National Institute for Health and Care Excellence

Final

Heart valve disease presenting in adults: investigation and management

[C] Evidence reviews for pharmacological management

NICE guideline NG208

Intervention evidence review underpinning recommendations 1.2.1 and 1.2.2 and research recommendations in the NICE guideline

November 2021

Final

This evidence review was developed by the National Guideline Centre, hosted by the Royal College of Physicians

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ISBN: 978-1-4731-4301-2

Contents

1 Introduction

The management of heart valve disease necessitates mechanical intervention. However, medical management may also play a role in the management of heart failure symptoms, particularly in heart failure with consequent secondary heart valve disease but also in primary heart valve disease with consequent valvular heart failure awaiting valve intervention. In the absence of heart failure, heart valve disease may impact the medical management of coexistent conditions, for example systemic hypertension. Furthermore, attempts to treat or slow down the progression of heart valve disease were made over the years with a variety of drugs. Consequently, it is important to determine the clinical and cost effectiveness of medical management in adults with heart valve disease with and without concomitant heart failure.

2 Pharmacological management of heart valve disease without concomitant heart failure

2.1 Review question: In adults with heart valve disease without concomitant heart failure, what is the clinical and cost effectiveness of alpha-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARBs), beta blockers, calcium channel blockers, digoxin, diuretics, statins and nitrates to improve clinical outcome?

2.1.1 PICO table

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 diagnosed heart valve disease (without concomitant heart failure) of at least moderate severity stratified by type: • Primary aortic [including bicuspid] stenosis • Primary aortic regurgitation • Primary mitral stenosis • Primary mitral regurgitation • Primary tricuspid regurgitation • Secondary heart valve disease – mitral regurgitation or tricuspid regurgitation A study will be considered to cover a population with heart valve disease without concomitant heart failure if it meets all of the following criteria: • Diagnosis of native heart valve disease • Asymptomatic or have only very mild/low-level symptoms that would not affect daily life (this would include those reported to be in class I of the NYHA classification) • A normal LVEF
Interventions	• Alpha blockers • Angiotensin-converting enzyme (ACE) inhibitors • Angiotensin-II receptor blockers (ARBs) • Beta blockers • Calcium channel blockers • Digoxin • Diuretics • Statins • Nitrates (including nitroprusside) • Any combination of 2 or more of the above
Comparison(s)	• Placebo or no treatment (usual care)

	• Other active comparator listed above, including combinations
Outcomes	Primary outcomes (critical outcomes): • All-cause mortality at ≥12 months (dichotomous) • Cardiac mortality at ≥12 months (dichotomous) • Health-related quality of life at 6 months and ≥12 months (continuous) • Onset of symptoms or progression in NYHA class at ≥12 months • Evidence of HVD progression on imaging (worsening of disease severity) at ≥ 12 months (dichotomous) • Need for heart valve intervention (surgical or transcatheter) at ≥12 months (dichotomous) Secondary outcomes (important outcomes): • Exercise tolerance reported as any of the following (in order of relevance) at 12 months: ○ Supine bicycle workload (watts or % difference from predicted watts) ○ Treadmill exercise time (duration) ○ Oxygen consumption on exercise testing (VO_2 max) ○ Time to near maximal dyspnoea ○ 6-minute walk test ○ Borg dyspnoea index (Continuous) • Withdrawal from the trial due to adverse events at 6 and 12 months (dichotomous)
Study design	Randomised controlled trials (RCTs) or systematic reviews of RCTs If no RCT data are available, observational data will not be considered for pharmacological interventions. This is due to the risk of confounding variables influencing the study results, reducing our confidence in the review results.

2.1.2 Clinical evidence

2.1.2.1 Included studies

Seventeen randomised controlled trials (RCTs) from twenty-seven papers were included in the review;[3, 13, 14, 20, 21, 25-28, 36, 41, 49, 58-60, 66, 71, 74, 104, 129, 131, 132, 143, 145, 146, 154, 177] these are summarised in Table 2 below. Note that the number of studies in the table is eighteen rather than seventeen as one study provided data for both aortic regurgitation and mitral regurgitation populations and is therefore included under each heading. Evidence from these studies is summarised in the clinical evidence summaries below (Table 3 to Table 14).

Studies identified investigated pharmacological management in people with aortic stenosis, aortic regurgitation and mitral regurgitation.

The identified studies included the following comparisons for each population stratum, with some studies reporting more than one comparison:

Primary aortic stenosis:

- ACE inhibitors compared to placebo: 1 study[21]
- Beta blockers compared to placebo: 1 study[66]
- Diuretics compared to placebo: 1 study[154]

- Statins compared to placebo: 4 studies (14 papers)[14, 25-28, 36, 41, 58-60, 71, 74, 131, 132]

Primary aortic regurgitation

- ACE inhibitors compared to placebo/no treatment: 2 studies[49, 177]
- ACE inhibitors compared to calcium channel blockers: 2 studies[13, 49]
- ARBs compared to beta blockers: 1 study[129]
- Beta blockers compared to placebo: 1 study[20]
- Calcium channel blockers compared to placebo/no treatment: 2 studies[49, 145]
- Digoxin compared to calcium channel blockers: 1 study[145]

Primary mitral regurgitation

- ACE inhibitors compared to placebo: 3 studies[104, 143, 177]
- Beta blockers compared to placebo: 1 study[4]

No relevant RCTs were identified investigating pharmacological management in people without concomitant heart failure in the following groups:

- primary mitral stenosis
- primary tricuspid regurgitation
- secondary heart valve disease (mitral regurgitation or tricuspid regurgitation).

No relevant RCTs were identified investigating the use of the following pharmacological interventions:

- alpha blockers
- nitrates
- combinations of treatment.

See also the study selection flow chart in Appendix C:, study evidence tables in Appendix D:, forest plots in Appendix E:and GRADE tables in Appendix F:.

2.1.2.2 Excluded studies

See the excluded studies list in Appendix I:.

2.1.2.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Aortic stenosis				
Bull 2015[21] RCT	**Angiotensin-converting enzyme (ACE) inhibitors** (n=50) Oral ramipril 2.5mg daily for 2 weeks, raised to 5mg daily until the 3 month follow up, raised to 10mg daily for the rest of the study or until maximal tolerable dose (?rationale for larger dose). **Placebo** (n=50) Oral placebo Concurrent medication/care: Not stated	**Primary aortic [including bicuspid] stenosis** (N=100) Severity: Moderate or severe Mechanism of disease: Not stated Defined by cardiac magnetic resonance imaging and echocardiography. Age (mean [SD]): 68.57 (14.22) years Disease mechanism for aortic and mitral stenosis: Not stated/unclear Presence or absence of uncontrolled systemic hypertension (140/85mmHg) at the end of the trial: Not stated/unclear (at the start of the study 11 people in the ACE inhibitor arm and 18 people in the placebo arm had hypertension).	Need for heart valve intervention at 12 months Exercise tolerance at 12 months Withdrawal due to adverse events at 12 months	RIAS study Academic or government funding (Heart Research UK, and the Oxford Comprehensive Biomedical Research Centre, funded by the National Institute of Health Research). Aims of the study: 1) To examine changes in myocardial physiology, in particular the regression of left ventricular mass, as well as other left ventricular physiological parameters using multi-parametric cardiac magnetic resonance in people with moderate to severe aortic stenosis. 2) to assess the safety and tolerability of ramipril in these people. 3) to examine potential improvements in effort tolerance.

Study	Intervention and comparison	Population	Outcomes	Comments
Chan 2010[27] Subsidiary papers: Chan 2011[25] Chan 2010[26] Chan 2007[28] RCT	**Statins** (n=136) Oral rosuvastatin 40mg once a day for 3.5 years. **Placebo** (n=136) Oral placebo Concurrent medication/care: Not stated	**Primary aortic [including bicuspid] stenosis** (N=272) Severity of disease: Mild-to-moderate (mean peak aortic velocity was 3.16 (0.42) in the intervention arm and 3.19 (0.42) in the control arm, considered moderate severity in the British Society of Echocardiography guidelines) Defined by echocardiography. Age (mean [SD]): 57.9 (13.6) years Disease mechanism for aortic stenosis: Mixed (50% of people had bicuspid aortic valve disease, otherwise not stated). Presence or absence of uncontrolled systemic hypertension (140/85mmHg) at the end of the trial: Not stated/unclear (initial blood pressure was not hypertensive). Presence of coronary artery disease: No (people with coronary artery disease or any other indication for statins [apart from presence	All-cause mortality at 3.5 years Cardiac mortality at 3.5 years Need for heart valve intervention at 3.5 years Withdrawal due to adverse events at 3.5 years	ASTRONOMER study Study funded by industry (AstraZeneca Canada) Aim of the study: To assess the effect of intensive lipid lowering with rosuvastatin on the progression of AS in asymptomatic people with mild to moderate AS and to assess the impact of intensive lipid lowering on adverse outcomes related to AS.

Study	Intervention and comparison	Population	Outcomes	Comments
		of hypercholesterolaemia] were excluded)		
Cowell 2005[36] Subsidiary papers: Houslay 2006[74] RCT	**Statins** (n=77) Oral atorvastatin 80mg once a day for 25 months. Concurrent medication/care: 43 taking aspirin, 12 taking ACE inhibitors, 21 taking beta blockers, 8 taking warfarin. **Placebo** (n=78) Oral placebo Concurrent medication/care: 40 taking aspirin, 14 taking ACE inhibitors, 27 taking beta blockers, 12 taking warfarin.	**Primary aortic [including bicuspid] stenosis** (N=155) Severity of disease: Severe (aortic jet velocity of at least 2.5m/s) Defined by echocardiography. Age (mean [SD]): 68 (10.5) years Disease mechanism for aortic stenosis: Calcific Presence or absence of uncontrolled systemic hypertension (140/85mmHg) at the end of the trial: Not stated/unclear (initial values were >140mmHg systolic but <85mmHg diastolic). Presence of coronary artery disease: 39 people had coronary artery disease. 20 had cerebrovascular disease.	Cardiac mortality at 25 months Onset of symptoms or progression of NYHA class at 25 months Need for heart valve intervention at 25 months Withdrawal due to adverse events at 25 months	SALTIRE study Funding not stated Aim of the study: To establish whether intensive lipid-lowering therapy with atorvastatin would halt the progression or induce regression of aortic jet velocity on Doppler echocardiography, and of the aortic-valve calcium score on computed tomography (CT), in people with calcific aortic stenosis.
Dichtl 2008[41] RCT	**Statins** (n=25) Oral atorvastatin 20mg once a day for 3-5 years. Concurrent medication/care: 7 people taking aspirin, 6 people taking ACE inhibitors, 1 person taking a calcium-channel	**Primary aortic [including bicuspid] stenosis** (N=50) Severity of disease: Severe (mean systolic gradients of ≥15mmHg and valvular stenosis flow velocities of ≥2.0m/s).	All-cause mortality at 5 years Cardiac mortality at 5 years Need for heart valve intervention at 5 years Withdrawal due to adverse events at <6 months	TASS study Equipment/drugs provided by industry (Pfizer Austria) Aim of the study: To further evaluate risk factors, the

Study	Intervention and comparison	Population	Outcomes	Comments
	blocker, 1 person taking a beta blocker, 1 person taking a vitamin K antagonist. **Placebo** (n=25) Oral placebo Concurrent medication/care: 14 people taking aspirin, 11 people taking ACE inhibitors, 2 people taking calcium-channel blockers, 5 taking beta blockers, 3 taking vitamin K antagonists.	Defined by transthoracic echocardiography. Age (mean [SD]): 67.0 (11.7) years Disease mechanism for aortic stenosis: Calcific Presence or absence of uncontrolled systemic hypertension (140/85mmHg) at the end of the trial: Not stated/unclear (states 9 people in the intervention arm and 14 in the control arm had hypertension. Antihypertensive medication as prescribed for these people). Presence of coronary artery disease: 13 people had coronary artery disease (5 more in the atorvastatin arm than the control arm)		progression rate of disease, and possible beneficial effects of new-onset lipid lowering therapy with atorvastatin at a standard daily dose of 20mg compared to placebo
Hansson 2017[66] RCT	**Beta blockers** (n=20) Oral extended-release metoprolol from 50mg up to a target daily dose of 200mg (over a six week titration period) or maximal dose without symptoms. Maintained for 5 months. **Placebo** (n=20)	**Primary aortic [including bicuspid] stenosis** (N=40) Severity of disease: Moderate-to-severe Defined by echocardiography and cardiac magnetic resonance imaging.	Quality of life at 5 months Exercise tolerance at 5 months Withdrawal due to adverse events at 5 months	Academic or government funding (Funded by the Lundbeck foundation, the Arvid Nilssons Foundation, the Health Research Fund of Central Denmark Region, Karen Elise Jensens Foundation, and Snedkermester Sophus Jacobsen and Hustru Astrid Jacobsens Foundation).

Study	Intervention and comparison	Population	Outcomes	Comments
	Oral placebo Concurrent medication/care: Not stated	Age (mean [SD]): 70.0 (5.1) years Disease mechanism for aortic stenosis: Not stated/unclear (7 people had bicuspid aortic valves, otherwise not stated). Presence or absence of uncontrolled systemic hypertension (140/85mmHg) at the end of the trial: Mixed (mean blood pressure metoprolol: 136/79 (13/8), mean blood pressure placebo: 140/81 (12/7)).		Aim of the study: To investigate whether metoprolol could improve myocardial efficiency (investigating the safety, haemodynamic and metabolic effects of metoprolol)
Rossebo 2008[132] Subsidiary papers: Bang 2012[14] Greve 2019[59] Greve 2018[58] Greve 2014[60] Holme 2010[71] Rossebø 2008[131] RCT	**Statins** (n=944) Oral simvastatin 40-80mg per day with Ezetimibe 10mg daily for 4.35 years. **Placebo** (n=929) Oral placebo Concurrent medication/care: Before starting the study, all people were given a single-blind placebo tablet and instructed to follow a lipid-lowering diet.	**Primary aortic [including bicuspid] stenosis** (N=1873) Severity of disease: Mild-to-moderate (While saying this, mean aortic valve area intervention group: 1.29 [0.48], placebo group: 1.27 [0.46] which is moderate severity according to the British Society of Echocardiography guidance). Defined by echocardiography. Age (mean [SD]): 67.6 (9.6) years	All-cause mortality at 4.35 years Cardiac mortality at 4.35 years Onset of symptoms or progression of NYHA class at 4.35 years Need for heart valve intervention at 4.35 years Withdrawal due to adverse events at 4.35 years	SEAS trial Study funded by industry (Merck and Schering-Ploug pharmaceuticals) Statin plus Ezetimibe. Reports time-to-event data and dichotomous data. Both have been reported with the dichotomous data being included in the relevant meta-analyses. Aim of the study: To study the effects of long-term, intensive cholesterol lowering with daily use of simvastatin and ezetimibe on clinical and echocardiographic outcomes in the population with no other indication for lipid-lowering treatment.

Study	Intervention and comparison	Population	Outcomes	Comments
		Disease mechanism of aortic stenosis: Mixed (5% had bicuspid aortic valve disease. No statement regarding other aetiology). Presence or absence of uncontrolled systemic hypertension (140/85mmHg) at the end of the trial: Not stated/unclear (initial blood pressure simvastatin-ezetimibe arm: 145.6/82 (20.4/10.6) mmHg; initial blood pressure placebo arm: 144.0/82.0 (20.0/10.0)mmHg) Presence of coronary artery disease: No (people with coronary artery disease, cerebrovascular disease, peripheral arterial disease and diabetes mellitus were excluded).		
Stewart 2008[154] RCT	**Diuretics** (n=33) Oral eplerenone 50mg daily increased up to 100mg after one month if serum potassium, creatinine and systolic blood pressure were within normal limits and no adverse events. **Placebo** (n=32) Oral placebo	**Primary aortic [including bicuspid] stenosis** (N=65) Severity of disease: Moderate to severe (peak velocity >3.0m/s) Defined by Doppler ultrasound and echocardiography.	All-cause mortality at 19 months Cardiac mortality at 19 months Quality of life at 19 months Onset of symptoms or progression of NYHA class at 19 months Withdrawal due to adverse events at 19 months	Study funded by industry (Pfizer) Aim of the study: To determine whether the aldosterone-receptor antagonist eplerenone delays the onset of LV systolic dysfunction or reduces progression of LV hypertrophy assessed by cardiac magnetic resonance imaging in asymptomatic people with moderate to severe aortic stenosis. Additionally, to

Study	Intervention and comparison	Population	Outcomes	Comments
	Concurrent medication/care: Other medications were at the discretion of the patient's usual doctor.	Age (mean [SD]): 67.5 (10.1) years Disease mechanism of aortic stenosis: Not stated/unclear Presence or absence of uncontrolled systemic hypertension (140/85mmHg) at the end of the trial: Not stated/unclear (initial blood pressure eplerenone, 145/83 (21/10)mmHg; initial blood pressure placebo: 144/81 (15/11)mmHg).		investigate the effects of eplerenone on non-invasive measures of LV diastolic function and progression of aortic valve stenosis.
Aortic regurgitation				
Banaszewski 1998[13] RCT	**Calcium-channel blockers (CCB)** (n=12) Oral nifedipine 10-20mg three times a day for 2.75 years. Mean daily dose of 40mg. **Angiotensin-converting enzyme (ACE) inhibitors** (n=13) Oral captopril 12.5-30mg three times a day for 2.75 years. Mean daily dose of 75mg. Concurrent medication/care: The study only included people who were not using ACE inhibitors, calcium-channel blockers, diuretics, beta blockers and digitalis prior to the study.	**Primary aortic regurgitation** (N=31) Severity of disease: Moderate to severe (AR grade range: 2-4) Mechanism of disease: Not stated Defined by echocardiography and cardiac catheterisation. Age (mean [SD]): 34.9 (10.1) years Presence or absence of uncontrolled systemic hypertension (140/85mmHg) at the end of the trial: Not stated/unclear (initial blood	Onset of symptoms or progression of NYHA class at 2.75 years Evidence of HVD progression on imaging (worsening of disease severity) at 2.75 years	The study included an acute phase where participants underwent cardiac catheterisation and exercise therapy after a single dose of nifedipine, which was then repeated after 24 hours with captopril. After a further 24 hours, a long term (randomised) phase of the study was started. Study aim: To look at the short-term haemodynamic effects of nifedipine and captopril on left ventricular volume responses, both at rest and at peak exercise, in asymptomatic people with moderate to severe isolated, untreated aortic regurgitation, enlarged left ventricle and normal left ventricular function, as well as

Study	Intervention and comparison	Population	Outcomes	Comments
		pressure was not hypertensive).		long term effects of the two drugs in this population.
Broch 2016[20] RCT	**Beta blockers** (n=37) Oral metoprolol CR/XL 25mg doubled every week up to a target daily dose of 200mg or the maximum tolerable dose. Maintained for 6 months. **Placebo** (n=38) Oral placebo Concurrent medication/care: All people were allowed to use other vasoactive drugs (6 in each group using ACE inhibitors/ARBs, 2 in beta blocker arm using calcium-channel blockers, 3 in placebo arm using calcium-channel blockers, 5 in both arms using statins, 8 in beta blocker arm using acetylsalicylic acid, 2 in placebo arm using acetylsalicylic acid).	**Primary aortic regurgitation** (N=75) Severity of disease: Severe (Vena contracta width 7.6 (1.6)cm) Mechanism of disease: Not stated Defined by cardiac magnetic resonance imaging and echocardiography. 55 (73%) of people had bicuspid aortic valves. Age (mean [SD]): 44 (14) years Presence or absence of uncontrolled systemic hypertension (140/85mmHg) at the end of the trial: Absent (final blood pressure <140/85mmHg)	Quality of life at 6 months Exercise tolerance at 6 months	Equipment/drugs provided by industry (AstraZeneca) Aim of the study: To examine the effect of metoprolol in asymptomatic people with chronic, moderate-to-severe aortic regurgitation, hypothesising the beta-blockade would reverse LV remodelling in these patients.
Evangelista 2005[49] RCT	**Calcium-channel blockers (CCB)** (n=32) Oral nifedipine 20mg every 12 hours for 7 years **Angiotensin-converting enzyme (ACE) inhibitors** (n=32)	**Primary aortic regurgitation** (N=95) Severity of disease: Severe Mechanism of disease: Not stated	All-cause mortality at 7 years Cardiac mortality at 7 years Onset of symptoms or progression of NYHA class at 7 years Evidence of HVD progression on imaging (worsening of disease severity) at 7 years	Academic or government funding (supported by a grant from the Red de Investigación Cooperativa de las Enfermedades Cardiovasculares from the Instituto de Salud Carlos III, Ministerio de Sanidad y Consumo, Spain)

Study	Intervention and comparison	Population	Outcomes	Comments
	Oral enalapril 20mg daily for 7 years **No treatment** (n=31) Concurrent medication/care not stated	Defined by physical examination, echocardiography, 12-lead electrocardiogram, chest radiography and radionuclide angiography at rest. 40 people had bicuspid aortic valve disease. Age (mean [SD]): 44.35 (13.19) years Presence or absence of uncontrolled systemic hypertension (140/85mmHg) at the end of the trial: Present (final systolic blood pressure >140mmHg, final diastolic blood pressure mixed)	Need for heart valve intervention at 7 years Withdrawal due to adverse events at 7 years	Aim of the study: To ascertain whether either nifedipine or enalapril reduces or delays the need for valve surgery and whether these drugs exert any effect on the size and function of the left ventricle in this population
Roberts 2018[129] RCT	**Angiotensin-II receptor antagonists (ARBs)** (n=17) Oral losartan up-titrated to a maximum of 100mg per day for 1-3 weeks. **Beta blockers** (n=17) Oral metoprolol CR to a maximum dose of 190mg for 1-3 weeks. Concurrent medication/care: People were allowed to use normal antihypertensive	**Primary aortic regurgitation** (N=46) Severity of disease: Severe (regurgitant volume 57.6 [35.8]mL) Mechanism of disease: Not stated Defined by echocardiography. Age (mean [SD]): 51.0 (14.1) years	Exercise tolerance at 3 weeks	Academic or government funding (funded by the Health Research Council of New Zealand) Cross-over study (0 day washout period). Aim of the study: To compare the effects of losartan and metoprolol on aortic regurgitant fraction, LV and aortic function at rest and during exercise in asymptomatic people with chronic aortic

Study	Intervention and comparison	Population	Outcomes	Comments
	medicines, which were then down-titrated or withdrawn completely while taking the drug.	Presence or absence of uncontrolled systemic hypertension (140/85mmHg) at the end of the trial: Absent (blood pressure ranged between 117-118/63-69mmHg).		regurgitation using cardiac magnetic resonance imaging.
Scognamiglio 1990[145] RCT	**Calcium-channel blockers (CCB)** (n=38) Oral nifedipine 20mg twice daily for 1 year. **Placebo** (n=34) Oral placebo Concurrent medication/care: No cardioactive therapies.	**Primary aortic regurgitation** (N=72) Severity of disease: Severe Mechanism of disease: Not stated Defined by Doppler colour flow imaging and confirmation by cardiac catheterisation. Age (mean [SD]): 35.9 (13.3) years Presence or absence of uncontrolled systemic hypertension (140/85mmHg) at the end of the trial: Not stated/unclear (initial blood pressure nifedipine, 154/60 (19/10)mmHg; initial blood pressure placebo: 155/62 (22/12)mmHg).	Need for heart valve intervention at 1 year Withdrawal due to adverse events at 1 year	Funding not stated Aim of the study: To verify whether long-term vasodilator therapy with nifedipine reduces left ventricular overloading and, hence, the left ventricular end diastolic volume and mass in the population.
Scognamiglio 1994[146]	**Digoxin** (n=74) Oral digoxin 0.25mg daily	**Primary aortic regurgitation** (N=143)	All-cause mortality at 6 years	Funding not stated

Study	Intervention and comparison	Population	Outcomes	Comments
RCT	**Calcium channel blockers** (n=69) Oral nifedipine 20mg twice daily Concurrent medication/care: No additional information	Severity of disease: Severe Mechanism of disease: Rheumatic in 87/143. Aortic valve prolapse in 24/143. Bicuspid aortic valve in 32/143. Defined by Doppler colour flow imaging. Age (mean [SD]): 35.0 (13.0) years Presence or absence of uncontrolled systemic hypertension (140/85mmHg) at the end of the trial: Not stated/unclear (initial blood pressure digoxin: 150/58 (22/14), initial blood pressure nifedipine: 154/60 (20/8).)	Onset of symptoms or progression of NYHA class at 6 years Evidence of HVD progression on imaging (worsening of disease severity) at 6 years Need for heart valve intervention at 6 years Withdrawal due to adverse events at 6 years	Aim of the study: To determine whether this therapy delayed or reduced the need for aortic valve replacement.
Wisenbaugh 1994[177] RCT	**Angiotensin-converting enzyme (ACE) inhibitors** (n=13 AR, 14 MR) Oral captopril 25mg three times a day for 6 months. **Placebo** (n=10 AR,18 MR) Oral placebo Concurrent medication/care: Other vasodilating drugs were not used. People who were on	**Primary aortic regurgitation** (n=23) Severity of disease: Severe Mechanism of disease: Not stated Defined by Doppler echocardiography and clinical examination. Age (mean): 28.1 years Presence or absence of uncontrolled systemic	All-cause mortality at 6 months Cardiac mortality at 6 months Onset of symptoms or progression of NYHA class at 6 months	Funding not stated Includes two strata, but outcomes reported separately. Aim of the study: To investigate the effect of captopril on “remodelling” in the population.

Study	Intervention and comparison	Population	Outcomes	Comments
	furosemide were maintained on a constant dose.	hypertension (140/85mmHg) at the end of the trial: Not stated/unclear (initial blood pressure captopril, 131/46mmHg; initial blood pressure placebo: 144/57mmHg). **Primary mitral regurgitation** (n=32) Severity of disease: Severe Mechanism of disease: Not stated Defined by Doppler echocardiography and clinical examination. Age (mean): 24.9 years Presence or absence of uncontrolled systemic hypertension (140/85mmHg) at the end of the trial: Not stated/unclear (initial blood pressure captopril, 117/67mmHg; initial blood pressure placebo: 110/63mmHg).		
Mitral regurgitation				
Ahmed 2012[4] RCT	**Beta blockers** (n=19) Oral metoprolol (Toprol XL) for 2 years. Starting dose of 12.5-25mg/day titrated up to the maximum tolerable dose at 2-	**Primary mitral regurgitation** (N=38) Severity of disease: Not stated	All-cause mortality at 2 years Cardiac mortality at 2 years Need for heart valve intervention at 2 years	Equipment/drugs provided by industry (AstraZeneca).

