical evidence summary below in Tables 20-32 below.

The assessment of the evidence quality was conducted with emphasis on test sensitivity, as this was identified by the committee as the primary measure in guiding decision-making as the priority would be to avoid missing cases (false negatives) and not sending them for further testing as a result. The committee set clinical decision thresholds as sensitivity = 0.60.

Reference standards

Only studies that had used echocardiography as a reference standard for confirming valve disease were included in this review as the older method of confirming valve disease (cardiac catheterisation) is not as good at assessing the severity of heart valve disease as

the current gold standard of echocardiography is, and this review focuses on the diagnosis of severe heart valve disease, which may differ between cardiac catheterisation and echocardiography.

Populations

Studies that involved screening for heart valve disease and murmurs in presumably healthy populations where there could be no reason for a suspicion of heart valve disease were excluded, for example, where screening was performed for everyone who experienced a hip fracture or in populations that were said to be healthy. However, studies where there was not necessarily a suspicion of heart valve disease but had some indication for either attendance at hospital or primary care, echocardiography or were experiencing cardiac symptoms were included, as there was limited evidence where the populations were defined as specifically being suspected of having heart valve disease.

Studies where the presence of a murmur was required for a participant to be included in a study were also included, despite the fact that this would mean all were already known to be index test positive before enrolment. Limited diagnostic accuracy data can be obtained from these studies, but it was agreed to include these given that murmur would be one of the main reasons for suspicion of heart valve disease and these studies could still provide information on the proportion of those with the murmur that actually had reference standard confirmed valve disease, in the form of the positive predictive ratio. The limitations of these studies were highlighted.

See also the study selection flow chart in Appendix C, sensitivity and specificity forest plots in Appendix E, and study evidence tables in Appendix D.

3.1.4.2 Excluded studies

See the excluded studies list in Appendix I.

3.1.5 Summary of studies included in the diagnostic evidence

Table 19: Summary of studies included in the evidence review

Study	Population	Target condition	Index test	Reference standard	Comments
Abe 2013[3] n=130 Japan	Patients with systolic ejection murmurs with grade ≥2 or known aortic stenosis and referred for echocardiography	Heart valve disease: severe aortic stenosis	Systolic ejection murmur + diminished second heart sound	Echocardiography confirmed aortic stenosis (subgroup for severe AS)	Population indirectness: 35% had known AS before study so may affect accuracy data Murmur + diminished heart sound: not clear if all had a murmur, but at least 65% did – could include some that just had a diminished

Study	Population	Target condition	Index test	Reference standard	Comments
					second heart sound
Aggarwal 2014[5] n=100 India	Outpatients presenting for echocardiography at Cardiology centre	Heart valve disease: significant valve lesion	Detection of murmur using stethoscope and specific software Systolic or diastolic murmurs	Echocardiography confirmed heart valve disease (subgroup for significant valve lesions)	Patients known to have pre-existing heart murmurs excluded ZargisCardioscan™ software used Target condition indirectness: significant lesion defined as any stenotic lesion and moderate-severe regurgitant lesions
Aronow 1987[17] n=75 USA	Unselected elderly patients in a long-term health care facility with echocardiography of aortic valve performed and aortic systolic ejection murmurs	Heart valve disease: severe aortic stenosis	Aortic systolic ejection murmurs (all had one to be included in the study)	Echocardiography confirmed aortic stenosis (subgroup for severe aortic stenosis)	
Aronow 1989[16] n=450 USA	Unselected elderly patients in a long-term health care facility with echocardiography of aortic valve performed	Heart valve disease: moderate or severe aortic regurgitation	Murmur of aortic regurgitation High frequency diastolic decrescendo murmur beginning with A2	Echocardiography confirmed moderate or severe aortic regurgitation	Potentially indirect population: unselected elderly patients in a long-term health care facility – not necessarily suspected HVD
Aronow 1991[18] n=781 USA	Unselected elderly patients in long term health care facility	Heart valve disease: severe aortic stenosis	Aortic systolic ejection murmur	Echocardiography confirmed AS (subgroup for severe disease)	
Attenhofer Jost, 2000[19] n=100	Those referred for echocardiography due to systolic murmur of unknown cause -	Heart valve disease: moderate or severe aortic stenosis or	Systolic murmur (all had one)	Echocardiography confirmed AS or valvular regurgitation (AR, TR, MR)	Reports separately for each type of HVD and not possible to combine into

Study	Population	Target condition	Index test	Reference standard	Comments
Switzerland	no prior echo examination	valvular regurgitation (AR, TR, MR)	Systolic murmur +diminished aortic closure sound (diagnostic association)	(subgroup for moderate or severe disease)	one group for severe disease.
Decoodt 1990[51] n=100 Belgium	Those with mitral valve prolapse confirmed by echocardiography	Heart valve disease: severe mitral regurgitation	Systolic murmur on auscultation (early systolic, late systolic or holosystolic)	Echocardiography confirmed mitral regurgitation (subgroup for severe mitral regurgitation)	Potential population indirectness: selected population that is more likely to have higher incidence of mitral regurgitation as they already have echo-confirmed mitral valve abnormality?
Etchells 1998[63] n=162 Canada	Hospital inpatients referred for echocardiography. Most had cardiac symptoms.	Heart valve disease: moderate or severe aortic stenosis	Systolic murmur	Echocardiography confirmed moderate or severe aortic stenosis	Results reported separately in the study for internist rather than cardiologist as fits better with setting of review Target condition indirectness: some had moderate rather than severe AS
Iversen 2008[89] n=2977 Denmark	All patients admitted to medical or surgical departments of a hospital	Heart valve disease (moderate or severe aortic stenosis, aortic regurgitation, mitral stenosis or mitral regurgitation)	Heart murmur	Echocardiography confirmed moderate or severe valve disease	Potential population indirectness: those admitted to a hospital, not necessarily suspected HVD but obviously some indication for them being in hospital Target condition indirectness: moderate or severe combined so

Study	Population	Target condition	Index test	Reference standard	Comments
					not all severe disease
Labovitz 1985[109] n=51 USA	Patients with mitral annular calcium detected on echocardiography	Heart valve disease: moderate or severe mitral regurgitation	Apical systolic murmur	Echocardiography confirmed moderate or severe mitral regurgitation	Potential population indirectness: selected population with likely increased incidence of disease as already had echocardiography performed? Target condition indirectness: moderate or severe combined so not all severe disease
Limacher 1985[117] n=81 USA	Pregnant women referred for evaluation of murmurs	Heart valve disease: severe tricuspid regurgitation	Cardiac murmur (all had one to be included in the study)	Echocardiography confirmed tricuspid regurgitation (data given for severe TR)	
Loperfido 1986[121] n=72 Italy	Patients diagnosed with myocardial infarction 1-3 months prior to the study at the coronary care unit based on chest pain, ECG and increase and decrease of creatine kinase-MB fraction	Heart valve disease: grade 3+ mitral regurgitation	Systolic murmur	Echocardiography confirmed mitral regurgitation (subgroup for grade 3+ MR)	Potential population indirectness: not necessarily suspected HVD but all have had MI with cardiac symptoms
McClelland 2020[131] n=350 USA	Consecutive patients ≥18 years referred for initial transthoracic echocardiography imaging with a heart murmur at single centre	Heart valve disease: severe heart valve disease Unclear which types of valve disease were included under severe valve	Heart murmur – no further details	Echocardiography confirmed severe valve disease	

Study	Population	Target condition	Index test	Reference standard	Comments
		disease, but report states moderate or severe cases of aortic regurgitation, mitral regurgitation, tricuspid regurgitation and aortic stenosis were identified.			
McGee 2010[132] n=376 USA	Non-intensive care unit patients undergoing echocardiography - around 16% already known to have valve disease	Heart valve disease: aortic stenosis (severe, Vmax ≥4.0 m/sec), moderate or severe mitral regurgitation or tricuspid regurgitation	Systolic heart murmur Broad apical-based systolic murmur + absence second heart sound	Echocardiography confirmed aortic stenosis, mitral regurgitation or tricuspid regurgitation (subgroup for severe can be obtained for AS, but moderate and severe cases combined for MR and TR)	Potential population indirectness: some already known to have valve disease Study reports details separately for different types of valve disease and not possible to combine Target condition indirectness: For MR and TR, moderate and severe cases are combined, so not all had severe disease.
McKillop 1991[134] n=35 UK	Elderly patients with systolic ejection murmurs	Heart valve disease: significant aortic stenosis (defined as gradient >30 mmHg) or mitral regurgitation (no definition provided for	Systolic ejection murmur (all had one to be included in the study)	Echocardiography confirmed significant aortic stenosis (defined as gradient >30 mmHg) or mitral regurgitation (no definition provided for significant disease)	Target condition indirectness: for AS, gradient of >30 mmHg doesn't necessarily indicate severe disease, and could include some moderate cases? No definition of significant

Study	Population	Target condition	Index test	Reference standard	Comments
		significant disease)			disease given for MR.
Panidis 1986[163] n=80 USA	Those with mitral valve prolapse confirmed on echocardiography and signs and symptoms	Heart valve disease: moderate or severe mitral regurgitation	Systolic murmur	Echocardiography confirmed mitral regurgitation (data available for moderate or severe disease)	Potential population indirectness: selected population that is more likely to have higher incidence of mitral regurgitation as they already have echo-confirmed mitral valve abnormality?
Rahko 1989[171] n=408 USA	Patients presenting to echocardiography laboratory	Heart valve disease: 3+ or 4+ (moderate-severe or severe) aortic regurgitation, mitral regurgitation or tricuspid regurgitation	Regurgitant murmur on auscultation	Echocardiography confirmed aortic regurgitation, mitral regurgitation or tricuspid regurgitation (data available for 3+ or 4+ regurgitation - moderate-severe or severe)	Potential population indirectness: not necessarily suspected HVD but some indication for echocardiography Study reports data for each type of regurgitation separately and not possible to combine as single 'regurgitation' group
Reardon 1996[174] n=148 UK	Acute medical patients aged >65 years admitted to geriatric ward of hospital – data reported only for those with systolic murmurs	Heart valve disease: significant (gradient >30 mmHg) aortic stenosis	Systolic murmur (all had one to be included in the analysis) Systolic murmur + reduced second heart sound Systolic murmur + symptoms (syncope) Systolic murmur + symptoms (angina)	Echocardiography confirmed aortic stenosis (subgroup for significant AS – gradient >30 mmHg)	Potential population indirectness: not necessarily suspected HVD but some indications to be admitted to hospital Target condition indirectness: gradient of >30 mmHg doesn't necessarily indicate severe disease, and could include

Study	Population	Target condition	Index test	Reference standard	Comments
			Systolic murmur + symptoms (dyspnoea) Systolic murmur + abnormal ECG (left ventricular hypertrophy) Systolic murmur + abnormal ECG (atrial fibrillation)		some moderate cases?
Sarasin 2002[191] n=20 Switzerland	Patients >18 years presenting with syncope in emergency department with systolic murmur Small subgroup of those with suspected AS due to presence of murmur + syncope on exertion with/without chest pain (n=20)	Heart valve disease: severe aortic stenosis	Systolic murmur + syncope on exertion with/without chest pain (all of those within the subgroup had this as an indicator)	Echocardiography confirmed severe aortic stenosis	

See Appendix D for full evidence tables.

3.1.6 Summary of the diagnostic evidence

The populations, target conditions and index tests used across the included studies were considered to be very broad and wide-ranging, and therefore no studies were pooled into a diagnostic meta-analysis. Sensitivity and specificity for each individual study is given below, separated into broad categories based on the population.

For studies where all of those included had to be positive for murmur with/without another characteristic (which was used as an index test in our review), sensitivity and specificity, as well as other measures, could not be calculated, and positive predictive values are instead presented.

Note that although all included studies detected heart valve disease as the target condition, the type of heart valve disease that was included in the studies varied. For example, some studies aimed to diagnose and report any type of valve disease (including aortic stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation and tricuspid regurgitation), while others focused specifically on one or two types of valve disease, such as aortic stenosis or

mitral stenosis and mitral regurgitation, or any type of regurgitation but not stenosis (i.e. aortic regurgitation, mitral regurgitation and tricuspid regurgitation). Where possible, results have been calculated for 'any valve disease'; however, in many cases results are reported separately for each type of valve disease as it was not possible to determine how many may have had more than one time of valve disease at the same time to calculate diagnostic accuracy results for overall heart valve disease in each study.

The assessment of the evidence quality was conducted with emphasis on test sensitivity and specificity as this was identified by the committee as the primary measure in guiding decision-making. The committee set a clinical decision threshold of 0.6 for sensitivity.

Table 20: Clinical evidence summary: murmur for moderate or severe heart valve disease in various settings in populations with various indications for assessment

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Detection of systolic or diastolic murmur on stethoscope with specific software for the diagnosis of significant valve disease – **community medicine physician**								
Outpatients presenting for echocardiography at Cardiology centre	100	Serious[1]	NA	Serious[2]	Very serious[3]	Sensitivity=0.64 (0.35 to 0.87)	VERY LOW	PPV: 0.29 NPV: 0.93 PLR: 2.51 NLR: 0.48 Prevalence on reference standard: 0.14
		Serious[1]	NA	Serious[2]	None	Specificity=0.74 (0.64 to 0.83)	LOW	
Murmur of AR (high frequency diastolic decrescendo murmur beginning with A2) for the diagnosis of moderate or severe AR – **experienced cardiologist**								
Unselected elderly patients in a long-term health care facility with echocardiography	450	Very serious[1]	NA	Very serious[2]	None	Sensitivity=0.95 (0.87 to 0.99)	VERY LOW	PPV: 0.62 NPV: 0.99 PLR: 8.27 NLR: 0.06 Prevalence on reference standard: 0.16
		Very serious[1]	NA	Very serious[2]	None	Specificity=0.89 (0.85 to 0.92)	VERY LOW	
Aortic systolic ejection murmur for the diagnosis of severe AS – **experienced cardiologist**								
Unselected elderly patients in long	781	Very serious[1]	NA	Serious[2]	None	Sensitivity=1.00 (0.82 to 1.00)	VERY LOW	Prevalence on reference standard: 0.02
		NA	NA	NA	NA	Specificity could not be calculated	NA	

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
term health care facility						as insufficient data provided		Other values could not be calculated
Systolic murmur for the diagnosis of moderate or severe AS – **third year resident/staff general internist**								
Hospital inpatients referred for echocardiography. Most had cardiac symptoms.	112	Serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=1.00 (0.77 to 1.00)	VERY LOW	PPV: 0.20 NPV: 1.00 PLR reported in the study (95% CI): 1.60 (1.20, 2.00) NLR reported in the study (95% CI): 0.00 (0.00, 0.71) Prevalence on reference standard: 0.13
		Serious[1]	NA	Serious[2]	Serious[3]	Specificity=0.43 (0.33 to 0.53)	VERY LOW	
Heart murmur for the diagnosis of moderate or severe AS, AR, MS or MR – **unclear who performed examination**								
All patients admitted to medical or surgical departments of a hospital	2977	Serious[1]	NA	Very serious[2]	None	Sensitivity=0.81 (0.73 to 0.87)	VERY LOW	PPV: 0.18 NPV: 0.99 PLR: 4.30 NLR: 0.24 Prevalence on reference standard: 0.05
		Serious[1]	NA	Very serious[2]	None	Specificity=0.81 (0.80 to 0.83)	VERY LOW	
Systolic murmur for the diagnosis of grade 3+ MR – **cardiologist (performed at coronary care unit)**								
Patients diagnosed with	72	Serious[1]	NA	Serious[2]	Very serious[3]	Sensitivity=0.50 (0.07 to 0.53)	VERY LOW	PPV: 0.13

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
myocardial infarction 1-3 months prior to the study at the coronary care		Serious[1]	NA	Serious[2]	Serious[3]	Specificity=0.79 (0.68 to 0.88)	VERY LOW	NPV: 0.96 PLR: 2.43 NLR: 0.63 Prevalence on reference standard: 0.06
Systolic heart murmur for the diagnosis of severe AS, or moderate or severe MR or TR – **physician in primary and specialist medical care department**								
Non-intensive care unit patients undergoing echocardiography	376	Severe aortic stenosis						PPV: 0.12 NPV: 1.0 PLR: 1.79 NLR: could not be calculated Prevalence on reference standard: 0.07
		Very serious[1]	NA	Serious[2]	None	Sensitivity=1.00 (0.87 to 1.00)	VERY LOW	
		Very serious[1]	NA	Serious[2]	None	Specificity=0.44 (0.39 to 0.49)	VERY LOW	
		Moderate or severe mitral regurgitation						PPV: 0.27 NPV: 0.91 PLR: 1.52 NLR: 0.41 Prevalence on reference standard: 0.20
		Very serious[1]	NA	Very serious[2]	None	Sensitivity=0.81 (0.70 to 0.89)	VERY LOW	
		Very serious[1]	NA	Very serious[2]	None	Specificity=0.47 (0.41 to 0.52)	VERY LOW	
		Moderate or severe tricuspid regurgitation						PPV: 0.21 NPV: 0.88 PLR: 1.29 NLR: 0.63 Prevalence on reference standard: 0.17
		Very serious[1]	NA	Very serious[2]	Serious[3]	Sensitivity=0.72 (0.60 to 0.83)	VERY LOW	
		Very serious[1]	NA	Very serious[2]	None	Specificity=0.44 (0.38 to 0.50)	VERY LOW	

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Regurgitant murmur on auscultation for the diagnosis of 3+ or 4+ (moderate-severe or severe) AR, MR or TR – **cardiologist**								
Patients presenting to an echocardiography laboratory	408	3+ or 4+ aortic regurgitation						PPV: 0.34 NPV: 0.99 PLR: 5.90 NLR: 0.11 Prevalence on reference standard: 0.08
		Very serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=0.91 (0.76 to 0.98)	VERY LOW	
		Very serious[1]	NA	Serious[2]	None	Specificity=0.85 (0.81 to 0.88)	VERY LOW	
		3+ or 4+ mitral regurgitation						PPV: 0.28 NPV: 0.98 PLR: 3.49 NLR: 0.20 Prevalence on reference standard: 0.10
		Very serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=0.85 (0.69 to 0.94)	VERY LOW	
		Very serious[1]	NA	Serious[2]	None	Specificity=0.76 (0.71 to 0.80)	VERY LOW	
		3+ or 4+ tricuspid regurgitation						PPV: 0.42 NPV: 0.97 PLR: 10.15 NLR: 0.41 Prevalence on reference standard: 0.07
		Very serious[1]	NA	Serious[2]	Very serious[3]	Sensitivity=0.62 (0.38 to 0.82)	VERY LOW	
		Very serious[1]	NA	Serious[2]	None	Specificity=0.94 (0.91 to 0.96)	VERY LOW	

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[2] *Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were considered to have a high degree of indirectness, and downgraded by 2 increments if the majority of studies were considered to have a very high degree of indirectness.*

[3] *Imprecision was assessed by considering the width of the confidence intervals around the sensitivity and specificity. A variation of 0-20% was considered precise, 20-40% serious imprecision, and >40% very serious imprecision.*

Table 21: Clinical evidence summary: murmur for moderate or severe heart valve disease in populations with MVP that has already been diagnosed by echocardiography

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Systolic murmur on auscultation (including early systolic, late systolic or holosystolic) for the diagnosis of severe MR – **unclear who did examination**								PPV: 0.19
Those with mitral valve prolapse confirmed by echocardiography	100	Very serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=1.00 (0.69 to 1.00)	VERY LOW	NPV: 1.0
		Very serious[1]	NA	Serious[2]	None	Specificity=0.53 (0.43 to 0.64)	VERY LOW	PLR: 2.14 NLR: could not be calculated Prevalence on reference standard: 0.10
Systolic murmur for the diagnosis of moderate or severe MR – **unclear who did examination**								PPV: 0.19
Those with mitral valve prolapse confirmed on echocardiography and signs and symptoms	80	Serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=1.00 (0.63 to 1.00)	VERY LOW	NPV: 1.00
		Serious[1]	NA	Serious[2]	Serious[3]	Specificity=0.51 (0.39 to 0.63)	VERY LOW	PLR: 2.06 Prevalence on reference standard: 0.10

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[2] *Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were considered to have a high degree of indirectness, and downgraded by 2 increments if the majority of studies were considered to have a very high degree of indirectness.*

[3] *Imprecision was assessed by considering the width of the confidence intervals around the sensitivity and specificity. A variation of 0-20% was considered precise, 20-40% serious imprecision, and >40% very serious imprecision.*

Table 22: Clinical evidence summary: murmur for moderate or severe heart valve disease in a population with mitral annular calcium observed by echocardiography

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Apical systolic murmur for the diagnosis of moderate or severe MR – **unclear who did examination**								PPV: 0.39

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Patients with mitral annular calcium detected on echocardiography	51	Very serious [1]	NA	Very serious [2]	Very serious [3]	Sensitivity=0.65 (0.38 to 0.86)	VERY LOW	NPV: 0.74 PLR: 1.29 NLR: 0.71 Prevalence on reference standard: 0.33
		Very serious [1]	NA	Very serious [2]	Serious [3]	Specificity=0.50 (0.32 to 0.68)	VERY LOW	

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[2] *Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were considered to have a high degree of indirectness, and downgraded by 2 increments if the majority of studies were considered to have a very high degree of indirectness.*

[3] *Imprecision was assessed by considering the width of the confidence intervals around the sensitivity and specificity. A variation of 0-20% was considered precise, 20-40% serious imprecision, and >40% very serious imprecision.*

Table 23: Clinical evidence summary: murmur for heart valve disease (all had a murmur to be included in the study)

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size [1]	Quality
Aortic systolic ejection murmur for the diagnosis of severe AS – prevalence 0.05 – **experienced cardiologist**							
Unselected elderly patients in a long-term health care facility with echocardiography	75	Serious[2]	NA	Serious[3]	Could not be assessed	PPV=0.05	VERY LOW
Systolic murmur for the diagnosis of moderate or severe AS or valvular regurgitation (AR, TR, MR) – **cardiologist**							
Those referred for echocardiography due to systolic murmur of unknown cause - no prior	100	<u>Moderate or severe aortic stenosis</u> – prevalence 0.15					
		Serious [2]	NA	Very serious[3]	Could not be assessed	PPV=0.15	VERY LOW
		<u>Moderate or severe aortic regurgitation</u> – prevalence 0.06					
		Serious [2]	NA	Very serious[3]	Could not be assessed	PPV=0.06	VERY LOW
		<u>Moderate or severe mitral regurgitation</u> – prevalence 0.06					

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size [1]	Quality
echo examination		Serious [2]	NA	Very serious[3]	Could not be assessed	PPV=0.06	VERY LOW
		<u>Moderate or severe tricuspid regurgitation</u> – prevalence 0.02					
		Serious [2]	NA	Very serious[3]	Could not be assessed	PPV=0.02	VERY LOW
Systolic ejection murmur for the diagnosis of significant AS (gradient >30 mmHg) or mitral regurgitation (no definition provided for significant MR) – prevalence 0.37 – **cardiologist and geriatrician**							
Elderly patients with systolic ejection murmurs	35	Very serious [2]	NA	Very serious[3]	Could not be assessed	PPV=0.37	VERY LOW
Systolic murmur for the diagnosis of significant AS (gradient >30 mmHg) – prevalence 0.26 – **junior hospital doctor and one of authors**							
Acute medical patients aged >65 years admitted to geriatric ward of hospital	148	Very serious [2]	NA	Very serious[3]	Could not be assessed	PPV=0.26	VERY LOW
Heart murmur for the diagnosis of severe heart valve disease – prevalence 0.04 – **unclear who assessed murmur**							
Referred for initial transthoracic echocardiography imaging with a heart murmur at single centre.	350	Very serious [2]	NA	Very serious[3]	Could not be assessed	PPV=0.04	VERY LOW

[1] *In these studies, all patients had to have a murmur to be included in the study. Therefore, sensitivity and specificity could not be calculated, and positive predictive values are instead presented for each study.95% confidence intervals could not be calculated for this effect measure.*

[2] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[3] *Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were considered to have a high degree of indirectness, and downgraded by 2 increments if the majority of studies were considered to have a very high degree of indirectness.*

Table 24: Clinical evidence summary: murmur in pregnant women for heart valve disease (all with murmur to be included)

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size [1]	Quality
Cardiac murmur for the diagnosis of severe TR – prevalence 0.0 – **referring physician**							
Pregnant women referred for evaluation of murmurs	81	Very serious[2]	NA	Very serious[3]	Could not be assessed	In all 81 patients with a murmur, none of them had severe TR.	VERY LOW

[1] *In this study, all patients had to have a murmur to be included in the study. Therefore, sensitivity and specificity could not be calculated. PPV could also not be calculated as all patients in the study were negative for severe TR.*

[2] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[3] *Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were considered to have a high degree of indirectness, and downgraded by 2 increments if the majority of studies were considered to have a very high degree of indirectness.*

Table 25: Clinical evidence summary: murmur + syncope for significant heart valve disease in acute medical patients admitted to geriatric ward of hospital

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Systolic murmur + symptoms (syncope) for the diagnosis of significant (gradient >30 mmHg) AS – **junior hospital doctor and one of authors**								PPV: 0.60 NPV: 0.76 PLR: 4.29 NLR: 0.89 Prevalence on reference standard: 0.26
Acute medical patients aged >65 years admitted to geriatric ward of hospital with confirmed systolic murmur present	148	Very serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=0.14 (0.03 to 0.36)	VERY LOW	
		Very serious[1]	NA	Serious[2]	None	Specificity=0.97 (0.88 to 1.00)	VERY LOW	

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[2] *Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were considered to have a high degree of indirectness, and downgraded by 2 increments if the majority of studies were considered to have a very high degree of indirectness.*

[3] *Imprecision was assessed by considering the width of the confidence intervals around the sensitivity and specificity. A variation of 0-20% was considered precise, 20-40% serious imprecision, and >40% very serious imprecision.*

Table 26: Clinical evidence summary: murmur + dyspnoea for significant heart valve disease in acute medical patients admitted to geriatric ward of hospital

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	
Systolic murmur + symptoms (dyspnoea) for the diagnosis of significant (gradient >30 mmHg) AS – **junior hospital doctor and one of authors**								PPV: 0.50
Acute medical patients aged >65 years admitted to geriatric ward of hospital with confirmed systolic murmur present	148	Very serious[1]	NA	Serious[2]	Very serious[3]	Sensitivity=0.43 (0.22 to 0.66)	VERY LOW	NPV: 0.81
		Very serious[1]	NA	Serious[2]	Serious[3]	Specificity=0.85 (0.73 to 0.93)	VERY LOW	PLR: 2.86 NLR: 0.67 Prevalence on reference standard: 0.26

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[2] *Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were considered to have a high degree of indirectness, and downgraded by 2 increments if the majority of studies were considered to have a very high degree of indirectness.*

[3] *Imprecision was assessed by considering the width of the confidence intervals around the sensitivity and specificity. A variation of 0-20% was considered precise, 20-40% serious imprecision, and >40% very serious imprecision.*

Table 27: Clinical evidence summary: murmur + angina for significant heart valve disease in acute medical patients admitted to geriatric ward of hospital

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Systolic murmur + symptoms (angina) for the diagnosis of significant (gradient >30 mmHg) AS – **junior hospital doctor and one of authors**								PPV: could not calculate as there were no true positives reported on index test
Acute medical patients aged >65 years admitted to geriatric ward of hospital with	148	Very serious[1]	NA	Serious[2]	None	Sensitivity=0.0 (0.0 to 0.16)	VERY LOW	NPV: 0.73
		Very serious[1]	NA	Serious[2]	None	Specificity=0.97 (0.88 to 1.00)	VERY LOW	PLR: could not

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
confirmed systolic murmur present								be calculated as there were true positives reported on index test NLR: 1.03 Prevalence on reference standard: 0.26

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[2] *Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were considered to have a high degree of indirectness, and downgraded by 2 increments if the majority of studies were considered to have a very high degree of indirectness.*

Table 28: Clinical evidence summary: systolic murmur + syncope on exertion with/without chest pain for heart valve disease (all had this combination to be included in the subgroup)

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size [1]	Quality
Systolic murmur + syncope on exertion with/without chest pain for the diagnosis of severe AS – prevalence 0.40 – **research physician in emergency department**							
Those presenting to emergency department with suspected AS due to presence of systolic murmur + syncope on exertion with/without chest pain	20	Very serious[2]	NA	Serious[3]	Could not be assessed	PPV=0.40	VERY LOW

[1] *In this study, all patients had a murmur + syncope on exertion with/without chest pain to be included in the analysis. Therefore, sensitivity and specificity could not be calculated, and the positive predictive value is instead presented.95% confidence intervals could not be calculated for this effect measure.*

[2] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[3] *Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were considered to have a high degree of indirectness, and downgraded by 2 increments if the majority of studies were considered to have a very high degree of indirectness.*

Table 29: Clinical evidence summary: systolic murmur +absent/reduced second heart sound for heart valve disease

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Systolic ejection murmur + diminished second heart sound for the diagnosis of severe AS – **experienced cardiologist**								PPV: 0.73 NPV: 0.91 PLR: 10.50 NLR: 0.39 Prevalence on reference standard: 0.21
Patients with systolic ejection murmurs with grade ≥2 or known aortic stenosis and referred for echocardiography	130	Very serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=0.63 (0.42 to 0.81)	VERY LOW	
		Very serious[1]	NA	Serious[2]	None	Specificity=0.94 (0.88 to 0.98)	VERY LOW	
Broad apical-based systolic heart murmur + absence of second heart sound for the diagnosis of moderate or severe MR – **physician in primary and specialist medical care department**								
Non-intensive care unit patients undergoing echocardiography	376	Very serious[1]	NA	Very serious[2]	Serious[4]	PLR[5]= 0.2 (0.0 to 1.5) (reported in the study)	VERY LOW	Prevalence on reference standard: 0.20 Other values could not be calculated
Systolic murmur + reduced second heart sound for the diagnosis of significant (gradient >30 mmHg) AS – **junior hospital doctor and one of authors**								PPV: 0.73 NPV: 0.96 PLR: 7.76 NLR: 0.11 Prevalence on
Acute medical patients aged >65 years admitted to geriatric	148	Very serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=0.90 (0.70 to 0.99)	VERY LOW	
		Very serious[1]	NA	Serious[2]	None	Specificity=0.88 (0.77 to 0.95)	VERY LOW	

Study population	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
ward of hospital with confirmed systolic murmur present								reference standard: 0.26

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[2] *Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were considered to have a high degree of indirectness, and downgraded by 2 increments if the majority of studies were considered to have a very high degree of indirectness.*

[3] *Imprecision was assessed by considering the width of the confidence intervals around the sensitivity and specificity. A variation of 0-20% was considered precise, 20-40% serious imprecision, and >40% very serious imprecision.*

[4] *For the PLR reported in the study, serious imprecision was considered to be present as the confidence intervals crossed 1.*

[5] *PLR was reported in this study and it was not possible to calculate sensitivity and specificity; PLR as reported in the study is therefore presented.*

Table 30: Clinical evidence summary: murmur + abnormal ECG (left ventricular hypertrophy) for heart valve disease in acute medical patients admitted to geriatric ward of hospital

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Systolic murmur + abnormal ECG (left ventricular hypertrophy) significant (gradient >30 mmHg) AS – **junior hospital doctor and one of authors**								PPV: 0.50
Acute medical patients aged >65 years admitted to geriatric ward of hospital	148	Very serious[1]	NA	Serious[2]	Very serious[3]	Sensitivity=0.38 (0.18 to 0.62)	VERY LOW	NPV: 0.80 PLR: 2.86 NLR: 0.71 Prevalence on reference standard: 0.26
		Very serious[1]	NA	Serious[2]	None	Specificity=0.87 (0.75 to 0.94)	VERY LOW	

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[2] *Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were considered to have a high degree of indirectness, and downgraded by 2 increments if the majority of studies were considered to have a very high degree of indirectness.*

[3] *Imprecision was assessed by considering the width of the confidence intervals around the sensitivity and specificity. A variation of 0-20% was considered precise, 20-40% serious imprecision, and >40% very serious imprecision.*

Table 31: Clinical evidence summary: murmur + abnormal ECG (atrial fibrillation) for heart valve disease in acute medical patients admitted to geriatric ward of hospital

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality	Other results
Systolic murmur + abnormal ECG (atrial fibrillation) significant (gradient >30 mmHg) AS – **junior hospital doctor and one of authors**								PPV: 0.21
Acute medical patients aged >65 years admitted to geriatric ward of hospital	148	Very serious[1]	NA	Serious[2]	Serious[3]	Sensitivity=0.14 (0.03 to 0.36)	VERY LOW	NPV: 0.73
		Very serious[1]	NA	Serious[2]	Serious[3]	Specificity=0.82 (0.70 to 0.90)	VERY LOW	PLR: 0.78 NLR: 1.05 Prevalence on reference standard: 0.26

[1] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

[2] *Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were considered to have a high degree of indirectness, and downgraded by 2 increments if the majority of studies were considered to have a very high degree of indirectness.*

[3] *Imprecision was assessed by considering the width of the confidence intervals around the sensitivity and specificity. A variation of 0-20% was considered precise, 20-40% serious imprecision, and >40% very serious imprecision.*

Table 32: Clinical evidence summary: Systolic murmur + diminished aortic closure sound vs. systolic murmur without diminished aortic closure sound – association with a diagnosis of moderate or severe AS

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Imprecision	GRADE Quality
Systolic murmur + diminished aortic closure sound vs. systolic murmur without diminished aortic closure sound (adjusted OR for the diagnosis of moderate or severe AS) (those referred for echocardiography due to systolic murmur of unknown cause)	1	Adjusted OR 14 (2.5-79.0)[1]	None[2]	⊕⊖⊖⊖ VERY LOW[3,4]

1. *Methods: multivariable analysis, covariates included are unclear, but may have included age (pre-specified in the protocol). Atrial fibrillation, also listed in the protocol, was not mentioned and therefore likely hasn't been adjusted for this. The other key confounder listed in the protocol was the type of murmur, and all participants in this study had the same type (systolic).*
2. *Imprecision was considered to be present if the 95% CI around the effect size crossed the null line.*
3. *Risk of bias was assessed using QUIPS and the study was considered to be at very high risk of bias, resulting in downgrading by 2 increments*
4. *Indirectness was considered to be present as the target condition was moderate or severe aortic stenosis grouped together, so not all are severe cases. The study was downgraded by 1 increment as a result.*

3.1.7 Economic evidence

3.1.7.1 Included studies

No health economic studies were included.

3.1.7.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix F.

3.1.8 Summary of included economic evidence

None

3.1.9 Economic model

This area was not prioritised for new cost-effectiveness analysis.

3.1.10 Unit costs

Table 33: UK appointment costs

Resource	No. of attendances	Unit cost	Source
Consultant led			
Non-Admitted Face-to-Face Attendance, First (a)	883,741	£172	NHS reference Costs 2018/19[150]
Non-consultant led			
Non-Admitted Face-to-Face Attendance, First (b)	303,851	£104	NHS reference Costs 2018/19[150]

(a) Currency code WF01B, was used to cost the consultant led appointments
(b) Currency code WF01B, was used to cost the non-consultant led appointments

4 The committee's discussion of the evidence

4.1 Interpreting the evidence

4.1.1 The diagnostic measures that matter most

Symptoms and signs indicating referral for echocardiography and direct referral to a specialist

For decision-making, it was agreed that sensitivity should be the primary measure taken into account, as avoiding false negatives was considered to be the priority over avoiding false positives, to avoid sending many people away early without further testing. This was because missing potentially severe cases of heart valve disease that may require intervention at the time of evaluation or further down the line, or non-severe heart valve disease that may progress to severe disease and requires monitoring, may result in negative consequences for patients.

A threshold of ≥60% was selected to represent suitable sensitivity to consider recommending a symptom or sign as an indicator for echocardiography or specialist referral, as although this is fairly low for sensitivity, the committee considered this to be a reasonable threshold for the heart valve disease population, as sensitivity of symptoms and signs for heart valve disease in general was considered to be low.

The specificity was still considered to be important and was considered alongside sensitivity to ensure that any recommendations made would not lead to a large proportion of people without heart valve disease being referred and to avoid an unnecessary strain on echocardiography and specialist services.

In studies where the inclusion criteria required all participants to have a particular symptom or sign, for example all with a murmur, the positive predictive value was the only diagnostic accuracy measure that could be obtained and was equivalent to the prevalence of heart valve disease in the population (for example, the prevalence of heart valve disease in those that present with a murmur). This gave useful information on the proportion with a murmur that would actually have echocardiography-confirmed heart valve disease or severe heart valve disease and helped guide the decision on when echocardiography or specialist referral should be offered or considered, alongside specificity values from other studies.

Women of childbearing age and pregnancy

The evidence is in the form of expert testimony and can be found in Appendix K. This testimony was further discussed at a committee meeting and used to inform recommendations in this area that were aimed at cardiologists. Expert testimony for recommendations in pregnant women or women considering pregnancy was agreed to be important by the committee across the guideline as it was a population where limited or no evidence was expected and identified depending on the individual review question and the committee did not feel able to make consensus recommendations for this population without expert testimony.

4.1.2 The quality of the evidence

The issues with the quality of the evidence were the same for both evidence reviews covered by this discussion document and are summarised below.

The characteristics of the included studies were very varied. The differences between the studies included:

- Different populations (e.g. some had to have a murmur to be included while others looked at a broader population of anyone that was referred for echocardiography evaluation)
- Type of heart valve disease they aimed to detect (e.g. some studies reported any detected heart valve disease while others were focused on a specific type, such as mitral regurgitation)
- The definition of symptoms and signs used (e.g. some studies defined murmur as any cardiac murmur while others focused on specific type of murmur, such as the high frequency diastolic decrescendo murmur beginning with A2 for the detection of aortic regurgitation)
- The type of clinician performing the clinical examination for the detection of the murmur (some were performed by the equivalent of primary care practitioners, but many were performed by experienced cardiologists)

The differences discussed above meant that for both reviews, no pooling of the studies was possible, and the committee had to consider each study separately, which made interpretation difficult.

In addition, the majority of the evidence for both reviews was of very low quality based on the assessment of risk of bias using the QUADAS-2 checklist, indirectness in relation to the protocols and a measure of imprecision for sensitivity and specificity.

- The main reasons that studies were downgraded for risk of bias were a lack of or no reporting of blinding between the index symptoms/signs and the reference standard used to confirm the presence of heart valve disease, as well as an unclear time interval between the two methods of evaluation.
- The main source of indirectness was the inclusion of people in whom heart valve disease may not have been suspected prior to the study.
- Studies where all had to have a particular symptom or sign to be included (e.g. murmur) were also downgraded for indirectness as this is not representative of the population presenting with suspected heart valve disease.
- A further issue with indirectness was the fact that in many of the studies the clinical examination for the detection of a murmur was performed by an experienced cardiologist rather than a primary care physician. The committee agreed that the experience of cardiologists means they should be able to determine whether a murmur is present, and whether it is pathological or not, with improved accuracy compared with primary care physicians. Therefore, the sensitivity and specificity values obtained from these studies may be indirect in relation to the protocols as both reviews are designed to cover the population that have not yet been referred to a cardiologist.
- Moderate or severe heart valve disease indirectness – direct referral to a specialist review: In addition to the factors described above, there was also indirectness for various studies included in the review on direct referral to a specialist, as some studies only gave information for the number of moderate or severe cases combined, rather than for only severe cases. This means that the sensitivity and specificity values obtained from these studies are indirect in relation to the protocol-defined diagnosis of severe heart valve disease.

The majority of the studies were considered to be small in size and many were not designed as diagnostic accuracy studies but had sufficient information available to be able to produce 2x2 tables and calculate sensitivity, specificity and other diagnostic accuracy measures.

Despite the limitations described above and the differences between the studies, the committee did feel able to make recommendations by carefully considering all the evidence presented and the impact any changes would have on current practice, while acknowledging the limitations associated with the evidence reviewed. These factors were also taken into account when deciding on the strength of recommendations.

4.1.3 Benefits and harms

The recommendations were based on evidence from both reviews listed above. Therefore, the discussion of the evidence from both reviews has been presented as single discussion document.

Referral for echocardiography

Murmur alone

The committee discussed that in current practice, not everyone with a murmur detected incidentally in primary care, in the absence of other symptoms or signs, would be referred for echocardiography. This is because murmurs can be pathological or innocent and in many cases primary care would not be able to distinguish between pathological and innocent murmurs based on clinical examination. Innocent murmurs are common in particular groups of people, for example in teenagers / young adults and during pregnancy. Referring anyone with a murmur in primary care would therefore include these groups with innocent murmurs and lead to a considerable proportion of those with innocent murmurs being referred for echocardiography. The committee agreed that in current practice those with a murmur and some suspicion of cardiac pathology would usually be referred for echocardiography.

On review of the evidence presented, the committee agreed that the sensitivity values obtained for the detection of heart valve disease of any severity varied substantially due to differences in study population, murmur definition, type of heart valve disease covered and the individual performing the clinical examination for detection of murmur. Most studies had a sensitivity value falling under the threshold of 60% specified in the protocol.

However, in general the specificity values reported across studies were reasonably good, with most being ≥80%. Despite these results suggesting that the presence of a murmur is a fairly specific indicator of heart valve disease being present, with a low proportion of false positives, results from studies where all had to have a murmur to be included reported a low prevalence of heart valve disease in those included in the study (all but one of the six studies reported prevalence <60%, including one study in pregnant women), suggesting that at least 40% of people with a murmur would not subsequently be confirmed to have heart valve disease on echocardiography.