Study	Intervention and comparison	Population	Outcomes	Comments
	week intervals. Maximum dose: 100mg/day. **Placebo** (n=19) Oral placebo No information on concurrent medication/care.	Mechanism of disease: Degenerative Defined by echocardiography (colour flow Doppler imaging). Age (mean [SD]): 52.9 (9.1) years Presence or absence of uncontrolled systemic hypertension (140/85mmHg) at the end of the trial: Not stated/unclear	Serious adverse events at 2 years	Study aim: To complete MRI analysis of the effects of treatment on left ventricular remodelling and function in people with chronic, isolated mitral regurgitation
Marcotte 1997[104] RCT	**Angiotensin-converting enzyme (ACE) inhibitors** (n=12) Oral lisinopril 5mg for two weeks, then doubled every two weeks until maximal dose of 20mg a day or maximal tolerable dose. Maintained for 1 year. **Placebo** (n=11) Oral placebo Concurrent medication/care: No other cardiovascular medications	**Primary mitral regurgitation** (N=23) Severity of disease: At least moderate Mechanism of disease: Organic Defined by echocardiography. Age (mean [SE]): 53.3 (2.4) years Presence or absence of uncontrolled systemic hypertension (140/85mmHg) at the end of the trial: Not stated/unclear (absent at the start of the study).	All-cause mortality at 1 year Cardiac mortality at 1 year Quality of life at 6 months Quality of life at 1 year Exercise tolerance at 1 year Withdrawal due to adverse events at 12 months	Study funded by industry (Merck Frosst Canada inc.) Population may include people with congenital mitral regurgitation. Aim of the study: To determine the effectiveness of lisinopril in reducing the severity of mitral regurgitation in the population and ultimately in altering favourably the natural history of the disease

Study	Intervention and comparison	Population	Outcomes	Comments
Sampaio 2005[143] RCT	**Angiotensin-converting enzyme (ACE) inhibitors** (n=27) Oral enalapril 5mg twice a day, titrated up to the maximal tolerated dose of at most 20mg twice a day (increased to 10mg at 2 weeks and 20mg at 4 weeks). Maintained for 1 year. **Placebo** (n=27) Oral placebo Concurrent medication/care: Not receiving therapy with any other vasodilators.	**Primary mitral regurgitation** (N=47) Severity of disease: Moderate to severe Mechanism of disease: Secondary to mitral prolapse or rheumatic heart disease Defined by echocardiography. Age (mean [SD]): 39 (15) years Presence or absence of uncontrolled systemic hypertension (140/85mmHg) at the end of the trial: Absent (final blood pressure ACE inhibitors: 122/78 (12/9)mmHg; final blood pressure placebo: 126/79 (12/8)mmHg).	Onset of symptoms or progression of NYHA class at 12 months Need for heart valve intervention at 12 months Exercise tolerance at 12 months	Academic or government funding (E.J. Zerbini foundation, São Paulo, Brazil) At the start of the study 20 people were NYHA class I, 17 people were NYHA class II. Aim of study: To evaluate the effects of enalapril on LV dimensions, LV systolic index, and functional capacity, with cardiopulmonary testing, after 12 months of therapy.
Wisenbaugh 1994[177] RCT	**Angiotensin-converting enzyme (ACE) inhibitors** (n=13 AR, 14 MR) Oral captopril 25mg three times a day for 6 months. **Placebo** (n=10 AR,18 MR) Oral placebo	**Primary aortic regurgitation** (n=23) Severity of disease: Severe Mechanism of disease: Not stated Defined by Doppler echocardiography and clinical examination.	All-cause mortality at 6 months Cardiac mortality at 6 months Onset of symptoms or progression of NYHA class at 6 months	Funding not stated Includes two strata, but outcomes reported separately. Aim of the study: To investigate the effect of captopril on “remodelling” in the population.

Study	Intervention and comparison	Population	Outcomes	Comments
	Concurrent medication/care: Other vasodilating drugs were not used. People who were on furosemide were maintained on a constant dose.	Age (mean): 28.1 years Presence or absence of uncontrolled systemic hypertension (140/85mmHg) at the end of the trial: Not stated/unclear (initial blood pressure captopril, 131/46mmHg; initial blood pressure placebo: 144/57mmHg). **Primary mitral regurgitation** (n=32) Severity of disease: Severe Mechanism of disease: Not stated Defined by Doppler echocardiography and clinical examination. Age (mean): 24.9 years Presence or absence of uncontrolled systemic hypertension (140/85mmHg) at the end of the trial: Not stated/unclear (initial blood pressure captopril, 117/67mmHg; initial blood pressure placebo: 110/63mmHg).		

See Appendix D:for full evidence tables.

2.1.2.4 Quality assessment of clinical studies included in the evidence review

2.1.2.4.1 Primary aortic [including bicuspid] stenosis

Table 3: Clinical evidence summary: ACE inhibitors compared to placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with ACE inhibitors (95% CI)
All-cause mortality - not reported	-	-	Not estimable	-	-
Cardiac mortality - not reported	-	-	Not estimable	-	-
Health-related quality of life - not reported	-	-	Not estimable	-	-
Health-related quality of life - not reported	-	-	Not estimable	-	-
Onset of symptoms or progression in NYHA class - not reported	-	-	Not estimable	-	-
Evidence of HVD progression on imaging (worsening of disease severity) - not reported	-	-	Not estimable	-	-
Need for heart valve intervention	83 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 2.15 (0.42 to 11.1)	47 per 1000	**54 more per 1000** (from 27 fewer to 475 more)
Exercise tolerance (change score) Exercise distance measured	67 (1 study) 12 months	⨁⨁⊖⊖ LOW[1,3] due to risk of bias		The mean exercise tolerance (change score) in the control groups was 29 meters	The mean exercise tolerance (change score) in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with ACE inhibitors (95% CI)
with treadmill exercise test (higher is better outcome)					**49 meters lower** (61.59 to 36.41 lower)
Withdrawal due to adverse events	80 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 2.21 (0.21 to 23.41)	24 per 1000	**29 more per 1000** (from 19 fewer to 538 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] MIDs used to assess imprecision were ±187.0

Table 4: Clinical evidence summary: beta blockers compared to placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with beta blockers (95% CI)
All-cause mortality - not reported	-	-	Not estimable	-	-
Cardiac mortality - not reported	-	-	Not estimable	-	-
Health-related quality of life (change score) Minnesota living with heart failure questionnaire. Scale from: 0 to 105 (high score is poor outcome).	38 (1 study) 5 months	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, imprecision		The mean health-related quality of life (change score) in the control groups was -1	The mean health-related quality of life (change score) in the intervention groups was **6 higher** (0.55 lower to 12.55 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with beta blockers (95% CI)
Health-related quality of life - not reported	-	-	Not estimable	-	-
Onset of symptoms or progression in NYHA class - not reported	-	-	Not estimable	-	-
Evidence of HVD progression on imaging (worsening of disease severity) - not reported	-	-	Not estimable	-	-
Need for heart valve intervention - not reported	-	-	Not estimable	-	-
Exercise tolerance (change score) 6-minute walk test distance (higher is better outcome)	38 (1 study) 5 months	⨁⊖⊖⊖ VERY LOW[1,2,4] due to risk of bias, imprecision		The mean exercise tolerance (change score) in the control groups was 14 meters	The mean exercise tolerance (change score) in the intervention groups was **12 meters lower** (42.22 lower to 18.22 higher)
Withdrawal or dose reduction due to adverse events	38 (1 study) 5 months	⨁⊖⊖⊖ VERY LOW[1,2,5] due to risk of bias, indirectness, imprecision	RR 2 (0.41 to 9.65)	105 per 1000	**105 more per 1000** (from 62 fewer to 908 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] MIDs used to assess imprecision were ±5.0
[4] MIDs used to assess imprecision were ±21.0
[5] Downgraded by 1 increment as the outcome includes people who had dose reductions or withdrawal due to adverse events

Table 5: Clinical evidence summary: diuretics compared to placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with diuretics (95% CI)
All-cause mortality	61 (1 study) 19 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.52 (0.05 to 5.4)	65 per 1000	**31 fewer per 1000** (from 62 fewer to 286 more)
Cardiac mortality	59 (1 study) 19 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 0.14 (0 to 7.06)	33 per 1000	**30 fewer per 1000** (from 120 fewer to 60 more)[3]
Health-related quality of life - not reported	-	-	Not estimable	-	-
Health-related quality of life (change score) SF-36 physical functioning subscale. Scale from: 0 to 100 (high score is good outcome).	59 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[1,2,4] due to risk of bias, imprecision		The mean health-related quality of life (change score) in the control groups was -9	The mean health-related quality of life (change score) in the intervention groups was **4 higher** (6.5 lower to 14.5 higher)
Health-related quality of life (change score) SF-36 role physical subscale. Scale from: 0 to 100 (high score is good outcome).	59 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[1,2,4] due to risk of bias, imprecision		The mean health-related quality of life (change score) in the control groups was -12	The mean health-related quality of life (change score) in the intervention groups was **3 higher** (15.12 lower to 21.12 higher)
Onset of symptoms or progression of NYHA class	59 (1 study) 19 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of	RR 1.34 (0.7 to 2.57)	333 per 1000	**113 more per 1000** (from 100 fewer to 523 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with diuretics (95% CI)
		bias, imprecision			
Evidence of HVD progression on imaging (worsening of disease severity) - not reported	-	-	Not estimable	-	-
Need for heart valve intervention - not reported	-	-	Not estimable	-	-
Withdrawal due to adverse events	62 (1 study) 19 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 6.94 (0.14 to 350.54)	0 per 1000	**30 more per 1000** (from 50 fewer to 120 more)[3]

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect calculated manually using risk difference as zero events in one arm of the study
[4] MIDs used to assess imprecision were ±3.0

Table 6: Clinical evidence summary: statins compared to placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with statins (95% CI)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with statins (95% CI)
All-cause mortality	2189 (3 studies) 4.3 years	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	RR 1.01 (0.79 to 1.3)	44 per 1000	**0 more per 1000** (from 9 fewer to 13 more)
All-cause mortality (time to event)	1873 (1 study) 4.4 years	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	HR 1.04 (0.79 to 1.37)	108 per 1000	**4 more per 1000** (from 22 fewer to 37 more)
Cardiac mortality	2344 (4 studies) 3.7 years	⨁⨁⊖⊖ LOW[2,3] due to indirectness, imprecision	RR 0.75 (0.54 to 1.03)	52 per 1000	**13 fewer per 1000** (from 24 fewer to 2 more)
Cardiac mortality (time to event)	1873 (1 study) 4.4 years	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	HR 0.83 (0.56 to 1.23)	60 per 1000	**10 fewer per 1000** (from 26 fewer to 13 more)
Health-related quality of life - not reported	-	-	Not estimable	-	-
Health-related quality of life - not reported	-	-	Not estimable	-	-

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with statins (95% CI)
Onset of symptoms or progression of NYHA class	2028 (2 studies) 3.2 years	⨁⊖⊖⊖ VERY LOW[2,3] due to indirectness, imprecision	RR 0.99 (0.59 to 1.66)	44 per 1000	**0 fewer per 1000** (from 18 fewer to 29 more)
Onset of symptoms or progression of NYHA class (time to event)	1873 (1 study) 4.4 years	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	HR 1.09 (0.62 to 1.92)	25 per 1000	**2 more per 1000** (from 9 fewer to 22 more)
Evidence of HVD progression on imaging (worsening of disease severity) - not reported	-	-	Not estimable	-	-
Need for heart valve intervention	2346 (4 studies) 3.7 years	⨁⊖⊖⊖ VERY LOW[2,3,4] due to inconsistency, indirectness, imprecision	RR 0.93 (0.7 to 1.24)	222 per 1000	**16 fewer per 1000** (from 67 fewer to 53 more)
Need for heart valve intervention (time to event)	1873 (1 study) 4.4 years	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, indirectness	HR 1 (0.84 to 1.19)	299 per 1000	**0 fewer per 1000** (from 41 fewer to 46 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with statins (95% CI)
Withdrawal due to adverse events	48 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[1,3] due to risk of bias, imprecision	Peto OR 6.82 (0.13 to 344.93)	0 per 1000	**40 more per 1000** (from 70 fewer to 150 more)[5]
Withdrawal due to adverse events	2296 (3 studies) 3.3 years	⨁⨁⊖⊖ LOW[2,3] due to indirectness, imprecision	RR 1.15 (0.94 to 1.4)	131 per 1000	**20 more per 1000** (from 8 fewer to 52 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment as one study included a statin and ezetimibe in the intervention group
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Downgraded by 1 as the point estimate varies widely across studies, with subgroup analysis not being possible due to the difference being seen in one study
[5] Absolute effect calculated manually using risk difference as zero events in one arm of the study

2.1.2.4.2 Primary aortic regurgitation

Table 7: Clinical evidence summary: ACE inhibitors compared to placebo/no treatment

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/no treatment	Risk difference with ACE-inhibitors (95% CI)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/no treatment	Risk difference with ACE-inhibitors (95% CI)
All-cause mortality	63 (1 study) 7 years	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.97 (0.06 to 14.82)	32 per 1000	**1 fewer per 1000** (from 30 fewer to 442 more)
Cardiac mortality	63 (1 study) 7 years	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 0.13 (0 to 6.61)	32 per 1000	**30 fewer per 1000** (from 120 fewer to 50 more)[3]
Health-related quality of life - not reported	-	-	Not estimable	-	-
Health-related quality of life - not reported	-	-	Not estimable	-	-
Onset of symptoms or progression of NYHA class	83 (2 studies) 7 years	⨁⊖⊖⊖ VERY LOW [1,4] due to risk of bias, imprecision	RD 0 (-0.13 to 0.22)	200 per 1000	**40 more per 1000** (from 130 fewer to 220 more)[5]
Evidence of HVD progression on imaging (worsening of disease severity)	63 (1 study) 7 years	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.36 (0.71 to 2.58)	323 per 1000	**116 more per 1000** (from 94 fewer to 510 more)
Need for heart valve intervention	63 (1 study) 7 years	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.29 (0.74 to 2.27)	387 per 1000	**112 more per 1000** (from 101 fewer to 491 more)
Withdrawal due to adverse events	63 (1 study) 7 years	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 7.65 (0.77 to 76.34)	0 per 1000	**90 more per 1000** (from 20 fewer to 210 more)[3]

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/no treatment	Risk difference with ACE-inhibitors (95% CI)

[3] Absolute effect calculated manually using risk difference as zero events in one arm of the study
[4] Imprecision was assessed based on OIS value as there were zero events in both arms of one of the studies. Downgraded by 2 increments as the OIS was <80%
[5] Absolute effect calculated manually using risk difference as zero events in both arms of a study

Table 8: Clinical evidence summary: ACE inhibitors compared to calcium channel blockers

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with calcium channel blockers	Risk difference with ACE inhibitors (95% CI)
All-cause mortality	64 (1 study) 7 years	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1 (0.07 to 15.3)	31 per 1000	**0 fewer per 1000** (from 29 fewer to 447 more)
Cardiac mortality	64 (1 study) 7 years	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 0.14 (0 to 6.82)	31 per 1000	**30 fewer per 1000** (from 110 fewer to 50 more)[3]
Health-related quality of life - not reported	-	-	Not estimable	-	-
Health-related quality of life - not reported	-	-	Not estimable	-	-

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with calcium channel blockers	Risk difference with ACE inhibitors (95% CI)
Onset of symptoms or progression of NYHA class	89 (2 studies) 4.8 years	⨁⊖⊖⊖ VERY LOW[1,4] due to risk of bias, imprecision	-RD 0.04 (-0.12 to 0.21)	125 per 1000	**40 more per 1000** (from 120 fewer to 210 more)[5]
Evidence of HVD progression on imaging (worsening of disease severity)	89 (2 studies) 4.8 years	⨁⊖⊖⊖ VERY LOW[1,2,6] due to risk of bias, inconsistency, imprecision	RR 0.84 (0.14 to 4.94)	240 per 1000	**20 fewer per 1000** (from 330 fewer to 290 more)[7]
Need for heart valve intervention	64 (1 study) 7 years	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.23 (0.71 to 2.12)	406 per 1000	**93 more per 1000** (from 118 fewer to 455 more)
Withdrawal due to adverse events	64 (1 study) 7 years	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.43 (0.12 to 1.51)	219 per 1000	**125 fewer per 1000** (from 193 fewer to 112 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

[3] Absolute effect calculated manually using risk difference as zero events in one arm of the study

[4] Imprecision was assessed based on OIS value as there were zero events in both arms of one of the studies. Downgraded by 2 increments as the OIS was <80%.

[5] Absolute effect calculated manually using risk difference as zero events in both arms of one study

[6] Downgraded by 1 increment as point estimates vary widely between the two studies

[7] Absolute effect calculated manually using risk difference as zero events in one arm of one study

Table 9: Clinical evidence summary: ARBs compared to beta blockers

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with beta blockers	Risk difference with ARBs (95% CI)
All-cause mortality - not reported	-	-	Not estimable	-	-
Cardiac mortality - not reported	-	-	Not estimable	-	-
Health-related quality of life - not reported	-	-	Not estimable	-	-
Health-related quality of life - not reported	-	-	Not estimable	-	-
Onset of symptoms or progression in NYHA class - not reported	-	-	Not estimable	-	-
Evidence of HVD progression on imaging (worsening of disease severity) - not reported	-	-	Not estimable	-	-
Need for heart valve intervention - not reported	-	-	Not estimable	-	-
Exercise tolerance (final value) exercise work rate using an ergometer (higher is better outcome)	34 (1 study) 3 weeks	⨁⊖⊖⊖ VERY LOW[1,2,3,4] due to risk of bias, indirectness, imprecision		The mean exercise tolerance (final value) in the control groups was 29 Watts	The mean exercise tolerance (final value) in the intervention groups was **0 Watts higher** (4.75 lower to 4.75 higher)[5]

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment as follow up less than 1 month
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] MIDs used to assess imprecision were ±4.0
[5] Insufficient information available to conduct a paired analysis

Table 10: Clinical evidence summary: Beta blockers compared to placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with beta blockers (95% CI)
All-cause mortality - not reported	-	-	Not estimable	-	-
Cardiac mortality - not reported	-	-	Not estimable	-	-
Onset of symptoms or progression in NYHA class - not reported	-	-	Not estimable	-	-
Quality of life (final value) EuroQol visual analogue scale. Scale from: 0 to 100 (high score is good outcome).	72 (1 study) 6 months	⨁⨁⨀⨀ LOW[1,2,3] due to risk of bias, imprecision		The mean quality of life (final value) in the control groups was 82	The mean quality of life (final value) in the intervention groups was **3 higher** (2.7 lower to 8.7 higher)
Quality of life (final value) KCCQ. Scale from: 0 to 100 (high score is good outcome).	72 (1 study) 6 months	⨁⨁⨀⨀ LOW[1,2,4] due to risk of bias, imprecision		The mean quality of life (final value) in the control groups was 96	The mean quality of life (final value) in the intervention groups was **2 higher** (17.76 lower to 21.76 higher)
Evidence of HVD progression on imaging (worsening of disease severity) - not reported	-	-	Not estimable	-	-
Need for heart valve intervention - not reported	-	-	Not estimable	-	-
Exercise tolerance Peak work (bicycle ergometer) (higher is better outcome)	72 (1 study) 6 months)	⨁⨁⨀⨀ LOW[1,2,5] due to risk of bias, imprecision		The mean exercise tolerance in the control groups was 241 watts	The mean exercise tolerance in the intervention groups was **12 watts lower** (40.64 lower to 16.64 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with beta blockers (95% CI)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] MIDs used to assess imprecision were ±5.00
[4] MIDs used to assess imprecision were ±21.39
[5] MIDs used to assess imprecision were ±31.50

Table 11: Clinical evidence summary: Calcium channel blockers compared to placebo/no treatment

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/no treatment	Risk difference with Calcium channel blockers (95% CI)
All-cause mortality	63 (1 study) 7 years	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.97 (0.06 to 14.82)	32 per 1000	**1 fewer per 1000** (from 30 fewer to 442 more)
Cardiac mortality	64 (1 study) 7 years	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1 (0.07 to 15.3)	31 per 1000	**0 fewer per 1000** (from 29 fewer to 443 more)
Health-related quality of life - not reported	-	-	Not estimable	-	-
Health-related quality of life - not reported	-	-	Not estimable	-	-
Onset of symptoms or progression of NYHA class	63 (1 study) 7 years	⨁⊖⊖⊖ VERY LOW[1,2]	RR 0.97 (0.42 to 2.26)	258 per 1000	**8 fewer per 1000** (from 150 fewer to 325 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/no treatment	Risk difference with Calcium channel blockers (95% CI)
		due to risk of bias, imprecision			
Evidence of HVD progression on imaging (worsening of disease severity)	63 (1 study) 7 years	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.97 (0.47 to 2)	323 per 1000	**10 fewer per 1000** (from 171 fewer to 323 more)
Need for heart valve intervention	135 (2 studies) 7 years	⨁⊖⊖⊖ VERY LOW[1,3] due to risk of biasimprecision	RD 0.01 (-0.11 to 0.13)	179 per 1000	**10 more per 1000** (from 110 fewer to 130 more)[4]
Withdrawal due to adverse events	135 (2 studies) 7 years	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias,imprecision	OR 9.64 (1.22 to 76.04)	0 per 1000	**120 more per 1000** (from 30 more to 200 more)[5]

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Imprecision was assessed based on OIS value as there were zero events in both arms of one of the studies. Downgraded by 2 increments as the OIS was <80%.
[4] Absolute effect calculated manually using risk difference as zero events in both arms of a study

[5] Absolute effect calculated manually using risk difference as zero events one arm of the study

Table 12: Clinical evidence summary: Digoxin compared to calcium channel blockers

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium channel blockers	Risk difference with Digoxin (95% CI)
All-cause mortality	135 (1 study) 6 years	⨁⊖⊖⊖ VERY LOW[2,3] due to risk of bias, imprecision	Peto OR 6.88 (0.14 to 347.65)	0 per 1000	**10 more per 1000** (from 30 fewer to 50 more)[1]
Cardiac mortality - not reported	-	-	Not estimable	-	-
Health-related quality of life - not reported	-	-	Not estimable	-	-
Health-related quality of life - not reported	-	-	Not estimable	-	-
Onset of symptoms of progression of NYHA class	135 (1 study) 6 years	⨁⨁⊖⊖ LOW[2,3] due to risk of bias, imprecision	RR 2.63 (1.11 to 6.26)	92 per 1000	**150 more per 1000** (from 10 more to 486 more)
Evidence of HVD progression on imaging (worsening of disease severity)	135 (1 study) 6 years	⨁⨁⊖⊖ LOW[2,3] due to risk of bias, imprecision	Peto OR 7.30 (1.23 to 43.33)	0 per 1000	**70 more per 1000** (from 10 more to 140 more)[1]
Need for heart valve intervention	135 (1 study) 6 years	⨁⨁⨁⊖ MODERATE[2] due to risk of bias	RR 3.10 (1.33 to 7.22)	92 per 1000	**194 more per 1000** (from 30 more to 574 more)
Withdrawal due to adverse events	135 (1 study) 6 years	⨁⨁⊖⊖ LOW[2,5] due to risk of bias, imprecision	RD 0 (-0.03 to 0.03)	0 per 1000	**0 fewer per 1000** (from 30 fewer to 30 more)[4]

[1] Absolute effect calculated from risk difference due to zero events in one study arm
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Calcium channel blockers	Risk difference with Digoxin (95% CI)

[4] Absolute effect calculated from risk difference due to zero events in both study arms
[5] Downgraded by 1 increment as sample size is between 75 and 350 with zero events in both arms

2.1.2.4.3 Primary mitral stenosis

No studies identified.

2.1.2.4.4 Primary mitral regurgitation

Table 13: Clinical evidence summary: ACE inhibitors compared to placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with ACE inhibitors (95% CI)
All-cause mortality	45 (2 studies) 6-12 months	⨁⊖⊖⊖ VERY LOW[2,3,4] due to risk of bias, indirectness, imprecision	-RD -0.04 (-0.18 to 0.11)	29 per 1000	**40 fewer per 1000** (from 180 fewer to 110 more)[1]
Cardiac mortality	45 (2 studies) 6-12 months	⨁⊖⊖⊖ VERY LOW[2,3,4] due to risk of bias, indirectness, imprecision	-RD -0.04 (-0.18 to 0.11)	29 per 1000	**40 fewer per 1000** (from 180 fewer to 110 more)[1]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with ACE inhibitors (95% CI)
Quality of life (change score) Life quality index. Scale from: 1 to 6 (high score is good outcome).	16 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[2,3,5] due to risk of bias, indirectness		The mean quality of life (change score) in the control groups was 0.4	The mean quality of life (change score) in the intervention groups was **0.2 lower** (1.03 lower to 0.63 higher)
Quality of life (change score) Life quality index. Scale from: 1 to 6 (high score is good outcome).	16 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW[2,3,5] due to risk of bias, indirectness		The mean quality of life (change score) in the control groups was 0.4	The mean quality of life (change score) in the intervention groups was **0.1 lower** (0.93 lower to 0.73 higher)
Onset of symptoms or progression of NYHA class	77 (2 studies) 6-12 months	⨁⊖⊖⊖ VERY LOW[2,3,6] due to risk of bias, indirectness, imprecision	RR 0.17 (0.02 to 1.26)	120 per 1000	**140 fewer per 1000** (from 270 fewer to 10 fewer)[1]
Evidence of HVD progression on imaging (worsening of disease severity) - not reported	-	-	Not estimable	-	-
Need for heart valve intervention	48 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW[2,6] due to risk of bias, imprecision	Peto OR 0.11 (0 to 5.76)	46 per 1000	**50 fewer per 1000** (from 160 fewer to 70 more)[1]
Exercise tolerance (change score) Bruce Protocol treadmill exercise time (seconds) (higher is better outcome)	16 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW[2,3,6,7] due to risk of bias, indirectness, imprecision		The mean exercise tolerance (change score) in the control groups was 18 seconds	The mean exercise tolerance (change score) in the intervention groups was **21 seconds higher** (42.97 lower to 84.97 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with ACE inhibitors (95% CI)
Exercise tolerance (final value) oxygen uptake at peak exercise (mL/min) (higher is better outcome)	47 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW[2,6,8] due to risk of bias, imprecision		The mean exercise tolerance (final value) in the control groups was 1433 mL/min	The mean exercise tolerance (final value) in the intervention groups was **361 mL/min higher** (50.91 to 671.09 higher)
Withdrawal due to adverse events	21 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW[2,3,6] due to risk of bias, indirectness, imprecision	RR 4.4 (0.59 to 33.07)	91 per 1000	**309 more per 1000** (from 37 fewer to 1000 more)

[1] Absolute effect calculated manually using risk difference as zero events in the studies
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Downgraded by 1 increment as some of the participants in one study may have had congenital valvular heart disease

[4] Imprecision was assessed based on OIS value as there were zero events in both arms of one of the studies. Downgraded by 2 increments as the OIS was <80%.
[5] MIDs used to assess imprecision were ±1.12
[6] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[7] MIDs used to assess imprecision were ±66.90
[8] MIDs used to assess imprecision were ±270.50

Table 14: Clinical evidence summary: beta blockers compared to placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with beta blockers (95% CI)
All-cause mortality	37 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW[2,3] due to risk of bias, imprecision	OR 7.01 (0.14 to 353.8)	0 per 1000	**50 more per 1000** (from 80 fewer to 190 more)[1]
Cardiac mortality	37 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW[2,3] due to risk of bias, imprecision	OR 7.01 (0.14 to 353.8)	0 per 1000	**50 more per 1000** (from 80 fewer to 190 more)[1]
Health-related quality of life - not reported	-	-	Not estimable	-	-
Health-related quality of life - not reported	-	-	Not estimable	-	-
Onset of symptoms or progression in NYHA class - not reported	-	-	Not estimable	-	-
Evidence of HVD progression on imaging (worsening of disease severity) - not reported	-	-	Not estimable	-	-
Need for heart valve intervention	36 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW[2,3] due to risk of bias, imprecision	RR 0.33 (0.08 to 1.44)	333 per 1000	**223 fewer per 1000** (from 306 fewer to 147 more)
Serious adverse events	36 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW[2,3,4] due to risk of bias, indirectness, imprecision	RR 0.43 (0.13 to 1.4)	389 per 1000	**222 fewer per 1000** (from 338 fewer to 156 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with beta blockers (95% CI)

[1] Absolute effect calculated manually using risk difference as zero events in the studies
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Downgraded by 1 increment as the study does not report withdrawal due to adverse events

2.1.2.4.5 Primary tricuspid regurgitation

No studies identified.

2.1.2.4.6 Secondary valvular heart disease – mitral regurgitation and tricuspid regurgitation

No studies identified.

For strata where evidence was identified as described in the tables above, see Appendix F: for full GRADE tables.

2.1.3 Economic evidence

2.1.3.1 Included studies

No health economic studies were included.

2.1.3.2 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 G:.

2.1.3.3 Health economic modelling

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

2.1.3.4 Unit costs

The following relevant unit costs have been included to inform the committee of the cost implications of different pharmacological management strategies.