Based on a discussion of sensitivity and specificity as described above, the committee agreed that in those that have a murmur alone and no other symptoms or signs, referral for echocardiography should be considered only if there is some suspicion that heart valve disease may be present, for example based on the nature of the murmur, family history or patient characteristics, such as age or medical history. This is because the evidence was not considered to be strong enough, as some studies suggested that a large proportion of false positives would be identified and sent for unnecessary further testing, to support referring everyone with a murmur for echocardiography, considering that this would represent a change in current practice and would increase pressure on echocardiography services. The committee also agreed that patient preferences should be taken into account regarding referral for echocardiography and future intervention. For example, it was highlighted that if a patient does not wish to undergo an intervention in the future then referring for echocardiography may not be necessary, but this should be discussed with the patient.

The committee noted that the aim was not to recommend screening for a murmur but that if a murmur was detected in those already presenting with suspected heart valve disease then echocardiography referral should be considered. The committee also acknowledged that, although the nature of the murmur may be the key factor that indicates a likely heart valve disease diagnosis, it may be difficult on auscultation to determine whether the nature of a murmur indicates heart valve disease. Typical examples of murmurs associated with heart valve disease are mid-systolic ejectional murmurs for aortic stenosis and holo-systolic (pan-systolic) regurgitant murmurs due to regurgitation of the mitral or tricuspid valve.

Systolic murmur with a reduced second heart sound

The committee agreed that there was evidence from two studies that few false positives are identified in terms of echocardiography-confirmed aortic stenosis when the presence of a systolic murmur + reduced second heart sound is detected, with one study reporting 100% specificity and the other reporting a positive likelihood ratio of 15.7. A recommendation involving this combination was therefore made. . The recommendation specifies ejection systolic murmur as this combined with a reduced second heart sound is a classic indicator of aortic stenosis and is most often present in severe aortic stenosis. Although information on false positives was only available from two studies, the committee agreed that people with these features should be referred for echocardiography, in line with current practice, but based on the limitations of the evidence this was also limited to those in whom heart valve disease was considered to be a possible explanation of these signs. The committee noted that sensitivity values of systolic murmur + reduced second heart sound were poorer than when murmur alone was used. This was explained by the fact that a systolic murmur with a reduced second heart sound is usually a sign of severe aortic stenosis, meaning mild and moderate cases would not usually present with this sign. As the aim of the review focusing on referral for echocardiography was to diagnose heart valve disease of any severity, this observation added to the importance of a consider recommendation for those with suspected heart valve disease and only a murmur, as detailed above under 'murmur alone'.

Murmur with other symptoms or signs

The definition of other symptoms and signs varied between studies but included abnormal ECG (atrial fibrillation or left ventricular hypertrophy) or symptoms such as angina, dyspnoea (breathlessness) or peripheral oedema. The committee agreed that based on the evidence presented, the specificity values for heart valve disease detection when murmur + other symptoms or signs (including atrial fibrillation or left ventricular hypertrophy on ECG, or symptoms or signs of heart failure such as angina, dyspnoea and peripheral oedema) was detected were generally higher than those for murmur alone, suggesting a stronger argument for echocardiography referral in this group of people. However, these observations were only based on a few studies. Therefore, a recommendation was made that echocardiography referral should be offered in individuals with a murmur and other symptoms or signs in line with current practice, but based on the limitations of the evidence this was also limited to those in whom heart valve disease was considered to be a possible explanation of these signs and symptoms. Peripheral oedema was recognised to be a very common presenting symptom in primary care that would not usually indicate the need for an echocardiogram, and so the recommendation specifies peripheral oedema consistent with heart failure. The committee noted that sensitivity values of murmur + other symptoms or signs for heart valve disease of any severity were poorer than when murmur alone was used, which added to the importance of a consider recommendation for those with suspected heart valve disease and only a murmur, as detailed above under 'murmur alone'.

No murmur

Although the sensitivity of a murmur alone or with other symptoms or signs was poor for detection of heart valve disease of any severity in many of the studies included in the review (most <60% for murmur alone and <40% for murmur in combination with other symptoms or signs), the presence of other symptoms or signs alone, without a murmur being present, was not covered by the review protocol and therefore recommendations for those with symptoms and signs but no murmur could not be made. However, the committee agreed that for adults with breathlessness and suspected valve disease but no murmur, recommendations in the NICE guideline on chronic heart failure should be followed. The committee agreed not to prioritise this area for research recommendations due to the difficulties in carry this out.

Direct referral to a specialist

Further information to support echocardiography referral recommendations

The sensitivity values obtained for murmur alone or murmur with a reduced or absent second heart sound for the diagnosis of severe heart valve disease were generally higher compared with the same signs for the detection of any heart valve disease severity. This means that the poorer sensitivity values observed for any heart valve disease severity may partially be a result of mild or moderate heart valve disease not presenting with these signs, including murmur, and therefore being missed, and that more cases of severe heart valve disease do present with these signs and are likely to be referred for echocardiography based on the recommendations the committee made. This information obtained from the direct referral to a specialist review added to the evidence obtained from the echocardiography referral review and contributed to the recommendations the committee made on echocardiography referral for murmur alone and systolic murmur with a reduced or absent second heart sound.

Recommendations on direct specialist referral

Despite improved sensitivity values for the diagnosis of severe heart valve disease, specificity values were in general poorer compared with for the diagnosis of heart valve disease of any severity because the signs and symptoms were not only present in those with severe heart valve disease and some with mild and moderate cases of heart valve disease presented with the same signs or symptoms. This included when murmur alone was used as a sign and also combinations of murmur and other symptoms or signs, such as murmur + dyspnoea and murmur + abnormal ECG. Similarly, in those studies where all participants had to have a particular sign or combination of signs and symptoms to be included, such as murmur alone or murmur + another indication, the positive predictive values as a measure of prevalence of severe heart valve disease were poorer for severe heart valve disease than any severity of heart valve disease covered in the previous review.

As a result of this, and the limitations associated with the evidence presented, recommendations concerning urgent assessment were limited to those with severe symptoms that limit daily activities (angina: Canadian Cardiovascular Society score≥3 or breathlessness: NYHA class ≥3 or more on minimal exertion or at rest, or exertional syncope), a murmur and a suspicion of heart valve disease. These thresholds of ≥3 on the mentioned scales were based on committee experience as they were considered to represent severe angina and breathlessness, respectively. This was to avoid unnecessary referrals to specialists, as specificity of the signs and symptoms investigated for diagnosis of severe heart valve disease was lower than for any heart valve disease severity, and severe heart valve disease is an indication for specialist referral in current practice as it is likely that intervention may be required.

The committee recommended that in people with suspected heart valve disease, exertional syncope and a systolic murmur urgent specialist assessment or urgent echocardiogram should be offered as in some cases an echocardiogram may be faster than direct specialist referral and the decision between these should be made based on the opinion of the examiner. This was made based on consensus as although there was some evidence to suggest a good specificity (97%) for the combination of syncope with a murmur for echocardiography-confirmed ‘significant’ aortic stenosis (gradient ≥30 mmHg), the evidence for exertional syncope with a systolic murmur was more limited as sensitivity and specificity values could not be calculated; the positive predictive value from this study was available and suggested that a large proportion of those with this combination would not have echocardiography-confirmed severe aortic stenosis. The strong offer recommendation was made in this group because, based on committee experience, if exertional syncope is caused by severe aortic stenosis it represents a high risk for poor outcome. Therefore, the diagnosis needs to be made quickly to allow appropriate management, which would likely include

intervention if severe aortic stenosis is confirmed. This was considered to be in line with current practice as usually anyone with a systolic murmur and exertional syncope is offered echocardiography or specialist review.

For people with suspected heart valve disease, severe angina or breathlessness (≥3 on Canadian Cardiovascular Society score or NYHA class, respectively) on minimal exertion or at rest and a murmur, urgent specialist assessment, which would include access to echocardiogram, should be considered. This was considered to be in line with current practice as this group of patients are usually referred for echocardiography first and then the urgency of a specialist review is decided upon.

The committee discussed whether the timeframe for urgent referral could be specified. The time frame of four weeks is consistent with current practice and should be before the disease progress significantly. The committee noted that non-exertional syncope is covered by the transient loss of consciousness guideline in terms of referral to a specialist, and therefore cross referral to this guideline should be made.

Similar to the review on referral for echocardiography, the presence of other symptoms or signs alone, without a murmur being present, was not covered by the review protocol and therefore recommendations for those with symptoms and signs but no murmur could not be made. The sensitivity values for severe disease in this review when murmur alone was used as the sign appeared in general to be better than the sensitivity values when any severity of valve disease was being detected with this sign; however, fewer studies reported data for the severe heart valve disease which was the focus of this direct referral to a specialist review and sensitivity values for murmur with another sign or symptom were still poor in this review (most <50%). However, the committee highlighted that recommendations in the NICE guideline on chronic heart failure should be followed for adults with breathlessness and suspected valve disease but no murmur, as recommendations for those without a murmur could not be made as part of this guideline.

Women of childbearing age and pregnancy Although recommendations in this specific population were made based on the discussion of expert testimony and consensus, some evidence in the evidence reviews was identified on the use of murmur as a sign of any heart valve disease (n=1 study) or tricuspid regurgitation in pregnant women (n=1 study). The latter study also provided results for severe tricuspid regurgitation as well as any severity of tricuspid regurgitation. The evidence from these studies was limited as in one study all of those included had a murmur, which meant only the sensitivity and specificity values could not be calculated. The other study allowed calculation of sensitivity and specificity for murmurs considered to be pathological by the senior cardiologist performing the assessment in terms of any valve disease confirmed on echocardiography, demonstrating good sensitivity (100%) and specificity values (82%). However, the committee noted that in practice assessments to detect valve disease would be done in primary care and not by senior cardiologists, meaning the evidence was too limited to base recommendations on. The committee noted that in their experience flow murmurs were common in many pregnant women that do not have echocardiography-confirmed valve disease, which was supported by the expert testimony discussed below.

As the evidence identified and discussed above was limited for this population, the committee made recommendations based on the discussion of the expert testimony. The committee recognised that the proportion of women who are pregnant and who have heart valve disease is small compared with the number of women of childbearing age who may be considering pregnancy. It was agreed that it was important that these women are given advice before making a treatment decision as they need to carefully consider the impact of treatment on any future pregnancy. It was noted that factors to consider should include the type of valve they receive if surgery is performed and that to inform this decision it may be appropriate for their clinician to seek specialist advice from a cardiologist with expertise in the

care of pregnant women. A recommendation was therefore made to consider seeking specialist advice on the choice of replacement valve in women of childbearing potential.

The committee noted that women may be inappropriately advised against becoming pregnant by health professionals who lack specialist expertise. The committee agreed that a woman diagnosed with heart valve disease who may wish to become pregnant or who is pregnant should be referred to a cardiologist with specialist expertise. The committee highlighted and recommended that it is only women with moderate or severe heart valve disease, bicuspid aortic valve disease with associated aortopathy or those with a mechanical valve that need to referred, as mild heart valve disease, for example, regurgitation secondary to mitral valve prolapse, is very common, haemodynamically insignificant and very unlikely to confer any additional risk or require any specific management in pregnancy. On balance the committee felt that these women could be safely and appropriately managed by general cardiology and obstetric services, though it should be emphasised that in any cases of doubt specialist advice should always be sought. The committee noted that there is no national accreditation for cardiologists with a specialist interest in pregnancy. The committee also acknowledged that an ejection systolic flow murmur is present in most pregnant women and is not a cause for concern. A recommendation highlighting that most women with valve disease can have a pregnancy without complications was made to acknowledge these points.

For guidance on intrapartum care in this population, the committee agreed to cross-refer to the NICE guideline on intrapartum care for women with existing medical conditions or obstetric complications and their babies.

4.2 Cost effectiveness and resource use

There was no published evidence of cost effectiveness. The committee were presented with unit costs for echocardiography and cardiology outpatient appointments. The cost effectiveness for specific symptoms for determining referral is uncertain. However, the recommendations do not represent a significant change from current practice and they imply that referral should not take place unless relevant symptoms are present.

4.3 Other factors the committee took into account

The recommendations are consistent with the NHS long term plan which refers to greater access to echocardiography in primary care to improve the investigation of those with breathlessness, and the early detection of heart failure and heart valve disease.

The committee agreed that the recommendations drafted should apply to anyone with a suspicion of heart valve disease and the signs or symptoms specified, including pregnant women if there is still a suspicion that heart valve disease may be present. Therefore, no separate recommendation is needed for pregnant women, although mitral stenosis is known to be a particular concern in pregnancy.

The committee acknowledged that informing patients that they have a murmur but that no further investigations, such as echocardiography, are needed because there are no reasons to suspect heart valve disease can cause anxiety in some patients and confirming the absence of heart valve disease on echocardiography could relieve this anxiety. However, recommendations for echocardiography referral were focused on those where there may be a suspicion of heart valve disease to avoid overwhelming echocardiography services with referrals that would subsequently be negative on echocardiography for heart valve disease.

The committee also noted that even if no murmur is heard, heart valve disease could still be present, and referral may be appropriate if, for example, severe symptoms are present. A recommendation on this could not however be made as the review protocols focused on looking at murmur with or without other signs or symptoms and did not allow evidence on

symptoms or signs on their own, without a murmur being present, to be included. As the evidence was not reviewed recommendations could not be made for those without a murmur.

The committee prioritised areas for research recommendations that were most practical to carry out.

4.2 Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.1-1.1.5.

5 Women of child bearing age and pregnancy

5.1 In women of child bearing age and women who are pregnant what issues across the review questions need to be considered?

5.1.1 Introduction

More women with valvular heart disease are reaching child-bearing age and considering pregnancy. The need for pre-conceptual advice is an important component of supporting the person to make informed decisions but access is highly varied. In addition, many women with significant valve disease are often are not aware of their diagnosis prior to pregnancy, without an opportunity for preconception advice and timely treatment before pregnancy.

Expert witness testimony was sought to inform recommendations in this population with heart valve disease as there was expected and confirmed to be a lack of evidence specifically in this population and there are important factors to be considered when managing heart valve disease in pregnant women or women of childbearing age. The expert witness testimony can be found in Appendix K. An expert was invited to attend a committee meeting to provide evidence from their experience and specific expertise. They answered questions from committee members and were invited to present evidence in the form of expert testimony.

This evidence review supports recommendations 1.1.8-1.1.11. A discussion of how this expert testimony was used to inform recommendations is provided in the benefits and harms section above, under 'women of childbearing age and pregnancy'.

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Appendices

Appendix A – Review protocols

Review protocol for symptoms and signs indicating echocardiography referral

ID	Field	Content
0.	PROSPERO registration number	CRD42020168662
1.	Review title	In adults with suspected heart valve disease what symptoms and signs indicate referral (for example from primary care) for echocardiography?
2.	Review question	In adults with suspected heart valve disease what symptoms and signs indicate referral (for example from primary care) for echocardiography?
3.	Objective	To determine the accuracy of presenting symptoms and signs to diagnose heart valve disease. This will inform a decision on which presenting factors indicate that referral for echocardiography is required to confirm the diagnosis in people with suspected heart valve disease.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language • Human studies • Letters and comments are excluded

		Other searches: • Inclusion lists of systematic reviews will be checked by the reviewer The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Suspected heart valve disease in adults aged 18 years and over: Aortic (including bicuspid) stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation, and tricuspid regurgitation.
6.	Population	Inclusion: Adults aged 18 years and over with suspected heart valve disease in any setting (for example, in primary care) Exclusion: Adults presenting with acute heart failure Children aged less than 18 years. Adults with congenital heart disease (excluding bicuspid aortic valves). Tricuspid stenosis and pulmonary valve disease.

7.	Symptoms and signs	**Clinical observations:**
		
		• Cardiac auscultation (standard or electronic):
		  ○ Presence of new murmur
		  ○ Character of heart sounds:
		  – no/soft 2nd heart sound (as in severe AS)
		  – added 3rd sound; gallop rhythm (as in severe MR)

		• Mild or atypical (non-exertional) symptoms or signs:
		  ○ Fatigue
		  ○ Palpitations
		  ○ Shortness of breath (NYHA class I-II)
		  ○ Peripheral oedema (swelling of ankles and legs)
		  ○ Chest pain (Canadian score class 1-2)
		  ○ Exertional dizziness or pre-syncope
		  ○ Abnormal ECG: for example signs of left ventricular hypertrophy or atrial fibrillation
		
		Include the following combinations:
		• murmur alone,
		• murmur + heart sounds,
		• murmur + symptoms,
		• murmur + heart sounds + symptoms
		(not symptoms alone nor heart sounds alone)

8.	Reference standard /
	Confounding factors
		Reference (gold) standard:
		• Confirmed diagnosis of HVD by transthoracic or transoesophageal echocardiography
		• Confirmed diagnosis of HVD by invasive cardiac catheterisation will be considered as indirect evidence to avoid excluding older studies
		
		Confounding factors (if diagnostic association studies are included):
		• Age (<65 years or ≥65 years)
		• Type of murmur:
		  ○ Innocent murmur
		  ○ Ejection systolic murmur
		  ○ Regurgitant systolic murmur
		  ○ Diastolic murmur

		• Presence/absence of anaemia • Presence/absence of pregnancy • Presence/absence of atrial fibrillation
9.	Types of study to be included	• Single-gate diagnostic studies (these may be called cohort studies or cross-sectional studies) will be included preferentially • If no/insufficient[1] diagnostic accuracy studies are identified prospective and retrospective cohort studies with multivariate analysis of the association between signs and symptoms and a confirmed diagnosis of heart valve disease will be included.
10.	Other exclusion criteria	Exclusion criteria: • Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study. • Case-control or 'two-gate' diagnostic studies • Non-English language studies
11.	Context	In clinical practice a number of symptoms and signs might indicate that a person has heart valve disease. An understanding of which symptoms and signs better indicate HVD as a cause can facilitate further investigations to confirm diagnosis and guide management.

12.	Primary outcomes (critical outcomes)	Diagnostic accuracy of symptoms and signs for a confirmed diagnosis of HVD of any severity.
		Measured by:
		• Accuracy data
		  ○ Sensitivity
		  ○ Specificity

[1] This will be assessed for the review as a whole. There is no strict definition, but in discussion with the GC we will consider whether we have enough to form the basis for a recommendation.

		○ Raw data to calculate 2x2 tables to calculate sensitivity and specificity (number of true positives, true negatives, false positives and false negatives).
13.	Secondary outcomes (important outcomes)	• Likelihood ratios • Positive Predictive Value (PPV) • Negative Predictive Value (NPV) If insufficient[2] accuracy data are found, diagnostic association of signs and symptoms with a confirmed diagnosis of HVD will be included. Measured by: • Association data ○ Adjusted RR or OR
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using QUADAS-2 for diagnostic accuracy. QUIPS will be used to assess diagnostic association reviews. 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:

[2] This will be assessed for the review as a whole. There is no strict definition, but in discussion with the GC we will consider whether we have enough to form the basis for a recommendation.

		• papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	**Diagnostic accuracy studies** Where possible data will be meta-analysed in WinBUGS (if at least 3 studies reporting data at the same diagnostic threshold). Summary diagnostic outcomes will be reported from the meta-analyses with their 95% confidence intervals in adapted GRADE tables. Assessment of the quality of evidence for each outcome will take into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Heterogeneity will be assessed by visual inspection of the sensitivity and specificity plots and summary area under the curve (AUC) plots. Particular attention will be placed on the measure determined by the committee to be the primary outcome for decision making. **Diagnostic association studies** Aggregate data on diagnostic association of signs and symptoms will be collected and synthesised in a quantitative data analysis. If more than one study covered the same combination of population, sign/symptom, outcome and confounding factors accounted for then meta-analysis will be used to pool results. Meta-analysis will be carried out using the generic inverse variance function on Review Manager using fixed effect model.

		Data synthesis will be completed by two reviewers, with any disagreements resolved by discussion, or if necessary a third independent reviewer. Data from the meta-analysis will be presented and quality assessed in adapted GRADE tables taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each sign/symptom. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. We will conduct sensitivity analyses based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. **All study types** If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software. Publication or other bias will only be taken into consideration in the quality assessment if it is apparent.

17.	Analysis of sub-groups	The following subgroups will be investigated if heterogeneity is apparent in the analysis:
		• Age (<65 years or ≥65 years)
		• Setting/population: GP screening/incidental findings, GP examination in response to symptoms, examination in a heart clinic, examination in a general hospital setting
		• Type of murmur:
		  ○ Innocent murmur
		  ○ Ejection systolic murmur
		  ○ Regurgitant systolic murmur
		  ○ Diastolic murmur
		• Presence/absence of exertional symptoms

		• Type of valve disease diagnosed (aortic stenosis [including bicuspid], aortic regurgitation, mitral stenosis, mitral regurgitation, tricuspid regurgitation) • Presence/absence of anaemia • Presence/absence of pregnancy • Presence/absence of atrial fibrillation			
18.	Type and method of review	☐	Intervention		
		☒	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
19.	Language	English			
20.	Country	England			
21.	Anticipated or actual start date	09/05/2019			
22.	Anticipated completion date	17/06/2021			
23.	Stage of review at time of this submission	Review stage		Started	Completed
		Preliminary searches		☑	☐
		Piloting of the study selection process		☐	☐
		Formal screening of search results against eligibility criteria		☐	☐

		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail HVD@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Sharon Swain [Guideline lead] Eleanor Samarasekera [Senior systematic reviewer] Nicole Downes [Systematic reviewer] George Wood [Systematic reviewer] Robert King [Health economist] Jill Cobb [Information specialist] Katie Broomfield [Project manager]		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		

27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10122
29.	Other registration details	None
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Aortic regurgitation; aortic stenosis; diagnosis; echocardiography; heart valve disease; mitral regurgitation; mitral stenosis; primary care; referral; tricuspid regurgitation
33.	Details of existing review of same topic by same authors	N/A

34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

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2 **Review protocol for symptoms and signs indicating direct referral to a specialist**

ID	Field	Content
0.	PROSPERO registration number	CRD42020168665
1.	Review title	In adults with suspected heart valve disease, what symptoms and signs indicate direct referral (for example from primary care) to a specialist?
2.	Review question	In adults with suspected heart valve disease, what symptoms and signs indicate direct referral (for example from primary care) to a specialist?
3.	Objective	To determine the accuracy of presenting symptoms and signs to diagnose severe heart valve disease. This will inform a decision on which presenting factors indicate that direct referral to a specialist is required in people with suspected heart valve disease.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Database of Systematic Reviews (CDSR) ○ Embase

		○ MEDLINE Searches will be restricted by: • English language • Human studies • Letters and comments are excluded Other searches: • Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant The full search strategies will be published in the final review.
5.	Condition or domain being studied	Suspected heart valve disease in adults aged 18 years and over: Aortic (including bicuspid) stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation and tricuspid regurgitation.
6.	Population	Inclusion: Adults aged 18 years and over with suspected heart valve disease in any setting (for example, in primary care) Exclusion: Children aged less than 18 years. Adults with congenital heart disease (excluding bicuspid aortic valves). Tricuspid stenosis and pulmonary valve disease. Adults presenting with acute heart failure
7.	Symptoms and signs	**Clinical observations:** • Cardiac auscultation (standard or electronic):

		○ Presence of new murmur ○ Character of heart sounds: – no/soft 2nd heart sound (as in severe AS) – added 3rd sound; gallop rhythm (as in severe MR) • Signs, severe symptoms or simple investigations: ○ Shortness of breath (exertional breathlessness, for example classified as NYHA class ≥2) ○ Shortness of breath + elevated serum natriuretic peptides (B‑type natriuretic peptide [BNP] or N‑terminal pro‑B‑type natriuretic peptide [NT‑proBNP]; for example NT‑proBNP 400-2000 or >2000 ng/litre) ○ Peripheral oedema (ie. swelling of ankles and legs) ○ Peripheral oedema (ie. swelling of ankles and legs) + BNP or NT proBNP (for example NT‑proBNP 400-2000 or >2000 ng/litre) ○ Pulmonary oedema ○ Exertional chest pain (Canadian score class 2+) ○ Exertional syncope (fainting) ○ Abnormal ECG: for example signs of LV hypertrophy or AF Include the following combinations: • murmur alone • murmur + heart sounds • murmur + any of the listed symptoms, signs, or investigative findings • murmur + heart sounds + any of the listed symptoms, signs, or investigative findings • murmur + heart failure (not symptoms alone nor heart sounds alone)

8.	Reference standard / Confounding factors	Reference (gold) standard: • Confirmed diagnosis of **severe** HVD by transthoracic or transoesophageal echocardiography Confounding factors (if diagnostic association studies are included): • Age (<65 years or ≥65 years) • Type of murmur: ○ Innocent murmur ○ Ejection systolic murmur ○ Regurgitant systolic murmur ○ Diastolic murmur • Presence/absence of atrial fibrillation
9.	Types of study to be included	• Single-gate diagnostic studies (these may be called cohort studies or cross-sectional studies) will be included preferentially • If no/insufficient[3] diagnostic accuracy studies are identified prospective and retrospective cohort studies with multivariate analysis of the association between signs and symptoms and a confirmed diagnosis of severe heart valve disease will be included.
10.	Other exclusion criteria	Exclusion criteria: • Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study. • Case-control or 'two-gate' diagnostic studies • Non-English language studies
11.	Context	In clinical practice a number of symptoms and signs might indicate that a person has severe heart valve disease. An understanding of which symptoms and signs

[3] This will be assessed for the review as a whole. There is no strict definition, but in discussion with the GC we will consider whether we have enough to form the basis for a recommendation.

		better indicate severe HVD as a cause can facilitate further investigations to confirm diagnosis and guide management.

12.	Primary outcomes (critical outcomes)	Diagnostic accuracy of symptoms and signs for **severe** HVD.
		
		Measured by:
		
		• Accuracy data
		  ○ Sensitivity
		  ○ Specificity
		  ○ Raw data to calculate 2x2 tables to calculate sensitivity and specificity (number of true positives, true negatives, false positives and false negatives).

13.	Secondary outcomes (important outcomes)	• Likelihood ratios • Positive Predictive Value (PPV) • Negative Predictive Value (NPV) • Receiver Operating Characteristic (ROC) curve or area under curve for BNP and NT pro-BNP If insufficient[4] accuracy data are found, diagnostic association of signs and symptoms with a confirmed diagnosis of severe HVD will be included. Measured by: • Association data ○ Adjusted RR or OR.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

[4] This will be assessed for the review as a whole. There is no strict definition, but in discussion with the GC we will consider whether we have enough to form the basis for a recommendation.

		The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using QUADAS-2 for diagnostic accuracy studies. QUIPS will be used to assess diagnostic association reviews. A 10% sample of the risk of bias assessments will be independently quality assured by a second reviewer. Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	**Diagnostic accuracy studies** Where possible data will be meta-analysed in WinBUGS (if at least 3 studies reporting data at the same diagnostic threshold). Summary diagnostic outcomes will be reported from the meta-analyses with their 95% confidence intervals in adapted GRADE tables. Assessment of the quality of evidence for each outcome will take into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Heterogeneity will be assessed by visual inspection of the sensitivity and specificity plots and summary area under the curve (AUC) plots. Particular attention will be placed on the measure determined by the committee to be the primary outcome for decision making. If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software. **Diagnostic association studies** Aggregate data on diagnostic association of signs and symptoms will be collected and synthesised in a quantitative data analysis.

		If more than one study covered the same combination of population, sign/symptom, outcome and confounding factors accounted for then meta-analysis will be used to pool results. Meta-analysis will be carried out using the generic inverse variance function on Review Manager using fixed effect model. Data synthesis will be completed by two reviewers, with any disagreements resolved by discussion, or if necessary a third independent reviewer. Data from the meta-analysis will be presented and quality assessed in adapted GRADE tables taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each sign/symptom. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. We will conduct sensitivity analyses based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. **All study types** A second reviewer will quality assure 10% of the data analyses. Discrepancies will be identified and resolved through discussion (with a third party where necessary). Publication or other bias will only be taken into consideration in the quality assessment if it is apparent.
17.	Analysis of sub-groups	The following subgroups will be investigated if heterogeneity is apparent in the analysis: • Age (<65 years or ≥65 years) • Setting/population: GP screening/incidental findings, GP examination in response to symptoms, examination in a heart clinic, examination in a general hospital setting • Type of valve disease diagnosed (aortic stenosis [including bicuspid], aortic regurgitation, mitral stenosis, mitral regurgitation, tricuspid regurgitation)? • Presence/absence of atrial fibrillation

		• Type of murmur: ○ Innocent murmur ○ Ejection systolic murmur ○ Regurgitant systolic murmur ○ Diastolic murmur		
18.	Type and method of review	☐	Intervention	
		☒	Diagnostic	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	09/05/2019		
22.	Anticipated completion date	17/06/2021		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑

		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail HVD@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Sharon Swain [Guideline lead] Eleanor Samarasekera [Senior systematic reviewer] Nicole Downes [Systematic reviewer] George Wood [Systematic reviewer] Robert King [Health economist] Jill Cobb [Information specialist] Katie Broomfield [Project manager]		

26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10122
29.	Other registration details	None
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.

32.	Keywords	Aortic regurgitation; aortic stenosis; clinical assessment; diagnosis; heart valve disease; mitral regurgitation; mitral stenosis; primary care; referral; tricuspid regurgitation	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

Table 34: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[149] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).

	• OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2004 or later that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'. • Studies published before 2004 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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Appendix B Literature search strategies

Heart valve disease – search strategy 1 – signs and symptoms

This literature search strategy was used for the following review questions:

- In adults with suspected heart valve disease what symptoms and signs indicate referral (for example from primary care) for echocardiography?
- In adults with suspected heart valve disease, what symptoms and signs indicate direct referral (for example from primary care) to a specialist?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[149]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 35: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 14 October 2020	Exclusions
Embase (OVID)	1974 – 14 October 2020	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 10 of 12	None

Medline (Ovid) search terms

1.	exp Heart Valve Diseases/
2.	exp heart valves/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.

16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
29.	27 not 28
30.	exp Heart Murmurs/
31.	murm*r*.ti,ab.
32.	Heart Sounds/
33.	((heart or cardiac) adj sound*).ti,ab.
34.	(wooshing or blowing or flutter* or rasping).ti,ab.
35.	(heart beat* or heartbeat*).ti,ab.
36.	turbulent blood flow.ti,ab.
37.	Heart Auscultation/
38.	auscultation*.ti,ab.
39.	or/30-38
40.	29 and 39

1 **Embase (Ovid) search terms**

1.	exp valvular heart disease/
2.	exp heart valve/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	Case report/ or Case study/
12.	(letter or comment*).ti.
13.	or/8-12
14.	randomized controlled trial/ or random*.ti,ab.

15.	13 not 14
16.	animal/ not human/
17.	Nonhuman/
18.	exp Animal Experiment/
19.	exp Experimental animal/
20.	Animal model/
21.	exp Rodent/
22.	(rat or rats or mouse or mice).ti.
23.	or/15-22
24.	7 not 23
25.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
26.	24 not 25
27.	limit 26 to English language
28.	exp heart murmur/
29.	murm*r*.ti,ab.
30.	((heart or cardiac) adj sound*).ti,ab.
31.	(wooshing or blowing or flutter* or rasping).ti,ab.
32.	(heart beat* or heartbeat*).ti,ab.
33.	turbulent blood flow.ti,ab.
34.	heart sound/
35.	heart auscultation/
36.	auscultation*.ti,ab.
37.	or/28-36
38.	27 and 37

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Heart Valve Diseases] explode all trees
#2.	MeSH descriptor: [Heart Valves] explode all trees
#3.	((primary or secondary) NEXT valv* disease*):ti,ab
#4.	((valv* or flap* or leaflet*) near/1 (heart or cardiac) NEXT (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)):ti,ab
#5.	((mitral or aortic or tricuspid or pulmon*) NEXT (valv* or flap* or leaflet*) NEXT (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)):ti,ab
#6.	((mitral or aortic or tricuspid or pulmon*) NEAR/3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)):ti,ab
#7.	(or #1-#6)
#8.	MeSH descriptor: [Heart Murmurs] explode all trees
#9.	murm*r*:ti,ab
#10.	MeSH descriptor: [Heart Sounds] this term only
#11.	((heart or cardiac) next sound*):ti,ab
#12.	(wooshing or blowing or flutter* or rasping):ti,ab
#13.	(heart next beat* or heartbeat*).ti,ab.
#14.	turbulent blood flow:ti,ab
#15.	MeSH descriptor: [Heart Auscultation] explode all trees

#16.	auscultation*:ti,ab
#17.	(or #8-#16)
#18.	#7 and #17

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to heart valve disease population in NHS Economic Evaluation Database (NHS EED) – (this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) – (this ceased to be updated after March 2018) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics.

Table 36: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2014 – 15 October 2020	Exclusions Health economics studies
Embase	01 January 2014 – 15 October 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 March 2018 NHSEED - Inception to 31 March 2015	None

Medline (Ovid) search terms

1.	exp Heart Valve Diseases/
2.	exp heart valves/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	Heart Valve Prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp Heart Murmurs/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter/
15.	editorial/
16.	news/
17.	exp historical article/

18.	Anecdotes as Topic/
19.	comment/
20.	case report/
21.	(letter or comment*).ti.
22.	or/14-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animals/ not humans/
26.	exp Animals, Laboratory/
27.	exp Animal Experimentation/
28.	exp Models, Animal/
29.	exp Rodentia/
30.	(rat or rats or mouse or mice).ti.
31.	or/24-30
32.	13 not 31
33.	limit 32 to english language
34.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
35.	33 not 34
36.	Economics/
37.	Value of life/
38.	exp "Costs and Cost Analysis"/
39.	exp Economics, Hospital/
40.	exp Economics, Medical/
41.	Economics, Nursing/
42.	Economics, Pharmaceutical/
43.	exp "Fees and Charges"/
44.	exp Budgets/
45.	budget*.ti,ab.
46.	cost*.ti.
47.	(economic* or pharmaco?economic*).ti.
48.	(price* or pricing*).ti,ab.
49.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
50.	(financ* or fee or fees).ti,ab.
51.	(value adj2 (money or monetary)).ti,ab.
52.	or/36-51
53.	35 and 52

1 **Embase (Ovid) search terms**

1.	exp valvular heart disease/
2.	exp heart valve/
3.	((primary or secondary) adj valv* disease*).ti,ab.

4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	exp heart valve prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp heart murmur/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter.pt. or letter/
15.	note.pt.
16.	editorial.pt.
17.	Case report/ or Case study/
18.	(letter or comment*).ti.
19.	or/14-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animal/ not human/
23.	Nonhuman/
24.	exp Animal Experiment/
25.	exp Experimental animal/
26.	Animal model/
27.	exp Rodent/
28.	(rat or rats or mouse or mice).ti.
29.	or/21-28
30.	13 not 29
31.	limit 30 to English language
32.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
33.	31 not 32
34.	health economics/
35.	exp economic evaluation/
36.	exp health care cost/
37.	exp fee/
38.	budget/
39.	funding/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.

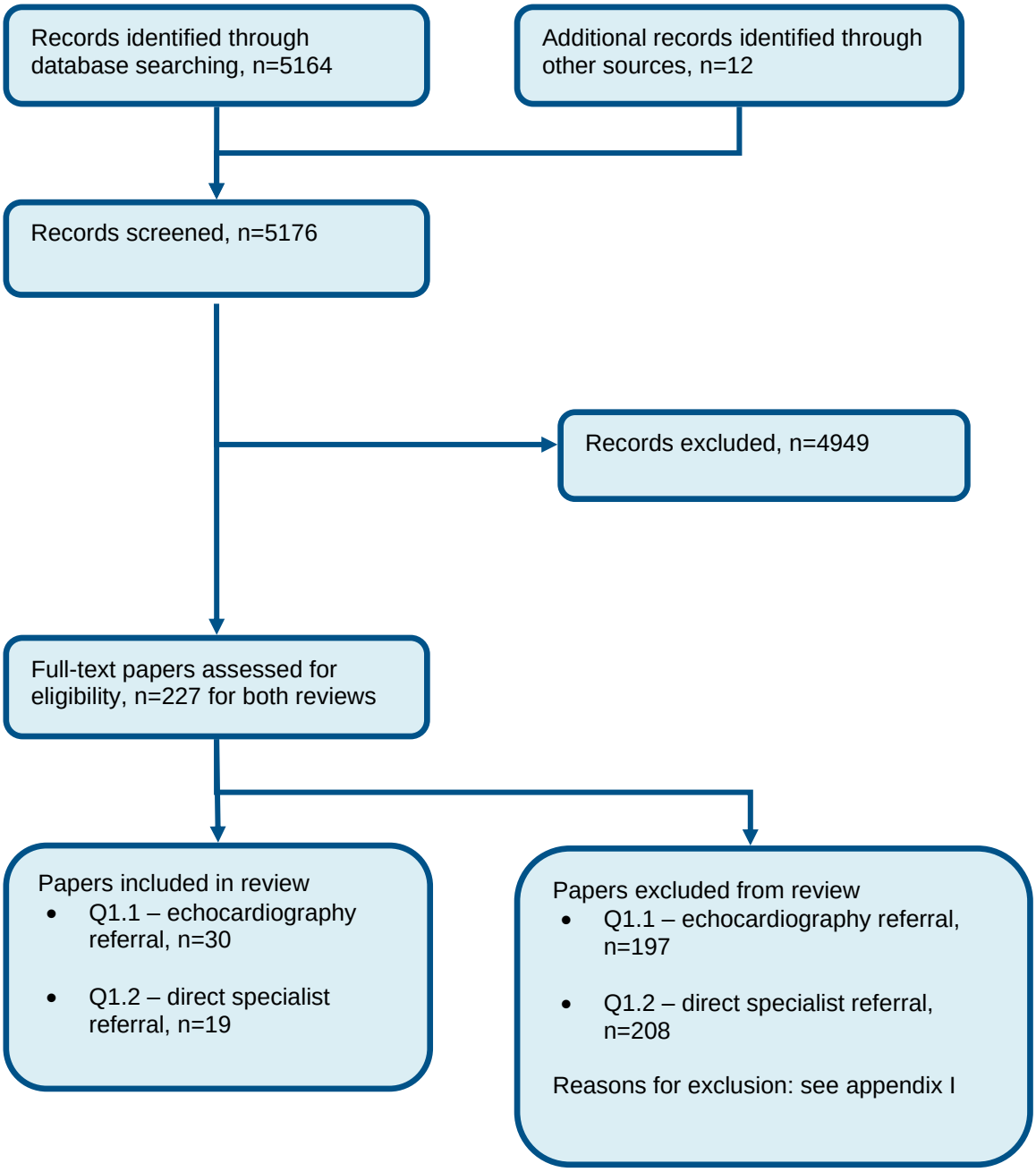
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.
46.	(value adj2 (money or monetary)).ti,ab.
47.	or/34-46
48.	33 and 47

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Heart Valve Diseases EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Heart Valves EXPLODE ALL TREES
#3.	(((primary or secondary) adj Valv* adj disease*))
#4.	(((valv* or flap* or leaflet*) adj (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)))
#5.	((heart or cardiac) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*))
#6.	(((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)))
#7.	(((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)))
#8.	MeSH DESCRIPTOR Heart Valve Prosthesis EXPLODE ALL TREES
#9.	(((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)))
#10.	(valve-in-valve)
#11.	((transcatheter adj2 (valve or valves)))
#12.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

Appendix C –Diagnostic evidence study selection

Figure 1: Flow chart of clinical study selection for the reviews of symptoms and signs indicating referral for echocardiography (1.1) and direct referral to a specialist (1.2)



Appendix D – Diagnostic evidence

D.1 Symptoms and signs indicating echocardiography referral

Reference	**Aggarwal 2014[5]**
Study type	Double blind prospective correlation study
Study methodology	Recruitment: consecutive (first 100 patients with inclusion criteria visiting the clinic)
Number of patients	n = 100
Patient characteristics	Age, mean (SD): 54.6 (sd not calculable) Gender (male to female ratio): 61:39 Ethnicity: Not reported Setting: Cardiology centre of an academic university hospital, in a rural area Country: India Inclusion criteria: Patients advised to undergo echocardiography when visiting the clinic Exclusion criteria: Known pre-existing heart murmurs No other characteristics provided
Target condition(s)	Any valve disease: stenosis or regurgitation
Index test(s) and reference standard	Index test Detection of murmur using stethoscope and specific software (ZargisCardioscan software) After taking informed consent, the principal investigator, a community medicine physician performed the auscultation of patients' hearts in sitting position. Subsequently, the ZargisCardioscan™ software was used to analyse the heart sounds auscultated by the 3M™ Littmann® Model 3200 stethoscope. The heart auscultation was performed at all four auscultation sites on the chest: aortic area in second intercostal space on right parasternal line, pulmonary area in second intercostal space on left parasternal line, tricuspid area in fourth intercostal space on left parasternal line and cardiac apex (mitral area) in fifth intercostal space on midclavicular line. The analysis by ZargisCardioscan™ about presence and absence of systolic and/or diastolic murmurs were recorded. Sub-analysis by ZargisCardioscan™ further confirmed whether the auscultated systolic murmur was Class I murmur based on its grade and occurrence-time in cardiac cycle; all auscultated diastolic murmurs were considered Class I murmur based on the American College of

<table>
<tr><td>Reference</td><td colspan="5">Aggarwal 2014[5]</td></tr>
<tr><td></td><td colspan="5">Cardiology/American Heart Association (ACC/AHA) Practice Guidelines for the Management of Patients with Valvular Heart Disease that classify murmurs in asymptomatic patients as Class I murmurs if they are diastolic or continuous or holosystolic or late systolic or mid-systolic (grade 3 or higher).