Table 15: Unit costs for different drugs used for pharmacological management of people with heart failure and concomitant heart valve disease

Class	Drug	Dose (tablet unless specified)	Unit cost
Alpha blockers	doxasozin	2mg	£ 0.04
ACE inhibitors	ramipril	1.25mg	£ 0.07
		2.5mg	£ 0.15
		5mg	£ 0.17
		10mg	£ 0.18
	captopril	12.5mg	£ 0.02
		25mg	£ 0.01
		50mg	£ 0.03
	enalapril	2.5mg	£ 0.18
		5mg, 10mg, 20mg	£ 0.06
	lisinopril	2.5mg, 5mg, 10mg, 20mg	£ 0.03
	quinapril	2.5mg, 5mg, 10mg	£ 0.31
		20mg	£ 0.39
		40mg	£ 0.13
	fosinopril	10mg	£ 0.15
		20mg	£ 0.14
Angiotensin II receptor blockers (ARBs)	candesartan cilexitil	2mg	£ 0.22
		4mg	£ 0.08
		8mg	£ 0.04

		16mg	£	0.06
		32mg	£	0.06
	losartan	12.5mg	£	0.11
		25mg	£	0.12
		50mg	£	0.07
		100mg	£	0.07
Beta blockers	bisoprolol	1.25mg	£	0.03
		3.75mg	£	0.03
		5mg	£	0.02
		10mg	£	0.03
	carvedilol	3.125mg	£	0.03
		6.25mg	£	0.03
		12.5mg	£	0.03
		25mg	£	0.04
	nebivolol	2.5mg	£	0.42
		5mg	£	0.16
		10mg	£	0.92
Diuretics	furosemide	20mg tablet	£	0.05
		40mg tablet	£	0.07
		10 mg per 1 ml solution for injection	£	1.74
	bumetanide	1mg tablet	£	0.05
		5mg tablet	£	0.25
	torasemide	2.5mg tablet	£	0.14
		5mg	£	0.20
		10mg	£	0.29
Calcium channel blockers	amlopodine	5mg, 10mg	£	0.03
Digoxin	-	62.5 micrograms	£	0.05
		125 micrograms	£	0.05
Nitrates	Isosorbide dinitrate	10mg	£	0.24
	Nitroprusside		No tariff price available	
Statins	Atorvastatin	10mg	£	0.03
		20mg	£	0.03
		80mg	£	0.07
	Fluvastin	20mg	£	0.08
		40mg	£	0.09
		80mg (modified release capsule)	£	0.69
	Pravastatin	10mg	£	0.03
		20mg	£	0.04
		40mg	£	0.05

	Rosuvastatin	5mg	£	0.06
		10mg	£	0.05
		20mg	£	0.07
		40mg	£	0.10
	Simvastatin	10mg	£	0.03
		20mg	£	0.03
		40mg	£	0.04
		80mg	£	0.06

Source: BNF 2018[79]

2.1.4 Evidence statements

2.1.4.1 Clinical evidence statements

See the summary of evidence in Table 3 to Table 14 .

2.1.4.2 Health economic evidence statements

No relevant economic evaluations were identified.

2.1.5 The committee's discussion of the evidence

2.1.5.1 Interpreting the evidence

2.1.5.1.1 The outcomes that matter most

The critical outcomes were all-cause mortality, cardiac mortality, health-related quality of life, onset of symptoms or progression in NYHA class, evidence of HVD progression on imaging and need for heart valve intervention. The important outcomes were exercise tolerance and withdrawal from the trial due to adverse events. Exercise tolerance was considered important due to its impact on quality of life and as a measure of symptom burden and withdrawal due to adverse events would provide information on any severe events associated with any of the drugs.

Physiological outcomes were not included as they are not clinically relevant endpoints, and the outcomes they aim to predict that are important to patients are captured by the included outcomes.

There was very limited evidence. All outcomes were reported in at least one study. However, there were gaps in outcomes reported for specific strata. For the aortic stenosis and mitral regurgitation strata, no studies reported evidence of HVD progression on imaging. For the aortic regurgitation stratum, no studies reported health-related quality of life at ≥12 months or withdrawal due to adverse events at <6 months.

2.1.5.1.2 The quality of the evidence

No relevant RCTs for mitral stenosis, tricuspid regurgitation and secondary heart valve disease were identified. No relevant RCTs investigating the use of alpha blockers or nitrates were identified. Seventeen RCTs were included in this review and evidence was only available for the following comparisons:

- Aortic stenosis
  - ACE-I versus placebo

  - Beta-blocker versus placebo
  - Diuretic versus placebo
  - Statin versus placebo
- Aortic regurgitation
  - ACE-I versus placebo/no treatment
  - ACE-I versus calcium channel blocker
  - ARB versus beta-blocker
  - Beta-blocker versus placebo
  - Calcium channel blocker versus placebo/no treatment
  - Digoxin versus calcium channel blocker
- Mitral regurgitation
  - ACE-I versus placebo
  - Beta-blocker versus placebo

Evidence ranged from moderate to very low quality, with the majority of the evidence being of very low quality and only one outcome having a moderate quality rating. Evidence was mainly downgraded due to risk of bias and imprecision. Analyses frequently included only a small number of participants and had low event rates resulting in great uncertainty. Additionally, some evidence was considered to be indirect because of inclusion of additional pharmacological agents not stated in the protocol (for example, ezetimibe with statins) or inclusion of people with congenital valve disease (while including an adequate proportion of the population without congenital valve disease to still fulfil the protocolised inclusion criteria). Two outcomes (need for heart valve intervention for statins compared to placebo in aortic stenosis and evidence of heart valve disease progression on imaging for ACE-I compared to calcium channel blockers in aortic regurgitation) showed inconsistency with heterogeneity that could not be explained by subgroup analysis.

2.1.5.1.3 Benefits and harms

Aortic stenosis

The evidence showed a small clinically important benefit of statins for cardiac mortality, with no clinically important difference in all-cause mortality, onset of symptoms, need for heart valve intervention, and withdrawal due to adverse events; however, for all of these outcomes confidence intervals demonstrated uncertainty in the effect. Although the evidence from these studies suggested increased withdrawal due to adverse events in the statin group compared to placebo, there was also uncertainty in this effect and the absolute effect was not considered to represent a clinically important difference. The committee agreed that statins are unlikely to directly affect the severity of the aortic valve lesion, which possibly explains why there was no clinically important difference in need for heart valve intervention observed, but they may help with other confounding variables that we cannot determine from this evidence that influence cardiac mortality. For example, aortic stenosis may be a marker for increased cardiovascular risk. Two of the four studies that were included in this analysis excluded people with a history of arteriopathy (including coronary artery disease, cerebrovascular disease, and peripheral vascular disease), although no history of arteriopathy does not necessarily mean it is not currently present. Both of these studies showed a clinically important benefit for cardiac mortality. It was agreed that the relative effect size showing a 25% reduced chance of death from cardiac causes, relating to 13 per 1000 fewer cases, would be important to people with aortic stenosis and that the meta-analysis was of sufficient size to provide evidence for this. Despite the evidence being graded low to very low quality for this comparison and uncertainty identified for all outcomes, the committee agreed that due to the likely impact on general cardiovascular health a cross-reference to the NICE guideline on lipid modification was appropriate, which includes recommendations on statin use. The committee highlighted that although this review focused

on those without heart failure and the pharmacological review protocol on heart valve disease with heart failure did not include statins, the results could also be applied to those with aortic stenosis and heart failure as statins are thought to affect general cardiovascular health rather than having an effect on aortic stenosis itself. Statins were not included in the heart valve disease with heart failure review protocol as this review aimed to focus on drugs that are commonly used to treat heart failure, which does not include statins.

The committee noted that statin use in moderate-to-severe aortic stenosis may be too late, and that advocates for the use of statins in aortic stenosis believe that starting statins in people with mild aortic stenosis may have more benefit in preventing progression of heart valve disease. This population was excluded in this review as it was noted that mild valve disease is rarely followed up and rarely progresses, and recommendations could therefore not be made.

There was insufficient evidence to draw conclusions about the relative benefits and harms of ACE-I, beta-blockers and diuretics based on the evidence available. Although ACE-I and beta-blockers showed increased events in those with moderate or severe aortic stenosis in terms of need for heart valve intervention at 12 months and withdrawal due to adverse events, respectively, in both cases only one small study with evidence graded very low quality was available for each comparison and imprecise estimates were reported that did not show a large enough difference in effect for the committee to be confident in the findings, with a difference of only two events between the groups in both cases that could have occurred by chance. Conversely, possible benefits in outcomes were seen when diuretics were compared to placebo. This was in one small study, with evidence graded very low quality and uncertainty observed for all outcomes, where the pharmacological agent was eplerenone, a mineralocorticoid receptor antagonist. The committee agreed that this may not be representative of other diuretics that have a different mechanism of action (as eplerenone acts on extrarenal pathways). In addition, there was a difference of only 1-3 events across the dichotomous outcomes meaning there was imprecision and uncertainty in these results. Uncertainty in the direction of the effect was also observed for quality of life outcomes. Given the limited evidence and the variation in current clinical practice, the committee could not make a recommendation for these agents and instead made a research recommendation that included ACE inhibitors, angiotensin II receptor antagonists, beta-blockers and diuretics in adults with severe aortic stenosis (see Appendix J.2 for details).

Aortic regurgitation

There was insufficient evidence to draw conclusions about the relative benefits and harms of ACE-I, ARB, beta-blockers and calcium channel blockers based on the evidence available. The results indicated that there may be a clinically important benefit of ACE-inhibitors and calcium channel blockers on the progression of heart valve disease on imaging, and a benefit of calcium channel blockers for onset of symptoms and need for heart valve intervention. However, the evidence was graded low to very low quality for all outcomes and comparisons and was based on a small number of studies with a small number of participants, which the committee agreed gave imprecise estimates and was insufficient to show a true benefit or harm. They noted that a lot of these studies are historical and so may not reflect current practice. Particularly they noted this for the comparison of digoxin to calcium channel blockers, where the dose of digoxin was a higher dose than is used in modern practiceand may influence the results in this group. They further noted that digoxin is not used currently for aortic regurgitation. The presence of one study using it in this population was explained by the fact that it is an old study and in the past digoxin was seen as a possible treatment for many heart conditions but this is no longer the case in aortic regurgitation. The committee also highlighted the lack of any placebo-controlled trials for ARBs and digoxin. Instead of recommending any treatment (and due to variation in current clinical practice), the committee made a research recommendation for more evidence, which included ACE inhibitors, ARBs, beta-blockers and calcium channel blockers in adults with

aortic regurgitation (see Appendix J.1.1 for details). Digoxin was not included in this research recommendation because it is no longer used in aortic regurgitation.

Primary mitral regurgitation

There was insufficient evidence to draw conclusions about the relative benefits and harms of ACE-I and beta-blockers. The results suggested that ACE inhibitors may be beneficial for preventing symptom onset, with a potential harm from adverse events. However, this was based on two studies, with evidence being graded very low quality and the studies having very small populations that did not report enough events to determine clinical importance, resulting in very serious imprecision in the estimate of effect. The committee noted that this population was younger than that which would be seen on average in the UK, and so may not be representative. Instead of recommending any treatment (and due to variation in current clinical practice), the committee made a research recommendation for more evidence, which included ACE inhibitors, angiotensin II receptor antagonists, beta-blockers and diuretics in adults with primary severe mitral regurgitation (see Appendix J.3.1 for details).

2.1.5.1.4 Key uncertainties

There was no clinical evidence for mitral stenosis and tricuspid regurgitation. The committee agreed that current practice does involve the use of pharmacological agents in tricuspid regurgitation (for example, diuretics) and were disappointed at the absence of evidence. There was a lack of consensus about what treatment was appropriate and variation in practice, meaning consensus recommendations could not be made for these populations. Research recommendations were also not made for these populations as areas within pharmacological treatment that were considered to be most feasible and useful were prioritised for research recommendations.

There was insufficient evidence to make recommendations for the majority of these conditions. This is a key area of concern in current UK practice as there is uncertainty about whether pharmacological management is required for people with heart valve disease to prevent progression or delay consequences of the disease and the effect of pharmacological treatment given for other conditions in those that also have heart valve disease . More specifically, there is uncertainty as to whether medications for the management of systemic hypertensions are more poorly tolerated in the presence of valve disease. In addition, there is uncertainty as to whether medications will delay the consequences of valve disease, for example symptoms. Research recommendations were made covering some areas where recommendations could not be made, however these were prioritised to the areas (aortic regurgitation, severe aortic stenosis and severe primary mitral regurgitation) thought to be most feasible and useful.

2.1.5.2 Cost effectiveness and resource use

No economic evaluations were found for this review question. The unit costs for the relevant drug classes used to the treat heart failure without concomitant heart valve disease were presented.

A cross-reference was made to the NICE guideline on lipid modification.

Due to a lack of clinical and economic evidence research recommendations were made for all the other medicines.

2.1.5.3 Other factors the committee took into account

Based on the recommendation, the committee agreed that there would not be a significant effect on current practice. Based on the economic evidence, there would not be a substantial cost implication from the use of statins.

2.1.6 Recommendations supported by this evidence review

This evidence review supports recommendation 1.2.1 and the research recommendations on pharmacological management.

3 Pharmacological management of heart failure with concomitant heart valve disease

3.1 Review question: In adults with heart failure and concomitant heart valve disease, what is the clinical and cost effectiveness of ACE inhibitors, ARBs, beta blockers, calcium channel blockers, digoxin, diuretics and nitrates to improve clinical outcome?

3.1.1 PICO table

For full details see the review protocol in Appendix A:.

Table 16: PICO characteristics of review question

Population	Adults aged 18 years and over with diagnosed heart failure and heart valve disease of at least moderate severity stratified by type: • Primary aortic [including bicuspid] stenosis • Primary aortic regurgitation • Primary mitral stenosis • Primary mitral regurgitation • Primary tricuspid regurgitation • Secondary heart valve disease – mitral regurgitation or tricuspid regurgitation
Interventions	• Angiotensin-converting enzyme (ACE) inhibitors • Angiotensin-II receptor blockers (ARBs) • Beta blockers • Calcium channel blockers (excluded for aortic stenosis) • Digoxin • Diuretics • Nitrates (including nitroprusside) • Any combination of 2 or more of the above
Comparisons	• Placebo or no treatment • Usual care (e.g. following standard heart failure guidelines: ACE + beta-blocker + diuretic) • Other active comparator listed above, including combinations
Outcomes	• All-cause mortality at 12 months (dichotomous) • Cardiac mortality at 12 months (dichotomous) • Hospital admission due to heart failure at 12 months (dichotomous) • Health-related quality of life at 6 months and 12 months (continuous)

	• Exercise tolerance reported as any of the following (in order of relevance): ○ Treadmill exercise time (duration) ○ Time to near maximal dyspnoea ○ 6-minute walk test ○ Borg dyspnoea index (continuous, final values or change scores) • Need for heart valve intervention (surgical or transcatheter) within 12 months (dichotomous) • Withdrawal from the trial due to adverse events at 6 months and 12 months (dichotomous)
Study design	Randomised control trials (RCTs) or systematic reviews of RCTs, including crossover trials If no RCT data are available, observational data will not be considered for pharmacological interventions. This is due to the risk of confounding variables influencing the study results, reducing our confidence in the review results.

3.1.2 Clinical evidence

3.1.2.1 Included studies

Ten randomised controlled trials were included in the review;[6, 15, 29, 38, 67, 87, 90, 123, 147, 150] these are summarised in Table 17 below. Evidence from these studies is summarised in the clinical evidence summary Table 18 to Table 23 below.

Evidence was only available for the following comparisons:

- Primary aortic stenosis:
  - ACE-I versus placebo: 2 studies[29, 38]
  - ARB versus placebo: 1 study[67]
- Primary mitral stenosis
  - Beta-blocker versus usual care: 2 studies[87, 150]
  - Beta-blocker versus placebo: 3 studies[15, 90, 123]
  - Beta-blocker versus calcium channel blocker: 1 study[6]
- Secondary heart valve disease (mitral regurgitation or tricuspid regurgitation)
  - ACE-I versus placebo: 1 study[147]

No relevant RCTs for primary aortic, mitral or tricuspid regurgitation were identified.

See also the study selection flow chart in Appendix C:, study evidence tables in Appendix D:, forest plots in Appendix E: and GRADE tables in Appendix F:.

Some of the studies included populations where it was unclear whether they directly matched our protocol, as follows:

- Age – Klein 1985[87],Kumar 1994[90] and Patel 1995[123] may have included participants under the age of 18 years, though the proportion was unclear
- Severity of heart valve disease – Klein 1985[87], Patel 1995[123] and Seneviratne 1994[147] did not provide information on the severity of heart valve disease for their population or details of any measurements (e.g. valve area) that are used to determine severity.

These were included in the review but downgrading for indirectness was considered based on the weighting in meta-analyses.

3.1.2.2 Excluded studies

See the excluded studies list in Appendix I:.

3.1.2.3 Summary of clinical studies included in the evidence review

Table 17: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Aortic stenosis				
Chockalingam 2004[29] RCT N=56	**ACE inhibitor (enalapril)** 2.5mg twice daily titrated up to 10mg twice daily over 2 weeks **Placebo**	Adults with symptomatic severe aortic stenosis waiting for surgery or unwilling to have surgery. NYHA class III and IV. Mean ± SD age Intervention group: 43±11, Control group: 46±12 India	Exercise tolerance at 4 weeks Withdrawal due to adverse events at 3 months	
Dalsgaard 2014[38] RCT N=44	**ACE inhibitor (trandolapril)** Daily increasing doses up to the maximum tolerated dose (maximum: 2mg). **Placebo**	Adults with severe symptomatic (32) and asymptomatic (12) aortic stenosis waiting for surgery. NYHA classes II to IV. Mean ± SD age 69.9±8.3. Denmark	Exercise tolerance at 3 days Withdrawal due to adverse events at 8 weeks	30 patients had comorbidities (including hypertension, ischaemic heart disease, and diabetes mellitus).
Helske-Suihko 2015[67] RCT	**ARB (candesartan)** 8mg once daily for 2 weeks, then 16mg once daily until 3 days before they have valve surgery (mean: 5.4 months).	Adults with symptomatic severe aortic stenosis waiting for surgery. Majority NYHA class II.	Hospitalisation due to heart failure at 2-12 months (mean: 5.4 months) Exercise tolerance at 2-12 months (mean: 5.4 months)	Reports the majority of patients had symptoms equivalent to NYHA class II. However, then selectively reports the proportion in class I/II vs. class III.

Study	Intervention and comparison	Population	Outcomes	Comments
N=51	**Placebo**	Mean ± SD age Intervention: 73±9, control: 70±12. 10% were in atrial fibrillation or pacemaker rhythm Finland	Withdrawal due to adverse events at 2-12 months (mean: 5.4 months) All-cause mortality at 2-12 months (mean: 5.4 months)	All analysed participants underwent valve replacement as part of the study protocol (so this is not reported as an outcome)
Mitral stenosis				
Alan 2002[6] RCT N=80	**Beta blocker (metoprolol)** Initially 5mg intravenous, followed by 50mg orally twice daily **Calcium channel blocker (diltiazem)** Initially 25mg intravenously, followed by 60mg orally three times daily	Adults with symptomatic mild-to-moderate mitral stenosis receiving chronic maintenance therapy. New York Heart Association (NYHA) class II and III. Mean ± SD age 38±6.8. Turkey	Exercise tolerance at 3 months Withdrawal due to adverse events at 3 months	Proportion with mild mitral stenosis not stated. Baseline total effort time not matched
Bassan 1987[15] RCT N=10	**Beta blocker (propranolol)** 40mg orally twice or three times daily (dependent on weight). **Placebo**	Adults with moderate symptomatic isolated mitral stenosis waiting for surgery (5 had surgery 1-24 months post-intervention). Median mitral valve area 1.1cm^2 (severity of valve disease not stated directly). NYHA class II and III. Mean age 38.7 (range: 19-56) Israel	Exercise tolerance at 1 week	Crossover RCT – insufficient data were available to account for the within-patient correlation and so the data were analysed as if it were a parallel trial
Klein 1985[87]	**Beta blockers (atenolol)** 100mg once daily for 2 weeks.	People (age range 15-35 years) with symptomatic	Exercise tolerance at 2 weeks	Crossover RCT – insufficient data were available to account for the

Study	Intervention and comparison	Population	Outcomes	Comments
RCT N=13	**Placebo**	significant isolated mitral stenosis in sinus rhythm receiving chronic maintenance therapy. Severity of valve disease not stated. NYHA class II and III. Age range 15-35 years. South Africa		within-patient correlation and so the data were analysed as if it were a parallel trial. Unclear what proportion <18 years of age were included.
Kumar 1994[90] RCT N=31	**Beta blockers (metoprolol)** 25mg twice daily increasing up to 50mg twice daily dependent on patient preference. **Placebo**	People with isolated symptomatic severe rheumatic mitral stenosis in sinus rhythm waiting for surgery or unwilling to have surgery. Mean mitral valve area 0.96±0.3cm^2 in placebo arm, 0.91±0.2cm^2 in intervention arm Severity of valve disease not stated directly. NYHA class II and III. Mean ± SD age Metoprolol mean: 23.6±7.7; Placebo mean: 22.8±8.2. India	Exercise tolerance at 6 months	Unclear if any <18 years of age were included.
Patel 1995[123] RCT N=19	**Beta blockers (acebutolol or atenolol)** Acebutolol 400mg once daily or atenolol 100mg daily for 1 week.	People with symptomatic isolated mitral stenosis admitted for percutaneous mitral valvotomy. Severity of valve disease not stated.	Exercise tolerance at 4 months	Crossover RCT – insufficient data were available to account for the within-patient correlation and so the data were analysed as if it were a parallel trial

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo	NYHA class II and III. Mean age 28(range 17-51 years). South Africa		Unclear what proportion <18 years of age were included.
Shu 2005[150] RCT N=88	**Beta blockers (bisoprolol)** Initial dose 1.25mg/day. Recommended maximum dose 10mg/day. Gradual titration over 3-5 days by 2-3 weeks. **Usual care** All patients received warfarin and basic therapy with one of the following: a diuretic, digoxin, ACE-inhibitors (or ARBs if contraindicated), or nitrates.	Adults with symptomatic significant mitral stenosis or aortic lesions and mitral regurgitation from uncorrected rheumatic heart valvular disease and atrial fibrillation receiving chronic maintenance therapy. Significant valve disease defined as: aortic stenosis with a gradient greater than 20mmHg; mitral stenosis with a valve area of less than 1.5cm^2, or mitral valve regurgitation lesions of at least moderate severity. Approximately 50% had significant mitral stenosis. NYHA class III and IV. Mean age Intervention: 40.6±6.8; Control: 43.5±7.4). China	Hospitalisation due to heart failure at 12 months Exercise tolerance at 6-12 months Withdrawal due to adverse events at 12 months	
Secondary mitral regurgitation				
Seneviratne 1994[147]	**ACE inhibitors (captopril)**	Adults with symptomatic secondary mitral	Quality of life at 12 weeks	Study funded by industry

Study	Intervention and comparison	Population	Outcomes	Comments
RCT N=28	6.25mg twice daily, increasing to 12.5mg twice daily after 4 weeks, increasing to 25mg twice daily after 8 weeks, increasing to 50mg twice daily at 12 weeks. **Placebo**	regurgitation receiving chronic maintenance therapy. Severity of mitral regurgitation was not stated. NYHA class II and III. Mean ± SD age Captopril mean: 72.3±5.4, Placebo mean: 71.5±7.2). Australia	Cardiac mortality at 12 weeks Withdrawal due to adverse events at 12 weeks	

See Appendix D: for full evidence tables.

3.1.2.4 Quality assessment of clinical studies included in the evidence review

3.1.2.4.1 Primary aortic stenosis

Table 18: Clinical evidence summary: ACE-I versus placebo in primary aortic stenosis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ACE-I (95% CI)
Exercise tolerance: change in exercise duration (minutes) semi-supine cycle exercise test (higher is better outcome)	43 (1 study) 3 days	⨁⨁⊖⊖ LOW[1,2.3] due to risk of bias, indirectness		The mean change in exercise duration (minutes) in the control groups was 0.2 minutes	The mean change in exercise duration (minutes) in the intervention groups was 0 higher (0.31 lower to 0.31 higher)
Exercise tolerance: 6-minute walk distance (meters)	52 (1 study) 4 weeks	⨁⨁⊖⊖ LOW[1,4,5]		The mean exercise tolerance: 6-minute walk distance (meters) in the	The mean exercise tolerance: 6-minute walk distance (meters) in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ACE-I (95% CI)
(higher is better outcome)		due to risk of bias, imprecision		control groups was 376 meters	26 higher (68.89 lower to 120.89 higher)
Withdrawal due to adverse events	100 (2 studies) 2-3 months	⨁⊖⊖⊖ VERY LOW[6,7,8] due to risk of bias, indirectness, imprecision	Peto OR 2.18 (0.34 to 14.17)	26 per 1000	29 more per 1000 (from 17 fewer to 248 more)

1 Downgraded by 1 increment because the evidence was at high risk of bias
2 Downgraded by 1 increment because the mean follow-up period was less than 1 month
3 MIDs used to assess imprecision were ±1.0
4 Downgraded by 1 increment because the confidence interval crossed one MID
4 Downgraded by 1 increment because the majority of evidence was at high risk of bias
5 MIDs used to assess imprecision were ±76.0
6 Downgraded by 1 increment because the mean follow-up period was less than 3 months
7 Downgraded by 2 increments because the confidence interval crossed both MIDs
8 Downgraded by 1 increment because the majority of evidence was at high risk of bias

Table 19: Clinical evidence summary: ARB versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ARB (95% CI)
All-cause mortality	51 (1 study) 2-12 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 0.14 (0 to 7.09)	39 per 1000	39 fewer per 1000 (from 140 fewer to 63 more)[6]
Acute heart failure	51 (1 study) 2-12 months	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	Peto OR 7.69 (0.15 to 387.87)	0 per 1000	40 more per 1000 (from 63 fewer to 143 more)[6]
Exercise tolerance: change from baseline 6-minute walking distance (meters) (higher is better outcome)	43 (1 study) 2-12 months	⨁⨁⨁⊖ MODERATE[4,5] due to risk of bias		The mean exercise tolerance: change from baseline 6-minute walking distance in the control groups was -2 meters	The mean change from baseline in 6-minute walking distance in the intervention groups was 18 metres lower (48.74 lower to 12.74 higher)
Withdrawal due to adverse events	51 (1 study) 2-12 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.04 (0.16 to 6.83)	77 per 1000	3 more per 1000 (from 65 fewer to 449 more)

[1] Downgraded by 2 increments because the evidence was at very high risk of bias
[2] Downgraded by 2 increments because the confidence interval crossed both MIDs

[3] Downgraded by 1 increment because of uncertainty as to the aetiology of reported acute heart failure
[4] Downgraded by 1 increment because the evidence was at high risk of bias

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ARB (95% CI)
[5] MIDs used to assess imprecision were ±74.0 [6] Absolute effect calculated manually using risk difference as zero events in one arm of the study					

3.1.2.4.2 Primary aortic regurgitation

No studies identified.

3.1.2.4.3 Primary mitral stenosis

Table 20: Clinical evidence summary: Beta-blocker versus usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Beta-blocker (95% CI)
Hospitalisation due to heart failure	67 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.31 (0.09 to 1.02)	294 per 1000	203 fewer per 1000 (from 268 fewer to 6 more)
Exercise tolerance: 6-minute walking distance (meters) (higher is better outcome)	67 (1 study) 6-12 months	⨁⨁⊖⊖ LOW[1,3] due to risk of bias		The mean exercise tolerance: 6-minute walking distance in the control groups was 290 meters	The mean exercise tolerance: 6-minute walking distance in the intervention groups was 133 meters higher (121.49 to 144.51 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Beta-blocker (95% CI)
Withdrawal due to adverse events (weakness, dizziness, dyspnoea)	88 (1 study) 12 months	⨁⨁⨀⨀ LOW[1] due to risk of bias	Peto OR 8.14 (1.35 to 48.97)	0 per 1000	114 more per 1000 (from 13 more to 214 more)[4]

[1] Downgraded by 2 increments because the evidence was at very high risk of bias
[2] Downgraded by 1 increment because the confidence interval crossed one MID
[3] MIDs used to assess imprecision were ±15.0

[4] Absolute effect calculated manually as zero events in one arm of the study

Table 21: Clinical evidence summary: Beta-blocker versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Beta blocker (95% CI)
Exercise tolerance: treadmill exercise time (minutes) to exhaustion (higher is better outcome)	84 (3 studies) 1-4 weeks	⨁⨀⨀⨀ VERY LOW[1,2,3,4,5] due to risk of bias, inconsistency, indirectness, imprecision,		The mean treadmill exercise time (minutes) to exhaustion in the control groups was 8.1 minutes	The mean treadmill exercise time (minutes) to exhaustion in the intervention groups was 0.33 higher (1.09 lower to 1.75 higher)
Exercise tolerance: Pulmonary capillary	26 (1 study) 6 months	⨁⨁⨀⨀ LOW[6,7,8]		The mean pulmonary capillary wedge pressure after exercise in the control group was	The mean pulmonary capillary wedge pressure after exercise in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Beta blocker (95% CI)
wedge pressure after exercise (lower is better outcome)		due to risk of bias, indirectness		50.5	14.8 lower (21.71 to 7.89 lower)

1 Downgraded by 2 increments because the majority of the evidence was at very high risk of bias
2 Downgraded by one increment because the I2 = 74% and heterogeneity was not explained by subgroup analyses.
3 Downgraded by 2 increments because the mean follow-up period is less than 1 month, and the majority of the studies appear to have included people under 18 years of age and do not specify the severity of mitral stenosis
4 Downgraded by 1 increment because the confidence interval crossed one MID
5 MIDs used to assess imprecision were ±0.9
6 Downgraded by 1 increment because the evidence was at high risk of bias
7 Downgraded by 1 increment because the outcome is a surrogate measure and the study appears to have included people under 18 years of age
8 MIDs used to assess imprecision were ±5.35

Table 22: Clinical evidence summary: Beta-blocker versus calcium channel blocker

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with calcium channel blocker	Risk difference with beta blocker (95% CI)
Exercise tolerance: total effort time on treadmill exercise test (higher is better outcome)	80 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, imprecision		The mean exercise tolerance: total effort time on treadmill exercise test in the control groups was 570 seconds[7]	The mean total effort time on treadmill exercise test in the intervention groups was 50 seconds lower (97.99 to 2.01 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with calcium channel blocker	Risk difference with beta blocker (95% CI)
Withdrawal due to adverse events	80 (1 study) 3 months	⨁⨁⊖⊖ LOW[4,6] due to risk of bias, imprecision	RD 0 (-0.048 to 0.048)	0 per 1000	0 fewer per 1000 (from 48 fewer to 48 more)[5]

[1] Downgraded by 2 increments because the evidence was at very high risk of bias: baseline total effort time not matched – beta-blocker: 452±120; calcium-channel blocker: 534±120
[2] Downgraded by 1 increment because the confidence interval crossed one MID
[3] MIDs used to assess imprecision were ±60.0
[4] Downgraded by 1 increment because the evidence was at high risk of bias
[5] Absolute effect calculated manually as zero events in both arms of the study
[6] Downgraded by 1 increment because sample size was >70 and <350 (imprecision was assessed based on sample size as zero events in both arms of the study)
[7] Baseline total effort time not matched

3.1.2.4.4 Primary mitral regurgitation

No studies identified.

3.1.2.4.5 Primary tricuspid regurgitation

No studies identified.

3.1.2.4.6 Secondary heart valve disease (mitral regurgitation or tricuspid regurgitation)

Table 23: Clinical evidence summary: ACE-I versus placebo in secondary heart valve disease

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ACE-I (95% CI)
Cardiac mortality	28 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	OR 0.14 (0 to 6.82)	71 per 1000	71 fewer per 1000 (from 248 fewer to 106 more)[9]
Quality of life: Duke activity index score Scale: 2.75 to 58.2 (high is good outcome)	23 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW[4,5,6,7] due to risk of bias, indirectness, imprecision		The mean Duke activity index score in the control group was 22.3	The mean Duke activity index score in the intervention groups was 6.7 higher (0.97 lower to 14.37 higher)
Withdrawal due to adverse events	27 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[1,2,8] due to risk of bias, indirectness, imprecision	RD 0 (-0.133 to 0.133)	0 per 1000	0 fewer per 1000 (from 133 fewer to 133 more)[10]

[1] Downgraded by 1 increment because the evidence was at high risk of bias
[2] Downgraded by 1 increment as the severity of heart valve disease was unclear
[3] Downgraded by 2 increments because the confidence interval crossed both MIDs
[4] Downgraded by 2 increments because the evidence was at very high risk of bias
[5] Downgraded by 1 increment because the reported measure only reports physical activity rather than other aspects of quality of life and the severity of heart valve disease is unclear
[6] Downgraded by 1 increment because the confidence interval crossed one MID
[7] MIDs used to assess imprecision were ±4.7
[8] Downgraded by 2 increments because sample size was <70 (imprecision was assessed based on sample size as zero events in both arms of the study)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with ACE-I (95% CI)

[9] Absolute effect calculated manually using risk difference as zero events in one arm of the study
[10] Absolute effect calculated manually as zero events in both arms of the study

For strata where evidence was identified as described in the tables above, see Appendix F: for full GRADE tables.

3.1.3 Economic evidence

3.1.3.1 Included studies

No health economic studies were included.

3.1.3.2 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 G:.

3.1.3.3 Summary of studies included in the economic evidence review

No economic studies were included in this review.

3.1.3.4 Unit costs

The following relevant unit costs have been included to inform the committee of the cost implications of different pharmacological management strategies.

Table 24: Unit costs for different drugs used for pharmacological management of people with heart failure and concomitant heart valve disease

Class	Drug	Dose (tablet unless specified)	Unit cost
ACE inhibitors	ramipril	1.25mg	£ 0.07
		2.5mg	£ 0.15
		5mg	£ 0.17
		10mg	£ 0.18
	captopril	12.5mg	£ 0.02
		25mg	£ 0.01
		50mg	£ 0.03
	enalapril	2.5mg	£ 0.18
		5mg, 10mg, 20mg	£ 0.06
	lisinopril	2.5mg, 5mg, 10mg, 20mg	£ 0.03
	quinapril	2.5mg, 5mg, 10mg	£ 0.31
		20mg	£ 0.39
		40mg	£ 0.13
	fosinopril	10mg	£ 0.15
		20mg	£ 0.14
Angiotensin II receptor blockers (ARBs)	candesartan cilexitil	2mg	£ 0.22
		4mg	£ 0.08
		8mg	£ 0.04
		16mg	£ 0.06
		32mg	£ 0.06
	losartan	12.5mg	£ 0.11
		25mg	£ 0.12
		50mg	£ 0.07
		100mg	£ 0.07
Beta blockers	bisoprolol	1.25mg	£ 0.03
		3.75mg	£ 0.03
		5mg	£ 0.02
		10mg	£ 0.03
	carvedilol	3.125mg	£ 0.03
		6.25mg	£ 0.03

		12.5mg	£	0.03
		25mg	£	0.04
	nebivolol	2.5mg	£	0.42
		5mg	£	0.16
		10mg	£	0.92
Diuretics	furosemide	20mg tablet	£	0.05
		40mg tablet	£	0.07
		10 mg per 1 ml solution for injection	£	1.74
	bumetanide	1mg tablet	£	0.05
		5mg tablet	£	0.25
	torasemide	2.5mg tablet	£	0.14
		5mg	£	0.20
		10mg	£	0.29
Calcium channel blockers	amlopodine	5mg, 10mg	£	0.03
Digoxin	-	62.5 micrograms	£	0.05
		125 micrograms	£	0.05
Nitrates	Isosorbide dinitrate	10mg	£	0.24

Source: BNF 2018[79]

3.1.4 Evidence statements

3.1.4.1 Clinical evidence statements

See the summary of evidence in Tables 19-24.

3.1.4.2 Health economic evidence statements

No relevant economic evaluations were identified.

3.1.5 The committee's discussion of the evidence

3.1.5.1 Interpreting the evidence

3.1.5.1.1 The outcomes that matter most

The critical outcomes were all-cause mortality, cardiac mortality, hospital admission due to heart failure and health-related quality of life. Important outcomes were exercise tolerance, need for heart valve intervention (surgical or transcatheter) and withdrawal from the study due to adverse events.

Physiological outcomes were not included in the protocol as they are not clinically relevant endpoints, and the outcomes they aim to predict that are important to patients are captured by the included outcomes. However, one study reported pulmonary wedge pressure

following exercise for the comparison of beta-blockers compared to placebo in primary mitral stenosis, which was included but downgraded for indirectness as it is a surrogate measure of exercise tolerance.

There was very limited evidence, especially for health-related quality of life. The need for heart valve intervention was not reported in any of the studies.

3.1.5.1.2 The quality of the evidence

No relevant RCTs for primary aortic, mitral or tricuspid regurgitation were identified. Ten RCTs were included in this review and evidence was only available for the following comparisons:

- Primary aortic stenosis:
  - ACE-I versus placebo
  - ARB versus placebo
- Primary mitral stenosis
  - Beta-blocker versus usual care
  - Beta-blocker versus placebo
  - Beta-blocker versus calcium channel blocker
- Secondary heart valve disease (mitral regurgitation or tricuspid regurgitation)
  - ACE-I versus placebo

Evidence ranged from moderate to very low quality, with the majority of the evidence being of low or very low quality. Evidence was mainly downgraded due to risk of bias and imprecision. Analyses frequently included only a small number of participants and had low event rates resulting in great uncertainty. Additionally, some evidence was considered to be indirect because of the inclusion of populations that did not reflect those seen in UK practice, the inclusion of those under 18 years of age, the severity of heart valve disease not being reported in studies or reporting at time points shorter than 3 months (or 1 month for exercise tolerance). One outcome (exercise tolerance measured by treadmill exercise time to exhaustion for beta-blockers compared to placebo in mitral stenosis) showed inconsistency with heterogeneity that could not be explained by subgroup analysis.

3.1.5.1.3 Benefits and harms

Primary aortic stenosis

There was insufficient evidence to draw conclusions about the relative benefits and harms of ACE-I or ARB compared with placebo, as there was only one very small study identified for each outcome and comparison, and no other comparisons were available for this stratum. No clinically important differences were seen for any of the reported outcomes, though uncertainty was observed for all outcomes and the majority of the evidence for all comparisons was graded low to very low quality. Due to variation in current clinical practice the committee were unable to make consensus recommendations. A research recommendation was therefore made to investigate the clinical and cost-effectiveness of pharmacological management of heart failure in adults with severe aortic stenosis (see Appendix J.5.1 for details). This research recommendation was also applied to the severe aortic regurgitation and severe mitral regurgitation populations, as no evidence was identified for these populations.

Primary mitral stenosis

For the comparison of beta blocker vs usual care (warfarin and basic therapy with either a diuretic, digoxin, ACE-inhibitors (or ARBs if contraindicated), or nitrates) clinically important benefits of beta blockers were seen for reduced hospitalisation due to heart failure and

increased exercise tolerance, though some uncertainty in the direction of the effect was observed for the hospitalisation due to heart failure outcome. However, there was also a clinically significant increase in the rate of withdrawals due to adverse events, namely weakness, dizziness and dyspnoea. This was based on evidence from a single, small study with evidence graded low to very low quality. Beta-blockers are widely used in patients with heart failure due to reduced ventricular systolic function and in patients with coronary artery disease and the same adverse events do not represent sufficient reason to negate potential benefit. The committee noted that in the study all participants were also in atrial fibrillation.

The evidence for the comparisons of beta blockers with placebo and calcium channel blockers was limited, based on factors such as inconsistency in results between studies and quality of the evidence being graded low to very low quality with very small population sizes, and it was not possible to draw any conclusions from the data. For the comparison between beta-blockers and calcium channel blockers, there was some suggestion of worse exercise tolerance with beta-blockers, but this evidence was considered to be limited given it was based on a single, small study and the size of the effect was uncertain based on confidence intervals, with the quality also being graded very low. For the comparison between beta-blockers and placebo, it was noted that the heterogeneity for the outcome of exercise tolerance could have been due to heart valve disease severity, as the study showing a benefit of beta blockers was in a population with 'significant' mitral stenosis while the other studies included moderate severity or did not specify the severity. However, due to the limited number of studies and the poorly defined populations it was not possible to assess this formally. It was also noted that the study showing a benefit included only people in sinus rhythm, while the others did not report the numbers in sinus rhythm or atrial fibrillation. This highlights the need to address whether beta blockers are effective in both sinus rhythm and atrial fibrillation, and a research recommendation was made to encourage research in this area (see Appendix J.4.1 for details).

The committee noted that all studies in this stratum related to a much younger population than the cohort seen in UK clinical practice and was often due to rheumatic fever, excluding those aged over 75 years. This is distinct from the cases seen in the UK which are commonly in older adults with calcific mitral stenosis. For this reason, the research recommendation described above on beta-blockers in mitral stenosis for those in sinus rhythm and those in atrial fibrillation was limited to adults ≥75 years in order to provide some direct evidence in this age group. The committee also acknowledged that one key study only included people in atrial fibrillation. However, the committee agreed that the findings align with their clinical experience in the UK population and can be extrapolated to this group. It is also plausible that lowering the heart rate in mitral stenosis should produce a benefit for patients.

Therefore, based on the evidence, supported by their clinical experience, the committee made a recommendation to consider beta blockers in people with moderate to severe mitral stenosis and concomitant heart failure. The recommendation was a consider recommendation based on the limitations associated with the included evidence, including the small study size, quality of the evidence being graded low to very low and uncertainty in the direction of the effect for many some outcomes. A separate recommendation was made rather than referring to the NICE chronic heart failure guideline as it was explained that in cases where heart failure is due to the heart valve disease, reduced systolic function may not be present so it would therefore not be appropriate to refer to this guideline. In addition, the research recommendation described in the previous paragraphs was also made to assess the clinical and cost-effectiveness of beta-blockers in adults ≥75 years, both in sinus rhythm and in atrial fibrillation, so that there is direct evidence for this older population with non-rheumatic/calcific mitral stenosis.

Secondary mitral or tricuspid regurgitation

A single, very small trial was available comparing ACE-I vs placebo. There was a possible benefit for improved quality of life based on functional ability assessed in the Duke Activity Index score, though there was uncertainty in the direction of the effect. However, overall there was insufficient evidence to draw conclusions, based on the size of the study, evidence being graded low to very low quality and uncertainty in the effect estimates for the other available outcomes of cardiac mortality and withdrawal due to adverse events. Due to variation in current clinical practice the committee were unable to make consensus recommendations.

Key uncertainties

Only 3 out of 6 of the studies in the mitral stenosis stratum specified whether the participants were in sinus rhythm or atrial fibrillation and none included older adults with calcific heart valve disease. Therefore, to inform future updates of this guidance the committee made a research recommendation around beta blockers, the key pharmacological intervention in this group, for older adults with non-rheumatic/calcific mitral stenosis including groups in sinus rhythm and in atrial fibrillation. This is to encourage research to clarify whether this form of pharmacological management is safe and effective in the population most relevant to UK clinical practice, both in people in sinus rhythm and those in atrial fibrillation, as there is currently no randomised evidence to answer these important clinical questions.

There was insufficient evidence to inform a recommendation for people with aortic stenosis. This is a key area of concern in current UK practice as there is uncertainty about whether pharmacological management in severe aortic stenosis is appropriate. Therefore, a research recommendation was made to encourage research into the clinical and cost effectiveness of pharmacological management of heart failure in adults with severe aortic stenosis. This research recommendation also applied to those with severe aortic regurgitation and severe mitral regurgitation, as no evidence was identified for these populations.

Although there was an absence of evidence for other areas included in the review protocol, including primary tricuspid regurgitation and secondary mitral and tricuspid regurgitation, consensus recommendations could not be made due to variation in practice and research recommendations were prioritised to the areas thought to be most feasible and useful.

3.1.5.1.4 Cost effectiveness and resource use

No economic evaluations were found for this review question. The unit costs for the relevant drug classes used to treat heart failure with concomitant heart valve disease were presented. The committee agreed that due to the low cost of all relevant drugs, the interventions costs for pharmacological management were unlikely to differ substantially from one drug class to another.

The clinical review demonstrated that using beta blockers to manage mitral stenosis may be associated with reduced hospital readmissions (due to heart failure) compared to usual care (warfarin and basic therapy with either a diuretic, digoxin, ACE-inhibitors (or ARBs if contraindicated), or nitrates), although there was uncertainty in the direction of effect for this outcome and evidence was only available from a single, small study with evidence graded very low quality. Therefore, there may be cost savings by considering beta blockers for this population over these comparators. However, some of these savings may be offset as people will need to be monitored for adverse events and no studies reported this outcome for beta-blockers compared with other comparators, such as placebo or calcium channel blockers.

Given that beta-blockers already form a large part of current practice for mitral stenosis, their recommendation is not likely to have a resource impact. There should be a focus on correct titration of beta blockers as improper titration may increase the need for monitoring.

3.1.5.2 Other factors the committee took into account

The committee made a research recommendation on the pharmacological management in adults with severe aortic stenosis, severe aortic regurgitation or severe mitral regurgitation to address the lack of evidence in this area.

When developing the protocol for this review the committee discussed the current focus on the neprilysin inhibitor sacubitril in combination with valsartan in heart failure research. It was noted that the current guideline must focus on the management of heart valve disease and cannot assess all pharmacological management options for heart failure if not currently used in people with heart valve disease, as it was agreed that this combination is not commonly used in heart valve disease. The committee were aware of the recommendations on the pharmacological management of chronic heart failure in the NICE guideline on the chronic heart failure (NG106). It was agreed that future updates of this guidance may be able to assess the use of this drug combination in heart valve disease with concomitant heart failure.

3.1.5.3 Recommendations supported by this evidence review

This evidence review supports recommendation 1.2.2 and the 5 research recommendations on pharmacological management.

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Appendices

Appendix A: Review protocols

A.1 Valve disease without heart failure

Table 25: Review protocol: pharmacological management of heart valve disease without concomitant heart failure

ID	Field	Content
0.	PROSPERO registration number	Not registered
1.	Review title	In adults with heart valve disease without concomitant heart failure, what is the clinical and cost effectiveness of alpha-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARBs), beta blockers, calcium channel blockers, digoxin, diuretics, statins and nitrates to improve clinical outcome?
2.	Review question	In adults with heart valve disease without concomitant heart failure, what is the clinical and cost effectiveness of alpha-blockers, ACE inhibitors, ARBs, beta blockers, calcium channel blockers, digoxin, diuretics, statins and nitrates to improve clinical outcome?
3.	Objective	To assess the clinical and cost-effectiveness of pharmacological interventions individually and in combination to manage asymptomatic heart valve disease in adults.
4.	Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Searches will be restricted by: English language studies

ID	Field	Content
		Human studies Letters and comments are excluded Validated study filters for systematic reviews and RCTs No date restrictions applied The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies database will be published in the final review.
5.	Condition or domain being studied	Diagnosed 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 diagnosed heart valve disease of at least moderate severity stratified by type: • Primary aortic [including bicuspid] stenosis • Primary aortic regurgitation • Primary mitral stenosis • Primary mitral regurgitation • Primary tricuspid regurgitation • Secondary heart valve disease – mitral regurgitation or tricuspid regurgitation A study will be considered to cover a population with heart valve disease without concomitant heart failure if it meets all of the following criteria: Diagnosis of native heart valve disease Asymptomatic or have only very mild/low-level symptoms that would not affect daily life (this would include those reported to be in class I of the NYHA classification) A normal LVEF Include only first line use of pharmacological management options. Inclusion of indirect evidence from mixed populations, to be considered separately for each strata and intervention:

ID	Field	Content
		Studies including adults with HVD where some also have concomitant heart failure will be included if <50% of the included patients had heart failure (those studies with ≥50% concomitant heart failure will be included in a separate review question focused on HVD and concomitant heart failure) .
7.	Intervention/Exposure/Test	Alpha blockers Angiotensin-converting enzyme (ACE) inhibitors Angiotensin-II receptor blockers (ARBs) Beta blockers Calcium channel blockers Digoxin Diuretics Statins Nitrates (including nitroprusside) Any combination of 2 or more of the above Primary studies with a mixed intervention (some in the 'active' arm received the intervention of interest and some a different intervention) will be included if at least 90% received the intervention of interest. A class effect will be used for analysis, combining all interventions within each drug class (regardless of mode of delivery, and dose – as long as within the licensed range). For crossover studies, there is no lower limit for the washout period because drug effects do not persist once a person is no longer taking the drug.
8.	Comparator/Reference standard/Confounding factors	Placebo or no treatment (usual care) Other active comparator listed above, including combinations
9.	Types of study to be included	Randomised control trials (RCTs) or systematic reviews of RCTs, including crossover trials If no RCT data are available, observational data will not be considered for pharmacological interventions. This is due to the risk of confounding variables influencing the study results, reducing our confidence in the review results.
10.	Other exclusion criteria	Exclusion criteria:

ID	Field	Content
		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. Non-randomised studies / observational studies Pharmacological management of HVD in adults with concomitant heart failure (where the proportion with heart failure is ≥50%) Pharmacological management of mild HVD Pharmacological management in the intra- or post-operative period Studies combining people with different types of valve disease (e.g. some with mitral regurgitation and some with aortic regurgitation). Pharmacological management in children Non-English language studies
11.	Context	Although not in the guideline Scope document it was agreed to be important because there is currently variation in practice. Also, pharmacological management in asymptomatic HVD can be used with the aim of preventing the development of heart failure as consequence of heart valve disease, so the impact is clinically relevant. Statins and alpha-blockers are relevant to the asymptomatic population but not those with concomitant heart failure and so have been added to this protocol although not listed in the Scope.
12.	Primary outcomes (critical outcomes)	All-cause mortality at ≥12 months (dichotomous) Cardiac mortality at ≥12 months (dichotomous) Health-related quality of life at 6 months and ≥12 months (continuous) Onset of symptoms or progression in NYHA class at ≥12 months Evidence of HVD progression on imaging (worsening of disease severity) at ≥ 12 months (dichotomous) Need for heart valve intervention (surgical or transcatheter) at ≥12 months (dichotomous) Follow-up: Include only the closest reported time to the 6 month time-point from each study if multiple time points are recorded. Report the longest follow-up time reported for the ≥12 month time-point if multiple time-points are recorded No minimum time-point for inclusion
13.	Secondary outcomes (important outcomes)	Exercise tolerance reported as any of the following (in order of relevance) at 12 months: Supine bicycle workload (watts or % difference from predicted watts)

ID	Field	Content
		Treadmill exercise time (duration) Oxygen consumption on exercise testing (VO2 max) Time to near maximal dyspnoea 6-minute walk test Borg dyspnoea index (Continuous, final values or change scores – choose the type most often reported in other studies if both available in a single study, combine change and final scores in meta-analysis if appropriate) Withdrawal from the trial due to adverse events at 6 and 12 months (dichotomous) Follow-up: Include only the closest reported time to the 6 month time-point from each study if multiple time points are recorded. Report the longest follow-up time reported for the ≥12 month time-point if multiple time-points are recorded No minimum time-point for inclusion
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. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. MS Excel will be used for data extraction and critical appraisal for health economic studies.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Checklists used in this intervention review are as follows for different types of study design:

ID	Field	Content
		Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: 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 party where necessary.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted 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. GRADEpro will be used to assess the quality of evidence for each outcome, 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 outcome. Publication bias is tested for when there are more than 5 studies for an outcome. WinBUGS will be used for network meta-analysis, if possible given the data identified. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. 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).
17.	Analysis of sub-groups	Groups that will be analysed separately (strata): Primary aortic [including bicuspid] stenosis Primary aortic regurgitation Primary mitral stenosis Primary mitral regurgitation

ID	Field	Content			
		Primary tricuspid regurgitation Secondary heart valve disease – mitral regurgitation or tricuspid regurgitation Subgroups that will be investigated if heterogeneity is present: Presence vs. absence of uncontrolled systemic hypertension (140/85 mmHg) at the end of trial intervention despite medication Age (<75 vs. ≥75 years) Disease mechanism: Aortic and mitral stenosis: calcific vs non-calcific			
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	☑	☑	

ID	Field	Content		
		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] Claire Townsend [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.		

ID	Field	Content	
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	N/A	
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	Heart valve disease; pharmacological treatment; medical treatment; asymptomatic; aortic stenosis; aortic regurgitation; mitral stenosis; mitral regurgitation; tricuspid regurgitation; angiotensin-converting enzyme inhibitors; angiotensin II receptor antagonists; beta blockers; calcium channel blockers; digoxin; diuretics; statins; nitrates.	
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	

A.2 Valve disease with heart failure

Table 26: Review protocol: pharmacological management with heart failure

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	In adults with heart failure and 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?
2.	Review question	In adults with heart failure and concomitant heart valve disease, what is the clinical and cost effectiveness of ACE inhibitors, ARBs, beta blockers, calcium channel blockers, digoxin, diuretics and nitrates to improve clinical outcome?
3.	Objective	To assess the clinical and cost-effectiveness of pharmacological interventions individually and in combination to manage heart failure specifically in adults with heart valve disease.
4.	Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Searches will be restricted by: • English language studies • Human studies • Letters and comments are excluded • Validated study filters for systematic reviews and RCTs • No date restrictions applied The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant.

ID	Field	Content
		The full search strategies database will be published in the final review.
5.	Condition or domain being studied	Diagnosed 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 diagnosed heart failure and heart valve disease of at least moderate severity stratified by type: Primary aortic [including bicuspid] stenosis Primary aortic regurgitation Primary mitral stenosis Primary mitral regurgitation Primary tricuspid regurgitation Secondary heart valve disease – mitral regurgitation or tricuspid regurgitation Any heart failure definition will be accepted as reported in the studies, with downgrading for risk of bias/indirectness if not adequately or appropriately defined. As stated in the NICE guideline on chronic heart failure (NG106), it is a complex clinical syndrome of symptoms and signs caused by impairment of the heart's action as a pump supporting the circulation. It is caused by structural or functional abnormalities of the heart. The demonstration of objective evidence of these cardiac abnormalities is necessary for the diagnosis of heart failure to be made. The symptoms most commonly encountered are breathlessness (exertional dyspnoea, orthopnoea and paroxysmal nocturnal dyspnoea), fatigue, and oedema. Signs in heart failure could be due to pulmonary and systemic congestion, or the structural abnormalities either causing or caused by heart failure. Therefore, the ideal definition includes symptoms and/or signs plus associated structural or functional abnormalities that can explain the symptoms and signs. Heart valve disease severity should be reported according to standard thresholds from echocardiography, as reported by the British Society of Echocardiography. However, study definitions will be accepted and discussed with the committee to determine whether they represent indirect evidence. If severity is not stated, the study will be included but downgraded for indirectness. Include both those with no current plan/need for intervention and those who are receiving drugs as bridging therapy while waiting for an intervention. These groups will be pooled initially but considered for subgroup analysis if heterogeneity is found. Include only first line use of pharmacological management options.

ID	Field	Content
		In cases of mixed heart valve disease (i.e. the patients each had more than one type of valve disease) the study will be classified according to the predominant valve lesion that drives medical decision making (e.g. in rheumatic heart disease, this may be mitral stenosis). Studies including adults with HVD but not all with concomitant heart failure will be included if ≥50% of the included patients had heart failure. Those with <50% having HF will be included in a separate question on HVD without heart failure. Groups from the equality impact assessment were considered. It was decided that they did not need to be considered separately for this question, Inclusion of indirect evidence from mixed populations, to be considered separately for each strata and intervention: If no/insufficient studies are found in the HVD population, studies including adults with heart failure from mixed causes will be included if >75% of the included patients had HVD. Exclusions: Pharmacological management in children (17 years and under) People with congenital heart valve disease, except bicuspid aortic valve disease.
7.	Intervention/Exposure/Test	Angiotensin-converting enzyme (ACE) inhibitors Angiotensin-II receptor blockers (ARBs) Beta blockers Calcium channel blockers Digoxin Diuretics Nitrates (including nitroprusside) Any combination of 2 or more of the above Primary studies with a mixed intervention (some in the 'active' arm received the intervention of interest and some a different intervention) will be included if at least 90% received the intervention of interest.