It appears that the index test categories were no murmur (-ve) and murmur [Class 1 and above] (+ve) but this is unclear from the methodological description.

<u>Reference standard</u>
Echocardiography confirmed valve disease, by blinded cardiologist. All except minimal-mild regurgitant valvular lesions were considered significant echocardiographic findings. Results have been extracted to include both minimal-mild regurgitant valvular lesions and significant valvular lesions as positives on gold standard for this review, as it covers heart valve disease regardless of severity.

Time between measurement of index test and reference standard: unclear</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4">Results have been extracted to include both minimal-mild regurgitant valvular lesions and significant valvular lesions as positives on gold standard for this review, as it covers heart valve disease regardless of severity. Though only a 2x2 table for significant regurgitant lesions was emphasised in the paper, sufficient data was available to be able to construct the 2x2 table ourselves for any severity of regurgitant lesion, which included significant regurgitant lesions as well as minimal-mild regurgitant lesions as positives on the reference standard.</td></tr>
<tr><td>Index test +</td><td>21</td><td>10</td><td>31</td></tr>
<tr><td>Index test −</td><td>30</td><td>39</td><td>69</td></tr>
<tr><td>Total</td><td>51</td><td>49</td><td>100</td></tr>
<tr><td>Statistical measures</td><td colspan="5"><u>Index text:</u> detection of murmur using stethoscope and specific software

Sensitivity: 0.41
Specificity: 0.80
PPV: 0.68
NPV: 0.57
PLR: 2.02
NLR: 0.74
Prevalence on reference standard: 0.51</td></tr>
</table>

Reference	**Aggarwal 2014[5]**
Source of funding	No funding was received from any agency for carrying out this research work. However, ZargisCardioscan™ software and 3M™ Littmann® Model 3200 stethoscope were provided by Deepak Gupta, MD, Anaesthesiologist, Detroit Medical Center/Wayne State University, Detroit, Michigan, United States from his personally owned equipments' inventory on loan basis (academic / research purposes only) only as a gesture of supporting medical research under the principal investigator at the institution. There was no competing interest between the authors of this research study.
Limitations	Risk of bias: serious (unclear duration between index and gold standard tests) Indirectness: serious – population is not necessarily those with suspected heart valve disease, but they have an indication for echocardiography
Comments	

1

Reference	**Amano 1986[11]**
Study type	Retrospective cross-sectional study
Study methodology	Recruitment: consecutive patients that were examined by auscultation, phonocardiography, 2D-echocardiography and pulsed Doppler echocardiography were reviewed – those with apical early or mid-systolic murmurs were included in the study.
Number of patients	n = 55
Patient characteristics	Age, mean (SD): not reported. Does appear to include some under the age of 18 but proportion unclear. Gender (male to female ratio): not reported Ethnicity: not reported Setting: unclear Country: Japan Inclusion criteria: had been examined by auscultation, phonocardiography, 2D-echocardiography and pulsed Doppler echocardiography; had apical early or mid-systolic murmurs Exclusion criteria: none reported No patient characteristics reported.
Target condition(s)	Heart valve disease: mitral regurgitation

<table>
<tr><td>Reference</td><td colspan="4">Amano 1986[11]</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="4">Index test
Presence of murmur – all had to have one to be included. These were apical early or mid-systolic murmurs. Murmurs appear to have been identified using auscultation and then analysed by phonocardiography. Prior to phonocardiography, careful auscultation was made with special attention to the point of the maximum intensity, area of transmission, timing, duration, intensity, pitch (high or medium), quality (blowing, harsh, rough, musical or vibratory and scratchy or clicky), and respiratory changes of murmurs.

Reference standard
Echocardiography confirmed mitral regurgitation. Pulsed Doppler echocardiography – Doppler signal recorded simultaneously with the M-mode echocardiogram, phonocardiogram and electrocardiogram using a strip chart recorder. Mitral regurgitation was estimated on basis of the location and area of distribution of abnormal systolic flow detected within the left atrium. 2D echocardiography – performed in supine or slightly left lateral position using commercially available, real-time scanner. Four cross-sectional images: long-axis, short-axis, apical four-chamber and subxiphoid views. Valve motion was carefully assessed to determine the lesions.

Time between measurement of index test and reference standard: unclear – performance of phonocardiography and echocardiography was described as simultaneous, but delay between hearing murmur on auscultation and phonocardiography and echocardiography is unclear. Likely to be short time period as described it as ‘before’, suggesting shortly before rather than there being a long time delay.</td></tr>
<tr><td>2×2 table</td><td colspan="4"><table>
<tr><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td></tr>
<tr><td>Index test +</td><td>29</td><td>26</td><td>55</td></tr>
<tr><td>Index test −</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Total</td><td>29</td><td>26</td><td>55</td></tr>
</table></td></tr>
<tr><td>Statistical measures</td><td colspan="4">Index test: Presence of murmur – all had to have one to be included

Sensitivity: could not calculate as all were index + to be included
Specificity: could not calculate as all were index + to be included
PPV: 0.53
NPV: could not calculate as all were index + to be included
PLR: could not calculate as all were index + to be included
NLR: could not calculate as all were index + to be included
Prevalence on reference standard: 0.53</td></tr>
<tr><td>Source of funding</td><td colspan="4">Not reported</td></tr>
<tr><td>Limitations</td><td colspan="4">Risk of bias: very serious – no reporting of blinding to index results; time interval between index test and reference standard unclear and exclusion criteria not listed.
Indirectness: serious – all had to have a murmur to be included, which is the index test for this review and limits the use of accuracy data</td></tr>
</table>

Reference	**Amano 1986[11]**
Comments	

1

Reference	**Aronow 1989[16]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: unselected elderly patients in a long-term health care facility
Number of patients	n = 450
Patient characteristics	Age, mean (SD): 82 (8) years, range 61-100 years Gender (male to female ratio): 114:336 Ethnicity: not reported Setting: long-term health care facility Country: USA Inclusion criteria: elderly patients in a long-term health care facility; had technically adequate M-mode and 2D echocardiograms and pulsed Doppler recordings of the aortic valve Exclusion criteria: not reported. No other characteristics of patients reported.
Target condition(s)	Heart valve disease: aortic regurgitation
Index test(s) and reference standard	Index test Murmur of aortic regurgitation. A high frequency decrescendo murmur beginning with A_2 was classified as an aortic regurgitation murmur. Cardiovascular examination was performed by an experienced cardiologist. Reference standard Echocardiography confirmed aortic regurgitation. M-mode and 2D echocardiograms and pulsed Doppler recordings of the aortic valve were obtained. Aortic regurgitation was diagnosed when an abnormal, high-velocity turbulent diastolic flow was detected in the left ventricular outflow tract. AR was considered mild when the signal was limited to the first centimetre proximal to the aortic valve, moderate

Reference	**Aronow 1989[16]**
	when signal was detected in the left ventricular outflow tract in the area beyond the first centimetre but not beyond the tip of the anterior mitral leaflet, and severe when the abnormal signal persisted to a distance beyond the tip of the anterior mitral leaflet and could be detected in the left ventricle. Echocardiograms and Doppler recordings were interpreted by an experienced echocardiographer. Time between measurement of index test and reference standard: unclear – all patients underwent a cardiovascular examination by an experienced cardiologist before interpretation of the echocardiograms and Doppler recordings.

2×2 table

	Reference standard +	Reference standard −	Total
Index test +	105	8	113
Index test −	26	311	337
Total	131	319	450

Statistical measures	Index text: murmur of aortic regurgitation Sensitivity: 0.80 Specificity: 0.97 PPV: 0.93 NPV: 0.92 PLR: 31.96 NLR: 0.20 Prevalence on reference standard: 0.29
Source of funding	Not reported
Limitations	Risk of bias: very serious – no reporting of blinding to index results; time interval between index test and reference standard unclear Indirectness: serious – population may not necessarily be suspected HVD and may be in long-term health care facility for other reasons
Comments	

1

Reference	**Aronow 1987[17]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: unselected elderly patients with aortic systolic ejection murmurs in a long-term health care facility
Number of patients	n = 75
Patient characteristics	Age, mean (SD): 83 (8) years (range, 62-100)

Reference	**Aronow 1987[17]**
	Gender (male to female ratio): 16:59 Ethnicity: not reported Setting: long-term health care facility Country: USA Inclusion criteria: elderly patients in a long-term health care facility; had technically adequate M-mode and 2D echocardiograms and pulsed Doppler recordings of the aortic valve Exclusion criteria: patients with more than mild aortic regurgitation as determined clinically or by Doppler echocardiography; patients with subvalvular stenosis. No other patient characteristics reported.
Target condition(s)	Heart valve disease: aortic stenosis
Index test(s) and reference standard	Index test Aortic systolic ejection murmur – all had to have one to be included in the study. All patients underwent a cardiovascular examination performed by an experienced cardiologist before interpretation of echocardiograms and Doppler recordings. A systolic ejection murmur heard in the second right intercostal space, down the left sternal border toward the apex or at the apex was classified as aortic systolic ejection murmur. Reference standard Echocardiography confirmed aortic stenosis. M-mode and 2D echocardiograms, and continuous wave Doppler measurement of aortic valve flow, were obtained. Valve flow velocities were assessed in multiple views, including apical, suprasternal and right parasternal views. Peak flow velocity across the aortic valve of 1.5 m/s or less was defined as normal. Peak aortic flow velocity 1.6-2.5 m/sec (peak gradient 10-25 mmHg), 2.6-3.5 m/sec (peak gradient 26-49 mmHg) and ≥3.6 m/sec (peak gradient ≥50 mmHg) were defined as mild, moderate and severe aortic stenosis, respectively. Echocardiographic and Doppler studies were interpreted by an experienced echocardiographer without knowledge of the cardiovascular findings. Time between measurement of index test and reference standard: unclear - cardiovascular examination was performed prior to interpretation of echocardiograms and Doppler recordings, but time interval unclear.

2×2 table

	Reference standard +	Reference standard −	Total
Index test +	42	33	75
Index test −	0	0	0

Reference	**Aronow 1987[17]**				
	Total	42	33	75	
Statistical measures	Index text: aortic systolic ejection murmur – all had to have one to be included in the study Sensitivity: could not calculate as all were index + to be included Specificity: could not calculate as all were index + to be included PPV: 0.56 NPV: could not calculate as all were index + to be included PLR: could not calculate as all were index + to be included NLR: could not calculate as all were index + to be included Prevalence on reference standard: 0.56				
Source of funding	Not reported				
Limitations	Risk of bias: serious – time interval between index test and reference standard unclear Indirectness: serious – all had to have a murmur to be included, which is the index test for this review and limits the use of accuracy data				
Comments					

1

Reference	**Aronow 1991[18]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: unselected elderly patients in a long-term health care facility
Number of patients	n = 781
Patient characteristics	Age, mean (SD): 82 (8) years (range, 62-100 years) Gender (male to female ratio): 223:558 Ethnicity: not reported Setting: long-term health care facility Country: USA Inclusion criteria: elderly patients in a long-term health care facility with technical Exclusion criteria: not reported. No other patient characteristics reported.

Reference	**Aronow 1991[18]**
Target condition(s)	Heart valve disease: aortic stenosis
Index test(s) and reference standard	Index test Aortic systolic ejection murmur. All patients underwent a cardiovascular examination performed by an experienced cardiologist before interpretation of echocardiograms and Doppler recordings. A systolic ejection murmur heard in the second right intercostal space, down the left sternal border toward the apex or at the apex was classified as aortic systolic ejection murmur. Reference standard Echocardiography confirmed aortic stenosis. M-mode and 2D echocardiograms, and continuous wave Doppler measurement of aortic valve flow, were obtained. Valve flow velocities were assessed in multiple views, including apical, suprasternal and right parasternal views. Peak flow velocity across the aortic valve of 1.5 m/s or less was defined as normal. Peak aortic flow velocity 1.6-2.5 m/sec (peak gradient 10-25 mmHg), 2.6-3.5 m/sec (peak gradient 26-49 mmHg) and ≥3.6 m/sec (peak gradient ≥50 mmHg) were defined as mild, moderate and severe aortic stenosis, respectively. Echocardiographic and Doppler studies were interpreted by an echocardiographer. Time between measurement of index test and reference standard: unclear - cardiovascular examination was performed prior to interpretation of echocardiograms and Doppler recordings, but time interval unclear.
2×2 table	

	Reference standard +	Reference standard −	Total
Index test +	138	Not reported	Not reported
Index test −	4	Not reported	Not reported
Total	142	639	781

Statistical measures	Index text: aortic systolic ejection murmur Sensitivity: 0.97 Specificity: could not calculate as no information regarding number of true negatives or false positives. PPV: could not calculate as no information regarding number of true negatives or false positives. NPV: could not calculate as no information regarding number of true negatives or false positives. PLR: could not calculate as no information regarding number of true negatives or false positives. NLR: could not calculate as no information regarding number of true negatives or false positives. Prevalence on reference standard: 0.18
Source of funding	Not reported
Limitations	Risk of bias: very serious – no reporting of blinding to index results; time interval between index test and reference standard unclear Indirectness: serious – population may not necessarily be suspected HVD and may be in long-term health care facility for other reasons
Comments	

1

Reference	**Attenhofer Jost 2000[19]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: consecutive patients referred to echocardiography laboratory because of a systolic murmur of unknown cause and who had not had previous echocardiographic examination
Number of patients	n = 100
Patient characteristics	Age, mean (SD): 58 (22) years (range, 17-92 years) Gender (male to female ratio): 43:57 Ethnicity: not reported Setting: echocardiography laboratory of a hospital Country: Switzerland Inclusion criteria: referred for echocardiography due to systolic murmur of unknown cause; no previous echocardiographic examination Exclusion criteria: not reported No other patient characteristics reported.
Target condition(s)	Heart valve disease: aortic stenosis or valvular regurgitation (AR, MR, TR) – reports separately for each type of valve disease
Index test(s) and reference standard	Index test 1. Systolic murmur – all had one to be included in the study 2. Systolic murmur + diminished aortic closure sound (AS and MR only) Immediately before echocardiography, patients were examined by two cardiologists blinded to the patient's history, electrocardiogram and other medical data. Clinical examination included estimate of jugular venous pressure, assessment of apical impulse and carotid artery upstroke, and auscultation at rest during quiet respiration, with assessment of heart sounds and murmurs and their radiation. Associated findings, such as thrills and systolic clicks, were noted. The Valsava manoeuvre was done in every patient and other dynamic manoeuvres were added if thought necessary. Characteristics of murmurs were classified at point of maximal intensity. Murmurs were located in aortic area, pulmonic area, base of the heart or apex. Timing and duration of murmurs were classified as early systolic, late systolic or holosystolic. The examiner had to state if the murmur was functional or organic. If thought to be organic, the examiner had to classify the underlying heart disease as significant or insignificant. Significant disease was defined as moderate or severe valvular heart disease, congenital shunts or intraventricular gradients. An isolated valvular lesion was defined if there was no clinical evidence of other types of heart disease – for the purposes of this review, information only on valve disease was extracted.

Reference	Attenhofer Jost 2000[19]				
	Reference standard Echocardiography confirmed aortic stenosis or valvular regurgitation (AR, MR, TR). Transthoracic 2D and Doppler echocardiography in the left supine position. Valvular regurgitation was graded as trivial, mild, moderate or severe based on a combination of factors, especially the vena contracta for the atrioventricular valves and the ratio of the regurgitant jet height to the outflow tract height for the semilunar valves. Aortic stenosis was classified as severe (mean systolic gradient ≥50 mmHg or aortic valve area ≤0.8 cm^2), moderate (mean systolic gradient 30-49 mmHg or aortic valve area 0.8-1.0 cm^2), mild (mean systolic gradient 10-29 mmHg or aortic valve area 1.1-1.9 cm^2) or trivial (mean systolic gradient <10 mmHg or aortic valve area ≥2.0 cm^2, but with thickening of bicuspid or tricuspid aortic valve). An intraventricular gradient (left or right ventricle) was defined as a peak systolic gradient ≥10 mmHg at rest or with Valsava within the left ventricular outflow tract or midventricular by continuous-wave Doppler with the typical shape (left convex) and the peak velocity occurring late in systole. Time between measurement of index test and reference standard: index test was performed immediately before echocardiography.				
2×2 tables	Systolic murmur - AS	Reference standard +	Reference standard −	Total	
	Index test +	29	71	100	
	Index test −	0	0	0	
	Total	29	71	100	
	Systolic murmur - AR	Reference standard +	Reference standard −	Total	
	Index test +	28	72	100	
	Index test −	0	0	0	
	Total	28	72	100	
	Systolic murmur - MR	Reference standard +	Reference standard −	Total	
	Index test +	30	70	100	
	Index test −	0	0	0	
	Total	30	70	100	
	Systolic murmur - TR	Reference standard +	Reference standard −	Total	
	Index test +	24	76	100	

Reference	**Attenhofer Jost 2000[19]**				
	Index test −	0	0	0	
	Total	24	76	100	
	Systolic murmur + diminished aortic closure sound - AS	Reference standard +	Reference standard −	Total	
	Index test +	8	Not reported	Not reported	
	Index test −	20	Not reported	Not reported	
	Total	28	72	100	
	Systolic murmur + diminished aortic closure sound - MR	Reference standard +	Reference standard −	Total	
	Index test +	3	Not reported	Not reported	
	Index test −	27	Not reported	Not reported	
	Total	30	70	100	
Statistical measures	Index text: AS - systolic murmur – all had one to be included in the study Sensitivity: could not calculate as all were index + to be included Specificity: could not calculate as all were index + to be included PPV: 0.29 NPV: could not calculate as all were index + to be included PLR: could not calculate as all were index + to be included NLR: could not calculate as all were index + to be included Prevalence on reference standard: 0.29 Index text: AR - systolic murmur – all had one to be included in the study Sensitivity: could not calculate as all were index + to be included Specificity: could not calculate as all were index + to be included				

Reference	Attenhofer Jost 2000[19]
	PPV: 0.28 NPV: could not calculate as all were index + to be included PLR: could not calculate as all were index + to be included NLR: could not calculate as all were index + to be included Prevalence on reference standard: 0.28 Index text: MR - systolic murmur – all had one to be included in the study Sensitivity: could not calculate as all were index + to be included Specificity: could not calculate as all were index + to be included PPV: 0.30 NPV: could not calculate as all were index + to be included PLR: could not calculate as all were index + to be included NLR: could not calculate as all were index + to be included Prevalence on reference standard: 0.30 Index text: TR - systolic murmur – all had one to be included in the study Sensitivity: could not calculate as all were index + to be included Specificity: could not calculate as all were index + to be included PPV: 0.24 NPV: could not calculate as all were index + to be included r PLR: could not calculate as all were index + to be included NLR: could not calculate as all were index + to be included Prevalence on reference standard: 0.24 Index text: AS systolic murmur + diminished aortic closure sound Sensitivity: 0.29 Specificity: could not calculate as no information regarding number of true negatives or false positives. PPV: could not calculate as no information regarding number of true negatives or false positives. NPV: could not calculate as no information regarding number of true negatives or false positives. PLR: could not calculate as no information regarding number of true negatives or false positives. NLR: could not calculate as no information regarding number of true negatives or false positives. Prevalence on reference standard: 0.29 Index text: MR systolic murmur + diminished aortic closure sound

Reference	**Attenhofer Jost 2000[19]**
	Sensitivity: 0.10 Specificity: could not calculate as no information regarding number of true negatives or false positives. PPV: could not calculate as no information regarding number of true negatives or false positives. NPV: could not calculate as no information regarding number of true negatives or false positives. PLR: could not calculate as no information regarding number of true negatives or false positives. NLR: could not calculate as no information regarding number of true negatives or false positives. Prevalence on reference standard: 0.30
Source of funding	Not reported
Limitations	Risk of bias: serious – certain manoeuvres may have been used for auscultation in some patients and not others Indirectness: serious – for the use of murmur alone as a diagnostic feature, all had to have a murmur to be included, which is the index test for this review and limits the use of accuracy data; for murmur + diminished aortic closure sound, insufficient information to calculate full diagnostic accuracy measures
Comments	

1

Reference	**Barron 1988[21]**
Study type	Cross-sectional study
Study methodology	Recruitment: consecutive patients referred to echocardiography for evaluation of suspected mitral valve prolapse
Number of patients	n = 140
Patient characteristics	Age, mean (SD): 36.8 (12.6) years Gender (male to female ratio): 23:117 Ethnicity: not reported Setting: 125 patients were outpatients and 15 were inpatients Country: USA Inclusion criteria: patients referred to echocardiography for evaluation of suspected mitral valve prolapse Exclusion criteria: not reported No other patient characteristics were reported.

Reference	**Barron 1988[21]**
Target condition(s)	Heart valve disease: mitral or tricuspid regurgitation
Index test(s) and reference standard	Index test Systolic murmur. Auscultation was performed by one investigator either immediately prior to or after echocardiographic and Doppler studies. Patients were examined in the supine left lateral decubitus, standing and squatting positions. Physical examination was positive for mitral valve prolapse if a midsystolic click was heard I supine position and if it moved toward the first heart sound with standing and toward the second heart sound with squatting. Clicks elicited only with standing or squatting were also deemed consistent with mitral valve prolapse. Presence of a systolic murmur heard in the left lower sternal border or apex, with or without radiation to the axilla, was noted in each position. Systolic murmurs heard loudest in the aortic or pulmonic areas were not consistent with mitral or tricuspid origin and therefore discounted. In the absence of a click, a systolic murmur alone was not considered indicative of mitral valve prolapse. For the purposes of this review, those with a murmur on auscultation were considered to be index positive – those with only clicks, and not a murmur, were not considered to be index test positive. Reference standard Echocardiography confirmed mitral or tricuspid regurgitation. 2D echocardiographs and Doppler studies were performed. The presence of mitral valve prolapse and tricuspid valve prolapse was assessed. Doppler flow studies were performed using pulsed Doppler sample volumes. The left atrium and right atrium above the valve leaflets were interrogated for valvular regurgitation. In the event of transmitral flow, the parasternal long-axis and apical four-chamber and two-chamber views were used. For the tricuspid valve, the parasternal right ventricular inflow tract view and apical four chamber views were used. Echocardiograms were interpreted by one investigator without knowledge of the auscultatory findings. Time between measurement of index test and reference standard: index test was performed by one investigator either immediately prior to or after echocardiographic and Doppler studies.
2×2 table	

	Reference standard +	Reference standard −	Total
Index test +	26	25	51
Index test −	23	66	89
Total	49	91	140

Statistical measures	Index text: systolic murmur Sensitivity: 0.53 Specificity: 0.73 PPV: 0.51 NPV: 0.74 PLR: 1.93 NLR: 0.65 Prevalence on reference standard: 0.35

Reference	Barron 1988[21]
Source of funding	Not reported.
Limitations	Risk of bias: serious – in some where index test was performed after reference standard it is unclear whether they were blinded to reference standard results Indirectness: none
Comments	

1

Reference	Barzilai 1988[22]
Study type	Prospective cross-sectional study
Study methodology	Recruitment: consecutive patients with documented acute myocardial infarction admitted to hospital cardiac care unit
Number of patients	n = 59
Patient characteristics	Age, mean (SD): 65 (2) years Gender (male to female ratio): 34:25 Ethnicity: not reported Setting: secondary care – Barnes Hospital Cardiac Care Unit Country: USA Inclusion criteria: admitted to hospital cardiac care unit between September 1985 and March 1986 with documented acute myocardial infarction and who could be examined within 48 h of the onset of infarction Exclusion criteria: not reported

Reference	**Barzilai 1988[22]**
	Type of myocardial infarction: n=35 with Q-wave acute MI and n=24 with non-Q-wave acute MI. The acute MI was anterior (Q-wave =18) in 24, inferior (Q-wave =16) in 34 and the locus could not be determined in 1 patient.
Target condition(s)	Heart valve disease: mitral regurgitation
Index test(s) and reference standard	Index test Systolic murmur. Relevant data from the history, an attending physician's physical examination, laboratory findings, including peak total and MB creatine kinase, and electrocardiograms were collected prospectively in all patients. Reference standard Echocardiography confirmed mitral regurgitation. Pulsed Doppler echocardiography was performed usually on the morning after admission. The presence of mitral regurgitation was determined from the apical 4 chamber and parasternal long-axis views with pulsed Doppler. Mitral regurgitation was diagnosed by the presence of a high pitched audio signal accompanied by turbulent systolic flow when the sample volume was placed in the left atrium. Only patients with flow velocities >150 cm/s were considered to have mitral regurgitation. The results of Doppler examination were not routinely revealed to physicians caring for the patients unless requested or unless unanticipated findings were documented. Time between measurement of index test and reference standard: unclear – potentially up to/longer than 24 h, as Doppler studies usually performed on the morning after admission.
2×2 table	

	Reference standard +	Reference standard −	Total
Index test +	10	6	16
Index test −	13	30	43
Total	23	36	59

Statistical measures	Index text: systolic murmur Sensitivity: 0.43 Specificity: 0.83 PPV: 0.63 NPV: 0.70 PLR: 2.61 NLR: 0.68 Prevalence on reference standard: 0.39
Source of funding	Not reported
Limitations	Risk of bias: very serious – no mention of blinding to index results when reference standard interpreted; time interval between the index test and reference standard being performed unclear and could have been up to/longer than 24 h

Reference	**Barzilai 1988[22]**
	Indirectness: serious – population is those admitted for acute myocardial infarction so may not necessarily have been suspicion of heart valve disease, but rather assessing its onset after acute myocardial infarction
Comments	

1

Reference	**Baur 2006[23]**
Study type	Prospective cohort study
Study methodology	Recruitment: 43 general practices were recruited, and each then referred any eligible patients to the study
Number of patients	n = 198 (43 general practices, covering 130,000 people; the 198 were those who were referred for echocardiography on the basis of approved indications)
Patient characteristics	Age, mean (SD): 64.5 (18.1) Gender (male to female ratio): 86:112 Ethnicity: Not reported Setting: Urban primary care Country: Netherlands Inclusion criteria: Patients at any of 43 general practices; suspected of having heart failure or valve disease, as shown by the following approved indications: shortness of breath, cardiac murmur and peripheral oedema of otherwise unexplained origin. Exclusion criteria: Other indications 34% cardiac murmur only; 28% dyspnea only; 3% peripheral oedema only; 13% cardiac murmur and dyspnea; 2% cardiac murmur and peripheral oedema; 1% cardiac murmur and dyspnea and peripheral oedema
Target condition(s)	Heart valve disease: aortic or mitral valve disease (including stenosis and regurgitation)
Index test(s) and reference standard	I Index test 1. Cardiac murmur 2. Cardiac murmur + other indication (e.g. dyspnoea, peripheral oedema or other) Reference standard

Reference	**Baur 2006[23]**				
	Echocardiography confirmed aortic or mitral valve disease (including stenosis and regurgitation). Results were interpreted by the cardiologist according to the criteria of the American and European Societies of Echocardiography. Systolic left ventricular dysfunction was defined as a left ventricular ejection fraction <40% measured by 2D echocardiography in the apical four-chamber and two-chamber view. Quantification of the echocardiograms was performed according to Simpson's rule. Diastolic dysfunction was defined as an abnormal flow pattern across the mitral valve and an abnormal flow pattern across the pulmonary vein. Because diastolic mitral flow is age-dependent, flow patterns were considered abnormal if the flow was beyond the mean and once the standard deviation of the normal flow of that age group. Left ventricular hypertrophy was defined as a mean wall thickness of >12 mm. Pulmonary hypertension was considered present if the measured systolic pulmonary pressure was >35 mmHg. Measurement of the systolic pulmonary pressure was done by measuring the maximal velocity of the tricuspid regurgitation and calculation of the systolic pressure gradient between the right ventricle and right atrium according to the Bernoulli equation. Right atrial pressure was estimated by looking to the diameter and the collapse of the inferior cava vein. Aortic insufficiency was measured using the criteria of Perry and Reynolds. Aortic valve insufficiency was assumed to be important if it was more than grade 2. Aortic valve stenosis was considered important if the maximal gradient was >30 mmHg and the mean gradient >20 mmHg. If one or more criteria were present the patient was assumed to have significant aortic valve disease. Mitral valve insufficiency was graded by measurement of the jet area and proximal jet width at the vena contracta in addition to measurement of the continuous wave flow and the pulsed wave flow in the pulmonary veins. Mitral valve regurgitation was assumed to be important if leakage was more than grade 2. Mitral valve stenosis was considered haemodynamically relevant when the maximal gradient was .10 mmHg. If one or both criteria were present, the patient was assumed to have significant mitral valve disease. Time between measurement of index test and reference standard: approximately 1 week				
2×2 tables	Cardiac murmur	Reference standard +	Reference standard −	Total	
	Index test +	19	82	101	
	Index test −	1	96	97	
	Total	20	178	198	
	Cardiac murmur + other indication (e.g. dyspnoea, peripheral oedema or other)	Reference standard +	Reference standard −	Total	
	Index test +	12	22	34	
	Index test −	8	156	164	

Reference	**Baur 2006[23]**				
	Total	20	178	198	
Statistical measures	Index text: cardiac murmur Sensitivity: 0.95 Specificity: 0.54 PPV: 0.19 NPV: 0.99 PLR: 2.06 NLR: 0.09 Prevalence on reference standard: 0.10 Index text: cardiac murmur + other indication (e.g. dyspnoea, peripheral oedema or other) Sensitivity: 0.60 Specificity: 0.88 PPV: 0.35 NPV: 0.95 PLR: 4.85 NLR: 0.46 Prevalence on reference standard: 0.10				
Source of funding	Not reported				
Limitations	Risk of bias: Very serious: 1 week duration between index and gold standard tests; no reporting of echo assessor blinding Indirectness: None				
Comments					

1

Reference	**Breisblatt 1988[27]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: patients referred for cardiac catheterisation with known ischaemic heart disease and no previous history of valvular disease, being assessed for the presence of mitral regurgitation. Unclear if consecutive.
Number of patients	n = 150
Patient characteristics	Age, mean (SD): 62 years (SD not reported), range 34-80 years Gender (male to female ratio): 112:38

Reference	Breisblatt 1988[27]
	Ethnicity: not reported Setting: 75% were evaluated in a coronary care unit or post-coronary care unit setting for unstable angina or myocardial infarction. Remaining patients were referred to radionuclide laboratory as patients who had previously been unstable and whose physicians wanted a pre-catheterisation assessment of left ventricular function. Country: USA Inclusion criteria: patients referred for cardiac catheterisation with known ischaemic heart disease; no previous history of valvular disease Exclusion criteria: not reported All patients had known or suspected coronary artery disease Previous transmural myocardial infarction, 52% Previous subendocardial myocardial infarction, 15% Three-vessel disease, 68% Two-vessel disease, 21% One-vessel disease, 11%
Target condition(s)	Heart valve disease: mitral regurgitation
Index test(s) and reference standard	Index test Systolic murmur. In pre-catheterisation assessment, patients were examined by two cardiologists who were blinded to radionuclide data. The presence of absence of a systolic murmur was noted, as well as whether the murmur was characteristic of mitral regurgitation – defined as a holosystolic apical murmur. Other systolic murmurs identified during the examination were assessed as suggestive of mitral regurgitation. Reference standard Radionuclide angiography confirmed mitral regurgitation. Right-sided catheterisation was performed in 85% patients with flow-directed balloon-tipped catheter and left ventricular end-diastolic pressure was recorded in all patients. Left ventriculography was performed. Mitral regurgitation was graded on a scale of 1+ to 4+. Post-extra systolic beats were excluded and only normal beats were evaluated. The degree of mitral regurgitation was based on consensus of two blinded angiographers. Equilibrium radionuclide angiocardiography performed at rest in all patients. A four-view study was performed in all patients (best septal view, anterior, left lateral and left posterior oblique). Both lateral views were obtained in the right-sided down decubitus position. Radionuclide interpretation was the consensus of two observers who were blinded to data from angiographic studies and physical examination. Regurgitant index was determined by the stroke volume method.

Reference	**Breisblatt 1988[27]**			
	Time between measurement of index test and reference standard: unclear.			
2×2 table		Reference standard +	Reference standard −	Total
	Index test +	26	36	62
	Index test −	3	85	88
	Total	29	121	150
Statistical measures	Index text: systolic murmur Sensitivity: 0.90 Specificity: 0.70 PPV: 0.42 NPV: 0.97 PLR: 3.01 NLR: 0.15 Prevalence on reference standard: 0.19			
Source of funding	Not reported			
Limitations	Risk of bias: serious – time interval between index test and reference standard unclear Indirectness: serious – population with known ischaemic heart disease, likely to have a different incidence to a more general population presenting for first time with a murmur with/without symptoms			
Comments				

1

Reference	**Cantley 1995[29]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: newly admitted patients in an acute assessment and rehabilitation unit at a general hospital who were found to have systolic murmurs on clinical examination. Recruited over an 8-week period.
Number of patients	n = 32
Patient characteristics	Age, mean (SD): 81.8 years (SD not reported), range 56-95 years Gender (male to female ratio): 9:23 Ethnicity: not reported Setting: those referred to acute assessment and rehabilitation unit at a general hospital

Reference	**Cantley 1995[29]**
	Country: Scotland, UK Inclusion criteria: referred to acute assessment and rehabilitation unit at general hospital; presence of systolic murmur on clinical examination Exclusion criteria: not reported
Target condition(s)	Heart valve disease: aortic stenosis, aortic regurgitation or mitral regurgitation (reported separately)
Index test(s) and reference standard	Index test Systolic murmur – all had to have one to be included. Systolic murmur noted on clinical examination – unclear who the clinical examination was performed by. Reference standard Echocardiography confirmed aortic stenosis, aortic regurgitation or mitral regurgitation. Each patient assessed independently by a registrar operator using mobile stand-alone continuous wave Doppler machine and by a consultant radiologist using full echocardiographic assessment, including Doppler techniques. The results from full echocardiographic assessment with Doppler were used as the reference standard results in terms of this review. The presence or absence of aortic stenosis was recorded and if present the pressure gradient across the valve was noted. A gradient >20 mmHg was considered to indicate aortic stenosis. The presence or absence of aortic and mitral regurgitation was also noted. Time between measurement of index test and reference standard: unclear.
2×2 tables	

Aortic stenosis	Reference standard +	Reference standard −	Total
Index test +	12	20	32
Index test −	0	0	0
Total	12	20	32

Aortic regurgitation	Reference standard +	Reference standard −	Total
Index test +	14	17	31
Index test −	0	0	0
Total	14	17	31

Reference	**Cantley 1995[29]**

Mitral regurgitation	Reference standard +	Reference standard −	Total
Index test +	17	14	31
Index test −	0	0	0
Total	17	14	31

Statistical measures

Aortic stenosis
Index text Systolic murmur – all had to have one to be included

Sensitivity: could not calculate as all were index + to be included
Specificity: could not calculate as all were index + to be included
PPV: 0.38
NPV: could not calculate as all were index + to be included
PLR: could not calculate as all were index + to be included
NLR: could not calculate as all were index + to be included
Prevalence on reference standard: 0.38

Aortic regurgitation
Index text Systolic murmur – all had to have one to be included

Sensitivity: could not calculate as all were index + to be included
Specificity: could not calculate as all were index + to be included
PPV: 0.45
NPV: could not calculate as all were index + to be included
PLR: could not calculate as all were index + to be included
NLR: could not calculate as all were index + to be included
Prevalence on reference standard: 0.45

Mitral regurgitation
Index text Systolic murmur – all had to have one to be included

Sensitivity: could not calculate as all were index + to be included
Specificity: could not calculate as all were index + to be included
PPV: 0.55
NPV: could not calculate as all were index + to be included
PLR: could not calculate as all were index + to be included

Reference	Cantley 1995[29]
	NLR: could not calculate as all were index + to be included Prevalence on reference standard: 0.55
Source of funding	Not reported
Limitations	Risk of bias: very serious – no mention of blinding to index test results when reference standard performed; unclear duration between the index and reference tests Indirectness: serious – all had to have a murmur to be included, which is the index test for this review and limits the use of accuracy data
Comments	

1

Reference	Chin 1992[34]
Study type	Prospective cross-sectional study
Study methodology	Recruitment: patients with previously diagnosed mitral valve prolapse over a period of 5 years. Unclear if consecutive.
Number of patients	n = 42
Patient characteristics	<u>For those that were included in the analysis (n=31)</u> Age, mean (SD): not reported. Range of ages reported to be 15-78 years. Gender (male to female ratio): 9:12 Ethnicity: not reported Setting: unclear Country: The Netherlands, Belgium Inclusion criteria: previously diagnosed mitral valve prolapse – defined as sagging of mitral closure lines at least 2 mm posterior to the CD line, a posterior excursion of >1 mm but <2 mm was called dubious. All cases were reviewed by 2D and Doppler echocardiography – the criteria were systolic bulging of one or both of the two mitral leaflets or their coaptation point into the left atrium beyond the mitral annulus in both views (parasternal long-axis and apical 4-chamber view)

Reference	**Chin 1992[34]**
	Exclusion criteria: not reported. No additional patient characteristics reported
Target condition(s)	Heart valve disease: mitral regurgitation
Index test(s) and reference standard	Index test Late systolic murmur. Immediately following ultrasound studies auscultation was performed in supine and left decubitus positions. Criteria for the diagnosis of MVP were a midsystolic click and/or late systolic murmur at the apex. The late systolic murmur was considered to be a sign of mitral regurgitation. Phonocardiographic recordings were also performed but results on auscultation reported separately. Reference standard Echocardiography confirmed mitral regurgitation. 2D and Doppler echocardiography used to confirm mitral valve prolapse. Detection of mitral regurgitation was performed using continuous and pulsed-wave Doppler recordings. In latter half of study, recordings could be made using colour-coded Doppler observations. Time between measurement of index test and reference standard: index test of murmur performed immediately after echocardiography.
2×2 table	

	Reference standard +	Reference standard −	Total
Index test +	9	2	11
Index test −	4	16	20
Total	13	18	31

Statistical measures	Index text: late systolic murmur Sensitivity: 0.69 Specificity: 0.89 PPV: 0.82 NPV: 0.80 PLR: 6.23 NLR: 0.35 Prevalence on reference standard: 0.42
Source of funding	Not reported
Limitations	Risk of bias: very serious – index test performed after reference standard and unclear if blinded; ~25% were not included in the analysis as not able to perform full assessment with reference standard or dubious results on the reference standard Indirectness: serious – already had confirmed mitral valve prolapse on echocardiography, may differ to the more general population with suspected HVD based on a murmur with/without symptoms only and no confirmation of existing structural problems

Reference	**Chin 1992[34]**
Comments	

1

Reference	**Decoodt 1990[51]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: patients with idiopathic mitral valve prolapse confirmed on echocardiography during 1 year period. Unclear if consecutive.
Number of patients	n = 100
Patient characteristics	Age, mean (SD): 53.5 years (SD not reported), range 18-83 years Gender (male to female ratio): 37:63 Ethnicity: not reported Setting: referred to a cardiology laboratory for echocardiography Country: Belgium Inclusion criteria: patients with idiopathic mitral valve prolapse – criteria based on M-mode and 2D echocardiography findings: late or holosystolic posterior movement of the valve of >2 mm below the CD line of coaptation of the mitral leaflets during systole (M-mode) and mitral coaptation of type 2-3. Prolapse criteria based on an apical view were avoided. Exclusion criteria: concomitant major cardiac abnormalities (hypertrophic cardiomyopathy, major aortic insufficiency, uncorrected atrial septal defect, surgically corrected atrial septal defects, corrected patent ductus arteriosus, dilated cardiomyopathy, ischaemic cardiopathies requiring transluminal dilatation and prior myocardial infarction). No other patient characteristics reported.
Target condition(s)	Heart valve disease: mitral regurgitation
Index test(s) and reference standard	Index test Systolic murmur – this included some with early systolic murmurs, late systolic murmurs and holosystolic murmurs. Auscultatory features were reported by another observer than the person performing the echocardiography. Reference standard Echocardiography confirmed mitral regurgitation. A 2.5 Mhz multi-element transducer was used for colour flow mapping study. Pulse repetition frequencies of 4, 6 or 8 KHz were available. Diagnostic range of 12 or 15 cm routinely used for mitral valve prolapse. When

Reference	**Decoodt 1990[51]**
	mitral regurgitation was found, the grade, direction of the jet and systolic timing were determined. For the grade, regurgitant flow on left atrial area ratio was obtained in the plane at which it appeared greatest. Same Doppler colour gain setting algorithm was used. Mitral regurgitation was classified as mild (ratio <20%), moderate (ratio 20-40%) and severe (ratio >40%). Time between measurement of index test and reference standard: unclear

2×2 table		Reference standard +	Reference standard −	Total
	Index test +	47	5	52
	Index test −	7	41	48
	Total	54	46	100

Statistical measures	Index text: systolic murmur Sensitivity: 0.87 Specificity: 0.89 PPV: 0.90 NPV: 0.85 PLR: 8.01 NLR: 0.15 Prevalence on reference standard: 0.54
Source of funding	Not reported
Limitations	Risk of bias: very serious – some of those with major concomitant heart abnormalities excluded; no blinding mentioned for performance of index test and reference standard; unclear time interval between index test and references standard Indirectness: serious – already had confirmed mitral valve prolapse on echocardiography, may differ to the more general population with suspected HVD based on a murmur with/without symptoms only and no confirmation of existing structural problems
Comments	

1

Reference	**Gardezi 2018[72]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: people undergoing echocardiography at two primary care sites participating in OxVALVE – prospective screening study to identify prevalence of undiagnosed valvular heart disease in asymptomatic subjects aged >65 years
Number of patients	n = 251
Patient characteristics	Age, mean (SD): 75 (6) years

Reference	**Gardezi 2018[72]**				
	Gender (male to female ratio): 128:123 Ethnicity: not reported Setting: primary care sites Country: UK Inclusion criteria: asymptomatic subjects >65 years undergoing screening for undiagnosed heart valve disease at two primary care sites enrolled in the OxVALVE study Exclusion criteria: history of valvular heart disease No other patient characteristics reported				
Target condition(s)	Heart valve disease: mild or significant valve disease				
Index test(s) and reference standard	Index test Murmur (systolic or diastolic) – as assessed by GPs. Systematic cardiac auscultation, incorporating assessment of pulse character and murmur radiation (where appropriate), was undertaken by one of two fully trained primary care/family doctors. Each participating primary care/family doctors had >10 years of clinical experience but had not received specialist cardiology training. They used an acoustic stethoscope under 'real world conditions' without the knowledge of the echocardiography results. Heart sounds were recorded using an electronic stethoscope and were analysed at a later date by two consultant cardiologists. Reference standard Echocardiography confirmed valve disease – reports separately for mild (aortic sclerosis or any mild regurgitation) and significant (at least moderate regurgitation or at least mild stenosis of any valve) valve disease. An investigating physician or sonographer performed detailed echocardiography immediately following auscultation using standard views according to the British Society of Echocardiography guidelines. Unclear if blinded to the index test results. Time between measurement of index test and reference standard: reference standard performed immediately after auscultation.				
2×2 table	Mild valve disease (aortic sclerosis or mild regurgitation)	Reference standard +	Reference standard −	Total	
	Index test +	55	27	82	

Reference	**Gardezi 2018[72]**				
	Index test −	115	54	169	
	Total	170	81	251	
	Significant valve disease (at least moderate regurgitation or at least mild stenosis of any valve)	Reference standard +	Reference standard −	Total	
	Index test +	16	66	82	
	Index test −	20	149	169	
	Total	36	215	251	
Statistical measures	Index test: murmur (systolic or diastolic) – mild valve disease (sclerosis or mild regurgitation) Sensitivity: 0.32 Specificity: 0.67 PPV: 0.67 NPV: 0.32 PLR: 0.97 NLR: 1.01 Prevalence on reference standard: 0.68 Index test: murmur (systolic or diastolic) – significant valve disease (at least moderate regurgitation or at least mild stenosis of any valve) Sensitivity: 0.44 Specificity: 0.69 PPV: 0.20 NPV: 0.88 PLR: 1.45 NLR: 0.80 Prevalence on reference standard: 0.14				

Reference	**Gardezi 2018[72]**
Source of funding	Supported by the National Institute for Health Research (NIHR) Biomedical Research Centre, Oxford, UK Reported to be no competing interests
Limitations	Risk of bias: serious – no mention of blinding to index test results when reference standard performed Indirectness: serious – appears to be a screening study in those over a certain age, and did not necessarily have any symptoms or signs that would lead to a suspicion of heart valve disease
Comments	

1

Reference	**Hoffmann 1983[86]**
Study type	Cross-sectional study
Study methodology	Recruitment: Consecutive patients
Number of patients	n = 102 in whole study (n=58 analysed as remaining 67 had Doppler ultrasound to assess aortic valve pressure gradient only, rather than to assess clinically ill-defined systolic murmur)
Patient characteristics	Age, range: 20-79 years Gender (male to female ratio): 57:45 Ethnicity: Not reported Note: above patient characteristics based on the whole cohort of n=102 patients, not limited to n=58 included in analysis of ill-defined systolic murmur. Setting: Cardiac catheter clinic (secondary care) Country: Switzerland Inclusion criteria: people undergoing right or left heart catheterisation for valvular or coronary heart disease, or both. Exclusion criteria: None reported Aortic stenosis: 22/102; mitral regurgitation 36/102; ventricular septal defect 8/102
Target condition(s)	Heart valve disease: aortic stenosis or mitral regurgitation. Aortic stenosis defined as pressure gradient >20 mmHg.