ID	Field	Content
		A class effect will be used for analysis, combining all interventions within each drug class (regardless of mode of delivery, and dose – as long as within the licensed range). Based on this class effect assumption, drugs not licenced for HF within a class that has some licenced agents could be considered as long as not contraindicated. For crossover studies, there is no lower limit for the washout period because drug effects do not persist once a person is no longer taking the drug.
8.	Comparator/Reference standard/Confounding factors	Placebo or no treatment Usual care (e.g. following standard heart failure guidelines: ACE + beta-blocker + diuretic) Other active comparator listed above, including combinations
9.	Types of study to be included	Randomised control trials (RCTs) or systematic reviews of RCTs, including crossover trials If no RCT data is available, observational data will not be considered for pharmacological interventions. This is due to the risk of confounding variables influencing the study results, reducing our confidence in the review results.
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. Non-randomised studies / observational studies Pharmacological management of heart failure in adults without HVD Pharmacological management of mild HVD with associated heart failure Pharmacological management in the intra- or post-operative period Studies combining people with different types of valve disease (e.g. some with mitral regurgitation and some with aortic regurgitation). Non-English language studies
11.	Context	This is important because there is uncertainty about the most appropriate medicines for pharmacological management, and whether this differs from the guidelines for heart failure not associated with HVD. There is also variation in practice.
12.	Primary outcomes (critical outcomes)	All-cause mortality at 12 months (dichotomous) Cardiac mortality at 12 months (dichotomous) Hospital admission due to heart failure at 12 months (dichotomous) Health-related quality of life at 6 months and 12 months (continuous) Follow-up:

ID	Field	Content
		include only the closest reported time to the 12- or 6-month time-points from each study if multiple time points are recorded no minimum time point for inclusion
13.	Secondary outcomes (important outcomes)	Exercise tolerance reported as any of the following (in order of relevance): Treadmill exercise time (duration) Time to near maximal dyspnoea 6-minute walk test Borg dyspnoea index (continuous, final values or change scores – choose the type most often reported in other studies if both available in a single study, combine change and final scores in meta-analysis if appropriate) Need for heart valve intervention (surgical or transcatheter) within 12 months (dichotomous) Withdrawal from the study due to adverse events at 6 months and 12 months (dichotomous) Follow-up: include only the closest reported time to the 12- or 6-month time-points from each study if multiple time points are recorded no minimum time point for inclusion
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. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. 10% of the sifting and extractions will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third party. MS Excel will be used for data extraction and critical appraisal for health economic studies.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Checklists used in this intervention review are as follows for different types of study design: Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)

ID	Field	Content
		Randomised Controlled Trial: Cochrane RoB (2.0) 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 party where necessary.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted 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. GRADEpro will be used to assess the quality of evidence for each outcome, 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 outcome. Publication bias is tested for when there are more than 5 studies for an outcome. WinBUGS will be used for network meta-analysis, if possible given the data identified. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. 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).
17.	Analysis of sub-groups	Groups that will be analysed separately (strata) Type of HVD: aortic [including bicuspid] stenosis aortic regurgitation mitral stenosis mitral regurgitation tricuspid regurgitation Subgroups that will be investigated if heterogeneity is present: Severe vs moderate HVD (as defined by the British Society of Echocardiography) Symptomatic vs asymptomatic Age (<75 versus ≥75)

ID	Field	Content			
		Disease mechanism: Aortic and mitral stenosis: calcific vs non-calcific Presence vs. absence of uncontrolled systemic hypertension (140/85 mmHg) at the end of trial intervention despite medication			
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	☑	☑	

ID	Field	Content
		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

ID	Field	Content	
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	Heart valve disease; Anticoagulation; Antiplatelet; Biological heart valve; Intervention; Surgical valve replacement; Transcatheter valve replacement	
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 27: 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).[112] **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.

Appendix B: Literature search strategies

B.1 Valve disease without heart failure

Heart valve disease – search strategy 6 - pharmacological management without heart failure

This literature search strategy was used for the following reviews:

- In adults with heart valve disease without concomitant heart failure, what is the clinical and cost effectiveness of alpha-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARBs), beta blockers, calcium channel blockers, digoxin, diuretics, statins and nitrates to improve clinical outcome?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[112]

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

B.1.1 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 28: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 - 14 October 2020	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974 - 14 October 2020	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 10 of 12 CENTRAL 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.	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.	randomized controlled trial.pt.
37.	controlled clinical trial.pt.
38.	randomi#ed.ti,ab.
39.	placebo.ab.
40.	randomly.ti,ab.
41.	Clinical Trials as topic.sh.
42.	trial.ti.
43.	or/36-42
44.	Meta-Analysis/
45.	exp Meta-Analysis as Topic/
46.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
47.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
48.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
49.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
50.	(search* adj4 literature).ab.
51.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
52.	cochrane.jw.
53.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
54.	or/44-52
55.	35 and (43 or 54)
56.	exp Angiotensin-Converting Enzyme Inhibitors/
57.	(("angiotensin-converting enzyme" or ace) adj2 (inhibitor* or antagonist*)).ti,ab.
58.	(Captopril or cilazapril or enalapril or enalaprilat or fosinopril or lisinopril or perindopril or quinapril or ramipril or teprotide or imidapril or trandolopril).ti,ab.
59.	exp Angiotensin Receptor Antagonists/

60.	(angiotensin adj3 receptor adj3 (antagonist* or blocker*)).ti,ab.
61.	(1-Sarcosine-8-Isoleucine or amlodipine or irbesartan or olmesartan or saralasin or telmisartan or valsartan or azilsartan or candesartan or eprosartan or losartan).ti,ab.
62.	exp Adrenergic beta-Antagonists/
63.	(Acebutolol or Atenolol or Bisoprolol or Carvedilol or Celiprolol or Esmolol or Labetalol or Metoprolol or Nadolol or Nebivolol or Oxprenolol or Propranolol or Pindolol or Sotalol or Timolol).ti,ab.
64.	(beta adj3 block*).ti,ab.
65.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj (block* or antagonist*)).ti,ab.
66.	(b adj3 block*).ti,ab.
67.	(beta adj2 antagonist*).ti,ab.
68.	exp Calcium Channel Blockers/
69.	(calcium adj3 (block* or antagonis* or inhibit*)).ti,ab.
70.	calcium channel receptor block*.ti,ab.
71.	(amlodipine or amrinone or bencyclane or bepridil or carvedilol or cinnarizine or conotoxin* or diltiazem or felodipine or fendiline or flunarizine or gallopamil or isradipine or lamotrigine or mibefradil or nicardipine or nifedipine or nimodipine or nisoldipine or nitrendipine or perhexiline or pregabalin or prenylamine or risedronic acid or tiapamil or verapamil or zonisamide or atenolol or clevidipine or lacidipine or lercanidipine or dihyropyridine*).ti,ab.
72.	exp Digoxin/
73.	digoxin.ti,ab.
74.	exp Diuretics/
75.	((oral* or subcut* or IV or intravenous* or iv or infusion* or drip or drips or augment* or sequential* or loop or "high ceiling") adj6 diuretic*).ti,ab.
76.	(augment* adj diuresis).ti,ab.
77.	(acetazolamide or amiloride or bendroflumenethiazide or bumentanide or chlorothiazide or chlorthalidone or clopamide or cyclopenhiazide or ethacrynic acid or ethoxzolamide or furosemide or hydrochlorothiazide or hydroflumethiazide or indapamide or mefruside or methazolamide or methyclothiazide or metolazone or muzolimine or polythiazide or potassium citrate or spironolactone or ticrynafen or torsemide or triamterene or trichlormethiazide or xipamide or isosorbide or mannitol or co-amilozide or co-triamterzide or co-flumactone or eplerenone or co-amilofruse).ti,ab.
78.	exp Nitrates/
79.	Nitroglycerin/
80.	Nitroprusside/
81.	Isosorbide Dinitrate/
82.	(nitroglycerin or gtn or nitrate* or nitroprusside*).ti,ab.
83.	(glyceryl trinitrate or isosorbide dinitrate or isosorbide mononitrate).ti,ab.
84.	*hydroxymethylglutaryl-coa reductase inhibitors/ or atorvastatin calcium/ or pravastatin/ or rosuvastatin calcium/ or exp simvastatin/
85.	(atorvastatin* or pravastatin* or rosuvastatin* or simvastatin* or fluvastatin*).ti,ab.
86.	((Hydroxymethylglutaryl-CoA or HMG-CoA or Hydroxymethylglutaryl-Coenzyme A) adj3 (reductase* or inhibitor*)).ti,ab.
87.	statin*.ti,ab.
88.	exp Adrenergic alpha-Antagonists/
89.	(alfuzosin or bunazosin or doxazosin or indoramin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).ti,ab.

90.	(alpha adrenergic antagonist* or alpha adrenergic receptor antagonist* or adrenergic alpha antagonist*).ti,ab.
91.	((alpha or alpha-adrenergic) adj2 block*).ti,ab.
92.	or/56-91
93.	55 and 92

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.	random*.ti,ab.

35.	factorial*.ti,ab.
36.	(crossover* or cross over*).ti,ab.
37.	((doubl* or singl*) adj blind*).ti,ab.
38.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
39.	crossover procedure/
40.	single blind procedure/
41.	randomized controlled trial/
42.	double blind procedure/
43.	or/34-42
44.	systematic review/
45.	meta-analysis/
46.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
47.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
48.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
49.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
50.	(search* adj4 literature).ab.
51.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
52.	((pool* or combined) adj2 (data or trials or studies or results)).ab.
53.	cochrane.jw.
54.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
55.	or/44-53
56.	33 and (43 or 55)
57.	exp dipeptidyl carboxypeptidase inhibitor/
58.	(("angiotensin-converting enzyme" or ace) adj2 (inhibitor* or antagonist*)).ti,ab.
59.	(Captopril or cilazapril or enalapril or enalaprilat or fosinopril or lisinopril or perindopril or quinapril or ramipril or teprotide or imidapril or trandolopril).ti,ab.
60.	exp angiotensin receptor antagonist/
61.	(angiotensin adj3 receptor adj3 (antagonist* or blocker*)).ti,ab.
62.	(1-Sarcosine-8-Isoleucine or amlodipine or irbesartan or olmesartan or saralasin or telmisartan or valsartan or azilsartan or candesartan or eprosartan or losartan).ti,ab.
63.	exp beta adrenergic receptor blocking agent/
64.	(Acebutolol or Atenolol or Bisoprolol or Carvedilol or Celiprolol or Esmolol or Labetalol or Metoprolol or Nadolol or Nebivolol or Oxprenolol or Propranolol or Pindolol or Sotalol or Timolol).ti,ab.
65.	(beta adj3 block*).ti,ab.
66.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj (block* or antagonist*)).ti,ab.
67.	(b adj3 block*).ti,ab.
68.	(beta adj2 antagonist*).ti,ab.
69.	exp Calcium Channel Blockers/
70.	(calcium adj3 (block* or antagonis* or inhibit*)).ti,ab.
71.	calcium channel receptor block*.ti,ab.
72.	(amlodipine or amrinone or bencyclane or bepridil or carvedilol or cinnarizine or conotoxin* or diltiazem or felodipine or fendiline or flunarizine or gallopamil or

	isradipine or lamotrigine or mibefradil or nicardipine or nifedipine or nimodipine or nisoldipine or nitrendipine or perhexiline or pregabalin or prenylamine or risedronic acid or tiapamil or verapamil or zonisamide or atenolol or clevidipine or lacidipine or lercanidipine or dihyropyridine*).ti,ab.
73.	digoxin/
74.	digoxin.ti,ab.
75.	exp diuretic agent/
76.	((oral* or subcut* or IV or intravenous* or iv or infusion* or drip or drips or augment* or sequential* or loop or "high ceiling") adj6 diuretic*).ti,ab.
77.	(augment* adj diuresis).ti,ab.
78.	(acetazolamide or amiloride or bendroflumenethiazide or bumentanide or chlorothiazide or chlorthalidone or clopamide or cyclopenhiazide or ethacrynic acid or ethoxzolamide or furosemide or hydrochlorothiazide or hydroflumethiazide or indapamide or mefruside or methazolamide or methyclothiazide or metolazone or muzolimine or polythiazide or potassium citrate or spironolactone or ticrynafen or torsemide or triamterene or trichlormethiazide or xipamide or isosorbide or mannitol or co-amilozide or co-triamterzide or co-flumactone or eplerenone or co-amilofruse).ti,ab.
79.	nitrate/
80.	glyceryl trinitrate/
81.	nitroprusside sodium/
82.	isosorbide mononitrate/
83.	isosorbide dinitrate/
84.	(nitroglycerin or gtn or nitrate* or nitroprusside*).ti,ab.
85.	(glyceryl trinitrate or isosorbide dinitrate or isosorbide mononitrate).ti,ab.
86.	*hydroxymethylglutaryl coenzyme a reductase inhibitor/ or exp atorvastatin/ or exp pravastatin/ or exp.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
87.	(atorvastatin* or pravastatin* or rosuvastatin* or simvastatin* or fluvastatin*).ti,ab.
88.	((Hydroxymethylglutaryl-CoA or HMG-CoA or Hydroxymethylglutaryl-Coenzyme A) adj3 (reductase* or inhibitor*)).ti,ab.
89.	statin*.ti,ab.
90.	exp alpha adrenergic receptor blocking agent/
91.	(alfuzosin or bunazosin or doxazosin or indoramin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).ti,ab.
92.	(alpha adrenergic antagonist* or alpha adrenergic receptor antagonist* or adrenergic alpha antagonist*).ti,ab.
93.	((alpha or alpha-adrenergic) adj2 block*).ti,ab.
94.	or/57-93
95.	56 and 94

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/2 (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.	MeSH descriptor: [Heart Valve Prosthesis] explode all trees
#8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) NEXT (valv* or flap* or leaflet*)):ti,ab
#9.	valve-in-valve:ti,ab
#10.	(transcatheter NEAR/2 (valve or valves)):ti,ab
#11.	MeSH descriptor: [Heart Murmurs] explode all trees
#12.	((heart or cardiac) NEXT murmur*):ti,ab
#13.	(or #1-#12)
#14.	MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees
#15.	(("angiotensin-converting enzyme" or ace) near/2 (inhibitor* or antagonist*)):ti,ab
#16.	(Captopril or cilazapril or enalapril or enalaprilat or fosinopril or lisinopril or perindopril or quinapril or ramipril or teprotide or imidapril or trandolopril):ti,ab
#17.	MeSH descriptor: [Angiotensin Receptor Antagonists] explode all trees
#18.	(angiotensin near/3 receptor near/3 (antagonist* or blocker*)):ti,ab
#19.	(amlodipine or irbesartan or olmesartan or saralasin or telmisartan or valsartan or azilsartan or candesartan or eprosartan or losartan):ti,ab
#20.	1-Sarcosine-8-Isoleucine:ti,ab
#21.	MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
#22.	(Acebutolol or Atenolol or Bisoprolol or Carvedilol or Celiprolol or Esmolol or Labetalol or Metoprolol or Nadolol or Nebivolol or Oxprenolol or Propranolol or Pindolol or Sotalol or Timolol):ti,ab
#23.	(beta near/3 block*):ti,ab
#24.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) NEXT (block* or antagonist*)):ti,ab
#25.	(b near/3 block*):ti,ab
#26.	(beta near/2 antagonist*):ti,ab
#27.	MeSH descriptor: [Calcium Channel Blockers] explode all trees
#28.	(calcium near/3 (block* or antagonis* or inhibit*)):ti,ab
#29.	'calcium channel receptor':ti,ab
#30.	(amlodipine or amrinone or bencyclane or bepridil or carvedilol or cinnarizine or conotoxin* or diltiazem or felodipine or fendiline or flunarizine or gallopamil or isradipine or lamotrigine or mibefradil or nicardipine or nifedipine or nimodipine or nisoldipine or nitrendipine or perhexiline or pregabalin or prenylamine or risedronic acid or tiapamil or verapamil or zonisamide or atenolol or clevidipine or lacidipine or lercanidipine or dihyropyridine*):ti,ab
#31.	MeSH descriptor: [Digoxin] explode all trees
#32.	digoxin:ti,ab
#33.	MeSH descriptor: [Diuretics] explode all trees
#34.	((oral* or subcut* or IV or intravenous* or iv or infusion* or drip or drips or augment* or sequential* or loop or "high ceiling") near/6 diuretic*):ti,ab
#35.	(acetazolamide or amiloride or bendroflumenethiazide or bumentanide or chlorothiazide or chlorthalidone or clopamide or cyclopenhiazide or ethacrynic acid or ethoxzolamide or furosemide or hydrochlorothiazide or hydroflumethiazide or indapamide or mefruside or methazolamide or methyclothiazide or metolazone or

	muzolimine or polythiazide or potassium citrate or spironolactone or ticrynafen or torsemide or triamterene or trichlormethiazide or xipamide or isosorbide or mannitol or co-amilozide or co-triamterzide or co-flumactone or eplerenone or co-amilofruse):ti,ab
#36.	MeSH descriptor: [Nitrates] explode all trees
#37.	MeSH descriptor: [Nitroglycerin] explode all trees
#38.	MeSH descriptor: [Nitroprusside] explode all trees
#39.	MeSH descriptor: [Isosorbide Dinitrate] explode all trees
#40.	(nitroglycerin or gtn or nitrate* or nitroprusside*):ti,ab
#41.	('glyceryl trinitrate' or 'isosorbide dinitrate' or 'isosorbide mononitrate'):ti,ab
#42.	MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees
#43.	MeSH descriptor: [Atorvastatin] explode all trees
#44.	MeSH descriptor: [Pravastatin] explode all trees
#45.	MeSH descriptor: [Rosuvastatin Calcium] explode all trees
#46.	MeSH descriptor: [Simvastatin] explode all trees
#47.	(atorvastatin* or pravastatin* or rosuvastatin* or simvastatin* or fluvastatin*):ti,ab
#48.	((Hydroxymethylglutaryl-CoA or HMG-CoA or Hydroxymethylglutaryl-Coenzyme A) near/3 (reductase* or inhibitor*)):ti,ab
#49.	statin*:ti,ab
#50.	MeSH descriptor: [Adrenergic alpha-Antagonists] explode all trees
#51.	(alfuzosin or bunazosin or doxazosin or indoramin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin):ti,ab
#52.	(alpha next adrenergic):ti,ab
#53.	(adrenergic next alpha):ti,ab
#54.	((alpha or alpha-adrenergic) near/2 block*).ti,ab
#55.	(or #14-#54)
#56.	#13 and #55

B.1.2 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 29: 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

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

B.2 Valve disease with heart failure

Heart valve disease – search strategy 5- pharmacological management with heart failure

This literature search strategy was used for the following reviews:

- In adults with heart failure and concomitant heart valve disease, what is the clinical and cost effectiveness of ACE inhibitors, ARBs, beta blockers, calcium channel blockers, digoxin, diuretics and nitrates to improve clinical outcome?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[112]

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

B.2.1 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 30: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 - 14 October 2020	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974 - 14 October 2020	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 10 of 12 CENTRAL to 2020 Issue 10 of 12	None

Medline (Ovid) search terms

94.	exp Heart Valve Diseases/
95.	exp heart valves/
96.	((primary or secondary) adj valv* disease*).ti,ab.
97.	((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.
98.	((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.
99.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
100.	Heart Valve Prosthesis/
101.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
102.	valve-in-valve.ti,ab.
103.	(transcatheter adj2 (valve or valves)).ti,ab.
104.	exp Heart Murmurs/
105.	((heart or cardiac) adj murmur*).ti,ab.
106.	or/1-12
107.	letter/
108.	editorial/
109.	news/
110.	exp historical article/
111.	Anecdotes as Topic/
112.	comment/

113.	case report/
114.	(letter or comment*).ti.
115.	or/14-21
116.	randomized controlled trial/ or random*.ti,ab.
117.	22 not 23
118.	animals/ not humans/
119.	exp Animals, Laboratory/
120.	exp Animal Experimentation/
121.	exp Models, Animal/
122.	exp Rodentia/
123.	(rat or rats or mouse or mice).ti.
124.	or/24-30
125.	13 not 31
126.	limit 32 to English language
127.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
128.	33 not 34
129.	randomized controlled trial.pt.
130.	controlled clinical trial.pt.
131.	randomi#ed.ti,ab.
132.	placebo.ab.
133.	randomly.ti,ab.
134.	Clinical Trials as topic.sh.
135.	trial.ti.
136.	or/36-42
137.	Meta-Analysis/
138.	exp Meta-Analysis as Topic/
139.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
140.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
141.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
142.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
143.	(search* adj4 literature).ab.
144.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
145.	cochrane.jw.
146.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
147.	or/44-52
148.	35 and (43 or 54)
149.	exp Angiotensin-Converting Enzyme Inhibitors/
150.	(("angiotensin-converting enzyme" or ace) adj2 (inhibitor* or antagonist*)).ti,ab.
151.	(Captopril or cilazapril or enalapril or enalaprilat or fosinopril or lisinopril or perindopril or quinapril or ramipril or teprotide or imidapril or trandolopril).ti,ab.
152.	exp Angiotensin Receptor Antagonists/

153.	(angiotensin adj3 receptor adj3 (antagonist* or blocker*)).ti,ab.
154.	(1-Sarcosine-8-Isoleucine or amlodipine or irbesartan or olmesartan or saralasin or telmisartan or valsartan or azilsartan or candesartan or eprosartan or losartan).ti,ab.
155.	exp Adrenergic beta-Antagonists/
156.	(Acebutolol or Atenolol or Bisoprolol or Carvedilol or Celiprolol or Esmolol or Labetalol or Metoprolol or Nadolol or Nebivolol or Oxprenolol or Propranolol or Pindolol or Sotalol or Timolol).ti,ab.
157.	(beta adj3 block*).ti,ab.
158.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj (block* or antagonist*)).ti,ab.
159.	(b adj3 block*).ti,ab.
160.	(beta adj2 antagonist*).ti,ab.
161.	exp Calcium Channel Blockers/
162.	(calcium adj3 (block* or antagonis* or inhibit*)).ti,ab.
163.	calcium channel receptor block*.ti,ab.
164.	(amlodipine or amrinone or bencyclane or bepridil or carvedilol or cinnarizine or conotoxin* or diltiazem or felodipine or fendiline or flunarizine or gallopamil or isradipine or lamotrigine or mibefradil or nicardipine or nifedipine or nimodipine or nisoldipine or nitrendipine or perhexiline or pregabalin or prenylamine or risedronic acid or tiapamil or verapamil or zonisamide or atenolol or clevidipine or lacidipine or lercanidipine or dihyropyridine*).ti,ab.
165.	exp Digoxin/
166.	digoxin.ti,ab.
167.	exp Diuretics/
168.	((oral* or subcut* or IV or intravenous* or iv or infusion* or drip or drips or augment* or sequential* or loop or "high ceiling") adj6 diuretic*).ti,ab.
169.	(augment* adj diuresis).ti,ab.
170.	(acetazolamide or amiloride or bendroflumenethiazide or bumentanide or chlorothiazide or chlorthalidone or clopamide or cyclopenhiazide or ethacrynic acid or ethoxzolamide or furosemide or hydrochlorothiazide or hydroflumethiazide or indapamide or mefruside or methazolamide or methyclothiazide or metolazone or muzolimine or polythiazide or potassium citrate or spironolactone or ticrynafen or torsemide or triamterene or trichlormethiazide or xipamide or isosorbide or mannitol or co-amilozide or co-triamterzide or co-flumactone or eplerenone or co-amilofruse).ti,ab.
171.	exp Nitrates/
172.	Nitroglycerin/
173.	Nitroprusside/
174.	Isosorbide Dinitrate/
175.	(nitroglycerin or gtn or nitrate* or nitroprusside*).ti,ab.
176.	(glyceryl trinitrate or isosorbide dinitrate or isosorbide mononitrate).ti,ab.
177.	or/56-83
178.	55 and 84

Embase (Ovid) search terms

96.	exp valvular heart disease/
97.	exp heart valve/
98.	((primary or secondary) adj valv* disease*).ti,ab.
99.	((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.