Reference	**Hoffmann 1983[86]**				
Index test(s) and reference standard	Index test Systolic murmur – all had one to be included Doppler US was the index test in the study but for the purpose of this review, data used to obtain information on the number of those with murmur that went on to have confirmed valve disease by cardiac catheterisation. Reference standard Cardiac catheterisation confirmed aortic stenosis or mitral regurgitation Time between measurement of index test and reference standard: unclear				
2×2 tables	Aortic stenosis	Reference standard +	Reference standard −	Total	Though flow murmurs are mentioned in the paper, they do not give numbers assessed as having flow murmurs on auscultation – the accuracy data given in the paper in terms of distinguishing between valve disease and flow murmurs appears to be for Doppler ultrasonography, not auscultation.
	Index test +	22	36	58	
	Index test −	0	0	0	
	Total	22	36	58	
	Mitral regurgitation	Reference standard +	Reference standard −	Total	Though flow murmurs are mentioned in the paper, they do not give numbers assessed as having flow murmurs on auscultation – the accuracy data given in the paper in terms of distinguishing between valve disease and flow murmurs appears to be for Doppler ultrasonography, not auscultation.
	Index test +	36	22	58	
	Index test −	0	0	0	
	Total	36	22	58	
Statistical measures	Index text: systolic murmur – AS Sensitivity: could not calculate as all were index + to be included Specificity: could not calculate as all were index + to be included PPV: 0.38 NPV: could not calculate as all were index + to be included PLR: could not calculate as all were index + to be included NLR: could not calculate as all were index + to be included Prevalence on reference standard: 0.38 Index text: systolic murmur – MR Sensitivity: could not calculate as all were index + to be included Specificity: could not calculate as all were index + to be included				

Reference	Hoffmann 1983[86]
	PPV: 0.62 NPV: could not calculate as all were index + to be included PLR: could not calculate as all were index + to be included NLR: could not calculate as all were index + to be included Prevalence on reference standard: 0.62
Source of funding	None reported
Limitations	Risk of bias: very serious: unclear duration between index and gold standard tests; no reporting of gold standard assessor blinding Indirectness: serious – all had to have a murmur to be included, which is the index test for this review and limits the use of accuracy data
Comments	

1

Reference	Kalinauskiene 2019[97]
Study type	Cross-sectional study
Study methodology	Recruitment: consecutive patients arriving at Kaunas Clinical Hospital meeting inclusion criteria
Number of patients	n = 30
Patient characteristics	Age, mean (SD): 68.7 (12.09) Gender (male to female ratio): 2:1 Ethnicity: Not reported Setting: 'Clinical Hospital' – unclear if primary or secondary care Country: Lithuania Inclusion criteria: BMI >30; aged >18 years; referred for echocardiogram Exclusion criteria: 'Severe' status; deemed unsuitable for inclusion Other characteristics: shortness of breath 83.33%; chest pain 76.67%; leg oedema 36.67%; fatigue 30%; echocardiography findings: mitral regurgitation 83.33%, tricuspid regurgitation 66.67%; aortic regurgitation 63.33%; pulmonary regurgitation 6.67%; aortic stenosis 3.33%.

Reference	**Kalinauskiene 2019[97]**
Target condition(s)	Heart valve disease: aortic stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation or tricuspid regurgitation
Index test(s) and reference standard	Index test Murmur via acoustic and electronic auscultation. Each subject received 4 auscultation examinations (Figure 1). Two auscultations were done by a cardiologist with about 20 years of experience using both an acoustic traditional stethoscope (3M Littman Cardiology III Mechanical Stethoscope, 3M Health Care, St. Paul, MN, USA) and an electronic stethoscope (3M Littmann 3200 Electronic Stethoscope,3MHealthCare, St. Paul, MN, USA). Two additional auscultations were done by a 3rd-year medical resident doctor also using both an acoustic traditional stethoscope and an electronic stethoscope. Half of the patients were auscultated by one cardiologist and one resident, and half, by another cardiologist and another resident. Based on the randomization for each subject, the auscultation may begin with either the 3M Littmann 3200 Electronic or 3M Littmann Cardiology III Mechanical stethoscope. Physicians had a 2-week period to gain experience in using the electronic stethoscope before the commencement of the study. Each auscultation consisted of heart murmurs being listened to in the following sites: mitral (apex), aortic (right second intercostal space), pulmonary (left second intercostal space), tricuspid (lower left sternal border), and Erb's (left third intercostal space). All physicians used the same ordinary methodology of Lithuanian University of Health Sciences: All physicians used the same ordinary methodology of Lithuanian University of Health (1) Using the bell listen first to the apex (mitral area) just above the apex beat (palpate the apex beat), then at the second right interspace parasternally (aortic area), at the second left interspace parasternally (pulmonic area), at the third interspace adjacent to the left sternal border (Erb's area), and, finally, at the left parasternal area at the lower part of the sternum (tricuspid area) in the supine position. (2) Shift to the diaphragm and return to all these areas. (3) Ask the patient to exhale completely and stop breathing, listen at the apex and aortic areas, and Erb's area with the bell and the diaphragm; ask the patient to inhale completely and stop breathing, listen at the pulmonic and tricuspid areas with the bell and the diaphragm. (4) Ask the patient to roll partly onto the left side, listen at the apex with the bell and the diaphragm, then also ask the patient to exhale completely and stop breathing, and again listen with the bell and the diaphragm. (5) Ask the patient to sit up, lean forward and put his/her arms on the head, listen at the aortic and Erb's areas only with the diaphragm, also repeat the auscultation at these areas in full held expiration. Physical conditions for all listeners were as in a real-life: all auscultations were performed in Sciences: 1) Using the bell listen first to the apex (mitral area) just above the apex beat (palpate the apex beat), then at the second right interspace parasternally (aortic area), at the second left interspace parasternally (pulmonic area), at the third interspace adjacent to the left sternal border (Erb's area), and, finally, at the left parasternal area at the lower part of the sternum (tricuspid area) in the supine position. 2) Shift to the diaphragm and return to all these areas. 3) Ask the patient to exhale completely and stop breathing, listen at the apex and aortic areas, and Erb's area with the bell and the diaphragm; ask the patient to inhale completely and stop breathing, listen at the pulmonic and tricuspid areas with the bell and the diaphragm. 4) Ask the patient to roll partly onto the left side, listen at the apex with the bell and the diaphragm, then also ask the patient to exhale completely and stop breathing, and again listen with the bell and the diaphragm. 5) Ask the patient to sit up, lean forward and put his/her arms on the head, listen at the aortic and Erb's areas only with the diaphragm, also repeat the auscultation at these areas in full held expiration. Reference standard Echocardiogram, carried after index tests who were blinded to index test results.

Reference	**Kalinauskiene 2019[97]**			
	Time between measurement of index test and reference standard: unclear			
2×2 table	**Resident/acoustic/mitral regurgitation**	Reference standard +	Reference standard −	Total
	Index test +	19	2	21
	Index test −	6	3	9
	Total	25	5	30
	Resident/electronic/mitral regurgitation	Reference standard +	Reference standard −	Total
	Index test +	21	3	24
	Index test −	4	2	6
	Total	25	5	30
	Resident/acoustic/aortic regurgitation	Reference standard +	Reference standard −	Total
	Index test +	5	0	5
	Index test −	14	11	25
	Total	19	11	30
	Resident/electronic/aortic regurgitation	Reference standard +	Reference standard −	Total
	Index test +	7	0	7
	Index test −	12	11	23
	Total	19	11	30
	Resident/acoustic/tricuspid regurgitation	Reference standard +	Reference standard −	Total
	Index test +	10	1	11
	Index test −	10	9	19
	Total	20	10	30

Reference	Kalinauskiene 2019[97]			
	Resident/electronic/tricuspid regurgitation	Reference standard +	Reference standard −	Total
	Index test +	13	2	15
	Index test −	7	8	15
	Total	20	10	30
	Resident/acoustic/mitral stenosis	Reference standard +	Reference standard −	Total
	Index test +	0	1	1
	Index test −	0	29	29
	Total	0	30	30
	Resident/electronic/mitral stenosis	Reference standard +	Reference standard −	Total
	Index test +	0	1	1
	Index test −	0	29	29
	Total	0	30	30
	Resident/acoustic/aortic stenosis	Reference standard +	Reference standard −	Total
	Index test +	1	3	4
	Index test −	2	24	26
	Total	3	27	30
	Resident/electronic/aortic stenosis	Reference standard +	Reference standard −	Total
	Index test +	1	3	4
	Index test −	2	24	26
	Total	3	27	30

Reference	Kalinauskiene 2019[97]
Statistical measures	Index text: **Resident/acoustic/mitral regurgitation** Sensitivity: 0.76 Specificity:0.60 PPV:0.90 NPV:0.33 PLR:1.90 NLR:0.40 Prevalence on reference standard:0.83 Index text **Resident/electronic/mitral regurgitation** Sensitivity: 0.84 Specificity:0.40 PPV:0.88 NPV:0.33 PLR:1.40 NLR:0.40 Prevalence on reference standard:0.83 Index text: **Resident/acoustic/aortic regurgitation** Sensitivity: 0.26 Specificity:1.00 PPV:1.00 NPV:0.44 PLR: Not calculable NLR:0.74 Prevalence on reference standard:0.63 Index text **Resident/electronic/aortic regurgitation** Sensitivity: 0.37 Specificity:1.00 PPV:1.00 NPV:0.48 PLR: Not calculable NLR:0.63 Prevalence on reference standard:0.63 Index text: **Resident/acoustic/tricuspid regurgitation**

Reference	Kalinauskiene 2019[97]
	Sensitivity: 0.50 Specificity:0.90 PPV:0.91 NPV:0.47 PLR:5.00 NLR:0.56 Prevalence on reference standard:0.67 Index text **Resident/electronic/tricuspid regurgitation** Sensitivity: 0.65 Specificity:0.80 PPV:0.87 NPV:0.53 PLR:3.25 NLR:0.44 Prevalence on reference standard:0.67 Index text: **Resident/acoustic/mitral stenosis** Sensitivity: not calculable Specificity: 0.97 PPV: 0.00 NPV: 1.00 PLR: not calculable NLR: not calculable Prevalence on reference standard: 0.00 Index text **Resident/electronic/mitral stenosis** Sensitivity: not calculable Specificity: 0.97 PPV: 0.00 NPV: 1.00 PLR: not calculable NLR: not calculable Prevalence on reference standard: 0.00 Index text: **Resident/acoustic/aortic stenosis** Sensitivity: 0.33

Reference	Kalinauskiene 2019[97]
	Specificity:0.89 PPV:0.25 NPV:0.92 PLR:3.00 NLR:0.75 Prevalence on reference standard:0.10 Index text **Resident/electronic/aortic stenosis** Sensitivity: 0.33 Specificity:0.89 PPV:0.25 NPV:0.92 PLR:3.00 NLR:0.75 Prevalence on reference standard:0.10
Source of funding	Sponsored by 3M, the manufacturers of the electronic and acoustic stethoscopes used in the study.
Limitations	Risk of bias: serious: unclear time interval between index tests and gold standard. No other limitations: index tests carried out before gold standard so these were effectively blinded from gold standard results; gold standard measured by different clinicians who were blinded to index test results; no attrition; consecutive sample. Indirectness: serious: these patients were those referred for an echo, but were from a sub-group with BMI >30. This sub-group may not be representative of the review population.
Comments	

1

Reference	Kinney 1988[103]
Study type	Retrospective review of hospital records
Study methodology	Recruitment: retrospective review of records of patients who had echocardiography performed between July 1982 and June 1985. Inpatients and outpatients included.
Number of patients	n = 294
Patient characteristics	Age, mean (SD): 59 (14) years Gender (male to female ratio): 100:0 – all patients were male Ethnicity: white, 70%; black, 30%

Reference	Kinney 1988[103]
	Setting: data from inpatients and outpatients included Country: USA Inclusion criteria: patients that had echocardiography performed between July 1982 and June 1985; data on self-reported heights and weights just before echocardiography Exclusion criteria: hospital charts too fragmentary to be useful; patients without Doppler study; equivocal Doppler results; Doppler studies of poor quality Most patients had one or more of the following conditions: • Hypertension, n=136 • Coronary artery disease, n=118. Of these, n=9 were within a week of acute myocardial infarction at time of Doppler echocardiography. • Alcoholism now or in the past, n=107 • Congestive heart failure now or in the past, n=70 • Symptomatic arrhythmias, n=16 • Prosthetic heart valves, n=5 (n=4 aortic prosthesis and n=1 mitral prosthesis) • Acute endocarditis, n=5 There were n=35 patients without apparent heart disease.
Target condition(s)	Heart valve disease: aortic regurgitation, mitral regurgitation or tricuspid regurgitation
Index test(s) and reference standard	Index test Murmur detected on auscultation. Auscultation performed as part of routine examination. Minimal requirement for using written examination notes in this study was that a cardiac examination had been recorded, and that the note was dated and signed. Information about each murmur was coded – whether it was systolic or diastolic, the location on the chest wall where it was heard best and its radiation, shape, loudness, duration and tonal quality. Auscultation was performed for various different examiners, of different experience levels, including students, interns, junior assistant residents, senior assistant residents and cardiology fellows. For the purpose of this review, data for junior and senior assistant residents were reported to match the setting of this review. Reference standard Echocardiography confirmed aortic regurgitation, mitral regurgitation or tricuspid regurgitation. M-mode, 2D and pulsed Doppler echocardiography were performed at the echocardiography laboratory unless there was equipment malfunction or a shortage of personnel. Presence or absence of aortic regurgitation was determined by pulsed Doppler by searching in the left ventricular outflow tract just below aortic valve in the apical 5-chamber plane. Aortic regurgitation was present if holodiastolic turbulence observed in left ventricular outflow tract. For mitral and tricuspid regurgitation, sample volume was placed below the mitral and tricuspid valves in the left

Reference	**Kinney 1988[103]**				
	and right atrium, respectively. Mitral regurgitation was diagnosed when holosystolic turbulence was observed in the left atrium, which was best recorded adjacent to the mitral valve. Tricuspid regurgitation was diagnosed when holosystolic turbulence was observed in the right atrium, which was best recorded adjacent to the tricuspid valve. When some but not all of the criteria for AR, MR and TR were present, the study was considered to be equivocal and the patients were not included in the study. The results of auscultation and cardiac catheterisation were not known at time of Doppler interpretation. Time between measurement of index test and reference standard: average time between index test and reference standard was 58 days – varied as some were inpatients while others were outpatients. However, interval was strongly skewed towards 1 day. Half of examinations done within 1 week of each other, and 65% of those were within 1 day.				
2×2 tables	Aortic regurgitation – junior assistant residents	Reference standard +	Reference standard −	Total	
	Index test +	3	7	9	
	Index test −	60	224	285	
	Total	63	231	294	
	Aortic regurgitation – senior assistant residents	Reference standard +	Reference standard −	Total	
	Index test +	0	21	21	
	Index test −	63	210	273	
	Total	63	231	294	
	Mitral regurgitation – junior assistant residents	Reference standard +	Reference standard −	Total	
	Index test +	27	30	57	
	Index test −	69	168	237	

Reference	Kinney 1988[103]				
	Total	96	198	294	
	Mitral regurgitation – senior assistant residents	Reference standard +	Reference standard −	Total	
	Index test +	12	20	32	
	Index test −	84	178	262	
	Total	96	198	294	
	Tricuspid regurgitation – junior assistant residents	Reference standard +	Reference standard −	Total	
	Index test +	13	0	13	
	Index test −	36	245	281	
	Total	49	245	294	
	Tricuspid regurgitation – senior assistant residents	Reference standard +	Reference standard −	Total	
	Index test +	16	0	16	
	Index test −	33	245	278	
	Total	49	245	294	

Reference	Kinney 1988[103]
Statistical measures	Index text: AR junior assistant residents - murmur Sensitivity: 0.04 Specificity: 0.97 PPV: 0.27 NPV: 0.79 PLR: 1.33 NLR: 0.99 Prevalence on reference standard: 0.214 Index text: AR senior assistant residents - murmur Sensitivity: 0.00 Specificity: 0.91 PPV: could not calculate as there were no true positives reported NPV: 0.77 PLR: could not calculate as there were no true positives reported NLR: 1.10 Prevalence on reference standard: 0.214 Index text: MR junior assistant residents - murmur Sensitivity: 0.28 Specificity: 0.85 PPV: 0.48 NPV: 0.71 PLR: 1.87 NLR: 0.85 Prevalence on reference standard: 0.327 Index text: MR senior assistant residents - murmur Sensitivity: 0.13 Specificity: 0.90 PPV: 0.39 NPV: 0.68 PLR: 1.30 NLR: 0.97 Prevalence on reference standard: 0.327 Index text: TR junior assistant residents - murmur

Reference	Kinney 1988[103]
	Sensitivity: 0.27 Specificity: 1.00 PPV: 1.00 NPV: 0.87 PLR: could not calculate as there were no false positives NLR: 0.73 Prevalence on reference standard: 0.167 Index text: TR senior assistant residents - murmur Sensitivity: 0.33 Specificity: 1.00 PPV: 1.00 NPV: 0.88 PLR: could not calculate as there were no false positives NLR: 0.67 Prevalence on reference standard: 0.167
Source of funding	Not reported
Limitations	Risk of bias: very serious – unclear whether blinded to index test results when reference standard performed; duration between index test and reference standard varied between patients and was >24 in a proportion of cases Indirectness: serious – population includes all patients referred for echocardiography and may not be limited to those with suspicion of heart valve disease, though all had some reason for referral for echocardiography
Comments	

1

Reference	Labovitz 1985[109]
Study type	Prospective cross-sectional study
Study methodology	Recruitment: consecutive series of patients with mitral annular calcium on echocardiography
Number of patients	n = 51
Patient characteristics	Age, mean (SD): 70 years (SD not reported), range 54-91 years Gender (male to female ratio): 21:30 Ethnicity: not reported

Reference	**Labovitz 1985[109]**				
	Setting: those that were originally referred for echocardiography Country: USA Inclusion criteria: echocardiographic diagnosis of mitral annular calcium – mitral annular calcium was diagnosed by echocardiography findings using standard criteria. Exclusion criteria: patients with calcified mitral valve leaflets Most patients were referred for symptoms of chest pain, congestive heart failure, dyspnoea or evaluation of a cardiac murmur. Hypertension, n=10 Coronary artery disease, n=7 Aortic valve replacement, n=4 Aortic stenosis, n=2 Cardiomyopathy, n=1 Chronic renal failure, n=3 Other patients had no associated cardiovascular abnormalities				
Target condition(s)	Heart valve disease: mitral stenosis or mitral regurgitation				
Index test(s) and reference standard	Index test Apical systolic murmur detected on clinical examination. No further details about the methods used. Reference standard Echocardiography confirmed mitral stenosis or mitral regurgitation. M-mode and 2D echocardiography and cardiac Doppler studies were performed. Mitral annular calcium was diagnosed by echocardiography findings using standard criteria. Doppler studies in pulsed or continuous- wave mode. Transmitral flow was sampled by placing the transducer at the cardiac apex and aligning the Doppler cursor parallel to flow using the 2D image from the 4-chamber view. The valve was scanned in continuous mode to determine maximal velocities of left ventricular inflow as well as to detect the presence of mitral regurgitation. Mitral regurgitation was defined as a holosystolic jet moving away from the transducer with velocity of >2 m/sec. If mitral regurgitation was present, it was quantified in pulsed mode and the extent of the regurgitant jet was mapped in the left atrium. Systolic flow away from the transducer seen 2 cm or more into the left atrium was considered significant (moderate to severe) mitral regurgitation. Jets that were <2 cm into the left atrium were considered mild mitral regurgitation. The mitral valve orifice area was determined by the pressure half-time method. Valve areas <2 cm^2 were classified as functional mitral stenosis. Time between measurement of index test and reference standard: unclear				
2×2 table		Reference standard +	Reference standard −	Total	

Reference	**Labovitz 1985[109]**				
	Index test +	19	9	28	
	Index test −	13	10	23	
	Total	32	19	51	
Statistical measures	Index text: apical systolic murmur Sensitivity: 0.59 Specificity: 0.53 PPV: 0.68 NPV: 0.43 PLR: 1.25 NLR: 0.77 Prevalence on reference standard: 0.63				
Source of funding	Not reported				
Limitations	Risk of bias: very serious –murmur assessment poorly reported and unclear whether reference standard was performed with blinding to index test results; time interval between index test and reference standard unclear Indirectness: serious – some already had known valve disease or had a prosthetic valve replacement (<10%) and all had echocardiography confirmed mitral annular calcium, which may mean the population differs from a more general one where heart valve disease may be suspected based on a murmur with/without symptoms				
Comments					

1

Reference	**Lehmann 1992[113]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: selected from those participating in phase I of the Thrombolysis in Myocardial Infarction (TIMI) trial. Unclear if consecutive and method of selection not described.
Number of patients	n = 206
Patient characteristics	Age, median (range): no MR, 57 (21-75) years; mild MR, 60 (26-74) years; moderate-severe MR, 68 (66-71) years Gender (male to female ratio): 170: 36 Ethnicity: not reported Setting: secondary care – acute presentation with myocardial infarction

Reference	Lehmann 1992[113]
	Country: USA Inclusion criteria: absence of previous myocardial infarction, cardiac surgery or dilated cardiomyopathy to help exclude pre-existent mitral regurgitation; good quality ventriculogram suitable for accurate quantification. In addition, the inclusion criteria of the TIMI trial were: age <76 years; severe ischaemic pain of at least 30 min duration; new or presumably new ST-segment elevation of at least 0.1 mV in two or more electrocardiographic leads; interval of <7 h between onset of symptoms and ventriculography; ability and willingness to grant informed consent Exclusion criteria: cardiogenic shock, uncontrolled hypertension or left bundle-branch block at presentation Site of infarction: anterior, 47%; inferior, 52%; uncertain, 1.9% Ejection fraction, mean (SD): 49.4 (10.1)%
Target condition(s)	Heart valve disease: mitral regurgitation
Index test(s) and reference standard	Index test Any murmur on auscultation. Auscultation performed by cardiology attending or fellow at presentation and the presence and characteristics of any murmur noted were recorded. Reference standard Cardiac catheterisation/ventriculography confirmed mitral regurgitation. Left heart catheterisation used to record intracardiac pressures. A contrast ventriculogram obtained in the 30 degree right anterior oblique position. After coronary angiography and attempted intravenous thrombolysis, the patient was transferred to cardiac care unit and standard care provided. Using a non-post extrasystolic beat, mitral regurgitation was graded 'none' if no contrast appeared in the left atrium, 'mild' if contrast did appear but was of insufficient quantity to completely fill the left atrium and moderate-severe if complete atrial opacification occurred. Artifactual regurgitation caused by catheter malposition was not included. Time between measurement of index test and reference standard: unclear, possibly short duration as presently within acute myocardial infarction but unclear.

2×2 table

	Reference standard +	Reference standard −	Total
Index test +	5	19	24
Index test −	22	160	182
Total	27	179	206

Reference	**Lehmann 1992[113]**
Statistical measures	Index text: murmur Sensitivity: 0.19 Specificity: 0.89 PPV: 0.21 NPV: 0.88 PLR: 1.74 NLR: 0.91 Prevalence on reference standard: 0.13
Source of funding	TIMI study was sponsored by National Heart, Lung and Blood Institute
Limitations	Risk of bias: very serious – unclear how patients were selected from the original trial and excluded those with history that may have meant mitral regurgitation was present before the acute myocardial infarction; no mention of blinding to index results when reference standard performed; time interval between index test and reference standard unclear Indirectness: serious – population is those admitted for acute myocardial infarction so may not necessarily have been suspicion of heart valve disease, but rather assessing its onset after acute myocardial infarction
Comments	

1

Reference	**Limacher 1985[117]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: pregnant women referred to echocardiography laboratory for evaluation of cardiac murmurs. Unclear if consecutive.
Number of patients	n = 81
Patient characteristics	Age, mean (SD): 22 (4) years Gender (male to female ratio): 0:81 – all were women Ethnicity: not reported Setting: those referred for echocardiography Country: USA Inclusion criteria: pregnant women referred to echocardiography laboratory for evaluation of cardiac murmurs Exclusion criteria: history of murmur or congenital or rheumatic heart disease

Reference	**Limacher 1985[117]**
	Pregnant women were in the 11th to 39th week of gestation (average, 30 weeks)
Target condition(s)	Heart valve disease: tricuspid regurgitation
Index test(s) and reference standard	Index test Murmur – all had one to be included in the study. Murmurs detected by the referring physician were described as early to midsystolic, best heard at the left sternal border, of grade I or II intensity. Reference standard Echocardiography confirmed tricuspid regurgitation. M-mode and 2D echocardiography were performed using standard views (parasternal long- and short-axis, apical 4-chamber, apical 2-chamber and subcostal). In the apical 4-chamber view, measurements of right atrial length and width were made at end-systole and the widest right ventricular diameter was measured at end-diastole. Tricuspid annular diameter was measured in the apical 4-chamber view during early diastole. Doppler studies performed with sampling in multiple views proximal and distal to all 3 valves and along the atrial and ventricular septae. Tricuspid regurgitation was diagnosed by holosystolic spectral dispersion of blood flow velocities (turbulence) with or without respiratory variation and by the presence of the typical harsh quality of the audio signal in systole. Time between measurement of index test and reference standard: unclear.
2×2 table	

	Reference standard +	Reference standard −	Total
Index test +	35	46	81
Index test −	0	0	0
Total	35	46	81

Statistical measures	Index text: murmur Sensitivity: could not calculate as all were index + to be included Specificity: could not calculate as all were index + to be included PPV: 0.43 NPV: could not calculate as all were index + to be included PLR: could not calculate as all were index + to be included NLR: could not calculate as all were index + to be included Prevalence on reference standard: 0.43
Source of funding	Not reported
Limitations	Risk of bias: very serious – some potentially inappropriate exclusions (those with a history of murmur and rheumatic/congenital heart disease); unclear whether blinded to index results when reference standard performed; time interval between index test and reference standard unclear Indirectness: serious – all had to have a murmur to be included, which is the index test for this review and limits the use of accuracy data

Reference	**Limacher 1985[117]**
Comments	

1

Reference	**Loperfido 1986[121]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: consecutive patients with myocardial infarction diagnosed 1-3 months before at coronary care unit on basis of chest pain, electrocardiogram and increase and decrease of creatine kinase-MB fraction
Number of patients	n = 72
Patient characteristics	Age, mean (SD): 53 (14) years, range 31-70 years Gender (male to female ratio): 62: 10 Ethnicity: not reported Setting: echocardiography performed in those who had had myocardial infarction 1-3 months prior Country: Italy Inclusion criteria: patients with myocardial infarction diagnosed 1-3 months before at coronary care unit on basis of chest pain, electrocardiogram and increase and decrease of creatine kinase-MB fraction; 2D echocardiography performed during acute myocardial infarction had excluded mitral leaflet abnormalities such as prolapse, vegetation or fibrosis Exclusion criteria: patients in clinical unstable condition at the time of Doppler study; complete bundle branch block; technically inadequate Doppler or echocardiographic studies Electrocardiogram: • Anterior myocardial infarction, n=42 • Inferior myocardial infarction, n=30
Target condition(s)	Heart valve disease: mitral regurgitation
Index test(s) and reference standard	Index test Systolic murmur. Cardiac auscultation was done at the time of Doppler examination with the patient in the left lateral decubitus position. An apical holosystolic or late systolic murmur was considered indicative of mitral regurgitation. A midsystolic murmur loudest at the apex was considered suggestive of mitral regurgitation.

Reference	**Loperfido 1986[121]**
	Reference standard Echocardiography confirmed mitral regurgitation. Doppler was performed at discharge (34±8 days following myocardial infarction) in 33 patients and during follow-up (101±6 days following myocardial infarction) in 39 patients. In 15 patients a Doppler study was obtained either at discharge or during follow-up. To assess mitral regurgitation, systolic turbulence was mapped within the left atrium using parasternal and apical approaches with the patient in the left lateral decubitus position. Mitral regurgitation diagnosed by presence of a high-pitched, whistling audio signal and confirmed by recording left atrial holosystolic turbulence in 5 consecutive cycles, excluding premature ventricular contractions. In the apical approach, care was taken to exclude the left ventricular outflow signal. Mitral regurgitation was semi-quantitatively graded according to extension of systolic turbulence below the mitral plane: 1+, up to 1 cm below the valve; 2+, up to half the superoinferior diameter of left atrium; and 3+, turbulence spreading even further. Time between measurement of index test and reference standard: not clear, but state auscultation was performed at the time of Doppler examination so possibly short time interval between them.
2×2 table	

	Reference standard +	Reference standard −	Total
Index test +	13	3	16
Index test −	27	29	56
Total	40	32	72

Statistical measures	Index text: systolic murmur Sensitivity: 0.33 Specificity: 0.91 PPV: 0.81 NPV: 0.52 PLR: 3.47 NLR: 0.74 Prevalence on reference standard: 0.56
Source of funding	Not reported
Limitations	Risk of bias: serious – unclear whether index test or reference standard performed first and no mention of any blinding to the results of the other Indirectness: serious – population is those previously admitted for acute myocardial infarction so may not necessarily have been suspicion of heart valve disease, but rather assessing its onset after myocardial infarction
Comments	

1

Reference	**McGee 2010[132]**
Study type	Prospective cross-sectional study

Reference	**McGee 2010[132]**
Study methodology	Recruitment: convenience sample of non-intensive care unit patients undergoing echocardiography during their hospital stay between 2001 and 2006
Number of patients	n = 376
Patient characteristics	Age, mean (SD): 69 (12) years, range 22-94 years (reported for the number assessed during the time period and includes those excluded for various reasons) Gender (male to female ratio): 399:10 (reported for the number assessed during the time period and includes those excluded for various reasons) Ethnicity: not reported Setting: hospitalised patients referred for echocardiography Country: USA Inclusion criteria: hospitalised non-intensive care unit patients undergoing echocardiography during their hospital stay between 2001 and 2006 Exclusion criteria: those with diastolic or systolic/diastolic murmurs; lacking complete echocardiogram Indications for echocardiography: assessment for structural heart disease, 59%; progression of pre-existing valvular disease, 16%; source of arterial emboli, 8%; suspected endocarditis, 7%; suspected pericardial disease, 2%. Only 7% of echocardiograms were to diagnosed unexplained murmurs.
Target condition(s)	Heart valve disease: aortic stenosis (mild, moderate or severe)
Index test(s) and reference standard	Index test 1. Systolic heart murmur 2. Broad apical-based systolic murmur + absent second heart sound With the exception of 14 cases, author unaware of patient diagnosis, indication for echocardiography or echocardiography results. Author recorded patient vital signs, arterial and venous pulsations, precordial pulsations, heart tones (first, second, third, fourth, and extra heart sounds and their characteristics) and murmurs (systolic, diastolic or both). Examination of the arteries, veins and precordium was performed prior to auscultation. The anterior chest from apex to clavicles was examined and radiation of murmurs completely described. Most patients examined in three positions (supine, left lateral decubitus and upright positions), but reported findings only refer to those in supine position. Murmurs defined as continuous sounds persisting during inspiration and expiration, though intensity could vary during

Reference	**McGee 2010[132]**				
	respiratory cycle. Continuous sounds that completely disappeared during inspiration or expiration were termed 'rubs'. All murmurs characterised using onomatopoeia and conventional grading. Reference standard Echocardiography confirmed aortic stenosis (mild, moderate or severe). All echocardiograms were interpreted by a cardiologist independent from bedside examination. Aortic stenosis was defined as peak aortic velocity ≥2.5 m/sec, with mild, moderate and severe aortic stenosis defined as peak aortic velocity 2.5-2.9 m/sec, 3.0-3.9 m/sec and ≥4.0 m/sec, respectively. Mitral regurgitation and tricuspid regurgitation were also assessed by echocardiography, but was only significant if moderate or severe regurgitation detected. No definition of this provided. No description of how mitral and tricuspid regurgitation confirmed on echocardiography. Time between measurement of index test and reference standard: unclear				
2×2 table	Systolic heart murmur - AS	Reference standard +	Reference standard −	Total	
	Index test +	71	146	217	
	Index test −	2	148	150	
	Total	73	294	367	
	Broad apical-based systolic murmur + absent second heart sound - AS	Reference standard +	Reference standard −	Total	
	Index test +	Not reported	Not reported	22	
	Index test −	Not reported	Not reported	354	
	Total	73	303	376	

Reference	McGee 2010[132]
Statistical measures	Index text: systolic heart murmur - AS Sensitivity: 0.97 Specificity: 0.50 PPV: 0.33 NPV: 0.99 PLR: 1.96 NLR: 0.05 Prevalence on reference standard: 0.20 Index text: broad apical-based systolic murmur + absent second heart sound - AS Sensitivity: could not be calculated Specificity: could not be calculated PPV: could not be calculated NPV: could not be calculated PLR (95% CI): 15.7 (1.0, 251) – reported in study. NLR(95% CI): not reported in study Prevalence on reference standard: 0.20
Source of funding	Not reported Reported to be no financial or personal relationships that could have biased the study
Limitations	Risk of bias: very serious – potentially inappropriate exclusions (those with diastolic murmurs or systolic/diastolic murmurs); unclear time interval between index test and reference standard being performed Indirectness: serious – not necessarily all suspected heart valve disease as some referred for echocardiography for other reasons, including 16% for evaluation of pre-existing heart valve disease
Comments	

1

Reference	Meyers 1982[139]
Study type	Prospective cross-sectional study
Study methodology	Recruitment: patients that had supravalvular aortogram to evaluate aortic valve disease during a two-year period. Unclear if consecutive.
Number of patients	n = 75
Patient characteristics	Age, mean (SD): not reported Gender (male to female ratio): not reported Ethnicity: not reported

Reference	**Meyers 1982[139]**
	Setting: referred for supravalvular aortogram to evaluate valve disease Country: USA Inclusion criteria: patients that had supravalvular aortogram to evaluate aortic valve disease during a two-year period Exclusion criteria: those without echocardiograms available to compare with angiograms; suboptimal echocardiograms; Starr-Edwards prosthetic valve in the mitral position Study population consists of a group in which there was a high pre-angiography clinical suspicion of aortic regurgitation.
Target condition(s)	Heart valve disease: aortic regurgitation
Index test(s) and reference standard	Index test Early diastolic murmur of aortic regurgitation. Presence or absence of the early diastolic murmur of aortic regurgitation on auscultation was noted by an attending cardiologist. Reference standard Angiography confirmed aortic regurgitation. Angiographic diagnosis of aortic regurgitation was made, with care taken to position the catheter correctly in the ascending aorta and to maintain this position, 4-6 cm above the aortic valve, during the injection to prevent spurious regurgitation due to catheter proximity to the valve and avoided missing a true regurgitation as a result of the catheter being too far from the valve. The presence or absence of regurgitation was also assessed on M-mode echocardiography by two experienced echocardiographers, independently and without the knowledge of the clinical and angiographic findings. Evidence of aortic regurgitation on echocardiography was defined by fine diastolic fluttering of anterior leaflet, posterior mitral leaflet or left ventricular surface of the septum, alone or in combination. Time between measurement of index test and reference standard: unclear
2×2 table	

	Reference standard +	Reference standard −	Total
Index test +	48	2	50
Index test −	18	7	25
Total	66	9	75

Reference	**Meyers 1982**[139]
Statistical measures	Index text: early diastolic murmur of aortic regurgitation Sensitivity: 0.73 Specificity: 0.78 PPV: 0.96 NPV: 0.28 PLR: 3.27 NLR: 0.35 Prevalence on reference standard: 0.88
Source of funding	Not reported
Limitations	Risk of bias: very serious – unclear whether blinded to results of index test when reference standard performed; unclear time interval between index test and reference standard Indirectness: none
Comments	

1

Reference	**Meyers 1986**[137]
Study type	Prospective cross-sectional study
Study methodology	Recruitment: patients evaluated by pulsed Doppler echocardiography, cardiac auscultation and left ventriculography – selection other than this unclear.
Number of patients	n = 35
Patient characteristics	Age, mean (SD): 55.4 (12.7) years Gender (male to female ratio): 16:19 Ethnicity: not reported Setting: undergoing echocardiography and left ventriculography – cardiology department Country: USA Inclusion criteria: patients evaluated by pulsed Doppler echocardiography, cardiac auscultation and left ventriculography Exclusion criteria: not reported

Reference	**Meyers 1986[137]**
	No other patient characteristics reported
Target condition(s)	Heart valve disease: mitral regurgitation
Index test(s) and reference standard	Index test Systolic murmur. The presence of absence of a characteristic apical systolic murmur of mitral regurgitation was noted during the precatheterisation evaluation. Reference standard Left ventriculography confirmed mitral regurgitation. All ventriculograms were evaluated for the presence or absence of mitral regurgitation by an investigator blinded to the Doppler findings. Semiquantitative estimates of severity were made angiographically on a scale of 1+ (mild) to 4+ (severe). Pulsed Doppler echocardiography also performed, by technicians blinded to the results of auscultation and angiography – described in detail in the paper but not used as the reference standard in this study. Time between measurement of index test and reference standard: all underwent diagnostic left ventriculography and Doppler echocardiography with a maximum interval between them of 10 days

2×2 table

	Reference standard +	Reference standard −	Total
Index test +	14	1	15
Index test −	5	15	20
Total	19	16	35

Statistical measures	Index text: Systolic murmur Sensitivity: 0.74 Specificity: 0.94 PPV: 0.93 NPV: 0.75 PLR: 11.79 NLR: 0.28 Prevalence on reference standard: 0.54
Source of funding	Not reported
Limitations	Risk of bias: very serious – selection of patients for the study poorly described; unclear if blinded to index test results when reference standard performed; unclear time interval between index test and reference standard Indirectness: serious – population may not necessarily be those with suspected heart valve disease, but are all undergoing cardiac assessment for some indication
Comments	

1

Reference	**Mishra, 1992** [143]				
Study type	Cross-sectional – audit of use of echocardiography between July 1989 and August 1991				
Study methodology	Recruitment: consecutive attendees referred for a cardiac opinion from the 4680 women attending an antenatal clinic in the period between July 1989 and August 1991.				
Number of patients	n = 103				
Patient characteristics	Age, mean (SD): no data Gender (male to female ratio): all women Ethnicity: no data Setting: Antenatal clinic Country: UK Inclusion criteria: pregnant women referred for a cardiac opinion Exclusion criteria: Known history of cardiac problems. No characteristics of patients reported.				
Target condition(s)	Heart valve disease: any type of echo abnormality – can obtain information for those relevant to our protocol				
Index test(s) and reference standard	Index test Murmur – three categorisations used, based on examination by a senior cardiologist. The first categorisation was ‘flow murmur’ and the second were ‘possibly pathological ‘ and ‘pathological’. We can regard the first category as non-pathological, based on the logic that if it is not ‘possibly pathological’ or ‘pathological’ it must be non-pathological. Hence anyone placed in the ‘possibly pathological’ and ‘pathological’ classes was index test + and anyone in the ‘flow murmur’ was index test -ve. Reference standard Echocardiography confirmed valve disease Time between measurement of index test and reference standard: unclear				
2×2 table		Reference standard +	Reference standard −	Total	Some of the echo ‘positives’ were not positives in the context of this review. So out of the 10 abnormal gold standard findings, only 4 of them
	Index test +	4	18	22	
	Index test −	0	81	81	

Reference	**Mishra, 1992** [143]				
	Total	4	99	103	were related to valve disease (the rest were cardiomyopathy findings, septal defect findings etc). Hence only these 4 cases were counted as gold standard positive.
Statistical measures	Index text: pathological or possibly pathological murmur Sensitivity: 1.00 Specificity: 0.82 PPV: 0.18 NPV: 1.00 PLR: 5.50 NLR: 0.00 Prevalence on reference standard: 0.04				
Source of funding	Not reported				

Limitations	Risk of bias: serious - unclear duration between index and gold standard test; otherwise no other limitations. Indirectness: serious – pregnant women sub-group may not be representative of the overall population
Comments	

1

Reference	**Panidis 1986[163]**
Study type	Cross-sectional study
Study methodology	Recruitment: consecutive patients referred by primary physician meeting inclusion criteria.
Number of patients	n = 80
Patient characteristics	Age, mean (SD): 38(16) Gender (male to female ratio): 22:58 Ethnicity: Not reported Setting: Secondary care – echocardiography laboratory Country: USA Inclusion criteria: Definite mitral valve prolapse on 2D echocardiography Exclusion criteria: Patients with potential causes of secondary mitral valve prolapse (such as rheumatic mitral valve disease, atrial septal defect, CAD with prior MI, significant pericardial effusion or cardiomyopathy) Chest pain 43/80; shortness of breath 28/80; palpitations 22/80; dizziness/near syncope 12/80; asymptomatic 16/80; AF 2/80
Target condition(s)	Heart valve disease: mitral regurgitation
Index test(s) and reference standard	Index test Systolic murmur on auscultation. Little information provided Reference standard Echocardiography confirmed mitral regurgitation, performed after index tests with blinding. Time between measurement of index test and reference standard: unclear

Reference	**Panidis 1986[163]**				
2×2 table		Reference standard +	Reference standard −	Total	
	Index test +	35	8	43	
	Index test −	20	17	37	
	Total	55	25	80	
Statistical measures	Index text: Systolic murmur Sensitivity: 0.64 Specificity: 0.68 PPV: 0.81 NPV: 0.46 PLR: 1.99 NLR: 0.53 Prevalence on reference standard: 0.69				
Source of funding	Not reported				
Limitations	Risk of bias: Serious: Unclear duration between index and gold standard tests Indirectness: Serious: all patients had mitral valve prolapse, which makes them a sub-group of the population in this review.				
Comments					

1

Reference	**Rahko 1989[171]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: consecutive series of patients who presented for clinical studies at echocardiography laboratory
Number of patients	n = 408
Patient characteristics	Age, mean (SD): 52 years (SD not reported), range 17-94 years Gender (male to female ratio): 210:198 Ethnicity: Setting: echocardiography laboratory Country: USA Inclusion criteria: echocardiogram of sufficient quality to analyse two valves completely; patient available for full auscultatory examination

Reference	**Rahko 1989[171]**				
	Exclusion criteria: not reported No other patient characteristics reported.				
Target condition(s)	Heart valve disease: aortic regurgitation, mitral regurgitation or tricuspid regurgitation				
Index test(s) and reference standard	Index test Regurgitant murmur on auscultation. Auscultation done in a quiet room after completion of the echocardiogram and after had had reviewed the study for technical adequacy. Patients were examined in the supine, left lateral and upright positions and the results were recorded on a standard form and coded for subsequent analysis. Clinical criteria were used to classify murmurs as a regurgitant murmur of one of the four valves, a systolic ejection murmur or a murmur of another type. Murmur intensity was graded on a scale of 1-6. Reference standard Echocardiography confirmed aortic regurgitation, mitral regurgitation or tricuspid regurgitation. Echocardiography was done by two experienced technologists. No special manoeuvres or agents were used to enhance the ability to detect valve regurgitation. Heart examined in multiple parasternal long-axis, parasternal shot-axis, apical and subcostal imaging planes using M-mode, 2D pulsed Doppler and continuous-wave Doppler modalities. Each valve interrogated using pulsed-Doppler mapping starting at the annular plane and moving forward until the full extent of any regurgitant jet was characterised fully. Mitral valve examined in parasternal long-axis, apical 4-chaamber, apical long-axis and apical 2-chamber views. Aortic valve examined in parasternal long-axis, apical 5-chamber and apical long-axis views. Tricuspid valve imaged using parasternal long-axis, parasternal short-axis and apical 4-chamber views. Doppler study was positive for valve regurgitation if an audio and spectral signal clearly present, if the spectral signal displayed turbulent flow and if the spectral signal was present for the duration of >50% of either systole or diastole for a particular valve. Severity of valve regurgitation was graded from 0 to 4+ for all valves but the pulmonary valve: 0, none; 1+, mild; 2+, moderate; 3+, moderate-severe; 4+, severe. For mitral and tricuspid valves, regurgitation was mild if turbulence confined to area within 1 cm of the valve plane, moderate if turbulence was confined to 1-2.5 cm from the valve plane, moderately severe if turbulence detected beyond the moderate zone but within the proximal half of the atrial chamber, and severe if turbulence extended into distal half of the atrial chamber. For the aortic valve, regurgitation was mild if turbulence confined to 1 cm of valve plane, moderate if turbulence was beyond 1 cm but no further than the tip of the anterior mitral leaflet in diastole, moderately severe if turbulence beyond mitral leaflet tip but confined to the proximal half of the left ventricle, and severe if turbulence extended into the distal half of the left ventricle. Each imaging plane graded separately and final regurgitation severity assigned based on view showing most severe regurgitation. Time between measurement of index test and reference standard: not clear, but seem to have been performed quite close together. Analysis of the results of Doppler studies were performed several months after completion and blinded to the results of auscultation.				
2×2 table	3+ or 4+ aortic regurgitation	Reference standard +	Reference standard −	Total	
	Index test +	30	57	87	

Reference	**Rahko 1989[171]**				
	Index test −	3	313	316	
	Total	33	370	403	
	3+ or 4+ mitral regurgitation	Reference standard +	Reference standard −	Total	
	Index test +	33	86	119	
	Index test −	6	269	275	
	Total	39	355	394	
	3+ or 4+ tricuspid regurgitation	Reference standard +	Reference standard −	Total	
	Index test +	13	18	31	
	Index test −	8	277	285	
	Total	21	295	316	
Statistical measures	Index text: regurgitant murmur - AR Sensitivity: 0.91 Specificity: 0.85 PPV: 0.34 NPV: 0.99 PLR: 5.90 NLR: 0.11 Prevalence on reference standard: 0.08 Index text: regurgitant murmur - MR Sensitivity: 0.85 Specificity: 0.76 PPV: 0.28 NPV: 0.98 PLR: 3.49 NLR: 0.20 Prevalence on reference standard: 0.10 Index text: regurgitant murmur - TR Sensitivity: 0.62 Specificity: 0.94				

Reference	Rahko 1989[171]
	PPV: 0.42 NPV: 0.97 PLR: 10.15 NLR: 0.41 Prevalence on reference standard: 0.07
Source of funding	Not reported
Limitations	Risk of bias: very serious – index test performed after reference standard assessed for technical adequacy by same physician so could have affected index test; some attrition and numbers in different tables within the paper do not match so possibly very slight errors in diagnostic accuracy measures Indirectness: serious – population consists of anyone referred for echocardiography, not necessarily suspected heart valve disease but some indication for heart examination
Comments	

1

Reference	Reardon 1996[174]
Study type	Prospective cross-sectional study
Study methodology	Recruitment: acute medical patients >65 years admitted to acute geriatric ward of a hospital during a 5 month period, with a basal systolic murmur detected
Number of patients	n = 148
Patient characteristics	Age, mean (SD): not reported for the subgroup with murmurs investigated in this study Gender (male to female ratio): not reported for the subgroup with murmurs investigated in this study Ethnicity: not reported Setting: acute medical patients admitted to hospital Country: UK Inclusion criteria: acute medical patient admitted to acute geriatric ward of a hospital during 5 month period; basal systolic murmur detected; >65 years of age

Reference	**Reardon 1996[174]**				
	Exclusion criteria: inability to complete echocardiography (patient refusal, patients being too ill to echocardiograph or deaths prior to echocardiography); unsatisfactory quality of a complete echocardiogram No other patient characteristics reported				
Target condition(s)	Heart valve disease: aortic stenosis				
Index test(s) and reference standard	Index test 1. Systolic murmur - all had one to be included in the analysis 2. Systolic murmur + reduced second heart sound 3. Systolic murmur + symptoms (angina – severity unclear) 4. Systolic murmur + symptoms (dyspnoea) 5. Systolic murmur + abnormal ECG (left ventricular hypertrophy) 6. Systolic murmur + abnormal ECG (atrial fibrillation) Patients examined by junior hospital doctor and one of the authors and if a basal systolic murmur was detected, the patient was asked about a history of rheumatic fever, stroke, angina, syncope or dyspnoea. They were also asked if they had known about the murmur previously and when it was first detected. Blood pressure was recorded and on auscultation the intensity of the murmur and their second heart sound was noted. If a palpable thrill was detected, it was recorded as was any radiation to the neck. Any aortic regurgitation that was audible was also noted. A standard 12-lead ECG performed and left ventricular hypertrophy assessed. The presence of atrial fibrillation and haemoglobin levels were also noted. Reference standard Echocardiography confirmed aortic stenosis. Echocardiography performed by one of the authors. Echocardiographs and Doppler studies were used to estimate the gradient across the aortic valve. Presence of calcification in the aortic valve was noted, as was mitral regurgitation and aortic regurgitation. Significant aortic stenosis defined as aortic gradient >30 mmHg Time between measurement of index test and reference standard: unclear				
2×2 tables	Systolic murmur	Reference standard +	Reference standard −	Total	
	Index test +	66	15	81	
	Index test −	0	0	0	
	Total	66	15	81	
	Systolic murmur + reduced	Reference standard +	Reference standard −	Total	

Reference	Reardon 1996[174]				
	second heart sound				
	Index test +	26	0	26	
	Index test −	40	15	55	
	Total	66	15	81	
	Systolic murmur + symptoms (angina)	Reference standard +	Reference standard −	Total	
	Index test +	2	0	2	
	Index test −	64	15	79	
	Total	66	15	81	
	Systolic murmur + symptoms (dyspnoea)	Reference standard +	Reference standard −	Total	
	Index test +	18	0	18	
	Index test −	48	15	63	
	Total	66	15	81	
	Systolic murmur + abnormal ECG (left ventricular hypertrophy)	Reference standard +	Reference standard −	Total	
	Index test +	15	1	16	
	Index test −	51	14	65	
	Total	66	15	81	
	Systolic murmur +	Reference standard +	Reference standard −	Total	

Reference	**Reardon 1996[174]**				
	abnormal ECG (atrial fibrillation)				
	Index test +	10	4	14	
	Index test −	56	11	67	
	Total	66	15	81	
Statistical measures	Index text: systolic murmur - all had one to be included in the analysis Sensitivity: could not calculate as all were index + to be included Specificity: could not calculate as all were index + to be included PPV: 0.81 NPV: could not calculate as all were index + to be included PLR: could not calculate as all were index + to be included NLR: could not calculate as all were index + to be included Prevalence on reference standard: 0.81 Index text: systolic murmur + reduced second heart sound Sensitivity: 0.39 Specificity: 1.00 PPV: 1.00 NPV: 0.27 PLR: could not be calculated as there were no false positives reported NLR: 0.61 Prevalence on reference standard: 0.81 Index text: systolic murmur + symptoms (angina) Sensitivity: 0.03 Specificity: 1.00 PPV: 1.00 NPV: 0.19 PLR: could not be calculated as there were no false positives reported NLR: 0.97 Prevalence on reference standard: 0.81 Index text: systolic murmur + symptoms (dyspnoea) Sensitivity: 0.27 Specificity: 1.00 PPV: 1.00				

Reference	Reardon 1996[174]
	NPV: 0.24 PLR: could not be calculated as there were no false positives reported NLR: 0.73 Prevalence on reference standard: 0.81 Index text: systolic murmur + abnormal ECG (left ventricular hypertrophy) Sensitivity: 0.23 Specificity: 0.93 PPV: 0.94 NPV: 0.22 PLR: 3.41 NLR: 0.83 Prevalence on reference standard: 0.81 Index text: systolic murmur + abnormal ECG (atrial fibrillation) Sensitivity: 0.15 Specificity: 0.73 PPV: 0.71 NPV: 0.16 PLR: 0.51 NLR: 1.16 Prevalence on reference standard: 0.81
Source of funding	Not reported
Limitations	Risk of bias: very serious – no mention of blinding to index test results when reference standard performed; unclear time interval between index test and reference standard being performed Indirectness: none to serious – for the use of murmur alone as a diagnostic feature, all had to have a murmur to be included, which is the index test for this review and limits the use of accuracy data
Comments	

1

Reference	Reichlin 2004[175]
Study type	Prospective cohort study
Study methodology	Recruitment: consecutive adult medical patients presenting to the medical ED
Number of patients	n = 203

Reference	**Reichlin 2004[175]**				
Patient characteristics	Age, mean (SD): 63.7 (22.3) Gender (male to female ratio): 85:118 Ethnicity: Not reported Setting: University Hospital Country: Switzerland Inclusion criteria: Not stated explicitly; appears that all patients recruited from the emergency department needed to have a systolic murmur confirmed by at least 2/3 examiners, and to have had an echo performed. Exclusion criteria: Not stated Other characteristics: bp> 160/100 mmHg 32%; current smoker 25%; chest pain 22%; pulse>100bpm 22%; pathologic CXR 53%; fever 18%; pathologic ECG 61%				
Target condition(s)	Heart valve disease: non-innocent murmurs indicating heart valve disease				
Index test(s) and reference standard	Index test Cardiac auscultation (almost certainly acoustic as not reported to be electronic) by emergency department attending physician. Examiner graded the murmur in loudness from 1 to 6 out of 6 and stated in writing if the murmur was innocent or indicated valvular heart disease. No other details provided. Reference standard 2-colour Doppler transthoracic echocardiography studies using Toshiba sonolayer SSH 140 A, performed independently by 2 experienced cardiologists within 24 hours of ED presentation. Blinded to history and index test results. Explicit criteria for 'valvular heart disease' on echo were: 1) aortic stenosis with maximal valvular pressure gradient >20 mmHg, 2) mitral regurgitation if jet >2mm width at base and crossed valve insertion, 3) other relevant valve abnormalities as defined by current guidelines. Carried out by 2 cardiologists, with a third cardiologist adjudicating if there was discordancy. Time between measurement of index test and reference standard: unclear but <24 hours				
2×2 table		Reference standard +	Reference standard −	Total	In text of paper it is stated that of the 71 true cases, 14 were missed by the examiner (14 false negatives). However that number does not tally with the calculated diagnostic accuracy data
	Index test +	58	41	99	
	Index test −	13	91	104	
	Total	71	132	203	

Reference	**Reichlin 2004[175]**				
					given in the paper, that is all consistent with13 false negatives and 41 false positives. A value of 14 false negatives would change the sensitivity, specificity, PPV and NPV to values that are not those reported in the paper. On the balance of the evidence it was decided to go with the most consistent result.
Statistical measures	Index text: murmur indicating heart valve disease Sensitivity: 0.82 Specificity: 0.69 PPV: 0.59 NPV: 0.88 PLR: 2.63 NLR: 0.27 Prevalence on reference standard: 0.35				
Source of funding	Not reported				
Limitations	Risk of bias: serious: time between index and gold standard tests up to 24 hours; no other limitations: index test before gold standard and gold standard tests blinded from index tests; no attrition reported. Indirectness: serious: only people with murmurs included, but investigator distinguished between innocent murmur and one indicating heart valve disease				
Comments					

1

Reference	**Yamashita 2020[230]**
Study type	Retrospective cohort study
Study methodology	Recruitment: inpatients diagnosed with infective endocarditis at a single hospital in Japan between September 2007 and August 2017
Number of patients	n = 74
Patient characteristics	Age, median (IQR): 66.5 (53.8-76.0) years; ≥60 years old, 68.9% Gender (male to female ratio): 42/32 (56.8%/43.2%) Ethnicity: not reported Setting: Secondary care – Saga University Hospital

Reference	Yamashita 2020[230]
	Country: Japan Inclusion criteria: in-patients diagnosed with “definite infective endocarditis” according to the modified Duke’s clinical criteria or pathological criteria between September 2007 and August 2017 Exclusion criteria: not reported Infective endocarditis hospitalisation: Mean duration of hospitalisation: 41.0 days (range, 28.8-60.5) days Transported by ambulance, 48.6% Nosocomial infection, 5.4% Valvular surgery performed, 47.3% Antibiotics administered prior to blood culture, 43.2% Comorbidities/history: Diabetes mellitus, 20.3% History of prosthetic valve replacement, 14.9% Presence of intravascular device (e.g. pacemaker or central intravenous catheter), 14.9% Administration of steroids or immunosuppressants, 12.2% Chronic dermatological disorder (e.g. atopic dermatitis), 10.8% Haemodialysis, 8.1% Dental disease, 39.2% Acute heart failure, 14.9% Visited dental clinical within past 6 months, 34.9% Invasive dental care within past 6 months, 17.6%
Target condition(s)	Any valve disease: including aortic regurgitation, mitral regurgitation and tricuspid regurgitation. Data reported separately for each of these three types as combined data also includes pulmonary regurgitation, which is excluded from this review.
Index test(s) and reference standard	Index test Audible cardiac murmur – method used to determine this unclear. Assessed at admission and obtained from medical charts. Data said to be available for 73/74 in the report but table suggests data for all 74 – may have assumed the patient without data did not have a murmur. No definition of cardiac murmurs considered to be positive for this murmur (e.g. innocent or pathological types). Reference standard Echocardiography (transthoracic in all and some also receiving transoesophageal) confirmed valve disease. Mild valve disease was defined as that below grade I. Transthoracic echocardiography was performed in all 74 patients and transoesophageal echocardiography

Reference	**Yamashita 2020[230]**				
	was performed in 26 patients (35.1%). For this review, this includes aortic regurgitation, mitral regurgitation and tricuspid regurgitation (pulmonary regurgitation also reported but is excluded from this review). Time between measurement of index test and reference standard: unclear. Cardiac murmur said to be assessed at admission and echocardiography appears to have been performed during the same admission, but timing between the two is unclear.				
2×2 tables	Aortic regurgitation	Reference standard +	Reference standard −	Total	Data includes aortic regurgitation below grade 1 in severity as well as grade 1 and above.
	Index test +	21	24	45	
	Index test −	7	22	29	
	Total	28	46	74	
	Mitral regurgitation	Reference standard +	Reference standard −	Total	Data includes mitral regurgitation below grade 1 in severity as well as grade 1 and above.
	Index test +	31	14	45	
	Index test −	16	13	29	
	Total	47	27	74	
	Tricuspid regurgitation	Reference standard +	Reference standard −	Total	Data includes tricuspid regurgitation below grade 1 in severity as well as grade 1 and above.
	Index test +	13	32	45	
	Index test −	8	21	29	
	Total	21	53	74	
Statistical measures	Index text: audible cardiac murmur – method used to determine this unclear. Aortic regurgitation Sensitivity: 0.75 Specificity: 0.48 PPV: 0.47 NPV: 0.76 PLR: 1.44 NLR: 0.52 Prevalence on reference standard: 0.38				

Reference	**Yamashita 2020[230]**
	Mitral regurgitation Sensitivity: 0.66 Specificity: 0.48 PPV: 0.69 NPV: 0.45 PLR: 1.27 NLR: 0.71 Prevalence on reference standard: 0.64 Tricuspid regurgitation Sensitivity: 0.62 Specificity: 0.40 PPV: 0.29 NPV: 0.72 PLR: 1.03 NLR: 0.96 Prevalence on reference standard: 0.28
Source of funding	Funding not reported.
Limitations	Risk of bias: very serious – definition and method of measuring index text unclear; no mention of blinding to index results when reference standard interpreted; time interval between the index test and reference standard being performed unclear; and some patients received transthoracic and transoesophageal echocardiography while others only received transthoracic echocardiography as the reference test Indirectness: serious – population includes 14.9% with acute heart failure as a complication of the infective endocarditis; and thresholds used to define valve disease on echocardiography not reported
Comments	

D.2 Symptoms and signs indicating direct referral to a specialist

Reference	**Abe 2013[3]**
Study type	Prospective cross-sectional study

Reference	Abe 2013[3]
Study methodology	Recruitment: consecutive patients >20 years of age with a systolic ejection murmur ≥ grade 2 or known aortic stenosis referred for echocardiography
Number of patients	n = 147
Patient characteristics	Age, mean (SD): 74 (10) years Gender (male to female ratio): 55:75 Ethnicity: not reported Setting: those referred for echocardiography – 59%, 16%, 14% and 12% referred from cardiology outpatient department, cardiology ward, non-cardiology outpatient department and non-cardiology ward, respectively. Country: Japan Inclusion criteria: >20 years of age; systolic ejection murmur ≥ grade 2 or known aortic stenosis referred for echocardiography Exclusion criteria: patents with atrial fibrillation; any other significant murmurs louder than the systolic ejection murmur; technical difficulty observing aortic valve cusps on pocket-sized echocardiography or in evaluating aortic valve area using continuity equation with high-end echocardiography; bicuspid aortic valves; any other significant disease leading to systolic ejection murmur such as left ventricular outflow tract obstruction; severe mitral regurgitation or tricuspid regurgitation on pocket echocardiography as holosytolic regurgitant murmurs had been misdiagnosed as systolic ejection murmurs in these patients Hypertension, 81% Dyslipidaemia, 62% Diabetes mellitus, 31% Smoking, 28% Dialysis, 12% Known coronary artery disease, 38% Known aortic stenosis, 35% Some symptoms (dyspnoea, palpitations, angina or syncope), 35% NYHA class III or IV, 5% Mean (SD) body surface area, 1.54 (0.17) m^2

Reference	**Abe 2013[3]**
Target condition(s)	Heart valve disease: **severe** aortic stenosis
Index test(s) and reference standard	Index test Murmur + diminished second heart sound (unclear whether all had a murmur but at least 65% did as this was indication for echocardiography in that proportion – may include some with diminished heart sound and no murmur, which is outside of protocol). Cardiac physical examination in supine position. Performed by experienced cardiologist, blinded to all other patient information. Presence or absence of following physical examination findings assessed: transmission of systolic ejection murmur to the neck; late peaking of systolic ejection murmur; diminished second heart sound; delayed carotid artery upstroke; carotid artery shudder. A diminished second heart sound was considered present if the aortic component of the second heart sound was significantly smaller than the first heart sound at the second or third left intercostal space. During normal breathing, the aortic component of the second heart sound was identified by its temporal relation to the pulmonary component that occurs later in the inspiratory period. Reference standard Echocardiography confirmed **severe** aortic stenosis. Complete examination with high-end echocardiography performed by a level 3 sonographer, who was blinded to all other patient information. LV diastolic dimension, systolic dimension, mass index and ejection fraction were evaluated. Doppler flow data obtained from LV outflow tract region in pulsed-wave mode using multiple transducer positions to obtain maximal velocity. Aortic valve area calculated using continuity equation. Aortic valve area index obtained by dividing aortic valve area by body surface area – indexed aortic valve area <0.60 cm^2 and 0.60 to 0.85 cm^2 considered to indicate severe and moderate aortic stenosis, respectively. Pocked echocardiography use also described, but this was not the reference standard for our review. Time between measurement of index test and reference standard: states that all tests were performed in sequence, but time interval unclear
2×2 table	

	Reference standard +	Reference standard −	Total
Index test +	17	6	23
Index test −	10	97	107
Total	27	103	130

Statistical measures	Index text: murmur + diminished second heart sound Sensitivity: 0.63 Specificity: 0.94 PPV: 0.73 NPV: 0.91 PLR: 10.50 NLR: 0.39 Prevalence on reference standard: 0.21

Reference	**Abe 2013[3]**
Source of funding	Not reported
Limitations	Risk of bias: very serious – some potentially inappropriate exclusions, including those that were misclassified as having systolic ejection murmurs but actually had regurgitant murmurs once reference standard had been performed; though sequentially, time interval between index test and echocardiography unclear Indirectness: serious – population included 35% that had known aortic stenosis before the study, but included in review due to lack of other information regarding a reduced second heart sound
Comments	

1

Reference	**Aggarwal 2014[5]**
Study type	Double blind prospective correlation study
Study methodology	Recruitment: consecutive (first 100 patients with inclusion criteria visiting the clinic)
Number of patients	n = 100
Patient characteristics	Age, mean (SD): 54.6 (sd not calculable) Gender (male to female ratio): 61:39 Ethnicity: Not reported Setting: Cardiology centre of an academic university hospital, in a rural area Country: India Inclusion criteria: Patients advised to undergo echocardiography when visiting the clinic Exclusion criteria: Known pre-existing heart murmurs No other characteristics provided
Target condition(s)	**Significant** valve disease
Index test(s) and reference standard	Index test Detection of murmur using stethoscope and specific software (ZargisCardioscan software) After taking informed consent, the principal investigator, a community medicine physician performed the auscultation of patients' hearts in sitting position. Subsequently, the ZargisCardioscan™ software was used to analyse the heart sounds auscultated by the 3M™ Littmann® Model 3200 stethoscope. The heart auscultation was performed at all four auscultation sites on the chest: aortic area in second intercostal

<table>
<tr><td>Reference</td><td colspan="5">Aggarwal 2014[5]</td></tr>
<tr><td></td><td colspan="5">space on right parasternal line, pulmonary area in second intercostal space on left parasternal line, tricuspid area in fourth intercostal space on left parasternal line and cardiac apex (mitral area) in fifth intercostal space on midclavicular line. The analysis by ZargisCardioscan™ about presence and absence of systolic and/or diastolic murmurs were recorded. Sub-analysis by ZargisCardioscan™ further confirmed whether the auscultated systolic murmur was Class I murmur based on its grade and occurrence-time in cardiac cycle; all auscultated diastolic murmurs were considered Class I murmur based on the American College of Cardiology/American Heart Association (ACC/AHA) Practice Guidelines for the Management of Patients with Valvular Heart Disease that classify murmurs in asymptomatic patients as Class I murmurs if they are diastolic or continuous or holosystolic or late systolic or mid-systolic (grade 3 or higher).

It appears that the index test categories were no murmur (-ve) and murmur [Class 1 and above] (+ve) but this is unclear from the methodological description.

<u>Reference standard</u>
Echocardiography confirmed significant valve disease (significant defined as any stenotic lesion or as anything other than minimal/mild for regurgitation), by blinded cardiologist .

Time between measurement of index test and reference standard: unclear</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4">Results have been extracted to include only significant valvular lesions as positives on gold standard for this review, as it covers severe heart valve disease.</td></tr>
<tr><td></td><td>Index test +</td><td>9</td><td>22</td><td>31</td></tr>
<tr><td></td><td>Index test −</td><td>5</td><td>64</td><td>69</td></tr>
<tr><td></td><td>Total</td><td>14</td><td>86</td><td>100</td></tr>
<tr><td>Statistical measures</td><td colspan="5"><u>Index text:</u> detection of murmur using stethoscope and specific software

Sensitivity: 0.64
Specificity: 0.74
PPV: 0.29
NPV: 0.93
PLR: 2.51
NLR: 0.48
Prevalence on reference standard: 0.14</td></tr>
<tr><td>Source of funding</td><td colspan="5">No funding was received from any agency for carrying out this research work. However, ZargisCardioscan™ software and 3M™ Littmann® Model 3200 stethoscope were provided by Deepak Gupta, MD, Anaesthesiologist, Detroit Medical Center/Wayne State University, Detroit, Michigan, United States from his personally owned equipments' inventory on loan basis (academic / research purposes only) only as a gesture of supporting medical research under the principal investigator at the institution. There was no</td></tr>
</table>

Reference	**Aggarwal 2014[5]**
	competing interest between the authors of this research study.
Limitations	Risk of bias: serious (unclear duration between index and gold standard tests) Indirectness: serious – even mild stenosis was included under the term 'significant' disease, so not all severe valve disease
Comments	

1

Reference	**Aronow 1987[17]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: unselected elderly patients with aortic systolic ejection murmurs in a long-term health care facility
Number of patients	n = 75
Patient characteristics	Age, mean (SD): 83 (8) years (range, 62-100) Gender (male to female ratio): 16:59 Ethnicity: not reported Setting: long-term health care facility Country: USA Inclusion criteria: elderly patients with aortic systolic ejection murmurs who had technically adequate M-mode and 2D echocardiograms of the aortic valve and continuous wave Doppler recordings of the aortic valve. Exclusion criteria: patients with more than mild aortic regurgitation as determined clinically or by Doppler echocardiography; patients with subvalvular stenosis. No other patient characteristics reported.
Target condition(s)	Heart valve disease: **severe** aortic stenosis
Index test(s) and reference standard	Index test Aortic systolic ejection murmur – all had to have one to be included in the study. All patients underwent a cardiovascular examination performed by an experienced cardiologist before interpretation of echocardiograms and Doppler recordings. A systolic ejection murmur heard in the second right intercostal space, down the left sternal border toward the apex or at the apex was classified as aortic systolic ejection murmur.

Reference	**Aronow 1987[17]**
	Reference standard Echocardiography confirmed **severe** aortic stenosis. M-mode and 2D echocardiograms, and continuous wave Doppler measurement of aortic valve flow, were obtained. Valve flow velocities were assessed in multiple views, including apical, suprasternal and right parasternal views. Peak flow velocity across the aortic valve of 1.5 m/s or less was defined as normal. Peak aortic flow velocity 1.6-2.5 m/sec (peak gradient 10-25 mmHg), 2.6-3.5 m/sec (peak gradient 26-49 mmHg) and ≥3.6 m/sec (peak gradient ≥50 mmHg) were defined as mild, moderate and severe aortic stenosis, respectively. Echocardiographic and Doppler studies were interpreted by an experienced echocardiographer without knowledge of the cardiovascular findings. Time between measurement of index test and reference standard: unclear - cardiovascular examination was performed prior to interpretation of echocardiograms and Doppler recordings, but time interval unclear.
2×2 table	

	Reference standard +	Reference standard −	Total
Index test +	4	71	75
Index test −	0	0	0
Total	4	71	75

Statistical measures	Index text: aortic systolic ejection murmur – all had to have one to be included in the study Sensitivity: could not calculate as all were index + to be included Specificity: could not calculate as all were index + to be included PPV: 0.05 NPV: could not calculate as all were index + to be included PLR: could not calculate as all were index + to be included NLR: could not calculate as all were index + to be included Prevalence on reference standard: 0.05
Source of funding	Not reported
Limitations	Risk of bias: serious – time interval between index test and reference standard unclear Indirectness: serious – all had to have a murmur to be included, which is the index test for this review and limits the use of accuracy data
Comments	

Reference	**Aronow 1989[16]**
Study type	Prospective cross-sectional study

Reference	**Aronow 1989[16]**
Study methodology	Recruitment: unselected elderly patients in a long-term health care facility
Number of patients	n = 450
Patient characteristics	Age, mean (SD): 82 (8) years, range 61-100 years Gender (male to female ratio): 114:336 Ethnicity: not reported Setting: long-term health care facility Country: USA Inclusion criteria: had technically adequate M-mode and 2D echocardiograms and pulsed Doppler recordings of the aortic valve Exclusion criteria: not reported. No other characteristics of patients reported.
Target condition(s)	Heart valve disease: **moderate or severe** aortic regurgitation
Index test(s) and reference standard	Index test Murmur of aortic regurgitation. A high frequency decrescendo murmur beginning with A_2 was classified as an aortic regurgitation murmur. Cardiovascular examination was performed by an experienced cardiologist. Reference standard Echocardiography confirmed **moderate or severe** aortic regurgitation. M-mode and 2D echocardiograms and pulsed Doppler recordings of the aortic valve were obtained. Aortic regurgitation was diagnosed when an abnormal, high-velocity turbulent diastolic flow was detected in the left ventricular outflow tract. AR was considered mild when the signal was limited to the first centimetre proximal to the aortic valve, moderate when signal was detected in the left ventricular outflow tract in the area beyond the first centimetre but not beyond the tip of the anterior mitral leaflet, and severe when the abnormal signal persisted to a distance beyond the tip of the anterior mitral leaflet and could be detected in the left ventricle. Echocardiograms and Doppler recordings were interpreted by an experienced echocardiographer.

Reference	**Aronow 1989[16]**
	Time between measurement of index test and reference standard: unclear – all patients underwent a cardiovascular examination by an experienced cardiologist before interpretation of the echocardiograms and Doppler recordings.
2×2 table	

	Reference standard +	Reference standard −	Total
Index test +	70	43	113
Index test −	4	333	337
Total	74	376	450

Statistical measures	Index text: murmur of aortic regurgitation Sensitivity: 0.95 Specificity: 0.89 PPV: 0.62 NPV: 0.99 PLR: 8.27 NLR: 0.06 Prevalence on reference standard: 0.16
Source of funding	Not reported
Limitations	Risk of bias: very serious – no reporting of blinding to index results; time interval between index test and reference standard unclear Indirectness: very serious – population may not necessarily be suspected HVD and may be in long-term health care facility for other reasons; moderate or severe aortic regurgitation grouped together so not all are severe cases.
Comments	

1

Reference	**Aronow 1991[18]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: unselected elderly patients in a long-term health care facility
Number of patients	n = 781
Patient characteristics	Age, mean (SD): 82 (8) years (range, 62-100 years) Gender (male to female ratio): 223:558

Reference	**Aronow 1991[18]**
	Ethnicity: not reported Setting: long-term health care facility Country: USA Inclusion criteria: elderly patients in a long-term health care facility with technical Exclusion criteria: not reported. No other patient characteristics reported.
Target condition(s)	Heart valve disease: **severe** aortic stenosis
Index test(s) and reference standard	Index test Aortic systolic ejection murmur. All patients underwent a cardiovascular examination performed by an experienced cardiologist before interpretation of echocardiograms and Doppler recordings. A systolic ejection murmur heard in the second right intercostal space, down the left sternal border toward the apex or at the apex was classified as aortic systolic ejection murmur. Reference standard Echocardiography confirmed **severe** aortic stenosis. M-mode and 2D echocardiograms, and continuous wave Doppler measurement of aortic valve flow, were obtained. Valve flow velocities were assessed in multiple views, including apical, suprasternal and right parasternal views. Peak flow velocity across the aortic valve of 1.5 m/s or less was defined as normal. Peak aortic flow velocity 1.6-2.5 m/sec (peak gradient 10-25 mmHg), 2.6-3.5 m/sec (peak gradient 26-49 mmHg) and ≥3.6 m/sec (peak gradient ≥50 mmHg) were defined as mild, moderate and severe aortic stenosis, respectively. Echocardiographic and Doppler studies were interpreted by an echocardiographer. Time between measurement of index test and reference standard: unclear - cardiovascular examination was performed prior to interpretation of echocardiograms and Doppler recordings, but time interval unclear.
2×2 table	

	Reference standard +	Reference standard −	Total
Index test +	19	Not reported	Not reported
Index test −	0	Not reported	Not reported
Total	19	762	781

Reference	**Aronow 1991[18]**
Statistical measures	Index text: aortic systolic ejection murmur Sensitivity: 1.00 Specificity: could not calculate as no information regarding number of true negatives or false positives. PPV: could not calculate as no information regarding number of true negatives or false positives. NPV: could not calculate as no information regarding number of true negatives or false positives. PLR: could not calculate as no information regarding number of true negatives or false positives. NLR: could not calculate as no information regarding number of true negatives or false positives. Prevalence on reference standard: 0.02
Source of funding	Not reported.
Limitations	Risk of bias: very serious – no reporting of blinding to index results; time interval between index test and reference standard unclear Indirectness: serious – population may not necessarily be suspected HVD and may be in long-term health care facility for other reasons
Comments	

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2

Reference	**Attenhofer Jost 2000[19]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: consecutive patients referred to echocardiography laboratory because of a systolic murmur of unknown cause and who had not had previous echocardiographic examination
Number of patients	n = 100
Patient characteristics	Age, mean (SD): 58 (22) years (range, 17-92 years) Gender (male to female ratio): 43:57 Ethnicity: not reported Setting: echocardiography laboratory of a hospital Country: Switzerland Inclusion criteria: referred for echocardiography due to systolic murmur of unknown cause; no previous echocardiographic examination Exclusion criteria: not reported

Reference	**Attenhofer Jost 2000[19]**
	No other patient characteristics reported.
Target condition(s)	Heart valve disease: **moderate or severe** aortic stenosis or valvular regurgitation (AR, MR, TR) – reports separately for each type of valve disease
Index test(s) and reference standard	Index test 1. Systolic murmur – all had one to be included in the study 2. Systolic murmur + diminished aortic closure sound (AS only) – given as adjusted odds ratio (diagnostic association) Immediately before echocardiography, patients were examined by two cardiologists blinded to the patient's history, electrocardiogram and other medical data. Clinical examination included estimate of jugular venous pressure, assessment of apical impulse and carotid artery upstroke, and auscultation at rest during quiet respiration, with assessment of heart sounds and murmurs and their radiation. Associated findings, such as thrills and systolic clicks, were noted. The Valsava manoeuvre was done in every patient and other dynamic manoeuvres were added if thought necessary. Characteristics of murmurs were classified at point of maximal intensity. Murmurs were located in aortic area, pulmonic area, base of the heart or apex. Timing and duration of murmurs were classified as early systolic, late systolic or holosystolic. The examiner had to state if the murmur was functional or organic. If thought to be organic, the examiner had to classify the underlying heart disease as significant or insignificant. Significant disease was defined as moderate or severe valvular heart disease, congenital shunts or intraventricular gradients. An isolated valvular lesion was defined if there was no clinical evidence of other types of heart disease – for the purposes of this review, information only on valve disease was extracted. Reference standard Echocardiography confirmed **moderate or severe** aortic stenosis or valvular regurgitation (AR, MR, TR). Transthoracic 2D and Doppler echocardiography in the left supine position. Valvular regurgitation was graded as trivial, mild, moderate or severe based on a combination of factors, especially the vena contracta for the atrioventricular valves and the ratio of the regurgitant jet height to the outflow tract height for the semilunar valves. Aortic stenosis was classified as severe (mean systolic gradient ≥50 mmHg or aortic valve area ≤0.8 cm^2), moderate (mean systolic gradient 30-49 mmHg or aortic valve area 0.8-1.0 cm^2), mild (mean systolic gradient 10-29 mmHg or aortic valve area 1.1-1.9 cm^2) or trivial (mean systolic gradient <10 mmHg or aortic valve area ≥2.0 cm^2, but with thickening of bicuspid or tricuspid aortic valve). An intraventricular gradient (left or right ventricle) was defined as a peak systolic gradient ≥10 mmHg at rest or with Valsalva within the left ventricular outflow tract or midventricular by continuous-wave Doppler with the typical shape (left convex) and the peak velocity occurring late in systole. Time between measurement of index test and reference standard: index test was performed immediately before echocardiography.
2×2 tables	

Systolic murmur - AS	Reference standard +	Reference standard −	Total
Index test +	15	85	100
Index test −	0	0	0
Total	15	85	100

Reference	**Attenhofer Jost 2000[19]**				
	Systolic murmur - AR	Reference standard +	Reference standard −	Total	
	Index test +	6	94	100	
	Index test −	0	0	0	
	Total	6	94	100	
	Systolic murmur - MR	Reference standard +	Reference standard −	Total	
	Index test +	6	94	100	
	Index test −	0	0	0	
	Total	6	94	100	
	Systolic murmur - TR	Reference standard +	Reference standard −	Total	
	Index test +	2	98	100	
	Index test −	0	0	0	
	Total	2	98	100	
Statistical measures	Index text: Moderate or severe AS - systolic murmur – all had one to be included in the study Sensitivity: could not calculate as all were index + to be included Specificity: could not calculate as all were index + to be included PPV: 0.15 NPV: could not calculate as all were index + to be included PLR: could not calculate as all were index + to be included NLR: could not calculate as all were index + to be included Prevalence on reference standard: 0.15 Index text: Moderate or severe AR - systolic murmur – all had one to be included in the study Sensitivity: could not calculate as all were index + to be included Specificity: could not calculate as all were index + to be included PPV: 0.06 NPV: could not calculate as all were index + to be included PLR: could not calculate as all were index + to be included				

Reference	Attenhofer Jost 2000[19]
	NLR: could not calculate as all were index + to be included Prevalence on reference standard: 0.06 Index text: Moderate or severe MR - systolic murmur Sensitivity: could not calculate as all were index + to be included Specificity: could not calculate as all were index + to be included PPV: 0.06 NPV: could not calculate as all were index + to be included PLR: could not calculate as all were index + to be included NLR: could not calculate as all were index + to be included Prevalence on reference standard: 0.06 Index text: Moderate or severe TR – systolic murmur Sensitivity: could not calculate as all were index + to be included Specificity: could not calculate as all were index + to be included PPV: 0.02 NPV: could not calculate as all were index + to be included PLR: could not calculate as all were index + to be included NLR: could not calculate as all were index + to be included Prevalence on reference standard: 0.02 Index text: Moderate or severe AS – systolic murmur + absent/diminished aortic closure sound No diagnostic accuracy data reported, but instead provides odds ratio obtained from multivariate analysis: **OR 14 (2.5-79.0)**. Clear that MVA performed, but list of factors adjusted for is unclear. Interpretation is that absent/diminished aortic closure sound is a predictor of moderate or severe AS.
Source of funding	Not reported
Limitations	Risk of bias: serious – certain manoeuvres may have been used for auscultation in some patients and not others Indirectness: serious to very serious – all had to have a murmur to be included, which is the index test for this review and limits the use of accuracy data; moderate or severe valve disease grouped together so not all are severe cases.
Comments	

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Reference	**Decoodt 1990[51]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: patients with idiopathic mitral valve prolapse confirmed on echocardiography during 1 year period. Unclear if consecutive.
Number of patients	n = 100
Patient characteristics	Age, mean (SD): 53.5 years (SD not reported), range 18-83 years Gender (male to female ratio): 37:63 Ethnicity: not reported Setting: referred to a cardiology laboratory for echocardiography Country: Belgium Inclusion criteria: patients with idiopathic mitral valve prolapse – criteria based on M-mode and 2D echocardiography findings: late or holosystolic posterior movement of the valve of >2 mm below the CD line of coaptation of the mitral leaflets during systole (M-mode) and mitral coaptation of type 2-3. Prolapse criteria based on an apical view were avoided. Exclusion criteria: concomitant major cardiac abnormalities (hypertrophic cardiomyopathy, major aortic insufficiency, uncorrected atrial septal defect, surgically corrected atrial septal defects, corrected patent ductus arteriosus, dilated cardiomyopathy, ischaemic cardiopathies requiring transluminal dilatation and prior myocardial infarction). No other patient characteristics reported.
Target condition(s)	Heart valve disease: **severe** mitral regurgitation
Index test(s) and reference standard	Index test Systolic murmur – this included some with early systolic murmurs, late systolic murmurs and holosystolic murmurs. Auscultatory features were reported by another observer than the person performing the echocardiography. Reference standard Echocardiography confirmed **severe** mitral regurgitation. A 2.5 Mhz multi-element transducer was used for colour flow mapping study. Pulse repetition frequencies of 4, 6 or 8 KHz were available. Diagnostic range of 12 or 15 cm routinely used for mitral valve prolapse. When mitral regurgitation was found, the grade, direction of the jet and systolic timing were determined. For the grade, regurgitant flow on left atrial area ratio was obtained in the plane at which it appeared greatest. Same Doppler colour gain setting algorithm was used. Mitral regurgitation was classified as mild (ratio <20%), moderate (ratio 20-40%) and severe (ratio >40%).