100.	((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.
101.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
102.	exp heart valve prosthesis/
103.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
104.	valve-in-valve.ti,ab.
105.	(transcatheter adj2 (valve or valves)).ti,ab.
106.	exp heart murmur/
107.	((heart or cardiac) adj murmur*).ti,ab.
108.	or/1-12
109.	letter.pt. or letter/
110.	note.pt.
111.	editorial.pt.
112.	Case report/ or Case study/
113.	(letter or comment*).ti.
114.	or/14-18
115.	randomized controlled trial/ or random*.ti,ab.
116.	19 not 20
117.	animal/ not human/
118.	Nonhuman/
119.	exp Animal Experiment/
120.	exp Experimental animal/
121.	Animal model/
122.	exp Rodent/
123.	(rat or rats or mouse or mice).ti.
124.	or/21-28
125.	13 not 29
126.	limit 30 to English language
127.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
128.	31 not 32
129.	random*.ti,ab.
130.	factorial*.ti,ab.
131.	(crossover* or cross over*).ti,ab.
132.	((doubl* or singl*) adj blind*).ti,ab.
133.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
134.	crossover procedure/
135.	single blind procedure/
136.	randomized controlled trial/
137.	double blind procedure/
138.	or/34-42
139.	systematic review/
140.	meta-analysis/

141.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
142.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
143.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
144.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
145.	(search* adj4 literature).ab.
146.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
147.	((pool* or combined) adj2 (data or trials or studies or results)).ab.
148.	cochrane.jw.
149.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
150.	or/44-53
151.	33 and (43 or 55)
152.	exp dipeptidyl carboxypeptidase inhibitor/
153.	(("angiotensin-converting enzyme" or ace) adj2 (inhibitor* or antagonist*)).ti,ab.
154.	(Captopril or cilazapril or enalapril or enalaprilat or fosinopril or lisinopril or perindopril or quinapril or ramipril or teprotide or imidapril or trandolopril).ti,ab.
155.	exp angiotensin receptor antagonist/
156.	(angiotensin adj3 receptor adj3 (antagonist* or blocker*)).ti,ab.
157.	(1-Sarcosine-8-Isoleucine or amlodipine or irbesartan or olmesartan or saralasin or telmisartan or valsartan or azilsartan or candesartan or eprosartan or losartan).ti,ab.
158.	exp beta adrenergic receptor blocking agent/
159.	(Acebutolol or Atenolol or Bisoprolol or Carvedilol or Celiprolol or Esmolol or Labetalol or Metoprolol or Nadolol or Nebivolol or Oxprenolol or Propranolol or Pindolol or Sotalol or Timolol).ti,ab.
160.	(beta adj3 block*).ti,ab.
161.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj (block* or antagonist*)).ti,ab.
162.	(b adj3 block*).ti,ab.
163.	(beta adj2 antagonist*).ti,ab.
164.	exp Calcium Channel Blockers/
165.	(calcium adj3 (block* or antagonis* or inhibit*)).ti,ab.
166.	calcium channel receptor block*.ti,ab.
167.	(amlodipine or amrinone or bencyclane or bepridil or carvedilol or cinnarizine or conotoxin* or diltiazem or felodipine or fendiline or flunarizine or gallopamil or isradipine or lamotrigine or mibefradil or nicardipine or nifedipine or nimodipine or nisoldipine or nitrendipine or perhexiline or pregabalin or prenylamine or risedronic acid or tiapamil or verapamil or zonisamide or atenolol or clevidipine or lacidipine or lercanidipine or dihyropyridine*).ti,ab.
168.	digoxin/
169.	digoxin.ti,ab.
170.	exp diuretic agent/
171.	((oral* or subcut* or IV or intravenous* or iv or infusion* or drip or drips or augment* or sequential* or loop or "high ceiling") adj6 diuretic*).ti,ab.
172.	(augment* adj diuresis).ti,ab.
173.	(acetazolamide or amiloride or bendroflumenethiazide or bumentanide or chlorothiazide or chlorthalidone or clopamide or cyclopenhiazide or ethacrynic acid or ethoxzolamide or furosemide or hydrochlorothiazide or hydroflumethiazide or

	indapamide or mefruside or methazolamide or methyclothiazide or metolazone or muzolimine or polythiazide or potassium citrate or spironolactone or ticrynafen or torsemide or triamterene or trichlormethiazide or xipamide or isosorbide or mannitol or co-amilozide or co-triamterzide or co-flumactone or eplerenone or co-amilofruse).ti,ab.
174.	nitrate/
175.	glyceryl trinitrate/
176.	nitroprusside sodium/
177.	isosorbide mononitrate/
178.	isosorbide dinitrate/
179.	(nitroglycerin or gtn or nitrate* or nitroprusside*).ti,ab.
180.	(glyceryl trinitrate or isosorbide dinitrate or isosorbide mononitrate).ti,ab.
181.	or/57-85
182.	56 and 86

Cochrane Library (Wiley) search terms

#57.	MeSH descriptor: [Heart Valve Diseases] explode all trees
#58.	MeSH descriptor: [Heart Valves] explode all trees
#59.	((primary or secondary) NEXT valv* disease*):ti,ab
#60.	((valv* or flap* or leaflet*) near/2 (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
#61.	((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
#62.	((mitral or aortic or tricuspid or pulmon*) NEAR/3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)):ti,ab
#63.	MeSH descriptor: [Heart Valve Prosthesis] explode all trees
#64.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) NEXT (valv* or flap* or leaflet*)):ti,ab
#65.	valve-in-valve:ti,ab
#66.	(transcatheter NEAR/2 (valve or valves)):ti,ab
#67.	MeSH descriptor: [Heart Murmurs] explode all trees
#68.	((heart or cardiac) NEXT murmur*):ti,ab
#69.	(or #1-#12)
#70.	MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees
#71.	(("angiotensin-converting enzyme" or ace) near/2 (inhibitor* or antagonist*)):ti,ab
#72.	(Captopril or cilazapril or enalapril or enalaprilat or fosinopril or lisinopril or perindopril or quinapril or ramipril or teprotide or imidapril or trandolopril):ti,ab
#73.	MeSH descriptor: [Angiotensin Receptor Antagonists] explode all trees
#74.	(angiotensin near/3 receptor near/3 (antagonist* or blocker*)):ti,ab
#75.	(amlodipine or irbesartan or olmesartan or saralasin or telmisartan or valsartan or azilsartan or candesartan or eprosartan or losartan):ti,ab
#76.	1-Sarcosine-8-Isoleucine:ti,ab
#77.	MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
#78.	(Acebutolol or Atenolol or Bisoprolol or Carvedilol or Celiprolol or Esmolol or Labetalol or Metoprolol or Nadolol or Nebivolol or Oxprenolol or Propranolol or Pindolol or Sotalol or Timolol):ti,ab
#79.	(beta near/3 block*):ti,ab

#80.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) NEXT (block* or antagonist*)):ti,ab
#81.	(b near/3 block*):ti,ab
#82.	(beta near/2 antagonist*):ti,ab
#83.	MeSH descriptor: [Calcium Channel Blockers] explode all trees
#84.	(calcium near/3 (block* or antagonis* or inhibit*)):ti,ab
#85.	'calcium channel receptor':ti,ab
#86.	(amlodipine or amrinone or bencyclane or bepridil or carvedilol or cinnarizine or conotoxin* or diltiazem or felodipine or fendiline or flunarizine or gallopamil or isradipine or lamotrigine or mibefradil or nicardipine or nifedipine or nimodipine or nisoldipine or nitrendipine or perhexiline or pregabalin or prenylamine or risedronic acid or tiapamil or verapamil or zonisamide or atenolol or clevidipine or lacidipine or lercanidipine or dihyropyridine*):ti,ab
#87.	MeSH descriptor: [Digoxin] explode all trees
#88.	digoxin:ti,ab
#89.	MeSH descriptor: [Diuretics] explode all trees
#90.	((oral* or subcut* or IV or intravenous* or iv or infusion* or drip or drips or augment* or sequential* or loop or "high ceiling") near/6 diuretic*):ti,ab
#91.	(acetazolamide or amiloride or bendroflumenethiazide or bumentanide or chlorothiazide or chlorthalidone or clopamide or cyclopenhiazide or ethacrynic acid or ethoxzolamide or furosemide or hydrochlorothiazide or hydroflumethiazide or indapamide or mefruside or methazolamide or methyclothiazide or metolazone or muzolimine or polythiazide or potassium citrate or spironolactone or ticrynafen or torsemide or triamterene or trichlormethiazide or xipamide or isosorbide or mannitol or co-amilozide or co-triamterzide or co-flumactone or eplerenone or co-amilofruse):ti,ab
#92.	MeSH descriptor: [Nitrates] explode all trees
#93.	MeSH descriptor: [Nitroglycerin] explode all trees
#94.	MeSH descriptor: [Nitroprusside] explode all trees
#95.	MeSH descriptor: [Isosorbide Dinitrate] explode all trees
#96.	(nitroglycerin or gtn or nitrate* or nitroprusside*):ti,ab
#97.	('glyceryl trinitrate' or 'isosorbide dinitrate' or 'isosorbide mononitrate'):ti,ab
#98.	(or #14-#41)
#99.	#13 and #42

B.2.2 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 31: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2014 – 15 October 2020	Exclusions Health economics studies

Database	Dates searched	Search filter used
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

54.	exp Heart Valve Diseases/
55.	exp heart valves/
56.	((primary or secondary) adj valv* disease*).ti,ab.
57.	((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.
58.	((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.
59.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
60.	Heart Valve Prosthesis/
61.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
62.	valve-in-valve.ti,ab.
63.	(transcatheter adj2 (valve or valves)).ti,ab.
64.	exp Heart Murmurs/
65.	((heart or cardiac) adj murmur*).ti,ab.
66.	or/1-12
67.	letter/
68.	editorial/
69.	news/
70.	exp historical article/
71.	Anecdotes as Topic/
72.	comment/
73.	case report/
74.	(letter or comment*).ti.
75.	or/14-21
76.	randomized controlled trial/ or random*.ti,ab.
77.	22 not 23
78.	animals/ not humans/
79.	exp Animals, Laboratory/
80.	exp Animal Experimentation/
81.	exp Models, Animal/
82.	exp Rodentia/
83.	(rat or rats or mouse or mice).ti.

84.	or/24-30
85.	13 not 31
86.	limit 32 to English language
87.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
88.	33 not 34
89.	Economics/
90.	Value of life/
91.	exp "Costs and Cost Analysis"/
92.	exp Economics, Hospital/
93.	exp Economics, Medical/
94.	Economics, Nursing/
95.	Economics, Pharmaceutical/
96.	exp "Fees and Charges"/
97.	exp Budgets/
98.	budget*.ti,ab.
99.	cost*.ti.
100.	(economic* or pharmaco?economic*).ti.
101.	(price* or pricing*).ti,ab.
102.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
103.	(financ* or fee or fees).ti,ab.
104.	(value adj2 (money or monetary)).ti,ab.
105.	or/36-51
106.	35 and 52

Embase (Ovid) search terms

49.	exp valvular heart disease/
50.	exp heart valve/
51.	((primary or secondary) adj valv* disease*).ti,ab.
52.	((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.
53.	((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.
54.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
55.	exp heart valve prosthesis/
56.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
57.	valve-in-valve.ti,ab.
58.	(transcatheter adj2 (valve or valves)).ti,ab.
59.	exp heart murmur/
60.	((heart or cardiac) adj murmur*).ti,ab.
61.	or/1-12
62.	letter.pt. or letter/

63.	note.pt.
64.	editorial.pt.
65.	Case report/ or Case study/
66.	(letter or comment*).ti.
67.	or/14-18
68.	randomized controlled trial/ or random*.ti,ab.
69.	19 not 20
70.	animal/ not human/
71.	Nonhuman/
72.	exp Animal Experiment/
73.	exp Experimental animal/
74.	Animal model/
75.	exp Rodent/
76.	(rat or rats or mouse or mice).ti.
77.	or/21-28
78.	13 not 29
79.	limit 30 to English language
80.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
81.	31 not 32
82.	health economics/
83.	exp economic evaluation/
84.	exp health care cost/
85.	exp fee/
86.	budget/
87.	funding/
88.	budget*.ti,ab.
89.	cost*.ti.
90.	(economic* or pharmaco?economic*).ti.
91.	(price* or pricing*).ti,ab.
92.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
93.	(financ* or fee or fees).ti,ab.
94.	(value adj2 (money or monetary)).ti,ab.
95.	or/34-46
96.	33 and 47

NHS EED and HTA (CRD) search terms

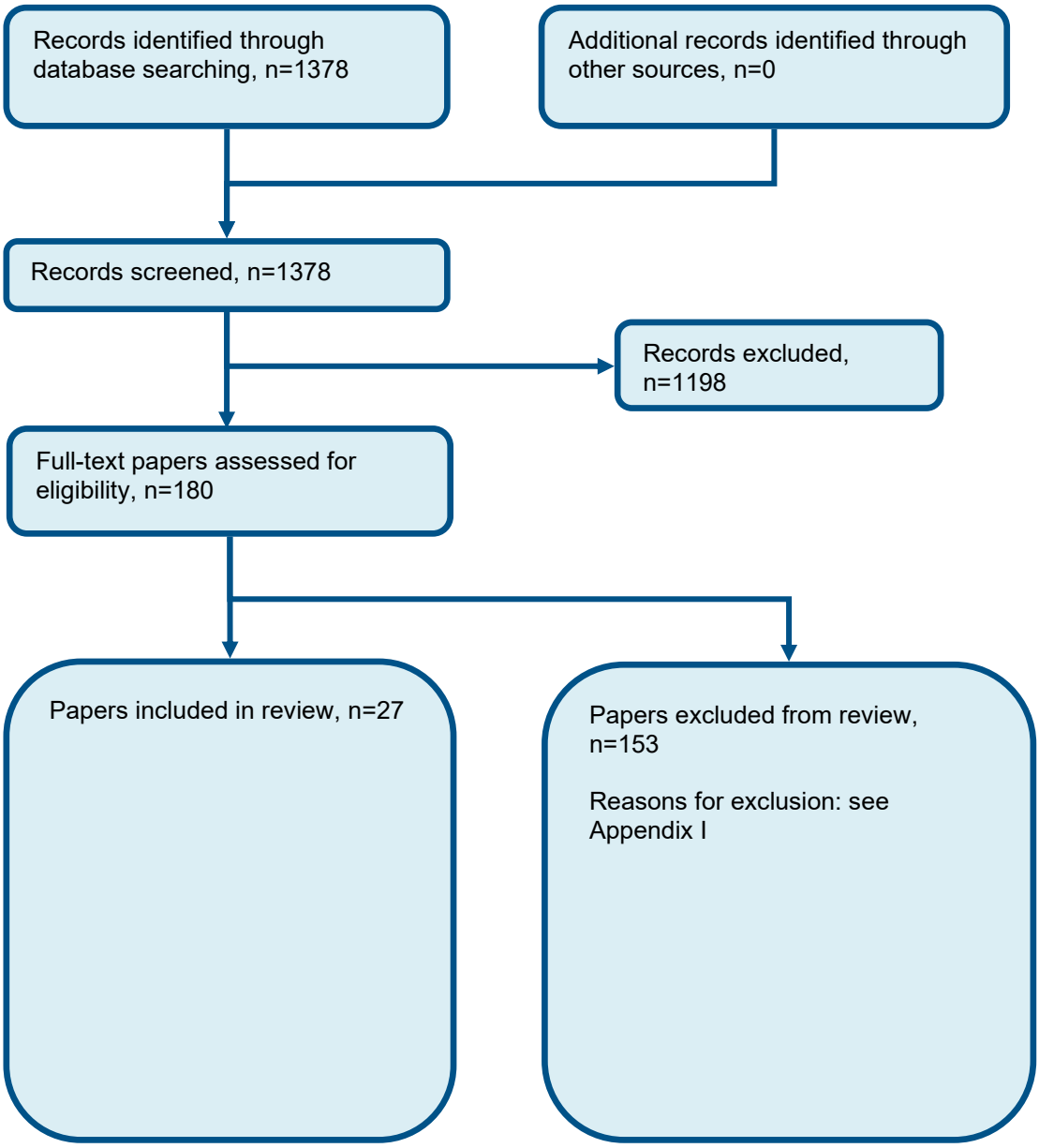
#13.	MeSH DESCRIPTOR Heart Valve Diseases EXPLODE ALL TREES
#14.	MeSH DESCRIPTOR Heart Valves EXPLODE ALL TREES
#15.	(((primary or secondary) adj Valv* adj disease*))
#16.	(((valv* or flap* or leaflet*) adj (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)))
#17.	((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*))

#18.	(((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*)))
#19.	(((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)))
#20.	MeSH DESCRIPTOR Heart Valve Prosthesis EXPLODE ALL TREES
#21.	(((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)))
#22.	(valve-in-valve)
#23.	((transcatheter adj2 (valve or valves)))
#24.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

Appendix C: Clinical evidence selection

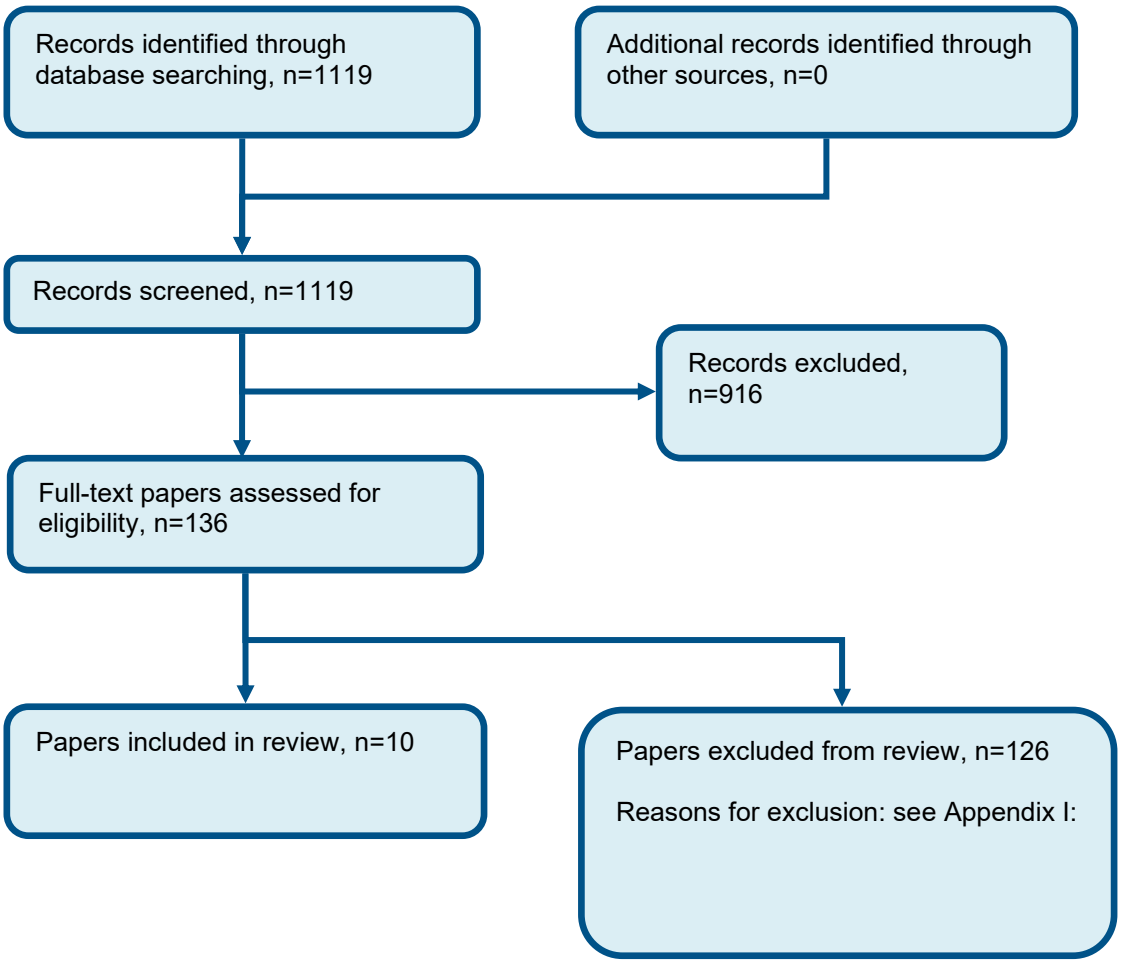
C.1 Valve disease without heart failure

Figure 1: Flow chart of clinical study selection for the review of pharmacological management of heart valve disease without concomitant heart failure



C.2 Valve disease with heart failure

Figure 2: Flow chart of clinical study selection for the review of pharmacological management



Appendix D: Clinical evidence tables

D.1 Valve disease without heart failure

Study	Ahmed 2012[4]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=38)
Countries and setting	Conducted in USA; Setting: Outpatient follow up
Line of therapy	1st line
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography - colour flow Doppler imaging
Stratum	Primary mitral regurgitation
Subgroup analysis within study	Not applicable
Inclusion criteria	Moderate or severe MR documented by color flow Doppler, LVEF >55%, LV end systolic dimension (ESD) < 40 mm, and echocardiographic thickening of the mitral valve leaflets and prolapse
Exclusion criteria	New York Heart Association class III or IV symptoms, previous myocardial infarction, significant coronary artery disease by exercise testing with myocardial perfusion imaging, significant other valvular disease, serum creatinine >2.5, and hypertension requiring medical treatment
Recruitment/selection of patients	Recruited in Birmingham, Alabama. No other details given.
Age, gender and ethnicity	Age - Mean (SD): Metoprolol: 52.9 (9.1). Placebo: 56 (9.2). Gender (M:F): 18:20. Ethnicity: Majority (92%) Caucasian
Further population details	1. Age: <75 years (Metoprolol: 52.9 (9.1). Placebo: 56 (9.2).). 2. Disease mechanism for aortic and mitral stenosis: Not applicable 3. Presence vs. absence of uncontrolled systemic hypertension (140/85 mmHg) at the end of trial intervention despite medication: Not stated / Unclear (At baseline: Metoprolol: 125/75 (14/8). Placebo: 121/75 (14/11).).
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Beta blockers - Metoprolol . Toprol XL (range 25 to 100mg/day) - starting dose of 12.5-25mg/day titrated up to the maximum tolerable dose at 2 week intervals up to a maximum of 100mg/day. Duration 2 years. Concurrent medication/care: No additional information given. Indirectness: No indirectness

	(n=19) Intervention 2: Placebo. Placebo. Duration 2 years. Concurrent medication/care: No additional information given. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Drug and placebo supplied by Astra-Zenica. The study was funded by NHLBI Specialised Centre for Clinically Oriented Research (SCCOR) in Cardiac Dysfunction)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METOPROLOL versus PLACEBO

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Primary mitral regurgitation: Death at 2 years; Group 1: 1/19, Group 2: 0/18; Comments: 1 death due to PE after a cosmetic procedure
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: 1 person withdrew from the study early on

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Primary mitral regurgitation: Death at 2 years; Group 1: 1/19, Group 2: 0/18; Comments: 1 death due to PE after a cosmetic procedure
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: 1 person withdrew from the study early on

Protocol outcome 3: Need for heart valve intervention at ≥12 months
- Actual outcome for Primary mitral regurgitation: Need to have valve replacement or surgery at 2 years; Group 1: 2/18, Group 2: 6/18
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 death; Group 2 Number missing: 1, Reason: 1 person withdrew from the study early on

Protocol outcome 4: Withdrawal due to adverse events at ≥12 months
- Actual outcome for Primary mitral regurgitation: Serious adverse events at 2 years; Group 1: 3/18, Group 2: 7/18; Comments: Events not stated
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Doesn't report withdrawal due to adverse

events; Group 1 Number missing: 1, Reason: 1 death; Group 2 Number missing: 1, Reason: 1 person withdrew from the study early on	
Protocol outcomes not reported by the study	Quality of life at 6 months; Quality of life at ≥12 months; Onset of symptoms or progression of NYHA class at ≥12 months ; Evidence of HVD progression on imaging (worsening of disease severity) at ≥12 months; Exercise tolerance at ≥12 months; Withdrawal due to adverse events at 6 months

Study (subsidiary papers)	ASTRONOMER trial: Chan 2010[27] (Chan 2011[25], Chan 2010[26], Chan 2007[28])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=272)
Countries and setting	Conducted in Canada; Setting: Outpatient follow up in secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: Median follow-up: 3.5 years (IQR: 2.1 to 4.5 years)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography - people were recruited from echocardiographic laboratories and cardiology clinics at participating sites.
Stratum	Primary aortic [including bicuspid] stenosis : While stated as including mild to moderate aortic stenosis, the mean peak aortic valve velocity was 3.16 (0.42) in the intervention arm, and 3.19 (0.42) in the control arm, considered moderate severity by the British Society of Echocardiography guidelines.
Subgroup analysis within study	Not applicable:
Inclusion criteria	People between 18 and 82 years of age with asymptomatic mild to moderate aortic stenosis defined by maximum aortic valve velocity between 2.5 and 4.0m/s.
Exclusion criteria	People with clinical indications for the use of statin as defined by Canadian guidelines such as coronary artery disease, cerebrovascular disease, peripheral vascular disease and diabetes. Baseline lipid values outside of the target levels for their respective risk category according to Canadian guidelines.
Recruitment/selection of patients	People recruited from echocardiographic laboratories and cardiology clinics at participating sites (5 sites listed in the study).
Age, gender and ethnicity	Age - Mean (SD): 57.9 (13.6). Gender (M:F): 166:103. Ethnicity: 98% were white. Asian people were excluded for the later part of the study due to concern regarding adverse events. 1 Asian person remained in the study due to no adverse events.
Further population details	1. Age: <75 years 2. Disease mechanism for aortic and mitral stenosis: Mixed (Not completely stated. However, they do state that around 50% of people had bicuspid aortic valve disease.). 3. Presence vs. absence of uncontrolled systemic hypertension (140/85 mmHg) at the end of trial intervention despite medication: Not stated / Unclear (Mean blood pressure at the start of study was not hypertensive. Intervention: 128.8/76.5 (15.67/10.04). Control: 128.4/75.9 (15.94/10.92).).
Indirectness of population	No indirectness

Interventions	(n=136) Intervention 1: Statins - Rosuvastatin . Rosuvastatin 40mg daily. Duration 3.5 years. Concurrent medication/care: No information provided. Indirectness: No indirectness (n=136) Intervention 2: Placebo. Placebo. Duration 3.5 years. Concurrent medication/care: No information provided. Indirectness: No indirectness
Funding	Study funded by industry (Supported by the Canada Institutes of Health Research, with additional support from AstraZeneca Canada Inc. Also several authors received travel grants from Astra Zeneca. One author has had consultancies for and/or research funds from St Jude Medical, Edward Life Sciences, and Medtronic.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ROSUVASTATIN versus PLACEBO

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : All-cause mortality at 3.5 years; Group 1: 3/134, Group 2: 5/135
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 136 allocated to rosuvastatin. 2 had a randomisation error and weren't eligible for randomisation - making 134 people who received rosuvastatin (included in intention to treat analysis). However, in actuality 57 people discontinued treatment: 25 for adverse events, 8 withdrew consent, 1 lost to follow-up, 1 investigator discretion, 3 patients died and 19 other (unclear).; Group 2 Number missing: 1, Reason: 136 allocated to placebo. 1 had a randomisation error and weren't eligible for randomisation - making 135 people who received placebo (included in the intention to treat analysis). However, in actuality 66 people discontinued treatment. 26 for adverse events. 2 for protocol non-compliance. 4 withdrew consent. 2 at investigator discretion. 5 patients died. 25 other (unclear).

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : Cardiac death at 3.5 years; Group 1: 2/134, Group 2: 5/135
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 136 allocated to rosuvastatin. 2 had a randomisation error and weren't eligible for randomisation - making 134 people who received rosuvastatin (included in intention to treat analysis). However, in actuality 57 people discontinued
treatment: 25 for adverse events, 8 withdrew consent, 1 lost to follow-up, 1 investigator discretion, 3 patients died and 19 other (unclear).

; Group 2 Number missing: 1, Reason: 136 allocated to placebo. 1 had a randomisation error and weren't eligible for randomisation - making 135 people who received placebo (included in the intention to treat analysis). However, in actuality 66 people discontinued
treatment. 26 for adverse events. 2 for protocol non-compliance. 4 withdrew consent. 2 at investigator discretion. 5 patients died. 25 other (unclear).

Protocol outcome 3: Need for heart valve intervention at ≥12 months - Actual outcome for Primary aortic [including bicuspid] stenosis : Aortic valve replacement at 3.5 years; Group 1: 28/134, Group 2: 27/135 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 136 allocated to rosuvastatin. 2 had a randomisation error and weren't eligible for randomisation - making 134 people who received rosuvastatin (included in intention to treat analysis). However, in actuality 57 people discontinued treatment: 25 for adverse events, 8 withdrew consent, 1 lost to follow-up, 1 investigator discretion, 3 patients died and 19 other (unclear).; Group 2 Number missing: 1, Reason: 136 allocated to placebo. 1 had a randomisation error and weren't eligible for randomisation - making 135 people who received placebo (included in the intention to treat analysis). However, in actuality 66 people discontinued treatment. 26 for adverse events. 2 for protocol non-compliance. 4 withdrew consent. 2 at investigator discretion. 5 patients died. 25 other (unclear). Protocol outcome 4: Withdrawal due to adverse events at ≥12 months - Actual outcome for Primary aortic [including bicuspid] stenosis : Withdrawal due to adverse events at 3.5 years; Group 1: 25/134, Group 2: 26/135 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 136 allocated to rosuvastatin. 2 had a randomisation error and weren't eligible for randomisation - making 134 people who received rosuvastatin (included in intention to treat analysis). However, in actuality 57 people discontinued treatment: 25 for adverse events, 8 withdrew consent, 1 lost to follow-up, 1 investigator discretion, 3 patients died and 19 other (unclear).; Group 2 Number missing: 1, Reason: 136 allocated to placebo. 1 had a randomisation error and weren't eligible for randomisation - making 135 people who received placebo (included in the intention to treat analysis). However, in actuality 66 people discontinued treatment. 26 for adverse events. 2 for protocol non-compliance. 4 withdrew consent. 2 at investigator discretion. 5 patients died. 25 other (unclear).	
Protocol outcomes not reported by the study	Quality of life at 6 months; Quality of life at ≥12 months; Onset of symptoms or progression of NYHA class at ≥12 months ; Evidence of HVD progression on imaging (worsening of disease severity) at ≥12 months; Exercise tolerance at ≥12 months; Withdrawal due to adverse events at 6 months

Study	Banaszewski 1998[13]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=31)
Countries and setting	Conducted in Poland; Setting: Initially secondary care, followed by outpatient follow up
Line of therapy	1st line
Duration of study	Intervention + follow up: 2.75 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography and cardiac catheterisation performed during the study - used echocardiographic parameters to determine severity of aortic regurgitation and exclude presence of other valve disease
Stratum	Primary aortic regurgitation
Subgroup analysis within study	Not applicable:
Inclusion criteria	Known history of aortic regurgitation for >24 months with a stable clinical course during that time; no clinical symptoms of heart failure, and echo-Doppler parameters of isolated (at least moderate) aortic insufficiency, LVEDD >56mm and LVEF >50%; signed, written informed consent
Exclusion criteria	A maximum aortic valvular pressure gradient >15mmHg; insufficiency and/or stenosis of any other valve; sustained or paroxysmal supra- and/or ventricular arrhythmias; coexistent coronary artery disease; previous therapy with ACE inhibitors, calcium channel blockers, diuretics, beta-blockers and/or digitalis
Recruitment/selection of patients	Does not give any additional information about where people were recruited from
Age, gender and ethnicity	Age - Mean (SD): 34.9 (10.1) (range: 18-60). Gender (M:F): 27:4. Ethnicity: Not stated
Further population details	1. Age: <75 years (Mean age: 34.9 (10.1) (range: 18-60)). 2. Disease mechanism for aortic and mitral stenosis: Not applicable 3. Presence vs. absence of uncontrolled systemic hypertension (140/85 mmHg) at the end of trial intervention despite medication: Not stated / Unclear (At the start of the trial: Mean systolic blood pressure 132.2 (14.3). Mean diastolic blood pressure 54.5 (10.4). Does not report at the end.).
Indirectness of population	No indirectness

Interventions	(n=12) Intervention 1: Calcium-channel blockers (CCB) - Nifedipine. Nifedipine 10-20mg three times a day - mean daily dose of 40mg. People were given the maximum tolerable dose. Duration 2.75 years. Concurrent medication/care: Exclusion criteria stated that people should not have been using ACE inhibitors, calcium channel blockers, diuretics, beta-blockers and/or digitalis prior to the study. No other information available. Indirectness: No indirectness (n=13) Intervention 2: Angiotensin-converting enzyme (ACE) inhibitors - Captopril. Captopril 12.5-30mg three times a day - mean daily dose of 75mg. People were given the maximum tolerable dose. Duration 2.75 years. Concurrent medication/care: Exclusion criteria stated that people should not have been using ACE inhibitors, calcium channel blockers, diuretics, beta-blockers and/or digitalis prior to the study. No other information available. Indirectness: No indirectness Comments: The study included an acute phase where participants underwent cardiac catheterisation and exercise therapy after a single dose of nifedipine, which was repeated after 24 hours (6 half-lives) with captopril. Another 24 hours were given and then the long term (randomised) phase of the study was started.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NIFEDIPINE versus CAPTOPRIL

Protocol outcome 1: Onset of symptoms or progression of NYHA class at ≥12 months
- Actual outcome for Primary aortic regurgitation : Development of symptoms at 2.75 years; Group 1: 0/12, Group 2: 0/13
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports the baseline characteristics for the combined cohort, but not for each intervention group.; Group 1 Number missing: 0, Reason: 5 people withdrew consent after the acute phase and 1 withdrew due to adverse events during the acute phase. However, it is not reported whether there was randomisation before this withdrawal so assuming no missing people.; Group 2 Number missing: 0, Reason: 5 people withdrew consent after the acute phase and 1 withdrew due to adverse events during the acute phase. However, it is not reported whether there was randomisation before this withdrawal so assuming no missing people.