Reference	**Decoodt 1990[51]**
	Time between measurement of index test and reference standard: unclear
2×2 table	

	Reference standard +	Reference standard −	Total
Index test +	10	42	52
Index test −	0	48	48
Total	10	90	100

Statistical measures	Index text: systolic murmur Sensitivity: 1.0 Specificity: 0.53 PPV: 0.19 NPV: 1.0 PLR: 2.14 NLR: could not be calculated as there were no false negatives (sensitivity was 1.0) Prevalence on reference standard: 0.10
Source of funding	Not reported
Limitations	Risk of bias: very serious – some of those with major concomitant heart abnormalities excluded; no blinding mentioned for performance of index test and reference standard; unclear time interval between index test and references standard Indirectness: serious – already had confirmed mitral valve prolapse on echocardiography, may differ to the more general population with suspected HVD based on a murmur with/without symptoms only and no confirmation of existing structural problems
Comments	

1

Reference	**Etchells 1998[63]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: consecutive hospital inpatients who had been referred for echocardiography by their treating physicians during September 1994 (reliability study) and September-October 1995 (accuracy study)
Number of patients	n = 162 (n=124 in accuracy study and 38 in reliability study)
Patient characteristics	Age, median (IQR): 68 (60-75) years (for n=123 patients) Gender (male to female ratio): 71:52 (for n=123 patients) Ethnicity: not reported

Reference	Etchells 1998[63]
	Setting: inpatients of hospital referred from treating physician – majority referred from general medical wards, providing secondary level generalist care, and cardiology wards, which provide tertiary/quaternary-level cardiology care Country: Canada Inclusion criteria: consecutive hospital inpatients who had been referred for echocardiography by their treating physicians Exclusion criteria: age <50 years; already discharged from hospital; admitted to the coronary care or intensive care unit; unstable angina within 48 hours; myocardial infarction within 6 weeks; recovering from cardiothoracic surgery; previous valve replacement; severe dyspnoea at rest; unable to provide informed consent. Patient history: Angina, 53% Congestive heart failure, 63% Myocardial infarction, 56% No patients had exertional syncope Functional NYHA class: I, 56%; II, 21%; III, 16%; IV, 7% 95% patients had at least one cardinal symptom or sign of aortic stenosis (history of angina, congestive heart failure or systolic murmur)
Target condition(s)	Heart valve disease: **moderate or severe** aortic stenosis
Index test(s) and reference standard	Index test Systolic murmur on physical examination. The examination included assessment of carotid artery volume and upstroke, second heart sound intensity, murmur intensity, location, and radiation. For the accuracy study, there were two study physicians: a third-year resident and a staff general internist. Each physician also obtained a focused clinical history from the patient prior to the physical examination. For the purposes of this review, only information related to the accuracy study has been extracted. All study physicians were unaware of the participants' diagnoses, echocardiographic data, and results of the examinations by other study physicians. Reference standard Echocardiography confirmed **moderate or severe** aortic stenosis. Echocardiograms were analysed by echocardiographers unaware of the results of the study physician examinations. Moderate to severe aortic stenosis was defined as either a calculated aortic valve area of 1.2 cm^2 or less, or a peak instantaneous transvalvular gradient of 25 mmHg or greater. An independent echocardiographer reviewed a subset (20%) of echocardiograms, with perfect agreement regarding the presence of moderate or severe aortic stenosis. Time between measurement of index test and reference standard: unclear

Reference	**Etchells 1998[63]**				
2×2 table	Resident	Reference standard +	Reference standard −	Total	
	Index test +	14	56	70	
	Index test −	0	42	42	
	Total	14	98	112	
Statistical measures	**Resident** Index text: systolic murmur Sensitivity: 1.0 - reported in study Specificity: 0.43 - reported in study PPV: 0.20 - calculated NPV: 1.00 - calculated PLR: 1.75 – PLR reported in the study (95% CI): 1.60 (1.20, 2.00) NLR: could not be calculated as no false negatives – NLR reported in the study (95% CI): 0.00 (0.00, 0.71) Prevalence on reference standard: 0.125 – calculated				
Source of funding	Not reported				
Limitations	Risk of bias: serious - ~10% not included in the analysis as both index test and reference standard couldn't be completed (main reasons for this were patient being discharged or unavailability of study physician) and unclear time interval between index test and reference standard Indirectness: serious – target condition was moderate or severe aortic stenosis, so is not limited to severe valve disease				
Comments					

1

2

Reference	**Iversen 2008[89]**
Study type	Retrospective review of data from patients included in the Copenhagen Hospital Heart Failure study (CHHF)
Study methodology	Recruitment: CHHF included all patients ≥40 years of age admitted to medical or surgical departments of local hospital between 1st April 1998 and 31st March 1999. Consecutive patients that agreed to participate.
Number of patients	n = 2977

Reference	Iversen 2008[89]
Patient characteristics	Age, mean (SD): 70.6 (14.3) years Gender (male to female ratio): 1215: 1762 Ethnicity: not reported Setting: inpatients of hospital Country: Denmark Inclusion criteria: CHHF included all patients ≥40 years of age admitted to medical or surgical departments of local hospital between 1st April 1998 and 31st March 1999; patients examined by both auscultation and echocardiography included in the current study; Exclusion criteria: not reported. Diabetes, 12.4% Previous myocardial infarction, 11.1% Previous lung disease, 18.0% Previous congestive heart failure, 12.5% Anaemia, 8.3% Mean (SD) ejection fraction, 59.1 (10.9)% Elevated NT-pro-BNP, 33.5%
Target condition(s)	Heart valve disease: **moderate or severe** aortic stenosis, aortic regurgitation, mitral stenosis or mitral regurgitation
Index test(s) and reference standard	Index test Murmur on physical examination. Within 24 h of hospital admission, patients underwent structured, comprehensive clinical examination including heart auscultation to determine whether a murmur was present. Structured medical history with focus on heart-related symptoms, without knowledge of the echocardiography results, was recorded. Information about hypertension, diabetes, dyslipidaemia, NYHA class, previous myocardial infarction, previously diagnosed congestive heart failure, angina pectoris, lung and liver disease obtained from self-reported medical history. Reference standard Echocardiography confirmed **moderate or severe** valve disease. Echocardiography was performed by one of two experience doctors. Echocardiograms performed without knowledge of results of clinical examination and patient history. Valvular disease was diagnosed on basis of echocardiographic evidence of valvular pathology in conjunction with structural changes of the left atrium of ventricle. Aortic stenosis defined as peak gradient >50 mmHg and left ventricular septum or posterior wall thicker than 11 mm on continuous-wave Doppler. Aortic regurgitation defined as presence of a moderate or severe regurgitant jet in the colour-flow echocardiogram as judged

Reference	**Iversen 2008[89]**
	visually by the examiner in conjunction with dilatation of the left ventricle (end diastolic diameter >60 mm for women and >63 mm for men). Mitral regurgitation defined as presence of moderate or severe regurgitant jet visually judged by examiner in conjunction with dilatation of the left atrium to >45 mm. Mitral stenosis defined at the discretion of the examiner. Time between measurement of index test and reference standard: unclear

2×2 table

Murmur	Reference standard +	Reference standard −	Total
Index test +	117	532	649
Index test −	28	2300	2328
Total	145	2832	2977

Statistical measures	Index text: murmur Sensitivity: 0.81 Specificity: 0.81 PPV: 0.18 NPV: 0.99 PLR: 4.30 NLR: 0.24 Prevalence on reference standard: 0.05
Source of funding	Study supported by unrestricted research grants from AstraZeneca (Copenhagen, Denmark), Roche (Basel, Switzerland) and the Danish Heart Foundation (Copenhagen, Denmark)
Limitations	Risk of bias: serious – time interval between index test and references standard unclear Indirectness: very serious – population not necessarily suspected heart valve disease as includes anyone hospitalised >40 years of age; target condition defined as moderate or severe valve disease, so not limited to severe disease
Comments	

1

Reference	**Labovitz 1985[109]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: consecutive series of patients with mitral annular calcium on echocardiography
Number of patients	n = 51
Patient characteristics	Age, mean (SD): 70 years (SD not reported), range 54-91 years Gender (male to female ratio): 21:30

Reference	**Labovitz 1985[109]**				
	Ethnicity: not reported Setting: those that were originally referred for echocardiography Country: USA Inclusion criteria: echocardiographic diagnosis of mitral annular calcium – mitral annular calcium was diagnosed by echocardiography findings using standard criteria. Exclusion criteria: patients with calcified mitral valve leaflets Most patients were referred for symptoms of chest pain, congestive heart failure, dyspnoea or evaluation of a cardiac murmur. Hypertension, n=10 Coronary artery disease, n=7 Aortic valve replacement, n=4 Aortic stenosis, n=2 Cardiomyopathy, n=1 Chronic renal failure, n=3 Other patients had no associated cardiovascular abnormalities				
Target condition(s)	Heart valve disease: **moderate or severe** mitral regurgitation				
Index test(s) and reference standard	Index test Apical systolic murmur detected on clinical examination. No further details about the methods used. Reference standard Echocardiography confirmed **moderate or severe** mitral regurgitation. M-mode and 2D echocardiography and cardiac Doppler studies were performed. Mitral annular calcium was diagnosed by echocardiography findings using standard criteria. Doppler studies in pulsed or continuous- wave mode. Transmitral flow was sampled by placing the transducer at the cardiac apex and aligning the Doppler cursor parallel to flow using the 2D image from the 4-chamber view. The valve was scanned in continuous mode to determine maximal velocities of left ventricular inflow as well as to detect the presence of mitral regurgitation. Mitral regurgitation was defined as a holosystolic jet moving away from the transducer with velocity of >2 m/sec. If mitral regurgitation was present, it was quantified in pulsed mode and the extent of the regurgitant jet was mapped in the left atrium. Systolic flow away from the transducer seen 2 cm or more into the left atrium was considered significant (moderate to severe) mitral regurgitation. Jets that were <2 cm into the left atrium were considered mild mitral regurgitation. The mitral valve orifice area was determined by the pressure half-time method. Time between measurement of index test and reference standard: unclear				
2×2 table		Reference standard +	Reference standard −	Total	

Reference	**Labovitz 1985[109]**				
	Index test +	11	17	28	
	Index test −	6	17	23	
	Total	17	34	51	
Statistical measures	Index text: apical systolic murmur Sensitivity: 0.65 Specificity: 0.50 PPV: 0.39 NPV: 0.74 PLR: 1.29 NLR: 0.71 Prevalence on reference standard: 0.33				
Source of funding	Not reported				
Limitations	Risk of bias: very serious –murmur assessment poorly reported and unclear whether reference standard was performed with blinding to index test results; time interval between index test and reference standard unclear Indirectness: very serious – some already had known valve disease or had a prosthetic valve replacement (<10%) and all had echocardiography confirmed mitral annular calcium, which may mean the population differs from a more general one where heart valve disease may be suspected based on a murmur with/without symptoms; target condition in this case is moderate or severe disease, so not limited to severe valve disease				
Comments					

1

Reference	**Limacher 1985[117]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: pregnant women referred to echocardiography laboratory for evaluation of cardiac murmurs. Unclear if consecutive.
Number of patients	n = 81
Patient characteristics	Age, mean (SD): 22 (4) years Gender (male to female ratio): 0:81 – all were women Ethnicity: not reported

Reference	**Limacher 1985[117]**
	Setting: those referred for echocardiography Country: USA Inclusion criteria: pregnant women referred to echocardiography laboratory for evaluation of cardiac murmurs Exclusion criteria: history of murmur or congenital or rheumatic heart disease Pregnant women were in the 11th to 39th week of gestation (average, 30 weeks)
Target condition(s)	Heart valve disease: **severe** tricuspid regurgitation
Index test(s) and reference standard	Index test Murmur – all had one to be included in the study. Murmurs detected by the referring physician were described as early to midsystolic, best heard at the left sternal border, of grade I or II intensity. Reference standard Echocardiography confirmed **severe** tricuspid regurgitation. M-mode and 2D echocardiography were performed using standard views (parasternal long- and short-axis, apical 4-chamber, apical 2-chamber and subcostal). In the apical 4-chamber view, measurements of right atrial length and width were made at end-systole and the widest right ventricular diameter was measured at end-diastole. Tricuspid annular diameter was measured in the apical 4-chamber view during early diastole. Doppler studies performed with sampling in multiple views proximal and distal to all 3 valves and along the atrial and ventricular septae. Tricuspid regurgitation was diagnosed by holosystolic spectral dispersion of blood flow velocities (turbulence) with or without respiratory variation and by the presence of the typical harsh quality of the audio signal in systole. Definition of severe tricuspid regurgitation not provided. Time between measurement of index test and reference standard: unclear
2×2 table	

	Reference standard +	Reference standard −	Total
Index test +	0	81	81
Index test −	0	0	0
Total	0	81	81

Reference	**Limacher 1985[117]**
Statistical measures	Index text: murmur Sensitivity: could not be calculated as there were none with severe TR in the study Specificity: could not be calculated as none were negatives for murmur PPV: could not be calculated as there were none with severe TR in the study NPV: could not be calculated as none were negatives for murmur PLR: could not be calculated as there were none with severe TR in the study NLR: could not be calculated as none were negatives for murmur Prevalence on reference standard: 0.00
Source of funding	Not reported
Limitations	Risk of bias: very serious – some potentially inappropriate exclusions (those with a history of murmur and rheumatic/congenital heart disease); unclear whether blinded to index results when reference standard performed; time interval between index test and reference standard unclear Indirectness: very serious – all had to have a murmur to be included, which is the index test for this review and limits the use of accuracy data; no definition of severe tricuspid regurgitation provided.
Comments	

1

2

Reference	**Loperfido 1986[121]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: consecutive patients with myocardial infarction diagnosed 1-3 months before at coronary care unit on basis of chest pain, electrocardiogram and increase and decrease of creatine kinase-MB fraction
Number of patients	n = 72
Patient characteristics	Age, mean (SD): 53 (14) years, range 31-70 years Gender (male to female ratio): 62: 10 Ethnicity: not reported Setting: echocardiography performed in those who had had myocardial infarction 1-3 months prior Country: Italy

Reference	**Loperfido 1986[121]**
	Inclusion criteria: patients with myocardial infarction diagnosed 1-3 months before at coronary care unit on basis of chest pain, electrocardiogram and increase and decrease of creatine kinase-MB fraction; 2D echocardiography performed during acute myocardial infarction had excluded mitral leaflet abnormalities such as prolapse, vegetation or fibrosis Exclusion criteria: patients in clinical unstable condition at the time of Doppler study; complete bundle branch block; technically inadequate Doppler or echocardiographic studies Electrocardiogram: • Anterior myocardial infarction, n=42 • Inferior myocardial infarction, n=30
Target condition(s)	Heart valve disease: **grade 3+ (moderate-severe or severe)** mitral regurgitation
Index test(s) and reference standard	Index test Systolic murmur. Cardiac auscultation was done at the time of Doppler examination with the patient in the left lateral decubitus position. An apical holosystolic or late systolic murmur was considered indicative of mitral regurgitation. A midsystolic murmur loudest at the apex was considered suggestive of mitral regurgitation. Reference standard Echocardiography confirmed **grade 3+ (moderate-severe or severe)** mitral regurgitation. Doppler was performed at discharge (34±8 days following myocardial infarction) in 33 patients and during follow-up (101±6 days following myocardial infarction) in 39 patients. In 15 patients a Doppler study was obtained either at discharge or during follow-up. To assess mitral regurgitation, systolic turbulence was mapped within the left atrium using parasternal and apical approaches with the patient in the left lateral decubitus position. Mitral regurgitation diagnosed by presence of a high-pitched, whistling audio signal and confirmed by recording left atrial holosystolic turbulence in 5 consecutive cycles, excluding premature ventricular contractions. In the apical approach, care was taken to exclude the left ventricular outflow signal. Mitral regurgitation was semi-quantitatively graded according to extension of systolic turbulence below the mitral plane: 1+, up to 1 cm below the valve; 2+, up to half the superoinferior diameter of left atrium; and 3+, turbulence spreading even further. Time between measurement of index test and reference standard: not clear, but state auscultation was performed at the time of Doppler examination so possibly short time interval between them.

2×2 table

	Reference standard +	Reference standard −	Total
Index test +	2	14	16
Index test −	2	54	56
Total	4	68	72

Reference	**Loperfido 1986[121]**
Statistical measures	Index text: systolic murmur Sensitivity: 0.50 Specificity: 0.79 PPV: 0.13 NPV: 0.96 PLR: 2.43 NLR: 0.63 Prevalence on reference standard: 0.06
Source of funding	Not reported
Limitations	Risk of bias: serious – unclear whether index test or reference standard performed first and no mention of any blinding to the results of the other Indirectness: serious – population is those previously admitted for acute myocardial infarction so may not necessarily have been suspicion of heart valve disease, but rather assessing its onset after myocardial infarction
Comments	

1

Reference	**McClelland 2020[131]**
Study type	Cohort, possibly retrospective
Study methodology	Recruitment: consecutive patients ≥18 years referred for initial transthoracic echocardiography imaging with a heart murmur at single centre. Unclear time period.
Number of patients	n = 350
Patient characteristics	Age, mean (no SD reported): 62.3 years Gender (male to female ratio): 126/224 (36%/64%) Ethnicity: not reported Setting: referred for transthoracic echocardiography at University of Chicago Medicine. Of these, 86% were reported to be outpatients. Country: USA Inclusion criteria: aged ≥18 years and referred for transthoracic echocardiography due to a heart murmur being present Exclusion criteria: not reported

Reference	**McClelland 2020[131]**				
	No other patient characteristics reported				
Target condition(s)	Heart valve disease: severe heart valve disease. Unclear which types of valve disease were included under severe valve disease, but report states moderate or severe cases of aortic regurgitation, mitral regurgitation, tricuspid regurgitation and aortic stenosis were identified.				
Index test(s) and reference standard	Index test Heart murmur – method used to determine this unclear. Murmur appears to have been detected elsewhere and a referral for echocardiography at this centre then set up. Types of murmurs included unclear. Reference standard Transthoracic echocardiography confirmed severe valve disease. Unclear definition of severe valve disease. Study reports that 4% of those included had severe valve disease detected on echocardiography. While the types of valve disease these severe cases included were unclear, the report states moderate or severe cases of aortic regurgitation, mitral regurgitation, tricuspid regurgitation and aortic stenosis were identified. Unclear whether other types (e.g. mitral stenosis) were searched for but no cases identified. Threshold used for severe valve disease is unclear. Time between measurement of index test and reference standard: unclear. Cardiac murmur appears to have been assessed elsewhere initially and then a referral for echocardiography at this centre set up.				
2×2 table	Severe valve disease	Reference standard +	Reference standard −	Total	Study reports that severe valve disease was identified in 4% of those in the study.
	Index test +	14	336	350	
	Index test −	0	0	0	
	Total	14	336	350	
Statistical measures	Index text: heart murmur – method used to determine this unclear. Severe valve disease Sensitivity: could not calculate as all were index + to be included Specificity: could not calculate as all were index + to be included PPV: 0.04 NPV: could not calculate as all were index + to be included PLR: could not calculate as all were index + to be included NLR: could not calculate as all were index + to be included Prevalence on reference standard: 0.04				
Source of funding	Funding not reported.				
Limitations	Risk of bias: very serious – definition and method of measuring index text unclear; no mention of blinding to index results when reference standard interpreted; and time interval between the index test and reference standard being performed unclear				

Reference	**McClelland 2020[131]**
	Indirectness: very serious – all had to have a murmur to be included, which is the index test for this review and limits the use of accuracy data; and definition of severe valve disease unclear (e.g. thresholds used not reported)
Comments	

1

2

Reference	**McGee 2010[132]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: convenience sample of non-intensive care unit patients undergoing echocardiography during their hospital stay between 2001 and 2006
Number of patients	n = 376
Patient characteristics	Age, mean (SD): 69 (12) years, range 22-94 years (reported for the number assessed during the time period and includes those excluded for various reasons) Gender (male to female ratio): 399:10 (reported for the number assessed during the time period and includes those excluded for various reasons) Ethnicity: not reported Setting: hospitalised patients referred for echocardiography Country: USA Inclusion criteria: hospitalised non-intensive care unit patients undergoing echocardiography during their hospital stay between 2001 and 2006 Exclusion criteria: those with diastolic or systolic/diastolic murmurs; lacking complete echocardiogram Indications for echocardiography: assessment for structural heart disease, 59%; progression of pre-existing valvular disease, 16%; source of arterial emboli, 8%; suspected endocarditis, 7%; suspected pericardial disease, 2%. Only 7% of echocardiograms were to diagnosed unexplained murmurs.
Target condition(s)	Heart valve disease: **severe (Vmax ≥4.0 m/sec)** aortic stenosis, **moderate or severe** mitral regurgitation or **moderate or severe** tricuspid regurgitation

Reference	**McGee 2010[132]**				
Index test(s) and reference standard	Index test 1. Systolic heart murmur 2. Broad apical-based systolic murmur + absent second heart sound With the exception of 14 cases, author unaware of patient diagnosis, indication for echocardiography or echocardiography results. Author recorded patient vital signs, arterial and venous pulsations, precordial pulsations, heart tones (first, second, third, fourth, and extra heart sounds and their characteristics) and murmurs (systolic, diastolic or both). Examination of the arteries, veins and precordium was performed prior to auscultation. The anterior chest from apex to clavicles was examined and radiation of murmurs completely described. Most patients examined in three positions (supine, left lateral decubitus and upright positions), but reported findings only refer to those in supine position. Murmurs defined as continuous sounds persisting during inspiration and expiration, though intensity could vary during respiratory cycle. Continuous sounds that completely disappeared during inspiration or expiration were termed 'rubs'. All murmurs characterised using onomatopoeia and conventional grading. Reference standard Echocardiography confirmed **severe (Vmax ≥4.0 m/sec)** aortic stenosis, **moderate or severe** mitral regurgitation or **moderate or severe** tricuspid regurgitation. All echocardiograms were interpreted by a cardiologist independent from bedside examination. Aortic stenosis was defined as peak aortic velocity ≥2.5 m/sec, with mild, moderate and severe aortic stenosis defined as peak aortic velocity 2.5-2.9 m/sec, 3.0-3.9 m/sec and ≥4.0 m/sec, respectively. Mitral regurgitation and tricuspid regurgitation were also assessed by echocardiography, but was only significant if moderate or severe regurgitation detected. No definition of this provided. No description of how mitral and tricuspid regurgitation confirmed on echocardiography. Time between measurement of index test and reference standard: unclear				
2×2 table	Systolic heart murmur – severe AS	Reference standard +	Reference standard −	Total	
	Index test +	26	191	217	
	Index test −	0	150	150	
	Total	26	341	367	
	Systolic heart murmur – moderate or severe MR	Reference standard +	Reference standard −	Total	
	Index test +	60	161	221	
	Index test −	14	141	155	
	Total	74	302	376	

Reference	**McGee 2010[132]**				
	Broad apical-based systolic murmur + absent second heart sound – moderate or severe MR	Reference standard +	Reference standard −	Total	
	Index test +	Not reported	Not reported	22	
	Index test −	Not reported	Not reported	354	
	Total	73	303	376	
	Systolic heart murmur – moderate or severe TR	Reference standard +	Reference standard −	Total	
	Index test +	47	174	221	
	Index test −	18	137	155	
	Total	65	311	376	
Statistical measures	Index text: systolic heart murmur – severe AS Sensitivity: 1.00 Specificity: 0.44 PPV: 0.12 NPV: 1.0 PLR: 1.79 NLR: could not be calculated as there were no false negatives reported Prevalence on reference standard: 0.07 Index text: systolic heart murmur – moderate or severe MR Sensitivity: 0.81 Specificity: 0.47 PPV: 0.27 NPV: 0.91				

Reference	McGee 2010[132]
	PLR: 1.52 NLR: 0.41 Prevalence on reference standard: 0.20 Index text: broad apical-based systolic murmur + absent second heart sound – moderate or severe MR Sensitivity: could not be calculated Specificity: could not be calculated PPV: could not be calculated NPV: could not be calculated PLR (95% CI): 0.2 (0, 1.5) – reported in study. NLR(95% CI): not reported in study Prevalence on reference standard: 0.20 Index text: systolic heart murmur – moderate or severe TR Sensitivity: 0.72 Specificity: 0.44 PPV: 0.21 NPV: 0.88 PLR: 1.29 NLR: 0.63 Prevalence on reference standard: 0.17
Source of funding	Not reported Reported to be no financial or personal relationships that could have biased the study
Limitations	Risk of bias: very serious – potentially inappropriate exclusions (those with diastolic murmurs or systolic/diastolic murmurs); unclear time interval between index test and reference standard being performed Indirectness: serious-very serious – not necessarily all suspected heart valve disease as some referred for echocardiography for other reasons, including 16% for evaluation of pre-existing heart valve disease; for mitral and tricuspid regurgitation, moderate and severe cases combined and no definition of what was considered to be moderate or worse
Comments	

1

Reference	McKillop 1991[134]
Study type	Prospective cross-sectional study
Study methodology	Recruitment: Recruitment was from among both general medical and geriatric inpatients and outpatients and from attenders at a geriatric day hospital. Consecutive patients with ejection systolic murmurs of any grade as judged by attending medical staff were recruited regardless of medical symptoms.

Reference	**McKillop 1991[134]**
Number of patients	n = 35 (39 recruited but 4 not analysed due to poor quality Doppler echography)
Patient characteristics	Age, mean (range): 77 (65-96) Gender (male to female ratio): Not reported Ethnicity: not reported Setting: General medical and geriatric inpatients and outpatients and from attenders at a geriatric day hospital. Country: UK Inclusion criteria: Ejection systolic murmurs of any grade as judged by attending medical staff Exclusion criteria: Overt cardiac failure; those unable to cooperate with echocardiography No other information on patient characteristics given.
Target condition(s)	Heart valve disease: aortic stenosis or mitral regurgitation
Index test(s) and reference standard	Index test Systolic ejection murmur – all had to have one to be included in study. Patients were assessed by a cardiologist and by a geriatrician. Grade of murmur, quality of the aortic second sound (reduced, normal, or increased), the presence or absence of aortic regurgitation, and finally a verdict on the presence or absence of significant aortic stenosis were recorded independently by the two clinicians, along with blood pressure and pulse pressure. Reference standard Echocardiography confirmed aortic stenosis or mitral regurgitation. Echocardiograms were recorded on VHS videotape and analysed later for valvular abnormalities (aortic stenosis or aortic regurgitation), aortic valve calcification and cusp separation on 2D and aortic valve gradient in systole and the presence of aortic regurgitation on Doppler. All echocardiographic and Doppler data was averaged over 3 cardiac cycles. No reporting of blinding. Doppler gradients of 30 mmHg were regarded as representing significant stenosis and those under 20 mmHg as not significant. Definition of significant mitral regurgitation not provided, but may include moderate and severe disease. Time between measurement of index test and reference standard: unclear

2×2 table

	Reference standard +	Reference standard −	Total
Index test +	13	22	35
Index test −	0	0	0
Total	13	22	35

Reference	**McKillop 1991[134]**
Statistical measures	Index text: systolic ejection murmur Sensitivity: could not calculate as all were index + to be included Specificity: could not calculate as all were index + to be included PPV: 0.37 NPV: could not calculate as all were index + to be included PLR: could not calculate as all were index + to be included NLR: could not calculate as all were index + to be included Prevalence on reference standard: 0.37
Source of funding	Not reported
Limitations	Risk of bias: very serious: no reporting of blinding; unclear duration between index and gold standard test; attrition of >10% which may have been of patients whose index tests would be systematically different to the average. Indirectness: very serious: all had to have a murmur to be included, which is the index test for this review and limits the use of accuracy data; threshold of >30 mmHg aortic valve gradient used for significant aortic stenosis, which may include moderate as well as severe valve disease (similarly, only 'significant' mitral regurgitation reported and definition unclear)
Comments	

1

Reference	**Panidis 1986[163]**
Study type	Cross-sectional study
Study methodology	Recruitment: consecutive patients referred by primary physician meeting inclusion criteria.
Number of patients	n = 80
Patient characteristics	Age, mean (SD): 38(16) Gender (male to female ratio): 22:58 Ethnicity: Not reported Setting: Secondary care – echocardiography laboratory Country: USA Inclusion criteria: Definite mitral valve prolapse on 2D echocardiography

Reference	**Panidis 1986**[163]
	Exclusion criteria: Patients with potential causes of secondary mitral valve prolapse (such as rheumatic mitral valve disease, atrial septal defect, CAD with prior MI, significant pericardial effusion or cardiomyopathy) Chest pain 43/80; shortness of breath 28/80; palpitations 22/80; dizziness/near syncope 12/80; asymptomatic 16/80; AF 2/80
Target condition(s)	Heart valve disease: **moderate or severe** mitral regurgitation
Index test(s) and reference standard	Index test Systolic murmur on auscultation. Little information provided Reference standard Echocardiography confirmed **moderate or severe** mitral regurgitation, performed after index tests with blinding. Mitral regurgitation was defined as minimal or mild when the regurgitant spectral signal was recorded just below the mitral valve or less than 2 cm from the mitral valve into the left atrium. Significant mitral regurgitation was considered to be present when the regurgitant jet was recorded in the mid- (moderate) or distal (severe) left atrial cavity. Time between measurement of index test and reference standard: unclear
2×2 table	
Statistical measures	Index text: Systolic murmur Sensitivity: 1.00 Specificity: 0.51 PPV: 0.19 NPV: 1.00 PLR: 2.06 NLR: could not calculate as there were no false negatives reported Prevalence on reference standard: 0.10
Source of funding	Not reported
Limitations	Risk of bias: Serious: Unclear duration between index and gold standard tests Indirectness: Serious: already had confirmed mitral valve prolapse on echocardiography, may differ to the more general population with suspected HVD based on a murmur with/without symptoms only and no confirmation of existing structural problems
Comments	

	Reference standard +	Reference standard −	Total
Index test +	8	35	43
Index test −	0	37	37
Total	8	72	80

1

Reference	**Rahko 1989[171]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: consecutive series of patients who presented for clinical studies at echocardiography laboratory
Number of patients	n = 408
Patient characteristics	Age, mean (SD): 52 years (SD not reported), range 17-94 years Gender (male to female ratio): 210:198 Ethnicity: Setting: echocardiography laboratory Country: USA Inclusion criteria: echocardiogram of sufficient quality to analyse two valves completely; patient available for full auscultatory examination Exclusion criteria: not reported No other patient characteristics reported.
Target condition(s)	Heart valve disease: **3+ or 4+ (moderate-severe or severe)** aortic regurgitation, mitral regurgitation or tricuspid regurgitation
Index test(s) and reference standard	Index test Regurgitant murmur on auscultation. Auscultation done in a quiet room after completion of the echocardiogram and after had had reviewed the study for technical adequacy. Patients were examined in the supine, left lateral and upright positions and the results were recorded on a standard form and coded for subsequent analysis. Clinical criteria were used to classify murmurs as a regurgitant murmur of one of the four valves, a systolic ejection murmur or a murmur of another type. Murmur intensity was graded on a scale of 1-6. Reference standard Echocardiography confirmed **3+ or 4+ (moderate-severe or severe)** aortic regurgitation, mitral regurgitation or tricuspid regurgitation. Echocardiography was done by two experienced technologists. No special manoeuvres or agents were used to enhance the ability to detect valve regurgitation. Heart examined in multiple parasternal long-axis, parasternal shot-axis, apical and subcostal imaging planes using M-mode, 2D pulsed Doppler and continuous-wave Doppler modalities. Each valve interrogated using pulsed-Doppler mapping starting at the annular plane and moving forward until the full extent of any regurgitant jet was characterised fully. Mitral valve examined in parasternal long-axis, apical 4-chaamber, apical long-axis and apical 2-chamber views. Aortic valve examined in parasternal long-axis, apical 5-chamber and apical long-axis views. Tricuspid valve imaged using parasternal long-axis, parasternal short-axis and apical 4-

Reference	**Rahko 1989[171]**				
	chamber views. Doppler study was positive for valve regurgitation if an audio and spectral signal clearly present, if the spectral signal displayed turbulent flow and if the spectral signal was present for the duration of >50% of either systole or diastole for a particular valve. Severity of valve regurgitation was graded from 0 to 4+ for all valves but the pulmonary valve: 0, none; 1+, mild; 2+, moderate; 3+, moderate-severe; 4+, severe. For mitral and tricuspid valves, regurgitation was mild if turbulence confined to area within 1 cm of the valve plane, moderate if turbulence was confined to 1-2.5 cm from the valve plane, moderately severe if turbulence detected beyond the moderate zone but within the proximal half of the atrial chamber, and severe if turbulence extended into distal half of the atrial chamber. For the aortic valve, regurgitation was mild if turbulence confined to 1 cm of valve plane, moderate if turbulence was beyond 1 cm but no further than the tip of the anterior mitral leaflet in diastole, moderately severe if turbulence beyond mitral leaflet tip but confined to the proximal half of the left ventricle, and severe if turbulence extended into the distal half of the left ventricle. Each imaging plane graded separately and final regurgitation severity assigned based on view showing most severe regurgitation. Time between measurement of index test and reference standard: not clear, but seem to have been performed quite close together. Analysis of the results of Doppler studies were performed several months after completion and blinded to the results of auscultation.				
2×2 table	3+ or 4+ aortic regurgitation	Reference standard +	Reference standard −	Total	
	Index test +	30	57	87	
	Index test −	3	313	316	
	Total	33	370	403	
	3+ or 4+ mitral regurgitation	Reference standard +	Reference standard −	Total	
	Index test +	33	86	119	
	Index test −	6	269	275	
	Total	39	355	394	
	3+ or 4+ tricuspid regurgitation	Reference standard +	Reference standard −	Total	
	Index test +	13	18	31	
	Index test −	8	277	285	
	Total	21	295	316	

Reference	Rahko 1989[171]
Statistical measures	Index text: regurgitant murmur - 3+ or 4+ AR Sensitivity: 0.91 Specificity: 0.85 PPV: 0.34 NPV: 0.99 PLR: 5.90 NLR: 0.11 Prevalence on reference standard: 0.08 Index text: regurgitant murmur - 3+ or 4+ MR Sensitivity: 0.85 Specificity: 0.76 PPV: 0.28 NPV: 0.98 PLR: 3.49 NLR: 0.20 Prevalence on reference standard: 0.10 Index text: regurgitant murmur - 3+ or 4+ TR Sensitivity: 0.62 Specificity: 0.94 PPV: 0.42 NPV: 0.97 PLR: 10.15 NLR: 0.41 Prevalence on reference standard: 0.07
Source of funding	Not reported
Limitations	Risk of bias: very serious – index test performed after reference standard assessed for technical adequacy by same physician so could have affected index test; some attrition and numbers in different tables within the paper do not match so possibly very slight errors in diagnostic accuracy measures Indirectness: serious – population consists of anyone referred for echocardiography, not necessarily suspected heart valve disease but some indication for heart examination
Comments	

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Reference	**Reardon 1996[174]**
Study type	Prospective cross-sectional study
Study methodology	Recruitment: acute medical patients >65 years admitted to acute geriatric ward of a hospital during a 5 month period, with a basal systolic murmur detected
Number of patients	n = 148
Patient characteristics	Age, mean (SD): not reported for the subgroup with murmurs investigated in this study Gender (male to female ratio): not reported for the subgroup with murmurs investigated in this study Ethnicity: not reported Setting: acute medical patients admitted to hospital Country: UK Inclusion criteria: acute medical patient admitted to acute geriatric ward of a hospital during 5 month period; basal systolic murmur detected; >65 years of age Exclusion criteria: inability to complete echocardiography (patient refusal, patients being too ill to echocardiograph or deaths prior to echocardiography); unsatisfactory quality of a complete echocardiogram No other patient characteristics reported
Target condition(s)	Heart valve disease: **significant (gradient >30 mmHg)** aortic stenosis
Index test(s) and reference standard	Index test 1. Systolic murmur - all had one to be included in the analysis 2. Systolic murmur + reduced second heart sound 3. Systolic murmur + symptoms (angina – severity unclear) 4. Systolic murmur + symptoms (dyspnoea) 5. Systolic murmur + abnormal ECG (left ventricular hypertrophy) 6. Systolic murmur + abnormal ECG (atrial fibrillation) Patients examined by junior hospital doctor and one of the authors and if a basal systolic murmur was detected, the patient was asked about a history of rheumatic fever, stroke, angina, syncope or dyspnoea. They were also asked if they had known about the murmur previously and when it was first detected. Blood pressure was recorded and on auscultation the intensity of the murmur and their second heart sound was noted. If a palpable thrill was detected, it was recorded as was any radiation to the neck. Any aortic regurgitation that was

Reference	Reardon 1996[174]				
	audible was also noted. A standard 12-lead ECG performed and left ventricular hypertrophy assessed. The presence of atrial fibrillation and haemoglobin levels were also noted. Reference standard Echocardiography confirmed **significant (gradient >30 mmHg)** aortic stenosis. Echocardiography performed by one of the authors. Echocardiographs and Doppler studies were used to estimate the gradient across the aortic valve. Presence of calcification in the aortic valve was noted, as was mitral regurgitation and aortic regurgitation. Significant aortic stenosis defined as aortic gradient >30 mmHg Time between measurement of index test and reference standard: unclear				
2×2 tables	Systolic murmur	Reference standard +	Reference standard −	Total	
	Index test +	21	60	81	
	Index test −	0	0	0	
	Total	21	60	81	
	Systolic murmur + reduced second heart sound	Reference standard +	Reference standard −	Total	
	Index test +	19	7	26	
	Index test −	2	53	55	
	Total	21	60	81	
	Systolic murmur + symptoms (syncope)	Reference standard +	Reference standard −	Total	
	Index test +	3	2	5	
	Index test −	18	58	76	
	Total	21	60	81	

Reference	Reardon 1996[174]				
	Systolic murmur + symptoms (angina)	Reference standard +	Reference standard −	Total	
	Index test +	0	2	2	
	Index test −	21	58	79	
	Total	21	60	81	
	Systolic murmur + symptoms (dyspnoea)	Reference standard +	Reference standard −	Total	
	Index test +	9	9	18	
	Index test −	12	51	63	
	Total	21	60	81	
	Systolic murmur + abnormal ECG (left ventricular hypertrophy)	Reference standard +	Reference standard −	Total	
	Index test +	8	8	16	
	Index test −	13	52	65	
	Total	21	60	81	
	Systolic murmur + abnormal ECG (atrial fibrillation)	Reference standard +	Reference standard −	Total	
	Index test +	3	11	14	
	Index test −	18	49	67	
	Total	21	60	81	

Reference	Reardon 1996[174]
Statistical measures	Index text: systolic murmur - all had one to be included in the analysis Sensitivity: could not calculate as all were index + to be included Specificity: could not calculate as all were index + to be included PPV: 0.26 NPV: could not calculate as all were index + to be included PLR: could not calculate as all were index + to be included NLR: could not calculate as all were index + to be included Prevalence on reference standard: 0.26 Index text: systolic murmur + reduced second heart sound Sensitivity: 0.90 Specificity: 0.88 PPV: 0.73 NPV: 0.96 PLR: 7.76 NLR: 0.11 Prevalence on reference standard: 0.26 Index text: systolic murmur + symptoms (syncope) Sensitivity: 0.14 Specificity: 0.97 PPV: 0.60 NPV: 0.76 PLR: 4.29 NLR: 0.89 Prevalence on reference standard: 0.26 Index text: systolic murmur + symptoms (angina) Sensitivity: 0.00 Specificity: 0.97 PPV: could not calculate as there were no true positives reported on index test NPV: 0.73 PLR: could not be calculated as there were true positives reported on index test NLR: 1.03 Prevalence on reference standard: 0.26

Reference	Reardon 1996[174]
	Index text: systolic murmur + symptoms (dyspnoea) Sensitivity: 0.43 Specificity: 0.85 PPV: 0.50 NPV: 0.81 PLR: 2.86 NLR: 0.67 Prevalence on reference standard: 0.26 Index text: systolic murmur + abnormal ECG (left ventricular hypertrophy) Sensitivity: 0.38 Specificity: 0.87 PPV: 0.50 NPV: 0.80 PLR: 2.86 NLR: 0.71 Prevalence on reference standard: 0.26 Index text: systolic murmur + abnormal ECG (atrial fibrillation) Sensitivity: 0.14 Specificity: 0.82 PPV: 0.21 NPV: 0.73 PLR: 0.78 NLR: 1.05 Prevalence on reference standard: 0.26
Source of funding	Not reported
Limitations	Risk of bias: very serious – no mention of blinding to index test results when reference standard performed; unclear time interval between index test and reference standard being performed Indirectness: serious to very serious – for the use of murmur alone as a diagnostic feature, all had to have a murmur to be included, which is the index test for this review and limits the use of accuracy data; definition of significant aortic stenosis is aortic valve gradient >30 mmHg, which may include moderate disease as well as severe disease
Comments	

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Reference	**Sarasin 2002[191]**
Study type	Prospective cohort study
Study methodology	Recruitment: patients were identified from daily visits to the departments (emergency department and inpatient services) by one of the investigators
Number of patients	n = 20 (subgroup of larger population within the study)
Patient characteristics	Age, mean (SD): not reported for the subgroup with suspected AS Gender (male to female ratio): not reported for the subgroup with suspected AS Ethnicity: not reported Setting: emergency department and the inpatient services of a hospital Country: Switzerland Inclusion criteria: >18 years of age; presenting with syncope as main complaint (defined as sudden transient loss of consciousness with an inability to maintain postural tone, and with spontaneous recovery). Exclusion criteria: not reported No other patient characteristics reported for the subgroup with suspected AS
Target condition(s)	Heart valve disease: **severe** aortic stenosis
Index test(s) and reference standard	Index test Murmur + syncope on exertion with/without chest pain – all within this subgroup had these features. Note that this is a much small proportion of the total population in the study, but is the population that is relevant to this review. Research physician collected baseline data on clinical and physical examination, current drug treatment, cardiovascular risk factors, and the results of all the tests. At admission, the patients were questioned using a standardised protocol recording the number of syncopal episodes, precipitating factors, and the occurrence and duration of prodromal and recovery symptoms, such as those suggesting aortic stenosis (aortic systolic murmur and syncope on exertion with or without chest pain), seizures, stroke or transient ischaemic attacks, and pulmonary embolism. Reference standard

Reference	**Sarasin 2002[191]**				
	Echocardiography confirmed **severe** aortic stenosis. Transthoracic echocardiographic examination was performed with cross-sectional Doppler ultrasound. Severe aortic stenosis was defied as mean aortic gradient >50mmHg and valvular area < 0.9 cm^2. Time between measurement of index test and reference standard: unclear				
2×2 table		Reference standard +	Reference standard −	Total	
	Index test +	8	12	20	
	Index test −	0	0	0	
	Total	8	12	20	
Statistical measures	Index text: murmur + syncope on exertion with/without chest pain – all within this subgroup had these features Sensitivity: could not calculate as all were index + to be included Specificity: could not calculate as all were index + to be included PPV: 0.40 NPV: could not calculate as all were index + to be included PLR: could not calculate as all were index + to be included NLR: could not calculate as all were index + to be included Prevalence on reference standard: 0.40				
Source of funding	Supported by grant 32-49853.96 from the Swiss National Research Foundation.				
Limitations	Risk of bias: very serious – unclear whether blinded to index test results when reference standard performed; unclear time interval between index test and reference standard Indirectness: serious – only a small subgroup of the study was those with suspected aortic stenosis, all based on having the same indication (murmur + syncope on exertion with/without chest pain) – when used as the index test for this review it limits the use of accuracy data				
Comments					

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Appendix E – Forest plots

E.1 Symptoms and signs for echocardiography referral

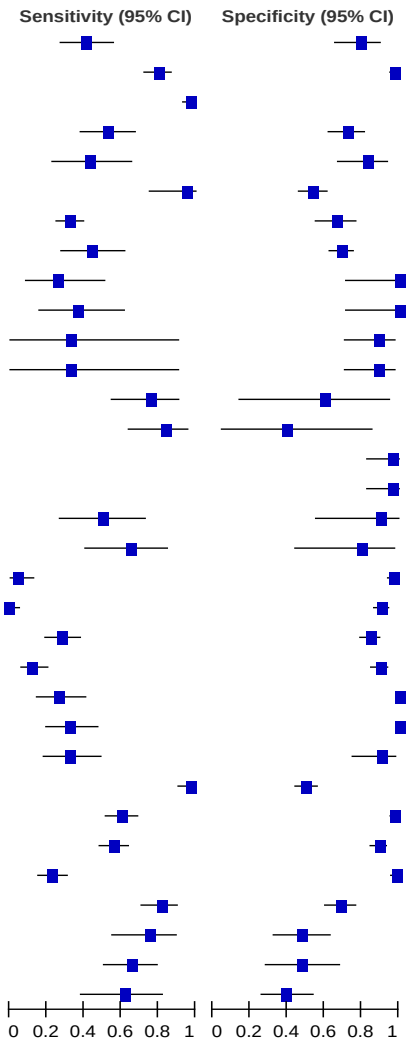
E.1.1 Coupled sensitivity and specificity forest plots

E.1.1.1 Reference standard – echocardiography

Note that sensitivity and specificity for studies where all had participants had to have a murmur to be included could not be calculated due to them all being index test positive. Positive predictive values have instead been reported for these studies to provide information on the proportion with a murmur that may actually go on to have echocardiography-confirmed heart valve disease.

Figure 2: Sensitivity and specificity of murmur for heart valve disease in various settings in populations with various indications for assessment

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Aggarwal 2014 any HVD	21	10	30	39	0.41 [0.28, 0.56]	0.80 [0.66, 0.90]
Aronow 1989 AR	105	8	26	311	0.80 [0.72, 0.87]	0.97 [0.95, 0.99]
Aronow 1991 AS	138	0	4	0	0.97 [0.93, 0.99]	Not estimable
Barron 1988 MR or TR	26	25	23	66	0.53 [0.38, 0.67]	0.73 [0.62, 0.81]
Barzilai 1988 MR	10	6	13	30	0.43 [0.23, 0.66]	0.83 [0.67, 0.94]
Baur 2006 AS/R, MS/R	19	82	1	96	0.95 [0.75, 1.00]	0.54 [0.46, 0.61]
Gardezi 2018 - mild (sclerosis or mild regurg)	55	27	115	54	0.32 [0.25, 0.40]	0.67 [0.55, 0.77]
Gardezi 2018 - signif. (mod regurg or mild steno)	16	66	20	149	0.44 [0.28, 0.62]	0.69 [0.63, 0.75]
Kalinauskiene 2019 AR aco	5	0	14	11	0.26 [0.09, 0.51]	1.00 [0.72, 1.00]
Kalinauskiene 2019 AR electronic	7	0	12	11	0.37 [0.16, 0.62]	1.00 [0.72, 1.00]
Kalinauskiene 2019 AS aco	1	3	2	24	0.33 [0.01, 0.91]	0.89 [0.71, 0.98]
Kalinauskiene 2019 AS electronic	1	3	2	24	0.33 [0.01, 0.91]	0.89 [0.71, 0.98]
Kalinauskiene 2019 MR aco	19	2	6	3	0.76 [0.55, 0.91]	0.60 [0.15, 0.95]
Kalinauskiene 2019 MR electronic	21	3	4	2	0.84 [0.64, 0.95]	0.40 [0.05, 0.85]
Kalinauskiene 2019 MS aco	0	1	0	29	Not estimable	0.97 [0.83, 1.00]
Kalinauskiene 2019 MS electronic	0	1	0	29	Not estimable	0.97 [0.83, 1.00]
Kalinauskiene 2019 TR aco	10	1	10	9	0.50 [0.27, 0.73]	0.90 [0.55, 1.00]
Kalinauskiene 2019 TR electronic	13	2	7	8	0.65 [0.41, 0.85]	0.80 [0.44, 0.97]
Kinney 1988 AR junior assistant residents	3	7	60	224	0.05 [0.01, 0.13]	0.97 [0.94, 0.99]
Kinney 1988 AR senior assistant residents	0	21	63	210	0.00 [0.00, 0.06]	0.91 [0.86, 0.94]
Kinney 1988 MR junior assistant residents	27	30	69	168	0.28 [0.19, 0.38]	0.85 [0.79, 0.90]
Kinney 1988 MR senior assistant residents	12	20	84	178	0.13 [0.07, 0.21]	0.90 [0.85, 0.94]
Kinney 1988 TR junior assistant residents	13	0	36	245	0.27 [0.15, 0.41]	1.00 [0.99, 1.00]
Kinney 1988 TR senior assistant residents	16	0	33	245	0.33 [0.20, 0.48]	1.00 [0.99, 1.00]
Loperfido 1986 MR	13	3	27	29	0.33 [0.19, 0.49]	0.91 [0.75, 0.98]
McGee 2010 AS	71	146	2	148	0.97 [0.90, 1.00]	0.50 [0.44, 0.56]
Rahko 1989 AR	81	6	53	263	0.60 [0.52, 0.69]	0.98 [0.95, 0.99]
Rahko 1989 MR	95	24	74	201	0.56 [0.48, 0.64]	0.89 [0.85, 0.93]
Rahko 1989 TR	28	3	95	190	0.23 [0.16, 0.31]	0.98 [0.96, 1.00]
Reichlin 2004 any HVD	58	41	13	91	0.82 [0.71, 0.90]	0.69 [0.60, 0.77]
Yamashita 2020 AR	21	24	7	22	0.75 [0.55, 0.89]	0.48 [0.33, 0.63]
Yamashita 2020 MR	31	14	16	13	0.66 [0.51, 0.79]	0.48 [0.29, 0.68]
Yamashita 2020 TR	13	32	8	21	0.62 [0.38, 0.82]	0.40 [0.26, 0.54]

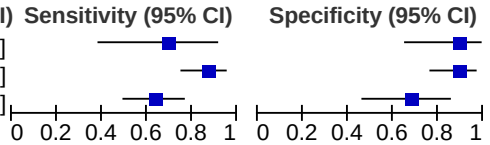


Please see individual clinical evidence tables for details concerning the population and setting of each of the above studies as these were quite broad for some studies and varied between the studies. Note that different studies detected different types of valve disease, which is indicated above in the figure.

1

Figure 3: Sensitivity and specificity of murmur for heart valve disease in populations with MVP that has already been diagnosed by echocardiography

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chin 1992 MR	9	2	4	16	0.69 [0.39, 0.91]	0.89 [0.65, 0.99]
Decoodt 1990 - MR	47	5	7	41	0.87 [0.75, 0.95]	0.89 [0.76, 0.96]
Panidis 1986 MR	35	8	20	17	0.64 [0.50, 0.76]	0.68 [0.46, 0.85]

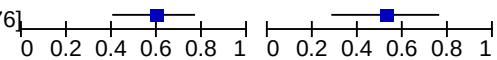


These were populations that had already had previously diagnosed mitral valve prolapse on echocardiography. All studies in this figure detected mitral regurgitation.

2

Figure 4: Sensitivity and specificity of murmur for heart valve disease in a population with mitral annular calcium observed by echocardiography

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Labovitz 1985 MR or MS	19	9	13	10	0.59 [0.41, 0.76]	0.53 [0.29, 0.76]

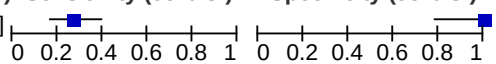


Participants in this study had previously had mitral annular calcium identified by echocardiography. This study detected mitral regurgitation or stenosis.

3

Figure 5: Sensitivity and specificity of murmur + dyspnoea for heart valve disease in acute medical patients admitted to geriatric ward of hospital

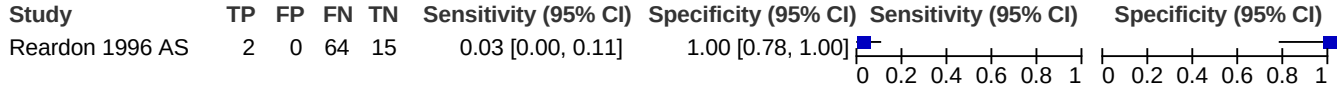
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Reardon 1996 AS	18	0	48	15	0.27 [0.17, 0.40]	1.00 [0.78, 1.00]



Participants in this study were >65 years of age and had to have systolic murmurs to be included. This study detected the presence of aortic stenosis.

1

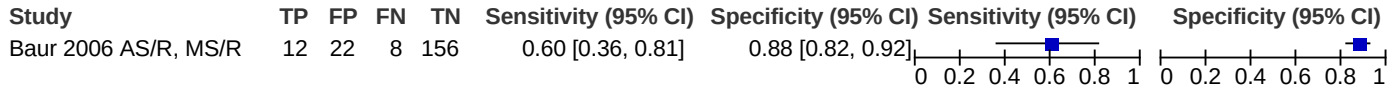
Figure 6: Sensitivity and specificity of murmur + angina for heart valve disease in acute medical patients admitted to geriatric ward of hospital



Participants in this study were >65 years of age and had to have systolic murmurs to be included. This study detected the presence of aortic stenosis.

2

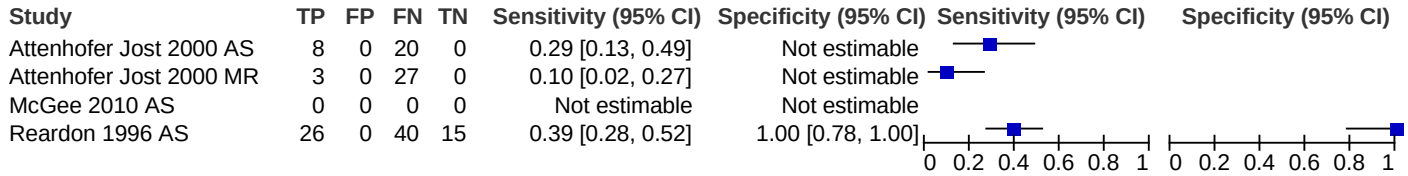
Figure 7: Sensitivity and specificity of murmur + other indication (dyspnoea, peripheral oedema or other) for heart valve disease in patients with suspected heart failure of heart valve disease)



Participants in this study were those with suspected heart failure or valve disease (restricted to: dyspnoea, cardiac murmur or peripheral oedema of unexplained origin). This study detected the presence of aortic stenosis, aortic regurgitation, mitral stenosis or mitral regurgitation.

3

Figure 8: Sensitivity and specificity of systolic murmur + absent/reduced second heart sound for heart valve disease



Please see individual clinical evidence tables for details concerning the population and setting of each of the above studies as these were quite broad for some studies and varied between the studies. Note that for McGee, the study reported a PLR value but did not provide sufficient information to calculate sensitivity or specificity. For Attenhofer Jost, sufficient information was available to calculate sensitivity, but there was insufficient data to calculate specificity.

1

Figure 9: Sensitivity and specificity of a non-flow murmur for heart valve disease in pregnant women

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Mishra 1992 any valve	4	18	0	81	1.00 [0.40, 1.00]	0.82 [0.73, 0.89]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

This study reported any valve abnormalities, and those included under our protocol were extracted as being reference standard positive. Any murmur that was considered to be pathological or possibly pathological by the auscultator in this study was considered to be index test positive, and flow murmurs were considered to be index test negative.

2

Figure 10: Sensitivity and specificity of murmur + abnormal ECG (left ventricular hypertrophy) for heart valve disease in acute medical patients admitted to geriatric ward of hospital

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Reardon 1996 AS	15	1	51	14	0.23 [0.13, 0.35]	0.93 [0.68, 1.00]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Participants in this study were >65 years of age and had to have systolic murmurs to be included. This study detected the presence of aortic stenosis.

3

Figure 11: Sensitivity and specificity of murmur + abnormal ECG (atrial fibrillation) for heart valve disease in acute medical patients admitted to geriatric ward of hospital

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Reardon 1996 AS	10	4	56	11	0.15 [0.08, 0.26]	0.73 [0.45, 0.92]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Participants in this study were >65 years of age and had to have systolic murmurs to be included. This study detected the presence of aortic stenosis.

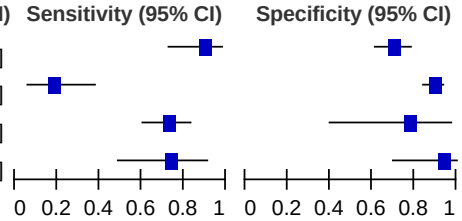
4

E.1.112 Reference standard – cardiac catheterisation

2 Note that sensitivity and specificity for studies where all had participants had to have a murmur to be included could not be calculated due to them
3 all being index test positive. Positive predictive values have instead been reported for these studies to provide information on the proportion with a
4 murmur that may actually go on to have echocardiography-confirmed heart valve disease.

Figure 12: Sensitivity and specificity of murmur for heart valve disease in various settings in populations with various indications for assessment

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Breisblatt 1988 MR	26	36	3	85	0.90 [0.73, 0.98]	0.70 [0.61, 0.78]
Lehmann 1992 MR	5	19	22	160	0.19 [0.06, 0.38]	0.89 [0.84, 0.93]
Meyers 1982 AR	48	2	18	7	0.73 [0.60, 0.83]	0.78 [0.40, 0.97]
Meyers 1986 MR	14	1	5	15	0.74 [0.49, 0.91]	0.94 [0.70, 1.00]



Please see individual clinical evidence tables for details concerning the population and setting of each of the above studies as these were quite broad for some studies and varied between the studies. Note that the type of murmur varied between studies.

5

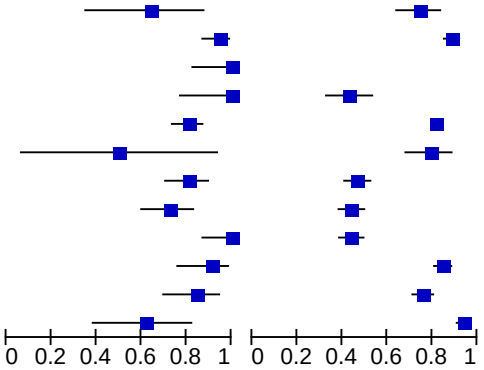
E.2 Symptoms and signs for direct referral to a specialist

E.2.1 Coupled sensitivity and specificity forest plots

Note that sensitivity and specificity from one study where all had participants had a murmur + syncope on exertion with or without chest pain to be included in the analysis could not be calculated due to them all being index test positive. Positive predictive values have instead been reported for this study to provide information on the proportion with this indication that may actually go on to have echocardiography-confirmed heart valve disease.

Figure 13: Sensitivity and specificity of murmur for moderate or severe heart valve disease in various settings in populations with various indications for assessment

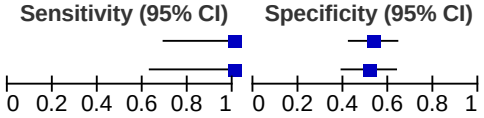
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Aggarwal 2014 significant HVD	9	22	5	64	0.64 [0.35, 0.87]	0.74 [0.64, 0.83]
Aronow 1989 moderate or severe AR	70	43	4	333	0.95 [0.87, 0.99]	0.89 [0.85, 0.92]
Aronow 1991 severe AS	19	0	0	0	1.00 [0.82, 1.00]	Not estimable
Etchells 1998 moderate or severe MR	14	56	0	42	1.00 [0.77, 1.00]	0.43 [0.33, 0.53]
Iversen 2008 moderate or severe AS, AR, MS or MR	117	532	28	2300	0.81 [0.73, 0.87]	0.81 [0.80, 0.83]
Loperfido 1986 grade 3+ MR	2	14	2	54	0.50 [0.07, 0.93]	0.79 [0.68, 0.88]
McGee 2010 moderate or severe MR	60	161	14	141	0.81 [0.70, 0.89]	0.47 [0.41, 0.52]
McGee 2010 moderate or severe TR	47	174	18	137	0.72 [0.60, 0.83]	0.44 [0.38, 0.50]
McGee 2010 severe AS	26	191	0	150	1.00 [0.87, 1.00]	0.44 [0.39, 0.49]
Rahko 1989 3+ or 4+ AR	30	57	3	313	0.91 [0.76, 0.98]	0.85 [0.81, 0.88]
Rahko 1989 3+ or 4+ MR	33	86	6	269	0.85 [0.69, 0.94]	0.76 [0.71, 0.80]
Rahko 1989 3+ or 4+ TR	13	18	8	277	0.62 [0.38, 0.82]	0.94 [0.91, 0.96]



Please see individual clinical evidence tables for details concerning the population and setting of each of the above studies as these were quite broad for some studies and varied between the studies. Note that different studies detected different types of valve disease, which is indicated above in the figure. Note that for some data was available for only severe disease, whereas others reported moderate or severe disease.

Figure 14: Sensitivity and specificity of murmur for moderate or severe heart valve disease in populations with MVP that has already been diagnosed by echocardiography

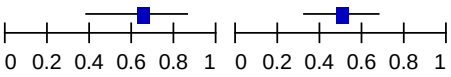
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Decoodt 1990 - severe MR	10	42	0	48	1.00 [0.69, 1.00]	0.53 [0.43, 0.64]
Panidis 1986 moderate or severe MR	8	35	0	37	1.00 [0.63, 1.00]	0.51 [0.39, 0.63]



These were populations that had already had previously diagnosed mitral valve prolapse on echocardiography. All studies in this figure detected mitral regurgitation.

Figure 15: Sensitivity and specificity of murmur for moderate or severe heart valve disease in a population with mitral annular calcium observed by echocardiography

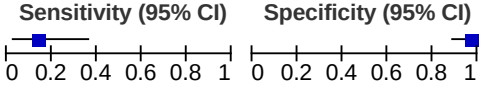
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Labovitz 1985 moderate or severe MR	11	17	6	17	0.65 [0.38, 0.86]	0.50 [0.32, 0.68]



Participants in this study had previously had mitral annular calcium identified by echocardiography. For moderate or severe disease, data were only provided for mitral regurgitation and not mitral stenosis.

Figure 16: Sensitivity and specificity of murmur + syncope for significant heart valve disease in acute medical patients admitted to geriatric ward of hospital

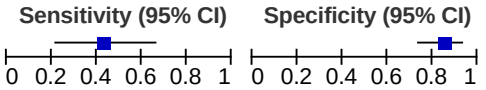
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Reardon 1996 significant AS (gradient 30 mmHg)	3	2	18	58	0.14 [0.03, 0.36]	0.97 [0.88, 1.00]



Note that it was unclear whether the peak or mean gradient was being referred to in the study to define significant aortic stenosis. Participants in this study were >65 years of age and had to have systolic murmurs to be included.

Figure 17: Sensitivity and specificity of murmur + dyspnoea for significant heart valve disease in acute medical patients admitted to geriatric ward of hospital

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Reardon 1996 significant AS (gradient 30 mmHg)	9	9	12	51	0.43 [0.22, 0.66]	0.85 [0.73, 0.93]

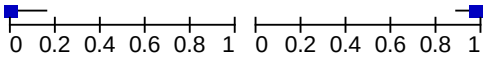


Note that it was unclear whether the peak or mean gradient was being referred to in the study to define significant aortic stenosis. Participants in this study were >65 years of age and had to have systolic murmurs to be included.

1

Figure 18: Sensitivity and specificity of murmur + angina for significant heart valve disease in acute medical patients admitted to geriatric ward of hospital

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Reardon 1996 significant AS (gradient 30 mmHg)	0	2	21	58	0.00 [0.00, 0.16]	0.97 [0.88, 1.00]

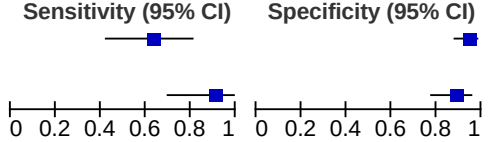


Note that it was unclear whether the peak or mean gradient was being referred to in the study to define significant aortic stenosis. Participants in this study were >65 years of age and had to have systolic murmurs to be included.

2

Figure 19: Sensitivity and specificity of systolic murmur +absent/reduced second heart sound for heart valve disease

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Abe 2013 severe AS	17	6	10	97	0.63 [0.42, 0.81]	0.94 [0.88, 0.98]
McGee 2010 moderate or severe MR	0	0	0	0	Not estimable	Not estimable
Reardon 1996 significant AS (gradient 30 mmHg)	19	7	2	53	0.90 [0.70, 0.99]	0.88 [0.77, 0.95]

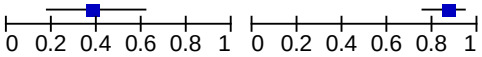


Please see individual clinical evidence tables for details concerning the population and setting of each of the above studies as these were quite broad for some studies and varied between the studies. Note that for McGee, the study reported a PLR value for moderate or severe MR but did not provide sufficient information to calculate sensitivity or specificity.

3

Figure 20: Sensitivity and specificity of murmur + abnormal ECG (left ventricular hypertrophy) for heart valve disease in acute medical patients admitted to geriatric ward of hospital

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Reardon 1996 significant AS (gradient 30 mmHg)	8	8	13	52	0.38 [0.18, 0.62]	0.87 [0.75, 0.94]		

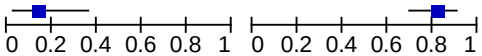


Note that it was unclear whether the peak or mean gradient was being referred to in the study to define significant aortic stenosis. Participants in this study were >65 years of age and had to have systolic murmurs to be included.

1

Figure 21: Sensitivity and specificity of murmur + abnormal ECG (atrial fibrillation) for heart valve disease in acute medical patients admitted to geriatric ward of hospital

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Reardon 1996 significant AS (gradient 30 mmHg)	3	11	18	49	0.14 [0.03, 0.36]	0.82 [0.70, 0.90]		



Note that it was unclear whether the peak or mean gradient was being referred to in the study to define significant aortic stenosis. Participants in this study were >65 years of age and had to have systolic murmurs to be included.

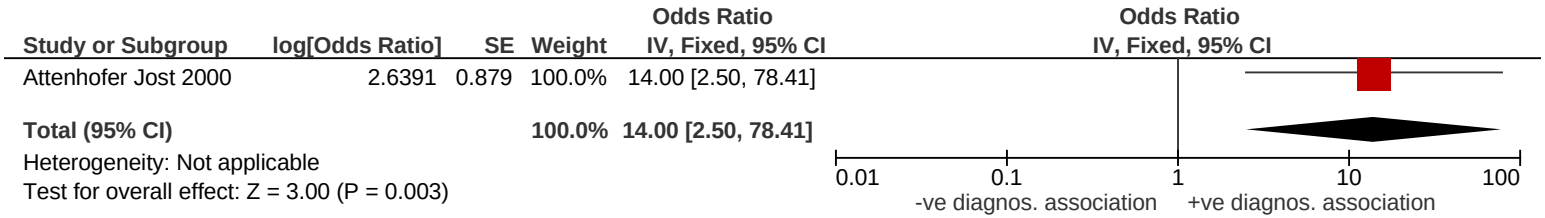
E.22 Diagnostic association plots

3

4 One study reported diagnostic association data, instead of diagnostic accuracy data, for the association of systolic murmur + diminished aortic
5 closure sound with a subsequent diagnosis of moderate or severe aortic stenosis.

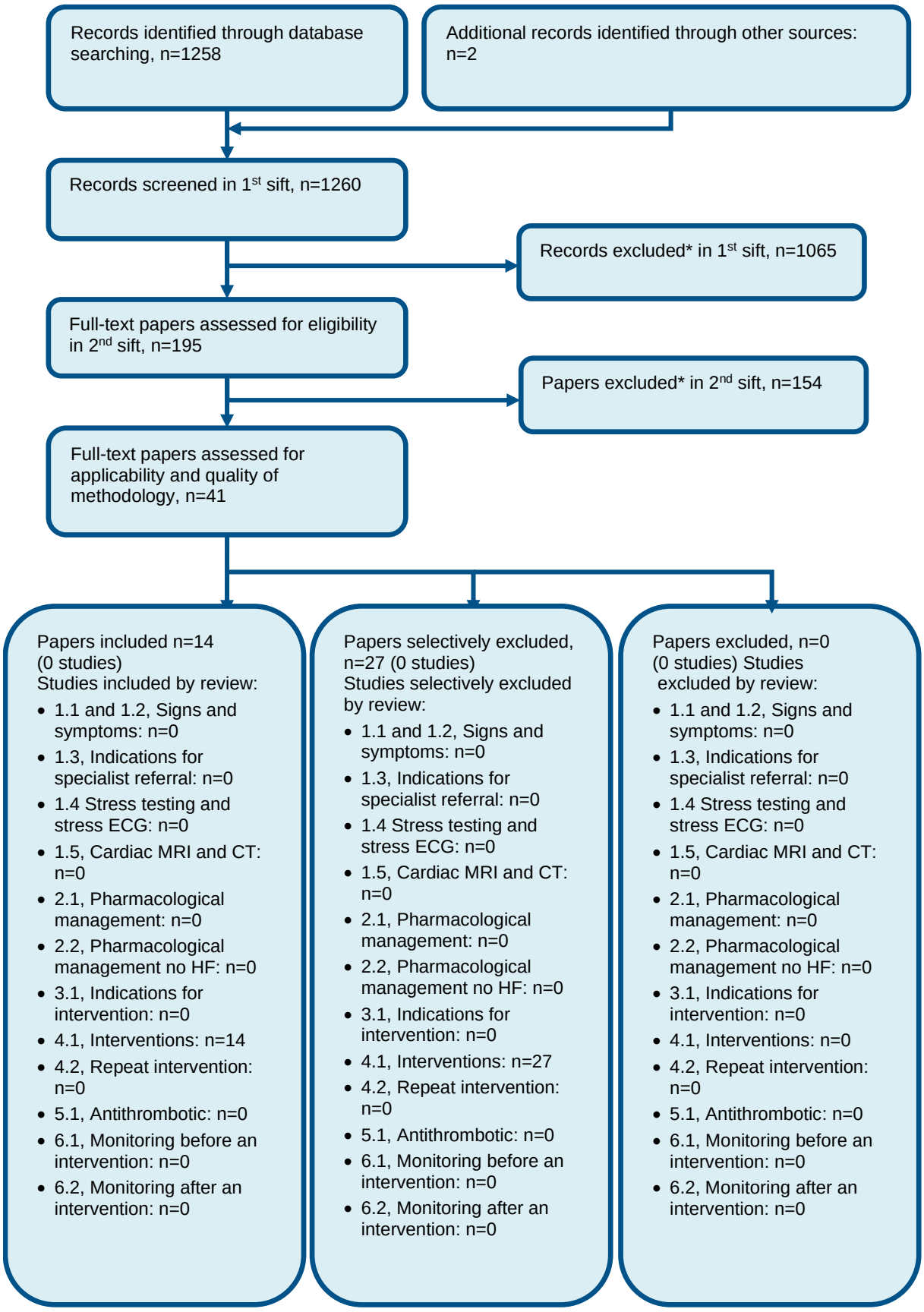
6

Figure 22: Diagnostic association OR for systolic murmur + diminished aortic closure sound and diagnosis of moderate or severe aortic stenosis



1

Appendix F – Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

1

Appendix G – Economic evidence tables

None.

Appendix H – Health economic model

No original economic modelling was undertaken.

1 Appendix I – Excluded studies

I.1 Symptoms and signs indicating echocardiography referral

3 Clinical studies

4 Table 37: Studies excluded from the clinical review

Reference	Reason for exclusion
Abbasi 1983[1]	Incorrect target condition - mitral valve prolapse. Incorrect index test/reference standard - echo as the index test. Incorrect study design - case-control.
Abdulla 1981[2]	Incorrect study design – two-gate (separate populations included - those with confirmed AR and those with absence of heart disease on catheterisation). Incorrect index test (heart sounds alone). Incorrect outcome/analysis - not diagnosis of HVD.
Abe 2013[3]	Incorrect target condition: limits to moderate or severe disease. Considered for inclusion in another review focusing on severe disease.
Abernethy 1994[4]	Incorrect population: all under 18 years of age
Ahlstrom 2006[7]	Incorrect index test - algorithms for classification of different types of valve disease.
Ahlstrom 2007[6]	Incorrect study design: not a diagnostic accuracy study
Ahmad 2019[8]	Incorrect index test: algorithm for classifying types of heart sounds/murmurs
Ahmed 2009[9]	Incorrect study design- two-gate, case control (all had murmur and MR already diagnosed).
Ahuja 1982[10]	Incorrect index test - ability of physician to distinguish between innocent and pathological murmur rather than presence or absence of murmur
Anjorin 1984[12]	Incorrect population: all already diagnosed with AS. Incorrect diagnosis: assessing severity in those with established AS rather than diagnosing AS.
Ansari 1985[13]	Incorrect population: suspected MVP and already had negative echo
Ari 2008[15]	Incorrect study design
Ari 2008[14]	Incorrect study design
Babaei 2009[20]	Incorrect index test - various algorithms for classification of different types of valve disease.
Betriu 1975[24]	Incorrect target condition: mitral valve prolapse
Bloch 2001[25]	Insufficient information to calculate diagnostic accuracy data.
Bodegard 2012[26]	Incorrect population: healthy cohort rather than suspected valve disease
Brusco 2005[28]	Incorrect index test: algorithm for classifying types of heart sounds/murmurs
Cha 1981[30]	Incorrect population, index test and reference standard
Chabchoub 2018[31]	Incorrect study design: known HVD vs control and classification algorithm not physician assessment
Chambers 2014[32]	Incorrect target condition: regurgitation/stenosis mixed in with other valve abnormalities that may just be structural

Reference	Reason for exclusion
Chen 2012[33]	Incorrect index test - algorithm used to distinguish between innocent and organic murmurs. No assessment of whether murmur diagnostic for HVD.
Choi 2010[36]	Incorrect index test: assessing accuracy of algorithm to classify different heart sounds
Choi 2015[35]	Incorrect study design: Known HVD vs normal heart sounds
Choudhry 1999[37]	Incorrect study design: narrative review. References checked.
Cohen 1987[38]	Incorrect population: known mitral valve prolapse Incorrect target condition: severity of MVP
Cohen 1988[40]	Incorrect study design: narrative review. References checked.
Cohen 1979[39]	Incorrect target condition: mitral valve prolapse rather than regurgitation/stenosis.
Comak 2007[42]	Incorrect index test: assessing accuracy of algorithm to classify different heart sounds
Comak 2012[41]	Incorrect index test: assessing accuracy of algorithm to classify different heart sounds
Come 1983[43]	Incorrect outcome/analysis: insufficient information to calculate accuracy data for mitral regurgitation
Come 1986[44]	Incorrect index test – auscultation or phonocardiogram Insufficient information to calculate accuracy data for TR and AR
Danielsen 1991[45]	Incorrect index test: no information on number with/without murmur. Incorrect diagnosis: no information on number with/without AS - only compares those with significant AS vs. those without significant AS, looking for predictors of more severe AS.
Darsee 1979[46]	Incorrect population: healthy young men Incorrect diagnosis: mitral valve prolapse rather than stenosis/regurgitation specifically.
Das 2000[47]	Incorrect study design - narrative review. References checked.
Das 2009[48]	Incorrect population and study design and unclear tests used
De Panfilis 2013[49]	Incorrect index test - algorithm used to distinguish between innocent and organic heart sounds.
Debbal 2005[50]	Incorrect study design/index test - no assessment of diagnostic accuracy of any signs/symptoms.
Deng 1990[52]	Incorrect target condition: MVP and incorrect index test
Denham 1977[53]	Incorrect diagnosis: valve abnormalities (structural) rather than presence of stenosis/regurgitation specifically. Incorrect reference standard/population: findings on post-mortem
Desjardins 1996[54]	Incorrect study design - two-gate (case-control) as separate groups of those with confirmed VD and those without VD.
Devereux 1989[56]	Incorrect study design: narrative review - references checked.
Devereux 1994[57]	Incorrect diagnosis: diagnosis of mitral valve prolapse, with no information on the number that also had mitral regurgitation/stenosis
Devereux 1986[55]	Incorrect target condition: mitral valve prolapse rather than stenosis/regurgitation specifically.
Dittmann 1987[58]	Incorrect index test: auscultation, but not clear whether this involved detection of murmur or whether other signs could also mean auscultation was positive.

Reference	Reason for exclusion
Draper 2019[59]	Incorrect diagnosis: some were diagnosed with non-valve disease conditions and included in the values reported – insufficient information to work out values for heart valve disease alone
Ellison 1976[60]	Incorrect population: congenital AS in children and young adults
Esper 1982[61]	Incorrect study design: predefined groups with and without murmur, and with and without AR
Etchells 1997[62]	Incorrect study design: systematic review and insufficient quality assessment. References checked.
Etchells 1998[63]	Incorrect target condition: limits to moderate or severe disease. Considered for inclusion in another review focusing on severe disease.
Fabich 2016[64]	Incorrect comparison: handheld vs standard echo
Fahad 2018[65]	Incorrect index test - algorithm used to distinguish between different types of heart sounds automatically.
Figueroa 2001[66]	Incorrect index test: clinical examination, unclear now positive test was defined
Fink 1994[67]	Incorrect target population: cardiac lesions (40% non-HVD diagnoses)
Forssell 1985[68]	Incorrect population: known HVD
Fukuda 1995[69]	Incorrect analysis / insufficient reporting
Gahl 1977[70]	Incorrect population: those undergoing cardiac surgery - not group that would be under consideration for echocardiography referral as they would have full cardiac assessment
Gamaza-Chulian 2020[71]	Incorrect population: all already diagnosed with valve disease
Gardin 1980[73]	Incorrect target condition: mitral valve prolapse rather than existence of stenosis/regurgitation specifically.
Gharehbaghi 2015[74]	Incorrect index test - algorithm used to distinguish between innocent and organic murmurs.
Goli 1993[75]	Incorrect population: all included had diagnosed aortic regurgitation. Incorrect diagnosis: aim was to assess severity of AR rather than diagnose it.
Grayburn 1986[76]	Incorrect population: already diagnosed with or without valve disease
Griffiths 1975[77]	Incorrect study design: no use of a reference standard to assess accuracy of murmur in diagnosis of valve disease
Guillermo 2015[78]	Incorrect study design: no accuracy or association data
Haikal 1982[79]	Incorrect target condition: diagnosis of mitral valve prolapse rather than regurgitation/stenosis.
Heidenreich 2004[80]	Incorrect population: Screening of a population at increased risk of HVD due to treatment received.
Herold 2005[81]	Incorrect index test: algorithm/features of the algorithm to diagnose/classify valve disease.
Hershman 1990[82]	Incorrect outcome/analysis: insufficient information to work out diagnostic accuracy for presence of murmur in HVD
Higuchi 2006[83]	Incorrect study design: no accuracy or association data
Hirata 1992[84]	Incorrect population: patients have a condition that means they will already be seeing specialists and being monitored by echocardiography
Hoagland 1986[85]	Incorrect target condition: limits to severe/surgical valve disease. Considered for inclusion in another review focusing on severe disease.