Protocol outcome 2: Evidence of HVD progression on imaging (worsening of disease severity) at ≥12 months
- Actual outcome for Primary aortic regurgitation : Aortic regurgitation grade worsening (by ≥1) at 2.75 years; Group 1: 2/12, Group 2: 0/13
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports the baseline characteristics for the combined cohort, but not for each intervention group.; Group 1 Number missing: 0, Reason: 5 people withdrew consent after the acute phase and 1

withdrew due to adverse events during the acute phase. However, it is not reported whether there was randomisation before this withdrawal so assuming no missing people.; Group 2 Number missing: 0, Reason: 5 people withdrew consent after the acute phase and 1 withdrew due to adverse events during the acute phase. However, it is not reported whether there was randomisation before this withdrawal so assuming no missing people.	
Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Cardiac mortality at ≥12 months; Quality of life at 6 months; Quality of life at ≥12 months; Need for heart valve intervention at ≥12 months; Exercise tolerance at ≥12 months; Withdrawal due to adverse events at 6 months; Withdrawal due to adverse events at ≥12 months

Study	Broch 2016[20]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in Denmark, Norway; Setting: Outpatient follow up
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cardiac MRI and echocardiography
Stratum	Primary aortic regurgitation
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged between 18 and 70 years with asymptomatic, haemodynamically significant aortic regurgitation, an LVEF >50% and an LVEDD >5.0cm (or an indexed value >30cm/m²).
Exclusion criteria	Symptoms of heart failure; a history of myocardial infarction or symptomatic coronary heart disease; significant aortic stenosis (valvular area <1.5cm²); additional haemodynamically significant valvular or congenital heart disease; an indication for aortic valve surgery (severe AR in conjunction with either symptoms of heart failure, an LVEF <50%, or an LV end diastolic/end systolic internal diameter >7.0/5.0cm); a second or third degree atrioventricular block; atrial fibrillation; an intra-cardiac device; serum creatinine >250 micromol/L; alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal; any illness of disorder that could severely limit survival; conditions or circumstances likely to lead to poor treatment adherence; and intolerance to metoprolol CR/XL.
Recruitment/selection of patients	Recruited from two centers.
Age, gender and ethnicity	Age - Mean (SD): 44 (14). Gender (M:F): 67:8. Ethnicity: Not stated
Further population details	1. Age: <75 years (44 (14)). 2. Disease mechanism for aortic and mitral stenosis: Not applicable 3. Presence vs. absence of uncontrolled systemic hypertension (140/85 mmHg) at the end of trial intervention despite medication: Absence of uncontrolled systemic hypertension (Final metoprolol: 124/58 (17/9). Final placebo: 134/67 (19/6).).
Extra comments	55 (73%) people had bicuspid aortic valves
Indirectness of population	No indirectness

Interventions	(n=37) Intervention 1: Beta blockers - Metoprolol . Metoprolol CR/XL 25mg doubled every week up to a target daily dose of 200mg or the maximum tolerable dose. Duration 6 months. Concurrent medication/care: All people were allowed to concomitantly use other vasoactive drugs. 6 on and ACE inhibitor/ARB. 2 on calcium channel blockers. 5 on statins. 7 on acetylsalicylic acid. 1 on another cardiovascular drug. Indirectness: No indirectness (n=38) Intervention 2: Placebo. Placebo. Duration 6 months. Concurrent medication/care: All people were allowed to concomitantly use other vasoactive drugs. 6 on and ACE inhibitor/ARB. 3 on calcium channel blockers. 5 on statins. 2 on acetylsalicylic acid. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Active drug and placebo provided by AstraZeneca. Unrestricted grants provided by the South-East Norway regional health authority and the Norwegian ExtraFoundation for Health and Rehabilitation through EXTRA funds.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METOPROLOL versus PLACEBO

Protocol outcome 1: Quality of life at 6 months
- Actual outcome for Primary aortic regurgitation : EuroQol VAS (0-100) at 6 months; Group 1: mean 85 (SD 7); n=36, Group 2: mean 82 (SD 16); n=36; EuroQoL visual analogue scale 0-100 Top=High is good outcome; Comments: Baseline metoprolol: 84 (9). Baseline placebo: 82 (11).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 withdrew; Group 2 Number missing: 2, Reason: 1 withdrew, 1 had a poor quality baseline MRI so their results were excluded
- Actual outcome for Primary aortic regurgitation : KCCQ overall clinical summary score at 6 months; Group 1: mean 98 (SD 42.78); n=36, Group 2: mean 96 (SD 42.78); n=36; KCCQ 0-100 Top=High is good outcome; Comments: SD calculated from p value. Reported p-value = 0.78. Standard error = 7.13.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 withdrew; Group 2 Number missing: 2, Reason: 1 withdrew, 1 had a poor quality baseline MRI so their results were excluded

Protocol outcome 2: Exercise tolerance at ≥12 months
- Actual outcome for Primary aortic regurgitation : Peak work (Watts) at 6 months; Group 1: mean 229 Watts (SD 62); n=36, Group 2: mean 241 Watts (SD 62); n=36; Comments: Baseline metoprolol: 240 (63). Baseline placebo: 237 (63).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 withdrew; Group 2

Number missing: 2, Reason: 1 withdrew, 1 had a poor quality baseline MRI so their results were excluded	
Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Cardiac mortality at ≥12 months; Quality of life at ≥12 months; Onset of symptoms or progression of NYHA class at ≥12 months ; Evidence of HVD progression on imaging (worsening of disease severity) at ≥12 months; Need for heart valve intervention at ≥12 months; Withdrawal due to adverse events at 6 months; Withdrawal due to adverse events at ≥12 months

Study	Bull 2015[21]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in United Kingdom; Setting: Outpatient follow up
Line of therapy	1st line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cardiovascular magnetic resonance imaging and echocardiography
Stratum	Primary aortic [including bicuspid] stenosis
Subgroup analysis within study	Not applicable
Inclusion criteria	All people aged >18 years with moderate or severe aortic stenosis by standard echocardiographic criteria (valve area <1.5cm², or peak velocity >3.0m/s (peak valve gradient >36mmHg)), who were asymptomatic as judged by patient-reported symptoms, and who did not have indications for valve replacement surgery.
Exclusion criteria	Abnormal LV function (LVEF <50% by echocardiography), other significant (>mild) valvular heart disease, excess hypo- or hypertension, intolerance to ACE inhibitors or ARBs or their prescription over the previous 3 months.
Recruitment/selection of patients	People recruited from clinics at the John Radcliffe Hospital and surrounding institutions.
Age, gender and ethnicity	Age - Mean (SD): 68.57 (14.22) years. Gender (M:F): 71:25. Ethnicity: Not stated
Further population details	1. Age: Mixed (68.57 (14.22) years. Confidence intervals would fall over the age boundary.). 2. Disease mechanism for aortic and mitral stenosis: Not stated / Unclear 3. Presence vs. absence of uncontrolled systemic hypertension (140/85 mmHg) at the end of trial intervention despite medication: Not stated / Unclear (At the start of the study 11 people in the ramipril arm and 17 people in the placebo arm had hypertension. No statement about the degree or progression during the study.).
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Angiotensin-converting enzyme (ACE) inhibitors - Ramipril. Ramipril 2.5mg daily for 2 weeks, raised to 5mg daily until the 3-month check, raised to 10mg daily for the rest of the study or to the maximal dose with no adverse events. Duration 1 year. Concurrent medication/care: Not stated.

	Indirectness: No indirectness (n=50) Intervention 2: Placebo. Placebo. Duration 1 year. Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Academic or government funding (Funded by a grant from Heart Research UK and supported by the Oxford Comprehensive Biomedical Research Centre, funded by the UK National Institute for Health Research. One author was supported by a British Heart Foundation Clinical Research Training Fellowship.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RAMIPRIL versus PLACEBO

Protocol outcome 1: Need for heart valve intervention at ≥12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : Aortic valve replacement at 12 months; Group 1: 4/40, Group 2: 2/43
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Placebo group generally has more hypertension, more medication usage and a worse exercise distance at baseline than the ramipril group.; Group 1 Number missing: 10, Reason: 50 allocated to ramipril. 1 withdrew consent before receiving the intervention. After receiving the allocated intervention: 6 withdrew consent, 2 withdrew due to a cough, 4 had an aortic valve replacement, 1 had a pacemaker implanted.; Group 2 Number missing: 7, Reason: 50 allocated to placebo. 2 withdrew consent and 1 had claustrophobia so withdrew from the study before receiving the intervention. After receiving the allocated intervention: 1 withdrew from the trial due to instruction from treating clinician, 2 withdrew consent, 1 withdrew due to a serious adverse event, 2 had an aortic valve replacement.

Protocol outcome 2: Exercise tolerance at ≥12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : Exercise distance (m) - measured with treadmill exercise test at 12 months; Group 1: mean -20 m (SD 26); n=26, Group 2: mean 29 m (SD 25); n=41; Comments: Baseline values ramipril: 1030 (386)m. Baseline values control: 985 (360)m.
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Placebo group generally has more hypertension, more medication usage and a worse exercise distance at baseline than the ramipril group.; Group 1 Number missing: 14, Reason: 50 allocated to ramipril. 1 withdrew consent before receiving the intervention. After receiving the allocated intervention: 6 withdrew consent, 2 withdrew due to a cough, 4 had an aortic valve replacement, 1 had a pacemaker implanted.; Group 2 Number missing: 9, Reason: 50 allocated to placebo. 2 withdrew consent and 1 had claustrophobia so withdrew from the study before receiving the intervention. After receiving the allocated intervention: 1 withdrew from the trial due to instruction from treating clinician, 2 withdrew consent, 1 withdrew due to a serious adverse event, 2 had an aortic valve replacement.

Protocol outcome 3: Withdrawal due to adverse events at ≥12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : Withdrawal due to adverse events at 12 months; Group 1: 2/38, Group 2: 1/42
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Placebo group generally has more

hypertension, more medication usage and a worse exercise distance at baseline than the ramipril group.; Group 1 Number missing: 12, Reason: 50 allocated to ramipril. 1 withdrew consent before receiving the intervention. After receiving the allocated intervention: 6 withdrew consent, 2 withdrew due to a cough, 4 had an aortic valve replacement, 1 had a pacemaker implanted.; Group 2 Number missing: 8, Reason: 50 allocated to placebo. 2 withdrew consent and 1 had claustrophobia so withdrew from the study before receiving the intervention. After receiving the allocated intervention: 1 withdrew from the trial due to instruction from treating clinician, 2 withdrew consent, 1 withdrew due to a serious adverse event, 2 had an aortic valve replacement.	
Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Cardiac mortality at ≥12 months; Quality of life at ≥12 months; Quality of life at 6 months; Onset of symptoms or progression of NYHA class at ≥12 months ; Evidence of HVD progression on imaging (worsening of disease severity) at ≥12 months; Withdrawal due to adverse events at 6 months

Study	Evangelista 2005[49]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=95)
Countries and setting	Conducted in Spain; Setting: Outpatient follow up
Line of therapy	1st line
Duration of study	Intervention + follow up: 7 years (range: 0.6 to 8.8 years)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Physical examination, echocardiography, 12-lead ECG, chest radiography and radionuclide angiography at rest.
Stratum	Primary aortic regurgitation
Subgroup analysis within study	Not applicable
Inclusion criteria	People with asymptomatic, chronic, severe aortic regurgitation (jet width exceeding 10mm and apical jet area exceeding 7cm² on colour Doppler ultrasonography, or when regurgitant fraction >60%) and normal left ventricular function.
Exclusion criteria	A decreased LVEF (<50%) during the preceding 6 months, other clinically significant associated valvular disease, associated valvular aortic stenosis (aortic mean gradient, more than 20mmHg), a diastolic blood pressure of more than 90mmHg, atrial fibrillation, or a history of coronary heart disease or other associated diseases that could affect the prognosis or functional class (including Marfan's syndrome or an ascending aortic aneurysm).
Recruitment/selection of patients	Consecutive people seen in the outpatient clinic
Age, gender and ethnicity	Age - Mean (SD): 44.35 (13.19). Gender (M:F): 74:21. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Disease mechanism for aortic and mitral stenosis: Not applicable 3. Presence vs. absence of uncontrolled systemic hypertension (140/85 mmHg) at the end of trial intervention despite medication: Presence of uncontrolled systemic hypertension (Final blood pressure in each group had a systolic value above 140mmHg. Diastolic values were below 85 (average around 75. However, standard deviations were on average 9).).
Extra comments	Morphological appearance of aortic valve varied. It was normal in 24 people, bicuspid in 40 people, degenerative in 23 people and rheumatic in 8 people.
Indirectness of population	No indirectness

Interventions	(n=32) Intervention 1: Calcium-channel blockers (CCB) - Nifedipine. Nifedipine 20mg every 12 hours. Duration 7 years. Concurrent medication/care: Not stated. Indirectness: No indirectness (n=32) Intervention 2: Angiotensin-converting enzyme (ACE) inhibitors - Enalapril . Enalapril 20mg daily. Duration 7 years. Concurrent medication/care: Not stated. Indirectness: No indirectness (n=31) Intervention 3: No treatment. No treatment. Duration 7 years. Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Academic or government funding (Supported by a grant from the Red de Investigación Cooperativa de las Enfermedades Cardiovasculares from the Instituto de Salud Carlos III, Ministerio de Sanidad y Consumo, Spain)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NIFEDIPINE versus ENALAPRIL

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Primary aortic regurgitation : All-cause mortality at 7 years; Group 1: 1/32, Group 2: 1/32
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: There are a lot more people with normal morphologic aortic valves in the control group compared to the other groups. There are more women in the control group compared to the others.; Group 1 Number missing: 0, Reason: Nifedipine: 32 people randomised to the treatment. 1 died (sudden death). 7 withdrew due to adverse events. 13 had an aortic valve replacement. Unclear is people reported
were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

; Group 2 Number missing: 0, Reason: Enalapril: 32 people randomised to the treatment. 1 died (Parkinson disease). 3 withdrew due to adverse events. 16 had an aortic valve replacement. Unclear is people reported were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Primary aortic regurgitation : Cardiac mortality at 7 years; Group 1: 1/32, Group 2: 0/32
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: There are a lot more people with normal morphologic aortic valves in the control group compared to the other groups. There are more women in the control group compared to the others.; Group 1 Number missing: 0, Reason: Nifedipine: 32 people randomised to the treatment. 1 died (sudden death). 7 withdrew due to adverse events. 13 had an aortic valve replacement. Unclear is people reported
were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

; Group 2 Number missing: 0, Reason: Enalapril: 32 people randomised to the treatment. 1 died (Parkinson disease). 3 withdrew due to adverse events. 16 had an aortic valve replacement. Unclear is people reported were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

Protocol outcome 3: Onset of symptoms or progression of NYHA class at ≥12 months
- Actual outcome for Primary aortic regurgitation : Presence of symptoms at 7 years; Group 1: 8/32, Group 2: 10/32
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: There are a lot more people with normal morphologic aortic valves in the control group compared to the other groups. There are more women in the control group compared to the others.; Group 1 Number missing: 0, Reason: Nifedipine: 32 people randomised to the treatment. 1 died (sudden death). 7 withdrew due to adverse events. 13 had an aortic valve replacement. Unclear is people reported
were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

; Group 2 Number missing: 0, Reason: Enalapril: 32 people randomised to the treatment. 1 died (Parkinson disease). 3 withdrew due to adverse events. 16 had an aortic valve replacement. Unclear is people reported were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

Protocol outcome 4: Evidence of HVD progression on imaging (worsening of disease severity) at ≥12 months
- Actual outcome for Primary aortic regurgitation : Left ventricular dysfunction or enlargement on imaging at 7 years; Group 1: 10/32, Group 2: 14/32
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: There are a lot more people with normal morphologic aortic valves in the control group compared to the other groups. There are more women in the control group compared to the others.; Group 1 Number missing: 0, Reason: Nifedipine: 32 people randomised to the treatment. 1 died (sudden death). 7 withdrew due to adverse events. 13 had an aortic valve replacement. Unclear is people reported
were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

; Group 2 Number missing: 0, Reason: Enalapril: 32 people randomised to the treatment. 1 died (Parkinson disease). 3 withdrew due to adverse events.

16 had an aortic valve replacement. Unclear is people reported were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

Protocol outcome 5: Need for heart valve intervention at ≥12 months
- Actual outcome for Primary aortic regurgitation : Aortic valve replacement at 7 years; Group 1: 13/32, Group 2: 16/32
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: There are a lot more people with normal morphologic aortic valves in the control group compared to the other groups. There are more women in the control group compared to the others.; Group 1 Number missing: 0, Reason: Nifedipine: 32 people randomised to the treatment. 1 died (sudden death). 7 withdrew due to adverse events. 13 had an aortic valve replacement. Unclear is people reported
were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

; Group 2 Number missing: 0, Reason: Enalapril: 32 people randomised to the treatment. 1 died (Parkinson disease). 3 withdrew due to adverse events. 16 had an aortic valve replacement. Unclear is people reported were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

Protocol outcome 6: Withdrawal due to adverse events at ≥12 months
- Actual outcome for Primary aortic regurgitation : Withdrawal due to adverse events at 7 years; Group 1: 7/32, Group 2: 3/32; Comments: Nifedipine: 7 developed either headache, flushing, oedema, epigastric pain or a combination of these. Enalapril: 2 developed cough, 1 developed hypotension
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: There are a lot more people with normal morphologic aortic valves in the control group compared to the other groups. There are more women in the control group compared to the others.; Group 1 Number missing: 0, Reason: Nifedipine: 32 people randomised to the treatment. 1 died (sudden death). 7 withdrew due to adverse events. 13 had an aortic valve replacement. Unclear is people reported
were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

; Group 2 Number missing: 0, Reason: Enalapril: 32 people randomised to the treatment. 1 died (Parkinson disease). 3 withdrew due to adverse events. 16 had an aortic valve replacement. Unclear is people reported were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NIFEDIPINE versus NO TREATMENT

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Primary aortic regurgitation : All-cause mortality at 7 years; Group 1: 1/32, Group 2: 1/31
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: There are a lot more people with normal morphologic aortic valves in the control group compared to the other groups. There are more women in the control group compared to the others.; Group 1 Number missing: 0, Reason: Nifedipine: 32 people randomised to the treatment. 1 died (sudden death). 7 withdrew due to adverse events. 13 had an aortic valve replacement. Unclear is people reported
were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

; Group 2 Number missing: 0, Reason: Placebo: 31 people randomised to the treatment. 1 died (of heart failure). 12 had an aortic valve replacement. Unclear is people reported were reported as having
these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Primary aortic regurgitation : Cardiac mortality at 7 years; Group 1: 1/32, Group 2: 1/31
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: There are a lot more people with normal morphologic aortic valves in the control group compared to the other groups. There are more women in the control group compared to the others.; Group 1 Number missing: 0, Reason: Nifedipine: 32 people randomised to the treatment. 1 died (sudden death). 7 withdrew due to adverse events. 13 had an aortic valve replacement. Unclear is people reported
were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

; Group 2 Number missing: 0, Reason: Placebo: 31 people randomised to the treatment. 1 died (of heart failure). 12 had an aortic valve replacement. Unclear is people reported were reported as having
these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

Protocol outcome 3: Onset of symptoms or progression of NYHA class at ≥12 months
- Actual outcome for Primary aortic regurgitation : Presence of symptoms at 7 years; Group 1: 8/32, Group 2: 8/31

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: There are a lot more people with normal morphologic aortic valves in the control group compared to the other groups. There are more women in the control group compared to the others.; Group 1 Number missing: 0, Reason: Nifedipine: 32 people randomised to the treatment. 1 died (sudden death). 7 withdrew due to adverse events. 13 had an aortic valve replacement. Unclear is people reported
were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

; Group 2 Number missing: 0, Reason: Placebo: 31 people randomised to the treatment. 1 died (of heart failure). 12 had an aortic valve replacement. Unclear is people reported were reported as having
these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

Protocol outcome 4: Evidence of HVD progression on imaging (worsening of disease severity) at ≥12 months
- Actual outcome for Primary aortic regurgitation : Left ventricular dysfunction or enlargement on imaging at 7 years; Group 1: 10/32, Group 2: 10/31
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: There are a lot more people with normal morphologic aortic valves in the control group compared to the other groups. There are more women in the control group compared to the others.; Group 1 Number missing: 0, Reason: Nifedipine: 32 people randomised to the treatment. 1 died (sudden death). 7 withdrew due to adverse events. 13 had an aortic valve replacement. Unclear is people reported
were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

; Group 2 Number missing: 0, Reason: Placebo: 31 people randomised to the treatment. 1 died (of heart failure). 12 had an aortic valve replacement. Unclear is people reported were reported as having
these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

Protocol outcome 5: Need for heart valve intervention at ≥12 months
- Actual outcome for Primary aortic regurgitation : Aortic valve replacement at 7 years; Group 1: 13/32, Group 2: 12/31
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: There are a lot more people with normal morphologic aortic valves in the control group compared to the other groups. There are more women in the control group compared to the others.; Group

1 Number missing: 0, Reason: Nifedipine: 32 people randomised to the treatment. 1 died (sudden death). 7 withdrew due to adverse events. 13 had an aortic valve replacement. Unclear is people reported
were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

; Group 2 Number missing: 0, Reason: Placebo: 31 people randomised to the treatment. 1 died (of heart failure). 12 had an aortic valve replacement. Unclear is people reported were reported as having
these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

Protocol outcome 6: Withdrawal due to adverse events at ≥12 months
- Actual outcome for Primary aortic regurgitation : Withdrawal due to adverse events at 7 years; Group 1: 7/32, Group 2: 0/31; Comments: Nifedipine: 7 developed either headache, flushing, oedema, epigastric pain or a combination of these.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: There are a lot more people with normal morphologic aortic valves in the control group compared to the other groups. There are more women in the control group compared to the others.; Group 1 Number missing: 0, Reason: Nifedipine: 32 people randomised to the treatment. 1 died (sudden death). 7 withdrew due to adverse events. 13 had an aortic valve replacement. Unclear is people reported
were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

; Group 2 Number missing: 0, Reason: Placebo: 31 people randomised to the treatment. 1 died (of heart failure). 12 had an aortic valve replacement. Unclear is people reported were reported as having
these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENALAPRIL versus NO TREATMENT

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Primary aortic regurgitation : All-cause mortality at 7 years; Group 1: 1/32, Group 2: 1/31
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: There are a lot more people with normal morphologic aortic valves in the control group compared to the other groups. There are more women in the control group compared to the others.; Group

1 Number missing: 0, Reason: Enalapril: 32 people randomised to the treatment. 1 died (Parkinson disease). 3 withdrew due to adverse events. 16 had an aortic valve replacement. Unclear is people reported were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

; Group 2 Number missing: 0, Reason: Placebo: 31 people randomised to the treatment. 1 died (of heart failure). 12 had an aortic valve replacement. Unclear is people reported were reported as having
these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Primary aortic regurgitation : Cardiac mortality at 7 years; Group 1: 0/32, Group 2: 1/31
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: There are a lot more people with normal morphologic aortic valves in the control group compared to the other groups. There are more women in the control group compared to the others.; Group 1 Number missing: 0, Reason: Enalapril: 32 people randomised to the treatment. 1 died (Parkinson disease). 3 withdrew due to adverse events. 16 had an aortic valve replacement. Unclear is people reported were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

; Group 2 Number missing: 0, Reason: Placebo: 31 people randomised to the treatment. 1 died (of heart failure). 12 had an aortic valve replacement. Unclear is people reported were reported as having
these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

Protocol outcome 3: Onset of symptoms or progression of NYHA class at ≥12 months
- Actual outcome for Primary aortic regurgitation : Presence of symptoms at 7 years; Group 1: 10/32, Group 2: 8/31
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: There are a lot more people with normal morphologic aortic valves in the control group compared to the other groups. There are more women in the control group compared to the others.; Group 1 Number missing: 0, Reason: Enalapril: 32 people randomised to the treatment. 1 died (Parkinson disease). 3 withdrew due to adverse events. 16 had an aortic valve replacement. Unclear is people reported were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

; Group 2 Number missing: 0, Reason: Placebo: 31 people randomised to the treatment. 1 died (of heart failure). 12 had an aortic valve replacement.

Unclear is people reported were reported as having
these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

Protocol outcome 4: Evidence of HVD progression on imaging (worsening of disease severity) at ≥12 months
- Actual outcome for Primary aortic regurgitation : Left ventricular dysfunction or enlargement on imaging at 7 years; Group 1: 14/32, Group 2: 10/31
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: There are a lot more people with normal morphologic aortic valves in the control group compared to the other groups. There are more women in the control group compared to the others.; Group 1 Number missing: 0, Reason: Enalapril: 32 people randomised to the treatment. 1 died (Parkinson disease). 3 withdrew due to adverse events. 16 had an aortic valve replacement. Unclear is people reported were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

; Group 2 Number missing: 0, Reason: Placebo: 31 people randomised to the treatment. 1 died (of heart failure). 12 had an aortic valve replacement. Unclear is people reported were reported as having
these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

Protocol outcome 5: Need for heart valve intervention at ≥12 months
- Actual outcome for Primary aortic regurgitation : Aortic valve replacement at 7 years; Group 1: 16/32, Group 2: 12/31
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: There are a lot more people with normal morphologic aortic valves in the control group compared to the other groups. There are more women in the control group compared to the others.; Group 1 Number missing: 0, Reason: Enalapril: 32 people randomised to the treatment. 1 died (Parkinson disease). 3 withdrew due to adverse events. 16 had an aortic valve replacement. Unclear is people reported were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

; Group 2 Number missing: 0, Reason: Placebo: 31 people randomised to the treatment. 1 died (of heart failure). 12 had an aortic valve replacement. Unclear is people reported were reported as having
these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.