Reference	Reason for exclusion
Homaeinezhad 2010[87]	Incorrect index test: assessing accuracy of algorithm to classify different heart sounds.
Ilmurzynska 1966[88]	Incorrect population: valve disease already diagnosed in all patients.
Iversen 2008[89]	Incorrect target condition: limits to moderate or severe disease. Considered for inclusion in another review focusing on severe disease.
Iversen 2006[90]	Incorrect population: valve disease already diagnosed prior to study
Jaffe 1988[91]	Incorrect index test: no information provided for the presence/absence of murmur in those diagnosed with/without valve disease by the reference standard. Only gives diagnostic accuracy results for significant valve disease and this was based on clinical measures other than a murmur.
Jeyaseelan 2007[92]	Incorrect index test: insufficient information to calculate accuracy data for murmur as diagnostic factor
Jick 1998[93]	Incorrect study design: retrospective review of records and echo not performed on all patients to confirm diagnosis
Johnson 1983[95]	Incorrect population: already diagnosed AS.
Johnson 1985[96]	Incorrect population: already diagnosed valve disease.
Johnson 1986[94]	Incorrect target condition: looking at diagnosis of mitral valve prolapse rather than regurgitation/stenosis specifically.
Kambe 1977[98]	Incorrect index test: murmur on phonocardiogram rather than auscultation
Karar 2017[99]	Incorrect index test: use of algorithm developed to automatically classify normal and various abnormal heart sounds.
Kavalier 1975[100]	Incorrect population: all had been diagnosed prior to the study. Incorrect study design: inclusion of cases and controls, 2-gate design. Incorrect index test and diagnosis: 4th heart sound alone and predicting severity of disease.
Kay 2017[101]	Incorrect index test - algorithm used to distinguish between different types of heart sounds automatically.
Kim 2003[102]	Incorrect population: all with previously diagnosed AS. Incorrect outcomes: comparing correlation between murmur features on auscultation and certain Doppler measurements.
Kinney 1989[104]	Incorrect study design: case series - all had confirmed MR.
Koegelenberg 2014[105]	Incorrect index test - algorithm used to distinguish between different types of heart sounds automatically.
Kolibash 1983[106]	Incorrect index test: auscultatory abnormalities could include clicks alone, without a murmur. Incorrect target condition: focus is on mitral valve prolapse rather than stenosis/regurgitation.
Krivokapich 1988[107]	Incorrect target condition: mitral valve prolapse.
Kumar 2008[108]	Incorrect index test - algorithm used to distinguish between different types of heart sounds automatically.
Landau 2008[110]	Incorrect population: screening of presumably healthy population - not suspected HVD
Lee 1995[111]	Not available: not in English language
Leech 1978[112]	Incorrect reference standard: stenosis diagnosed at operation/necroscopy in some and may have been time gap between this and when murmur first detected.
Lembo 1988[114]	Incorrect study design: known valve disease prior to study

Reference	Reason for exclusion
Liberfarb 1986[115]	Incorrect target condition: mitral valve prolapse rather than stenosis/regurgitation specifically.
Liberthson 1986[116]	Incorrect target condition: mitral valve prolapse.
Lingamneni 1979[118]	Incorrect population: valve disease already diagnosed
Lippman 1985[119]	Incorrect target condition: mitral valve prolapse rather than stenosis/regurgitation specifically.
Lockhart 1989[120]	Incorrect target condition: diagnosis of mitral valve prolapse rather than stenosis/regurgitation
Lopez 1985[122]	Incorrect study design: case-control, 2-gate. Includes group with confirmed HVD and a normal control group.
Loxdale 2012[123]	Incorrect population: Those with hip fractures - no further reasons to suspect HVD so is more of a screening study.
Luisada 1980[124]	Incorrect study design: case control, 2-gate.
Maglogiannis 2009[125]	Incorrect population and study design and unclear tests used
Maisel 1984[126]	Incorrect study design: case control two-gate - all known to have/not have valve disease prior to study.
Markiewicz 1976[127]	Incorrect population - presumably healthy individuals so is a screening study - not those with suspected HVD. Incorrect target condition: prolapse rather than stenosis/regurgitation being present.
Marsalese 1989[128]	Incorrect study design - compares outcomes for different interventions rather than accuracy of different diagnostic factors for valve disease. Insufficient information to calculate diagnostic accuracy of murmur for HVD.
Martin 2009[129]	Incorrect index test: physical exam in general which included physician interpretation of their findings. No information regarding presence/absence of murmur and diagnosis of HVD.
McBrien 2009[130]	Incorrect population: hip fractures, more of a screening study as no reason to suspect HVD
McClelland 2020[131]	Incorrect target conditions: combines valve disease with other abnormalities
McGee 2011[133]	Incorrect study design - abstract only
McKillop 1991[134]	Incorrect target condition: limits to severe/surgical valve disease. Considered for inclusion in another review focusing on severe disease.
Mehta 2014[135]	Incorrect index test: physical examination, not specifically the presence/absence of murmur.
Menahem 1986[136]	Incorrect population: all under 18 years of age
Meyers 1985[138]	Incorrect index test: auscultation with no mention of whether murmur was considered to be positive test - could have also referred to heart sounds alone, or may have been on physician interpretation as to whether a murmur was innocent or pathological.
Meziani 2013[141]	Incorrect study design: no accuracy or association data
Meziani 2018[140]	Incorrect study design: not a diagnostic accuracy study
Minich 1997[142]	Incorrect population: children
Missri 1985[144]	Incorrect study design: two gate, case control design. Confirmed TR and a control group with no disease.

Reference	Reason for exclusion
Movahed 2007[145]	Incorrect study design/population: retrospective analysis of all who had echo. May be many with murmur detected who were not sent for echo and so not included in this analysis
Munt 1999[146]	Incorrect population: known HVD
Nakamura 1984[147]	Incorrect population: known AS (diagnosing severity)
Naseri 2013[148]	Incorrect index test: assesses accuracy of an algorithm
Nienaber 1993 [152]	Incorrect index test: no information for number with murmur and subsequent AR detected
Nitta 1987[153]	Incorrect population: all with known AS. Incorrect index test: no use of murmur alone to detect presence/absence of HVD.
Noah 1987[154]	Incorrect population: healthy sample rather than those with suspected valve disease - differs from population likely to be used in. Incorrect target condition: mitral valve prolapse
Noble 1982[155]	Incorrect study design: different groups with or without evidence of prolapse on both auscultation and echo enrolled - different cohorts. Incorrect target condition: mitral valve prolapse
Nygaard 1993[156]	Incorrect population - all with diagnosed aortic stenosis. Incorrect target condition: assessing severity in those with established AS rather than diagnosing AS.
Nygaard 1993[157]	Incorrect outcome/analysis: cannot calculate diagnostic accuracy.
Nylander 1986[158]	Incorrect population: all had established AS before the study. Incorrect target condition: assessing severity of AS rather than presence/absence of it.
Oh 2020[159]	Incorrect index test: algorithm used to classify different types of HVD
Oladapo 2001[160]	Incorrect population: presumably healthy volunteers. Screening study rather than those with suspected HVD.
Olive 1990[161]	Incorrect target condition: diagnosis of mitral valve prolapse (structural) rather than stenosis/regurgitation specifically.
Oweis 2014[162]	Incorrect index test - algorithm used to distinguish between different types of heart sounds automatically.
Papadaniil 2014[164]	Incorrect study design and index test (heart sounds alone)
Parras 2015[165]	Incorrect population: all previously diagnosed with valve disease
Patel 2017[166]	Incorrect index test - auscultation rather than detection of murmur specifically. No information with regards to those with/without diagnosis of HVD and number with/without murmur in each case
Patidar 2013[167]	Incorrect index test - algorithm used to distinguish between different types of heart sounds automatically.
Patnaik 2019[168]	Incorrect study design: narrative review – references checked.
Phoon 2001[169]	Incorrect population: known HVD. Incorrect index test and analysis (correlation only)
Procacci 1976[170]	Incorrect population: healthy young women rather than those with suspected valve disease. Incorrect target condition: mitral valve prolapse
Rama 1999[172]	Incorrect population: all had diagnosed AS. Incorrect target condition: aim is to assess correlation of murmur intensity and other physical findings with severity of AS.
Ranganathan 1976[173]	Incorrect outcomes/analysis: insufficient information to calculate diagnostic accuracy for HVD

Reference	Reason for exclusion
Rispler 1995[176]	Incorrect study design - case series. All had diagnosed AS and clinical characteristics were reviewed to compare between those where it was suspected and those where it was not suspected prior to echo.
Roldan 1996[179]	Incorrect population - large proportion (48%) were presumably healthy and remaining population were those with connective tissue diseases but no further symptoms of heart disease. Does not represent population with suspected HVD.
Roldan 1997[177]	Incorrect population - large proportion (48%) were presumably healthy, and remaining population were those with connective tissue diseases but no further symptoms of heart disease. Does not represent population with suspected HVD.
Roldan 2000[178]	Incorrect population: Screening of a population at increased risk of it due to treatment received.
Rouhani 2012[180]	Incorrect study design: no accuracy or association data
Rueda 1988[181]	Incorrect study design: narrative review. References checked
Rujoie 2020[182]	Incorrect index test - algorithm used to distinguish between different types of heart sounds automatically.
Saal 1985[183]	Incorrect population: valve disease already diagnosed
Saeidi 2017[185]	Incorrect index test - algorithm used to distinguish between different types of heart sounds automatically.
Saeidi 2020[184]	Incorrect study design: deriving an algorithm using data from known HVD and controls
Safara 2012[188]	Incorrect index test - algorithm used to automatically classify heart sounds into different pathologies.
Safara 2013[187]	Incorrect index test - algorithm used to automatically classify heart sounds into different pathologies.
Safara 2015[186]	Incorrect index test - algorithm used to automatically classify heart sounds into different pathologies.
Salah 2020[189]	Incorrect index test - algorithm used to distinguish between different types of heart sounds and diagnose HVD automatically.
Saraf 2019[190]	Incorrect index test – algorithm used to diagnose HVD
Sarasin 2002[191]	Incorrect target condition: limits to moderate or severe disease. Considered for inclusion in another review focusing on severe disease.
Sathesh 2020[192]	Incorrect index test – algorithm used to classify auscultation sounds
Sbarbaro 1979[193]	Incorrect population: sample of healthy individuals, not suspected HVD (more like a screening study). Incorrect target condition: mitral valve prolapse (structural feature) rather than stenosis/regurgitation specifically.
Schnittger 1988[194]	Incorrect outcome/analysis: insufficient information to be able to calculate diagnostic accuracy measures
Sengur 2008[195]	Incorrect index test: algorithm used to automatically classify heart sounds.
Shry 2001[196]	Incorrect population: healthy individuals screened for presence of murmur. No other indication for suspicion of HVD.
Shub 2003[197]	Incorrect study design: narrative review. References checked
Sinha 2007[198]	Incorrect index test: algorithm used to automatically classify heart sounds.
Smith 1977 [199]	Incorrect target condition: mitral valve prolapse rather than stenosis or regurgitation
Spencer 2001 [200]	Incorrect study design: diagnosis already known

Reference	Reason for exclusion
Stanger 2019[201]	Incorrect index test: SR of studies looking at diagnostic accuracy of handheld echo in valve disease - references checked
Strauss 1987[202]	Incorrect population: acute heart failure
Streib 1985[203]	Incorrect target condition: mitral valve prolapse
Sun 2005[204]	Incorrect study design: case control, 2-gate - presence/absence of AS already known on enrolment. Incorrect target condition: aim was to identify factors associated with different AS severity, not diagnosis of AS
Sztajzel 2010[205]	Incorrect index test: no info regarding presence/absence of murmur in the patients and results may be due to physician interpretation.
Thiyagaraja 2018[206]	Incorrect index test: classification model
Thomas 2016[208]	Incorrect study design: no accuracy or association data
Thomas 2018[207]	Incorrect reference test: hand-held echo
Thompson 2001[209]	Incorrect population: under 18 years of age. Incorrect index test: algorithm developed and accuracy for diagnosing different heart sounds assessed.
Thompson 2019[210]	Incorrect index test: algorithm used to automatically classify abnormal heart sounds/murmurs.
Tofler 1990[211]	Incorrect target condition: mitral valve prolapse Incorrect outcome/analysis: insufficient to be able to calculate diagnostic accuracy
Tokuda 2020[212]	Incorrect study design – assessing improvement in auscultation skills after a training session
Tribouilloy 2001[213]	Incorrect study design: case-control; and index test (3rd heart sound alone)
Turkoglu 2003[214]	Incorrect index test: classification model
Tutar 2005[215]	Incorrect population: children
Uguz 2012[216]	Incorrect index test: algorithm used to automatically classify heart sounds.
Uretsky 1982[217]	Incorrect study design: not all of the participants had echo or an alternative reference standard performed - some classified just based on auscultatory findings. Incorrect target condition: mitral valve prolapse
van Klei 2006[218]	Incorrect population: screening all of those undergoing non-cardiac surgery. Not representative of the population that would usually be considered for referral in current practice and is more of a screening study.
Varadarajan 2006[219]	Incorrect population: congestive heart failure monitoring by echocardiography already covered by NICE chronic heart failure guideline
Vargas-Barron 1984[220]	Incorrect population: children
Voelkel 1980[221]	Incorrect index test: no use of murmur as an index test/sign. Incorrect study design: all included had known and confirmed aortic stenosis, divided into severities.
Voss 2005[222]	Incorrect index test: algorithm used to automatically classify heart sounds.
Vourvouri 2005[223]	Incorrect index test: no indication of number with murmur in study and number subsequently diagnosed with valve disease

Reference	Reason for exclusion
Wang 1984[224]	Incorrect study design - 2-gate case control, aortic regurgitation and controls already diagnosed before study. Incorrect outcome/analysis: insufficient to be able to calculate any accuracy measures.
Wann 1983[225]	Incorrect population: healthy young women so represents a screening study - not suspected HVD. Incorrect target condition: mitral valve prolapse
Ward 1977[226]	Incorrect population: includes children
Weis 1995[227]	Incorrect index test: heart sounds alone. Incorrect target condition: mitral valve prolapse
Wong 1983[228]	Incorrect target condition: Valve abnormalities rather than specifically stenosis or regurgitation.
Xu 1993[229]	Incorrect population: uses number of scans rather than number of patients to report results, meaning certain patients would be included more than once. Also appears to be large proportion <18 years of age included.

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.

I.2 Symptoms and signs indicating direct referral to a specialist

Clinical studies

Table 38: Studies excluded from the clinical review

Reference	Reason for exclusion
Abbasi 1983[1]	Incorrect target condition - mitral valve prolapse. Incorrect index test/reference standard - echo as the index test. Incorrect study design - case-control.
Abdulla 1981[2]	Incorrect study design – two-gate (separate populations included - those with confirmed AR and those with absence of heart disease on catheterisation). Incorrect index test (heart sounds alone). Incorrect outcome/analysis - not diagnosis of HVD.
Abernethy 1994[4]	Incorrect population: all under 18 years of age
Ahlstrom 2006[7]	Incorrect index test - algorithms for classification of different types of valve disease.
Ahlstrom 2007[6]	Incorrect study design: not a diagnostic accuracy study
Ahmad 2019[8]	Incorrect index test: algorithm for classifying types of heart sounds/murmurs
Ahmed 2009[9]	Incorrect study design- two-gate, case control (all had murmur and MR already diagnosed). Not able to calculate ay accuracy data as all had the disease and diagnostic feature (murmur)

Reference	Reason for exclusion
Ahuja 1982[10]	Incorrect index test - ability of physician to distinguish between innocent and pathological murmur rather than presence or absence of murmur
Amano 1986[11]	Incorrect target condition: no information for severe valve disease specifically
Anjorin 1984[12]	Incorrect population: all already diagnosed with AS. Incorrect diagnosis: assessing severity in those with established AS rather than diagnosing AS.
Ansari 1985[13]	Incorrect population: suspected MVP and already had negative echo
Ari 2008[15]	Incorrect study design
Ari 2008[14]	Incorrect study design
Babaei 2009[20]	Incorrect index test - various algorithms for classification of different types of valve disease.
Barron 1988[21]	Incorrect target condition: no information for severe valve disease specifically
Barzilai 1988[22]	Incorrect target condition: no information for severe valve disease specifically
Baur 2006[23]	Incorrect target condition: no information for severe valve disease specifically
Betriu 1975[24]	Incorrect target condition: mitral valve prolapse
Bloch 2001[25]	Insufficient information to calculate diagnostic accuracy data.
Bodegard 2012[26]	Incorrect population: healthy cohort rather than suspected valve disease
Breisblatt 1988[27]	Incorrect reference standard: cardiac catheterisation not as good as echocardiography at quantifying severity of valve disease
Brusco 2005[28]	Incorrect index test: algorithm for classifying types of heart sounds/murmurs
Cantley 1995[29]	Incorrect target condition: no information for severe valve disease specifically
Cha 1981[30]	Incorrect population, index test and reference standard
Chabchoub 2018[31]	Incorrect study design: known HVD vs control and classification algorithm not physician assessment
Chambers 2014[32]	Incorrect target condition: regurgitation/stenosis mixed in with other valve abnormalities that may just be structural
Chen 2012[33]	Incorrect index test - algorithm used to distinguish between innocent and organic murmurs.
Chin 1992[34]	Incorrect target condition: no information for severe valve disease specifically
Choi 2010[36]	Incorrect index test: assessing accuracy of algorithm to classify different heart sounds
Choi 2015[35]	Incorrect study design: Known HVD vs normal heart sounds
Choudhry 1999[37]	Incorrect study design: narrative review. References checked.
Cohen 1987[38]	Incorrect population: known mitral valve prolapse Incorrect target condition: severity of MVP
Cohen 1988[40]	Incorrect study design: narrative review. References checked.
Cohen, 1979 [39]	Incorrect target condition: mitral valve prolapse rather than regurgitation/stenosis.
Comak 2007[42]	Incorrect index test: assessing accuracy of algorithm to classify different heart sounds

Reference	Reason for exclusion
Comak 2012[41]	Incorrect index test: assessing accuracy of algorithm to classify different heart sounds
Come 1983[43]	Incorrect outcome/analysis: insufficient information to calculate accuracy data for mitral regurgitation
Come 1986[44]	Incorrect index test – auscultation or phonocardiogram Insufficient information to calculate accuracy data for TR and AR
Danielsen 1991[45]	Incorrect index test: no information on number with/without murmur. Incorrect diagnosis: no information on number with/without AS - only compares those with significant AS vs. those without significant AS, looking for predictors of more severe AS.
Darsee 1979[46]	Incorrect population: healthy young men. Incorrect diagnosis: mitral valve prolapse rather than stenosis/regurgitation specifically.
Das 2000[47]	Incorrect study design - narrative review. References checked.
Das 2009[48]	Incorrect population and study design and unclear tests used
De Panfilis 2013[49]	Incorrect index test - algorithm used to distinguish between innocent and organic heart sounds.
Debbal 2005[50]	Incorrect study design/index test - no assessment of diagnostic accuracy of any signs/symptoms.
Deng 1990[52]	Incorrect target condition: MVP and incorrect index test
Denham 1977[53]	Incorrect diagnosis: valve abnormalities (structural) rather than presence of stenosis/regurgitation specifically. Incorrect reference standard/population: findings on post-mortem
Desjardins 1996[54]	Incorrect study design - two-gate (case-control) as separate groups of those with confirmed VD and those without VD.
Devereux 1989[56]	Incorrect study design: narrative review - references checked.
Devereux 1994[57]	Incorrect diagnosis: diagnosis of mitral valve prolapse, with no information on the number that also had mitral regurgitation/stenosis
Devereux 1986[55]	Incorrect target condition: mitral valve prolapse rather than stenosis/regurgitation specifically.
Dittmann 1987[58]	Incorrect index test: auscultation, but not clear whether this involved detection of murmur or whether other signs could also mean auscultation was positive.
Draper 2019[59]	Incorrect diagnosis: some were diagnosed with non-valve disease conditions and included in the values reported – insufficient information to work out values for heart valve disease alone
Ellison 1976[60]	Incorrect population: congenital AS in children and young adults
Esper 1982[61]	Incorrect study design: predefined groups with and without murmur, and with and without AR
Etchells 1997[62]	Incorrect study design: systematic review and insufficient quality assessment. References checked.
Fabich 2016[64]	Incorrect comparison: handheld vs standard echo
Fahad 2018[65]	Incorrect index test - algorithm used to distinguish between different types of heart sounds automatically.
Figueroa 2001[66]	Incorrect index test: clinical examination, unclear now positive test was defined
Fink 1994[67]	Incorrect target population
Forssell 1985[68]	Incorrect population: known HVD
Fukuda 1995[69]	Incorrect analysis / insufficient reporting

Reference	Reason for exclusion
Gahl 1977[70]	Incorrect population: those undergoing cardiac surgery - not group that would be under consideration for echocardiography referral as they would have full cardiac assessment
Gamaza-Chulian 2020[71]	Incorrect population: all already diagnosed with valve disease
Gardezi 2018[72]	Incorrect target condition: no information for severe valve disease specifically
Gardin 1980[73]	Incorrect target condition: mitral valve prolapse rather than existence of stenosis/regurgitation specifically.
Gharehbaghi 2015[74]	Incorrect index test - algorithm used to distinguish between innocent and organic murmurs.
Goli 1993[75]	Incorrect population: all included had diagnosed aortic regurgitation. Incorrect diagnosis: aim was to assess severity of AR rather than diagnose it.
Grayburn 1986[76]	Incorrect population: already diagnosed with or without valve disease
Griffiths 1975[77]	Incorrect study design: no use of a reference standard to assess accuracy of murmur in diagnosis of valve disease
Guillermo 2015[78]	Incorrect study design: no accuracy or association data
Haikal 1982[79]	Incorrect target condition: diagnosis of mitral valve prolapse rather than regurgitation/stenosis.
Heidenreich 2004[80]	Incorrect population: Screening of a population at increased risk of HVD due to treatment received.
Herold 2005[81]	Incorrect index test: algorithm/features of the algorithm to diagnose/classify valve disease.
Hershman 1990[82]	Incorrect outcome/analysis: insufficient information to work out diagnostic accuracy for presence of murmur in HVD
Higuchi 2006[83]	Incorrect study design: no accuracy or association data
Hirata 1992[84]	Incorrect population: patients have a condition that means they will already be seeing specialists and being monitored by echocardiography
Hoagland 1986[85]	Incorrect target condition: limits to severe/surgical valve disease. Considered for inclusion in another review focusing on severe disease.
Hoffmann 1983[86]	Incorrect target condition: no information for severe valve disease specifically. Incorrect reference standard: cardiac catheterisation not as good as echocardiography at quantifying severity of valve disease
Homaeinezhad 2010[87]	incorrect index test: assessing accuracy of algorithm to classify different heart sounds
Ilmurzynska 1966[88]	Incorrect population: valve disease already diagnosed in all patients.
Iversen 2006 [90]	Incorrect population: valve disease already diagnosed prior to study
Jaffe 1988[91]	Incorrect index test: no information provided for the presence/absence of murmur in those diagnosed with/without valve disease by the reference standard. Only gives diagnostic accuracy results for significant valve disease and this was based on clinical measures other than a murmur.
Jeyaseelan 2007[92]	Incorrect index test: insufficient information to calculate accuracy data for murmur as diagnostic factor
Jick 1998 [93]	Incorrect study design: retrospective review of records and echo not performed on all patients to confirm diagnosis
Johnson 1983[95]	Incorrect population: already diagnosed AS.

Reference	Reason for exclusion
Johnson 1985[96]	Incorrect population: already diagnosed valve disease.
Johnson 1986[94]	Incorrect target condition: looking at diagnosis of mitral valve prolapse rather than regurgitation/stenosis specifically.
Kalinauskiene 2019[97]	Incorrect target condition: no information for severe valve disease specifically
Kambe 1977[98]	Incorrect reference standard: cardiac catheterisation not as good as echocardiography at quantifying severity of valve disease. Incorrect index test: murmur on phonocardiogram rather than auscultation.
Karar 2017[99]	Incorrect index test: use of algorithm developed to automatically classify normal and various abnormal heart sounds.
Kavalier 1975[100]	Incorrect population: all had been diagnosed prior to the study. Incorrect study design: inclusion of cases and controls, 2-gate design. Incorrect index test and diagnosis: 4th heart sound alone and predicting severity of disease.
Kay 2017[101]	Incorrect index test - algorithm used to distinguish between different types of heart sounds automatically.
Kim 2003[102]	Incorrect population: all with previously diagnosed AS. Incorrect outcomes: comparing correlation between murmur features on auscultation and certain Doppler measurements.
Kinney 1988[103]	Incorrect target condition: no information for severe valve disease specifically
Kinney 1989[104]	Incorrect study design: case series - all had confirmed MR.
Koegelenberg 2014[105]	Incorrect index test - algorithm used to distinguish between different types of heart sounds automatically.
Kolibash 1983[106]	Incorrect index test: auscultatory abnormalities could include clicks alone, without a murmur. Incorrect target condition: focus is on mitral valve prolapse rather than stenosis/regurgitation.
Krivokapich 1988[107]	Incorrect target condition: mitral valve prolapse
Kumar 2008[108]	Incorrect index test - algorithm used to distinguish between different types of heart sounds automatically.
Landau 2008[110]	Incorrect population: screening of presumably healthy population - not suspected HVD
Lee 1995[111]	Not available: not in English language
Leech 1978[112]	Incorrect reference standard: stenosis diagnosed at operation/necroscopy in some and may have been time gap between this and when murmur first detected.
Lehmann 1992[113]	Incorrect study design: known valve disease prior to study
Lembo 1988[114]	Incorrect target condition: mitral valve prolapse rather than stenosis/regurgitation specifically.
Liberfarb 1986[115]	Incorrect target condition: mitral valve prolapse.
Liberthson 1986[116]	Incorrect population: screening of presumably healthy population - not suspected HVD
Lingamneni 1979[118]	Incorrect population: valve disease already diagnosed
Lippman 1985[119]	Incorrect target condition: mitral valve prolapse rather than stenosis/regurgitation specifically
Lockhart 1989[120]	Incorrect target condition: diagnosis of mitral valve prolapse rather than stenosis/regurgitation

Reference	Reason for exclusion
Lopez 1985[122]	Incorrect study design: case-control, 2-gate. Includes group with confirmed HVD and a normal control group.
Loxdale 2012[123]	Incorrect population: Those with hip fractures - no further reasons to suspect HVD so is more of a screening study.
Luisada 1980[124]	Incorrect study design: case control, 2-gate.
Maglogiannis 2009[125]	Incorrect population and study design and unclear tests used
Maisel 1984[126]	Incorrect study design: case control two-gate - all known to have/not have valve disease prior to study.
Markiewicz 1976[127]	Incorrect population - presumably healthy individuals so is a screening study - not those with suspected HVD. Incorrect target condition: prolapse rather than stenosis/regurgitation being present.
Marsalese 1989[128]	Incorrect study design - compares outcomes for different interventions rather than accuracy of different diagnostic factors for valve disease. Insufficient information to calculate diagnostic accuracy of murmur for HVD.
Martin 2009[129]	Incorrect index test: physical exam in general which included physician interpretation of their findings. No information regarding presence/absence of murmur and diagnosis of HVD.
McBrien 2009[130]	Incorrect population: hip fractures, more of a screening study as no reason to suspect HVD
McGee 2011[133]	Incorrect study design - abstract only
Mehta 2014[135]	Incorrect index test: physical examination, not specifically the presence/absence of murmur.
Menahem 1986[136]	Incorrect population: all under 18 years of age
Meyers 1982[139]	Incorrect reference standard: cardiac catheterisation not as good as echocardiography at quantifying severity of valve disease
Meyers 1985[138]	Incorrect index test: auscultation with no mention of whether murmur was considered to be positive test - could have also referred to heart sounds alone, or may have been on physician interpretation as to whether a murmur was innocent or pathological.
Meyers 1986[137]	Incorrect reference standard: cardiac catheterisation not as good as echocardiography at quantifying severity of valve disease
Meziani 2013[141]	Incorrect study design: no accuracy or association data
Meziani 2018[140]	Incorrect study design: not a diagnostic accuracy study
Minich 1997[142]	Incorrect population: children
Mishra 1992[143]	Incorrect target condition: no information for severe valve disease specifically
Missri 1985[144]	Incorrect study design: two gate, case control design. Confirmed TR and a control group with no disease.
Movahed 2007[145]	Incorrect study design/population: retrospective analysis of all who had echo. May be many with murmur detected who were not sent for echo and so not included in this analysis
Munt 1999[146]	Incorrect population: known HVD
Nakamura 1984[147]	Incorrect population: known AS (diagnosing severity)
Naseri 2013[148]	Incorrect index test: assesses accuracy of an algorithm
Nienaber 1993[152]	Incorrect index test: no information for number with murmur and subsequent AR detected

Reference	Reason for exclusion
Nitta 1987[153]	Incorrect population: all with known AS. Incorrect index test: no use of murmur alone to detect presence/absence of HVD.
Noah 1987[154]	Incorrect population: healthy sample rather than those with suspected valve disease - differs from population likely to be used in. Incorrect target condition: mitral valve prolapse
Noble 1982[155]	Incorrect study design: different groups with or without evidence of prolapse on both auscultation and echo enrolled - different cohorts. Incorrect target condition: mitral valve prolapse
Nygaard 1993[156]	Incorrect population - all with diagnosed aortic stenosis. Incorrect target condition: assessing severity in those with established AS rather than diagnosing AS.
Nygaard 1993[157]	Incorrect outcome/analysis: cannot calculate diagnostic accuracy.
Nylander 1986[158]	Incorrect population: all had established AS before the study. Incorrect target condition: assessing severity of AS rather than presence/absence of it.
Oh 2020[159]	Incorrect index test: algorithm used to classify different types of HVD
Oladapo 2001[160]	Incorrect population: presumably healthy volunteers. Screening study rather than those with suspected HVD.
Olive 1990[161]	Incorrect target condition: diagnosis of mitral valve prolapse (structural) rather than stenosis/regurgitation specifically.
Oweis 2014[162]	Incorrect index test - algorithm used to distinguish between different types of heart sounds automatically.
Papadaniil 2014[164]	Incorrect study design and index test (heart sounds alone)
Parras 2015[165]	Incorrect population: all previously diagnosed with valve disease
Patel 2017[166]	Incorrect index test - auscultation rather than detection of murmur specifically. No information with regards to those with/without diagnosis of HVD and number with/without murmur in each case
Patidar 2013[167]	Incorrect index test - algorithm used to distinguish between different types of heart sounds automatically.
Patnaik 2019[168]	Incorrect study design: narrative review – references checked.
Phoon 2001[169]	Incorrect population: known HVD. Incorrect index test and analysis (correlation only)
Procacci 1976[170]	Incorrect population: healthy young women rather than those with suspected valve disease. Incorrect target condition: mitral valve prolapse
Rama 1999[172]	Incorrect population: all had diagnosed AS. Incorrect target condition: aim is to assess correlation of murmur intensity and other physical findings with severity of AS.
Ranganathan 1976[173]	Incorrect outcomes/analysis: insufficient information to calculate diagnostic accuracy for HVD
Reichlin 2004[175]	Incorrect target condition: no information for severe valve disease specifically
Rispler 1995[176]	Incorrect population: known HVD. Incorrect index test and analysis (correlation only)
Roldan 1996[179]	Incorrect population - large proportion (48%) were presumably healthy and remaining population were those with connective tissue diseases but no further symptoms of heart disease. Does not represent population with suspected HVD.
Roldan 1997[177]	Incorrect population - large proportion (48%) were presumably healthy, and remaining population were those with connective tissue diseases

Reference	Reason for exclusion
	but no further symptoms of heart disease. Does not represent population with suspected HVD.
Roldan 2000[178]	Incorrect population: Screening of a population at increased risk of it due to treatment received.
Rouhani 2012[180]	Incorrect study design: no accuracy or association data
Rueda 1988[181]	Incorrect study design: narrative review. References checked
Rujoie 2020[182]	Incorrect index test - algorithm used to distinguish between different types of heart sounds automatically.
Saal 1985[183]	Incorrect population: valve disease already diagnosed
Saeidi 2017[185]	Incorrect index test - algorithm used to distinguish between different types of heart sounds automatically.
Saeidi 2020[184]	Incorrect study design: deriving an algorithm using data from known HVD and controls
Safara 2012[188]	Incorrect index test - algorithm used to automatically classify heart sounds into different pathologies.
Safara 2013[187]	Incorrect index test - algorithm used to automatically classify heart sounds into different pathologies.
Safara 2015[186]	Incorrect index test - algorithm used to automatically classify heart sounds into different pathologies.
Salah 2020[189]	Incorrect index test - algorithm used to distinguish between different types of heart sounds and diagnose HVD automatically.
Saraf 2019[190]	Incorrect index test – algorithm used to diagnose HVD
Sathesh 2020[192]	Incorrect index test – algorithm used to classify auscultation sounds
Sbarbaro 1979[193]	Incorrect population: sample of healthy individuals, not suspected HVD (more like a screening study). Incorrect target condition: mitral valve prolapse (structural feature) rather than stenosis/regurgitation specifically.
Schnittger 1988[194]	Incorrect outcome/analysis: insufficient information to be able to calculate diagnostic accuracy measures
Sengur 2008[195]	Incorrect index test: algorithm used to automatically classify heart sounds.
Shry 2001[196]	Incorrect population: healthy individuals screened for presence of murmur. No other indication for suspicion of HVD.
Shub 2003[197]	Incorrect study design: narrative review. References checked
Sinha 2007[198]	Incorrect index test: algorithm used to automatically classify heart sounds.
Smith 1977[199]	Incorrect target condition: mitral valve prolapse rather than stenosis or regurgitation
Spencer 2001[200]	Incorrect study design: diagnosis already known
Stanger 2019[201]	Incorrect index test: SR of studies looking at diagnostic accuracy of handheld echo in valve disease -– references checked
Strauss 1987[202]	Incorrect population: acute heart failure
Streib 1985[203]	Incorrect target condition: mitral valve prolapse
Sun 2005[204]	Incorrect study design: case control, 2-gate - presence/absence of AS already known on enrolment. Incorrect target condition: aim was to identify factors associated with different AS severity, not diagnosis of AS
Sztajzel 2010[205]	Incorrect index test: no info regarding presence/absence of murmur in the patients and results may be due to physician interpretation.

Reference	Reason for exclusion
Thiyagaraja 2018[206]	Incorrect index test: classification model
Thomas 2016[208]	Incorrect study design: no accuracy or association data
Thomas 2018[207]	Incorrect reference test: hand-held echo
Thompson 2001[209]	Incorrect population: under 18 years of age. Incorrect index test: algorithm developed and accuracy for diagnosing different heart sounds assessed.
Thompson 2019[210]	Incorrect index test: algorithm used to automatically classify abnormal heart sounds/murmurs.
Tofler 1990[211]	Incorrect target condition: mitral valve prolapse Incorrect outcome/analysis: insufficient to be able to calculate diagnostic accuracy
Tokuda 2020[212]	Incorrect study design – assessing improvement in auscultation skills after a training session
Tribouilloy 2001[213]	Incorrect study design: case-control; and index test (3rd heart sound alone)
Turkoglu 2003[214]	Incorrect index test: classification model
Tutar 2005[215]	Incorrect population: children
Uguz 2012[216]	Incorrect index test: algorithm used to automatically classify heart sounds.
Uretsky 1982[217]	Incorrect study design: not all of the participants had echo or an alternative reference standard performed - some classified just based on auscultatory findings. Incorrect target condition: mitral valve prolapse
van Klei 2006[218]	Incorrect population: screening all of those undergoing non-cardiac surgery. Not representative of the population that would usually be considered for referral in current practice and is more of a screening study.
Varadarajan 2006[219]	Incorrect population: congestive heart failure monitoring by echocardiography already covered by NICE chronic heart failure guideline
Vargas-Barron 1984[220]	Incorrect population: children
Voelkel 1980[221]	Incorrect index test: no use of murmur as an index test/sign. Incorrect study design: all included had known and confirmed aortic stenosis, divided into severities.
Voss 2005[222]	Incorrect index test: algorithm used to automatically classify heart sounds.
Vourvouri, 2005 [223]	Incorrect index test: no indication of number with murmur in study and number subsequently diagnosed with valve disease
Wang 1984[224]	Incorrect study design - 2-gate case control, aortic regurgitation and controls already diagnosed before study. Incorrect outcome/analysis: insufficient to be able to calculate any accuracy measures.
Wann 1983[225]	Incorrect population: healthy young women so represents a screening study - not suspected HVD. Incorrect target condition: mitral valve prolapse
Ward 1977[226]	Incorrect population: includes children
Weis 1995[227]	Incorrect index test: heart sounds alone. Incorrect target condition: mitral valve prolapse

Reference	Reason for exclusion
Wong 1983[228]	Incorrect target condition: Valve abnormalities rather than specifically stenosis or regurgitation.
Xu 1993[229]	Incorrect population: uses number of scans rather than number of patients to report results, meaning certain patients would be included more than once. Also appears to be large proportion <18 years of age included.
Yamashita 2020[230]	Incorrect target condition: no information for severe valve disease specifically

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.

Appendix J – Research recommendations – full details

None

Appendix K – Expert witness testimony

Name: Dr Catherine Head

Role: Consultant Cardiologist

Institution/Organisation

(where applicable):

Contact information

To be redacted prior to publication

Norfolk and Norwich University Hospital

Norwich NR4 7UY

Guideline title: Heart valve disease

Guideline committee: Heart valve disease

Subject of expert testimony: Pregnant women and women considering pregnancy

Evidence gaps or uncertainties: There is limited information across the guideline for the population including pregnant women and women of childbearing age and information relating to this population in terms of the review questions listed below would be useful

No.	Review question
1	In adults with suspected heart valve disease, what symptoms and signs indicate referral (for example from primary care) for echocardiography?
2	In adults with suspected heart valve disease, what symptoms and signs indicate direct referral (for example from primary care) to a specialist?
3	In adults who have had echocardiography, what are the indications for referral to a specialist?
4	In adults with heart valve disease, what is the predictive accuracy and cost effectiveness of stress testing and stress echocardiography to determine the need for intervention?
5	In adults with heart valve disease, what is the predictive accuracy and cost effectiveness of cardiac MRI and cardiac CT to determine the need for intervention?
6	In adults with heart failure and concomitant heart valve disease, what is the clinical and cost effectiveness of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers, calcium channel blockers, digoxin, diuretics and nitrates to improve clinical outcome?

7	In adults with heart valve disease without concomitant heart failure, what is the clinical and cost effectiveness of ACE inhibitors, ARBs, alpha-blockers, beta blockers, calcium channel blockers, digoxin, diuretics, statins and nitrates to improve clinical outcome?
8	What are the indications that interventions should be offered to adults with asymptomatic, severe heart valve disease?
9	What is the clinical and cost effectiveness of transcatheter intervention, surgery (with mechanical or biological valves) and conservative management compared with each other for adults with heart valve disease?
10	What is the clinical and cost effectiveness of transcatheter or surgical repeat valve intervention for prosthetic biological valve degeneration?
11	What is the clinical and cost effectiveness of anticoagulant and/or antiplatelet therapy for adults with transcatheter or surgical biological prosthetic valves or after valve repair?
12	Where there is no current indication for intervention, what is the most clinically and cost-effective type and frequency of test for monitoring in adults with heart valve disease?
13	What is the most clinically and cost-effective frequency of echocardiography or clinical review for monitoring in adults with repaired or replaced heart valves?
14	What information and advice should adults with heart valve disease and their family and carers receive?

Summary testimony

Please use the space below to summarise your testimony in 250–1000 words. Continue over page if necessary]

Indications for referral for echo

Echo systolic murmur is present in approximately 90% of women and therefore murmur alone should not be used as an indication for referral.

Pharmacological management

The interventions should be used in accordance with the BNF, for example statins are contraindicated in pregnancy

Indications for referral for intervention

Any women with heart valve disease should be referred to a cardiologist with specialist expertise

Diagnosis

Exercise testing is safe in pregnancy and pre-pregnancy. Low flow low gradient stenosis is not relevant for pregnancy

Monitoring before an intervention A woman who is pregnancy needs a different frequency and type of monitoring. This needs to be determined by a multi-disciplinary team (MDT) Interventions The choice of a mechanical or biological valve needs to take into account the possibility of a future pregnancy. The decision should be taken in consultation with a MDT. The choice between TAVI and surgery is the same as for all people with heart valve disease. Monitoring after an intervention Whilst the women is pregnant monitoring needs to take place within the context of an MDT. After pregnancy monitoring is the same as for all people with heart valve disease Anticoagulation This is a highly specialised area and needs to be individualised to the type of valve, site of valve and risk factors
References to other work or publications to support your testimony (if applicable):

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