Protocol outcome 6: Withdrawal due to adverse events at ≥12 months - Actual outcome for Primary aortic regurgitation : Withdrawal due to adverse events at 7 years; Group 1: 3/32, Group 2: 0/31; Comments: Enalapril: 2 developed cough, 1 developed hypotension Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: There are a lot more people with normal morphologic aortic valves in the control group compared to the other groups. There are more women in the control group compared to the others.; Group 1 Number missing: 0, Reason: Enalapril: 32 people randomised to the treatment. 1 died (Parkinson disease). 3 withdrew due to adverse events. 16 had an aortic valve replacement. Unclear is people reported were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated. ; Group 2 Number missing: 0, Reason: Placebo: 31 people randomised to the treatment. 1 died (of heart failure). 12 had an aortic valve replacement. Unclear is people reported were reported as having these events. 1 person is reported to have not received full follow up, their allocated arm was not stated.	
Protocol outcomes not reported by the study	Quality of life at 6 months; Quality of life at ≥12 months; Exercise tolerance at ≥12 months; Withdrawal due to adverse events at 6 months

Study	Hansson 2017[66]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Denmark; Setting: Outpatient follow up
Line of therapy	1st line
Duration of study	Intervention + follow up: 22 weeks (5 months)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography and cardiac MR
Stratum	Primary aortic [including bicuspid] stenosis
Subgroup analysis within study	Not applicable
Inclusion criteria	Asymptomatic aortic stenosis with an aortic valve area ≤1.2cm² or transaortic maximal velocity ≥3.0m/s and sinus rhythm with an HR ≥60/min.
Exclusion criteria	Ongoing treatment with beta blockers, significant aortic valve regurgitation (vena contracta ≥5mm), or ischaemic heart disease evaluated by symptoms or signs of myocardial ischaemia (i.e. angina pectoris, abnormal echocardiography, wall motion abnormalities). In addition, people with previous coronary angiography proving a ≥70% luminal stenosis were excluded.
Recruitment/selection of patients	Recruitment from outpatient clinics at 3 centres between August 2013 and April 2016.
Age, gender and ethnicity	Age - Mean (SD): 70.0 (5.1). Gender (M:F): 24:14. Ethnicity: Not stated
Further population details	1. Age: Mixed (Based on mean age and standard deviation). 2. Disease mechanism for aortic and mitral stenosis: Not stated / Unclear (States that 7 people had bicuspid aortic valves, but no other information.). 3. Presence vs. absence of uncontrolled systemic hypertension (140/85 mmHg) at the end of trial intervention despite medication: Mixed (Mean blood pressure at follow up metoprolol: 136/79 (13/8). Placebo: 140/81 (12/7).
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Beta blockers - Metoprolol. Extended-release metoprolol from 50mg up to a target dose of 200mg or maximal dose without symptoms. Achieved during a 6-week uptitration period. Duration 5 months. Concurrent medication/care: Not stated. Indirectness: No indirectness (n=20) Intervention 2: Placebo. Placebo. Duration 5 months. Concurrent

	medication/care: Not stated. Indirectness: No indirectness
Funding	Academic or government funding (Funded by the Lundbeck foundation, the Arvid Nilssons Foundation, the Health Research Fund of Central Denmark Region, Karen Elise Jensens Foundation, and Snedkermester Sophus Jacobsen and Hustru Astrid Jacobsens Foundation.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METOPROLOL versus PLACEBO

Protocol outcome 1: Quality of life at 6 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : Minnesota living with heart failure questionnaire at 5 months; Group 1: mean 5 (SD 14); n=19, Group 2: mean -1 (SD 4); n=19; Minnesota living with heart failure questionnaire 0-105 Top=High is poor outcome; Comments: Baseline (median (IQR)) metoprolol: 3 (1-6). Baseline placebo: 4 (2-8). Final metoprolol: 5 (2-9). Final placebo: 3 (0-8).
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Generally people in the placebo group had more comorbidities (hypertension and diabetes mellitus) and used more medication than the metoprolol group. However, this is based on a very small number of people.; Group 1 Number missing: 1, Reason: 1 excluded due to having an LVEF <50% after randomisation.; Group 2 Number missing: 1, Reason: 1 excluded due to having an LVEF <50% after randomisation.

Protocol outcome 2: Exercise tolerance at ≥12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : 6 minute walk test distance, m at 5 months; Group 1: mean 2 m (SD 46); n=19, Group 2: mean 14 m (SD 49); n=19; Comments: Baseline metoprolol: 543 (46)m. Baseline placebo: 538 (36)m. Final metoprolol: 546 (48)m. Final placebo: 550 (49)m.
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Generally people in the placebo group had more comorbidities (hypertension and diabetes mellitus) and used more medication than the metoprolol group. However, this is based on a very small number of people.; Group 1 Number missing: 1, Reason: 1 excluded due to having an LVEF <50% after randomisation.; Group 2 Number missing: 1, Reason: 1 excluded due to having an LVEF <50% after randomisation.

Protocol outcome 3: Withdrawal due to adverse events at 6 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : Withdrawal or dose reduction due to adverse events at 5 months; Group 1: 4/19, Group 2: 2/19
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Includes people who had a dose reduction and then continued the trial with no additional adverse events; Baseline details: Generally people in the placebo group had more comorbidities (hypertension and diabetes mellitus) and used more medication than the metoprolol group. However, this is based on a very small number of people.; Group 1 Number missing: 1, Reason: 1 excluded due to having an LVEF <50% after randomisation.; Group 2 Number missing: 1, Reason: 1 excluded due

to having an LVEF <50% after randomisation.	
Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Cardiac mortality at ≥12 months; Quality of life at ≥12 months; Onset of symptoms or progression of NYHA class at ≥12 months ; Evidence of HVD progression on imaging (worsening of disease severity) at ≥12 months; Need for heart valve intervention at ≥12 months; Withdrawal due to adverse events at ≥12 months

Study	Marcotte 1997[104]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=23)
Countries and setting	Conducted in Canada; Setting: Outpatient follow up
Line of therapy	1st line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography (Hewlett-Packard Sonos 1500 ultrasonograph) with 2.5 and 3.5 mHz transducers
Stratum	Primary mitral regurgitation
Subgroup analysis within study	Not applicable
Inclusion criteria	Asymptomatic adults (18 to 75 years) with at least moderate, organic (degenerative, rheumatic, postinfectious or congenital), isolated mitral regurgitation (grade 3+ or more). People were in sinus rhythm, taking no cardiovascular medication at the time of enrolment. They needed to have had a good quality echocardiogram showing a maximal MR colour jet area >4cm² or greater than 25% of the LA area in at least two different views, and normal LVEF (>60%).
Exclusion criteria	Clinically documented coronary artery disease (including angina, prior myocardial infarction and prior revascularisation); mitral stenosis (valve area less than 2.5cm²); significant ventricular or atrial arrhythmia (including atrial fibrillation); significant aortic valve disease (either moderate to severe aortic regurgitation or the presence of aortic stenosis, defined as a valve area less than 2.0cm²); hypertension under therapy before randomisation or untreated hypertension with a DBP >90mmHg or hypotension with an SBP <90mmHg; chronic renal failure; contraindication to receiving ACE inhibitors; abnormal LV systolic function by echocardiography (<60%); severe LV dilation; or resting or stress-induced regional wall motion abnormalities.
Recruitment/selection of patients	10,054 people underwent echocardiography at the author's institution. 248 satisfied the echocardiographic inclusion criteria. 211 refused to participate in the study, were judged to be symptomatic, had undergone mitral valve surgery, or presented clinical or echocardiographic exclusion criteria. 37 attended a screening visit, of which 5 refused to participate and 9 were found to have clinical or echocardiographic exclusion factors.
Age, gender and ethnicity	Age - Other: 53.3 (standard error: 2.4). Gender (M:F): 16:7. Ethnicity: Not stated

Further population details	1. Age: <75 years (Mean age: 53.3 (standard error: 2.4)). 2. Disease mechanism for aortic and mitral stenosis: Not applicable 3. Presence vs. absence of uncontrolled systemic hypertension (140/85 mmHg) at the end of trial intervention despite medication: Not stated / Unclear (None at the start of the study, but not reported at the end).
Indirectness of population	Serious indirectness: Population may include people with congenital mitral regurgitation
Interventions	(n=12) Intervention 1: Angiotensin-converting enzyme (ACE) inhibitors - Lisinopril. Lisinopril 5mg for two weeks, then doubled every two weeks until the maximal dose of 20mg a day was reached or they developed symptoms of hypotension, in which the dose was titrated to the maximal tolerable dose. Duration 1 year. Concurrent medication/care: No other cardiovascular medications. Indirectness: No indirectness (n=11) Intervention 2: Placebo. Placebo. Duration 1 year. Concurrent medication/care: No other cardiovascular medications. Indirectness: No indirectness
Funding	Study funded by industry (Supported by a grant from Merck Frosst Canada inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LISINOPRIL versus PLACEBO

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Primary mitral regurgitation: Death at 1 year; Group 1: 0/6, Group 2: 0/10
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Exercise time different between the two groups (lisinopril = 581 (37), placebo = 637 (56)). This may affect the results of exercise time.; Group 1 Number missing: 6, Reason: 4 withdrew due to adverse events. 2 additional people were lost due to need for surgical intervention or urgent medical therapy.; Group 2 Number missing: 1, Reason: 1 withdrawal due to adverse events.

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Primary mitral regurgitation: Death at 1 year; Group 1: 0/6, Group 2: 0/10
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Exercise time different between the two groups (lisinopril = 581 (37), placebo = 637 (56)). This may affect the results of exercise time.; Group 1 Number missing: 6, Reason: 4 withdrew due to adverse events. 2 additional people were lost due to need for surgical intervention or urgent medical therapy.; Group 2 Number missing: 1, Reason: 1

withdrawal due to adverse events.

Protocol outcome 3: Quality of life at 6 months
- Actual outcome for Primary mitral regurgitation: Life quality index at 6 months; Group 1: mean 0.2 (SD 0.73); n=6, Group 2: mean 0.4 (SD 0.95); n=10; Life quality index 1-6 Top=High is good outcome; Comments: Life quality index is a measurement for asymptomatic hypertensive people where they rate their energy level on the scale from 1 (no energy) to 6 (full of energy). Reports standard error. Lisinopril 6 months: +0.2 (0.3). Placebo 6 months: +0.3 (0.3). Lisinopril baseline: 4.6 (0.4). Placebo baseline: 4.8 (0.4).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Exercise time different between the two groups (lisinopril = 581 (37), placebo = 637 (56)). This may affect the results of exercise time.; Group 1 Number missing: 6, Reason: 4 withdrew due to adverse events. 2 additional people were lost due to need for surgical intervention or urgent medical therapy.; Group 2 Number missing: 1, Reason: 1 withdrawal due to adverse events.

Protocol outcome 4: Quality of life at ≥12 months
- Actual outcome for Primary mitral regurgitation: Life quality index at 1 year; Group 1: mean 0.3 (SD 0.73); n=6, Group 2: mean 0.4 (SD 0.95); n=10; Life quality index 1-6 Top=High is good outcome; Comments: Life quality index is a measurement for asymptomatic hypertensive people where they rate their energy level on the scale from 1 (no energy) to 6 (full of energy). Reports standard error. Lisinopril 1 year: +0.3 (0.3). Placebo 1 year: +0.4 (0.3). Lisinopril baseline: 4.6 (0.4). Placebo baseline: 4.8 (0.4).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Exercise time different between the two groups (lisinopril = 581 (37), placebo = 637 (56)). This may affect the results of exercise time.; Group 1 Number missing: 6, Reason: 4 withdrew due to adverse events. 2 additional people were lost due to need for surgical intervention or urgent medical therapy.; Group 2 Number missing: 1, Reason: 1 withdrawal due to adverse events.

Protocol outcome 5: Exercise tolerance at ≥12 months
- Actual outcome for Primary mitral regurgitation: Treadmill exercise time (Bruce protocol) at 1 year; Group 1: mean 39 seconds (SD 61.2); n=6, Group 2: mean 18 seconds (SD 66.4); n=10; Comments: Reported with standard errors. Lisinopril 1 year: 39 (25)s. Placebo 1 year: 18 (21)s. Lisinopril baseline: 581 (37)s. Placebo baseline: 637 (56)s.
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Exercise time different between the two groups (lisinopril = 581 (37), placebo = 637 (56)). This may affect the results of exercise time.; Group 1 Number missing: 6, Reason: 4 withdrew due to adverse events. 2 additional people were lost due to need for surgical intervention or urgent medical therapy.; Group 2 Number missing: 1, Reason: 1 withdrawal due to adverse events.

Protocol outcome 6: Withdrawal due to adverse events at ≥12 months
- Actual outcome for Primary mitral regurgitation: Withdrawal due to adverse events at 12 months; Group 1: 4/10, Group 2: 1/11; Comments: The study reports withdrawal due to adverse events as a whole rather than when people withdrew from the study. Therefore, the results are being reported for the

longest time period possible only. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Exercise time different between the two groups (lisinopril = 581 (37), placebo = 637 (56)). This may affect the results of exercise time.; Group 1 Number missing: 2, Reason: 2 people were lost due to need for surgical intervention or urgent medical therapy.; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Onset of symptoms or progression of NYHA class at ≥12 months ; Evidence of HVD progression on imaging (worsening of disease severity) at ≥12 months; Need for heart valve intervention at ≥12 months; Withdrawal due to adverse events at 6 months

Study	Roberts 2018[129]
Study type	RCT (Patient randomised; Crossover: 0 days)
Number of studies (number of participants)	1 (n=46)
Countries and setting	Conducted in New Zealand; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: Maximum 7 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography (people were recruited from a clinical echocardiography database).
Stratum	Primary aortic regurgitation
Subgroup analysis within study	Not applicable
Inclusion criteria	People with moderate to severe chronic aortic regurgitation (two or more of the following present on echocardiography: aortic regurgitant central jet width >25% of left ventricular outflow tract, vena contracta width >0.3cm, presence of early diastolic flow reversal in the descending aorta, pressure half time or aortic regurgitant velocity <500ms, and left ventricular end diastolic dimension or volume above the normal reference range) and normal left ventricular systolic function (ejection fraction >50%).
Exclusion criteria	Age <18 or >80 years; contraindications to cardiac magnetic resonance imaging; inability to complete study exercise protocol or procedures; other documented significant cardiac diseases; contraindications to study medications or withdrawal of usual antihypertensive medications.
Recruitment/selection of patients	Recruited from a clinical echocardiography database at Auckland City Hospital.
Age, gender and ethnicity	Age - Mean (SD): 51.0 (14.1). Gender (M:F): 14:3. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Disease mechanism for aortic and mitral stenosis: Not applicable 3. Presence vs. absence of uncontrolled systemic hypertension (140/85 mmHg) at the end of trial intervention despite medication: Absence of uncontrolled systemic hypertension (Blood pressure ranged between 117-118/63-69.).
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: Angiotensin-II receptor antagonists (ARBs) - Losartan . Losartan up-titrated to a maximum of 100mg per day. Duration 1-3 weeks. Concurrent medication/care: People were allowed to use normal antihypertensive medicines, which were then downtitrated or withdrawn completely while taking the

	drug. Indirectness: Serious indirectness; Indirectness comment: Inadequate duration of treatment (n=17) Intervention 2: Beta blockers - Metoprolol . Metoprolol CR to a maximum dose of 190mg. Duration 1-3 weeks. Concurrent medication/care: People were allowed to use normal antihypertensive medicines, which were then downtitrated or withdrawn completely while taking the drug. Indirectness: Serious indirectness; Indirectness comment: Inadequate duration of treatment
Funding	Academic or government funding (Funded by the Health Research Council of New Zealand)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOSARTAN versus METOPROLOL Protocol outcome 1: Exercise tolerance at ≥12 months - Actual outcome for Primary aortic regurgitation : Exercise work rate (Watts) - using an ergometer at 3 weeks; Group 1: mean 29 Watts (SD 6); n=17, Group 2: mean 29 Watts (SD 8); n=17; Comments: Not provided with baseline values Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Time period for treatment was less than 1 month; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Cardiac mortality at ≥12 months; Quality of life at ≥12 months; Quality of life at 6 months; Onset of symptoms or progression of NYHA class at ≥12 months ; Evidence of HVD progression on imaging (worsening of disease severity) at ≥12 months; Need for heart valve intervention at ≥12 months; Withdrawal due to adverse events at 6 months; Withdrawal due to adverse events at ≥12 months

Study (subsidiary papers)	SALTIRE trial: Cowell 2005[36] (Houslay 2006[74])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=155)
Countries and setting	Conducted in United Kingdom; Setting: Outpatient follow up
Line of therapy	1st line
Duration of study	Intervention + follow up: 25 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography
Stratum	Primary aortic [including bicuspid] stenosis
Subgroup analysis within study	Not applicable
Inclusion criteria	People older than 18 years with calcific aortic stenosis, an aortic-jet velocity of at least 2.5m/s, and aortic-valve calcification on echocardiography.
Exclusion criteria	Child-bearing potential without contraception, active or chronic liver disease, a history of alcohol or drug abuse, severe mitral-valve stenosis (mitral-valve area <1cm²), severe mitral or aortic regurgitation, left ventricular dysfunction (EF <35%), a planned aortic-valve replacement, intolerance of statins, statin therapy or a potential benefit from statin therapy (according to the treating physician), a baseline serum total cholesterol concentration of less than 150mg/dL (4.0mmol/L), and presence of a permanent pacemaker or cardiodefibrillator.
Recruitment/selection of patients	Recruited from eight centers.
Age, gender and ethnicity	Age - Mean (SD): 68 (10.5). Gender (M:F): 140:15. Ethnicity: Not stated
Further population details	1. Age: Mixed (Confidence intervals fall either side of 75 years.). 2. Disease mechanism for aortic and mitral stenosis: Calcific 3. Presence vs. absence of uncontrolled systemic hypertension (140/85 mmHg) at the end of trial intervention despite medication: Not stated / Unclear (Baseline atorvastatin: 144/82 (18/10). Baseline placebo: 144.81 (21/12). No final value stated.).
Indirectness of population	No indirectness
Interventions	(n=77) Intervention 1: Statins - Atorvastatin . Atorvastatin 80mg once a day. Duration 25 months. Concurrent medication/care: 43 taking aspirin, 12 taking ACE inhibitors, 21 taking beta-blockers, 8 taking warfarin. Otherwise not stated. Indirectness: No indirectness (n=78) Intervention 2: Placebo. Placebo. Duration 25 months. Concurrent

	medication/care: 40 took aspirin, 14 took ACE inhibitors, 27 took beta-blockers, 12 took warfarin. Otherwise not stated. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN versus PLACEBO

Protocol outcome 1: Cardiac mortality at ≥12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : Death from cardiovascular causes at 25 months; Group 1: 3/77, Group 2: 3/78
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Onset of symptoms or progression of NYHA class at ≥12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : Hospitalisation for severe aortic stenosis at 25 months; Group 1: 3/77, Group 2: 5/78
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Need for heart valve intervention at ≥12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : Aortic valve replacement at 25 months; Group 1: 11/77, Group 2: 19/78
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Withdrawal due to adverse events at ≥12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : Withdrawal due to adverse events at 25 months; Group 1: 7/77, Group 2: 4/78
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Quality of life at 6 months; Quality of life at ≥12 months; Evidence of HVD progression on imaging (worsening of disease severity) at ≥12 months; Exercise tolerance at ≥12 months; Withdrawal due to adverse events at 6 months

Study	Sampaio 2005[143]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=47)
Countries and setting	Conducted in Brazil; Setting: Outpatient follow up
Line of therapy	1st line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography
Stratum	Primary mitral regurgitation
Subgroup analysis within study	Not applicable
Inclusion criteria	People with moderate to severe mitral regurgitation according to echocardiographic criteria: mitral regurgitation jet area >40% of the left atrium or no evidence of leaflet coaptation; absolute MR jet area >8cm² associated with left chamber dilation; MR jet into pulmonary veins.
Exclusion criteria	Atrial fibrillation; systolic blood pressure <100 or >160 mmHg; receiving therapy with other vasodilators.
Recruitment/selection of patients	No additional information given
Age, gender and ethnicity	Age - Mean (SD): 39 (15) years. Gender (M:F): 27:20. Ethnicity: Not stated
Further population details	1. Age: <75 years (Mean age: 39 (15) years). 2. Disease mechanism for aortic and mitral stenosis: Not applicable 3. Presence vs. absence of uncontrolled systemic hypertension (140/85 mmHg) at the end of trial intervention despite medication: Absence of uncontrolled systemic hypertension (At 12 months the mean systolic blood pressure for the enalapril arm: 122 (13)mmHg. Placebo arm: 126 (12)mmHg. Mean diastolic blood pressure for the enalapril arm: 78 (9). Placebo arm: 79 (8).).
Extra comments	. At the start of the study, 20 people were NYHA class I, 17 people were NYHA class II.
Indirectness of population	Serious indirectness
Interventions	(n=27) Intervention 1: Angiotensin-converting enzyme (ACE) inhibitors - Enalapril . Enalapril 5mg twice a day, titrated up to the maximal tolerated dose of at most 20mg twice a day with increases to 10mg and then 20mg at 2 weekly intervals if systolic blood pressure remained >100mmHg. Duration 1 year. Concurrent medication/care: Not receiving therapy with any other vasodilators.

	(n=27) Intervention 2: Placebo. Placebo. Duration 1 year. Concurrent medication/care: Not receiving therapy with any other vasodilators. Indirectness: No indirectness
Funding	Academic or government funding (Received grants from the E.J. Zerbini foundation, São Paulo, Brazil)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENALAPRIL versus PLACEBO

Protocol outcome 1: Onset of symptoms or progression of NYHA class at ≥12 months
- Actual outcome for Primary mitral regurgitation: Onset of symptoms or progression of NYHA class at 12 months; Group 1: 0/26, Group 2: 4/22
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: People in the placebo arm appear to have more severe valve disease and worse exercise tolerance than the enalapril arm.; Group 1 Number missing: 5, Reason: 5 withdrew due to nonadherence; Group 2 Number missing: 1, Reason: 1 withdrew due to nonadherence

Protocol outcome 2: Need for heart valve intervention at ≥12 months
- Actual outcome for Primary mitral regurgitation: Need for heart valve intervention at 12 months; Group 1: 0/26, Group 2: 1/22
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: People in the placebo arm appear to have more severe valve disease and worse exercise tolerance than the enalapril arm.; Group 1 Number missing: 5, Reason: 5 withdrew due to nonadherence; Group 2 Number missing: 1, Reason: 1 withdrew due to nonadherence

Protocol outcome 3: Exercise tolerance at ≥12 months
- Actual outcome for Primary mitral regurgitation: Oxygen uptake at peak exercise (mL/min) at 12 months; Group 1: mean 1794 mL/min (SD 561); n=26, Group 2: mean 1433 mL/min (SD 521); n=21; Comments: Baseline enalapril: 1690 (561). Baseline placebo: 1437 (521).
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: People in the placebo arm appear to have more severe valve disease and worse exercise tolerance than the enalapril arm.; Group 1 Number missing: 6, Reason: 5 withdrew due to nonadherence, 1 developed symptoms and had valve replacement surgery; Group 2 Number missing: 1, Reason: 1 withdrew due to nonadherence

Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Cardiac mortality at ≥12 months; Quality of life at ≥12 months; Quality of life at 6 months; Evidence of HVD progression on imaging (worsening of disease severity) at ≥12 months; Withdrawal due to adverse events at 6 months; Withdrawal due to adverse events at ≥12 months

Study	Scognamiglio 1990[145]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=72)
Countries and setting	Conducted in Italy; Setting: Outpatient follow up
Line of therapy	1st line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Doppler color flow imaging and confirmation by cardiac catheterisation
Stratum	Primary aortic regurgitation
Subgroup analysis within study	Not applicable
Inclusion criteria	People with chronic severe aortic stenosis (grade 3+ to 4+) who were asymptomatic.
Exclusion criteria	Atrial fibrillation, diastolic blood pressure >90mmHg, history of recent development or worsening of the aortic regurgitation (within the preceding 6 months), history of coronary artery disease, mixed aortic stenosis and regurgitation, evidence of additional valvular or congenital heart disease by cardiac catheterisation or echocardiographic and Doppler evaluation, or both, and previous vasodilator or diuretic drug or inotropic therapy (previous therapy with cardioactive drugs).
Recruitment/selection of patients	No additional information stated.
Age, gender and ethnicity	Age - Mean (SD): 35.9 (13.3) years. Gender (M:F): 62:10. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Disease mechanism for aortic and mitral stenosis: Not applicable 3. Presence vs. absence of uncontrolled systemic hypertension (140/85 mmHg) at the end of trial intervention despite medication: Not stated / Unclear (At the start of the study, nifedipine: 154/60 (19/10), placebo: 155/62 (22/12). No measurements after this. It is likely that the placebo group continued to have hypertension, but no clear reporting of this.).
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Calcium-channel blockers (CCB) - Nifedipine. Nifedipine 20mg twice daily. Duration 1 year. Concurrent medication/care: No cardioactive therapies. No other information provided. Indirectness: No indirectness (n=34) Intervention 2: Placebo. Placebo. Duration 1 year. Concurrent

	medication/care: No cardioactive therapies. No other information provided. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NIFEDIPINE versus PLACEBO Protocol outcome 1: Need for heart valve intervention at ≥12 months - Actual outcome for Primary aortic regurgitation : Surgery at 1 year; Group 1: 0/36, Group 2: 0/34 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 1 withdrew due to adverse events (leg oedema), 1 refused the monthly return visit after 3 months of therapy.; Group 2 Number missing: 0 Protocol outcome 2: Withdrawal due to adverse events at ≥12 months - Actual outcome for Primary aortic regurgitation : Withdrawal due to adverse event at 1 year; Group 1: 1/38, Group 2: 0/34 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Cardiac mortality at ≥12 months; Quality of life at 6 months; Quality of life at ≥12 months; Onset of symptoms or progression of NYHA class at ≥12 months ; Evidence of HVD progression on imaging (worsening of disease severity) at ≥12 months; Exercise tolerance at ≥12 months; Withdrawal due to adverse events at 6 months

Study	Scognamiglio 1994[146]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=143)
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Isolated, chronic, severe aortic regurgitation and normal left ventricular systolic function confirmed by Doppler colour-flow imaging
Stratum	Primary aortic regurgitation
Subgroup analysis within study	Not applicable
Inclusion criteria	Asymptomatic people with isolated, chronic, severe aortic regurgitation and normal left ventricular systolic function.
Exclusion criteria	Recent development or worsening of aortic regurgitation (within the preceding six months); diastolic blood pressure above 90mmHg, a history of coronary artery disease; mixed aortic stenosis and regurgitation (valve gradients ≥20mmHg); evidence of additional valvular or congenital heart disease on echocardiographic or Doppler study; absence of high-quality echocardiographic study of the left ventricle; and an abnormal left ventricular ejection fraction (<50%).
Recruitment/selection of patients	Consecutive people seen at the University of Padua, Italy
Age, gender and ethnicity	Age - Mean (SD): 35.0 (13.0) years. Gender (M:F): 122:21. Ethnicity: Not stated
Further population details	1. Age: <75 years 2. Disease mechanism for aortic and mitral stenosis: Not applicable 3. Presence vs. absence of uncontrolled systemic hypertension (140/85 mmHg) at the end of trial intervention despite medication: Not stated / Unclear (Pre-treatment blood pressure - Digoxin: 150/58 (22/14). Nifedipine: 154/60 (20/8).).
Indirectness of population	No indirectness
Interventions	(n=74) Intervention 1: Digoxin. Digoxin 0.25mg daily. Duration 6 years. Concurrent medication/care: No additional information provided. Indirectness: No indirectness (n=69) Intervention 2: Calcium-channel blockers (CCB) - Nifedipine. Nifedipine 20mg twice daily. Duration 6 years. Concurrent medication/care: No additional

	information. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIGOXIN versus NIFEDIPINE

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Primary aortic regurgitation : Perioperative death at 6 years; Group 1: 1/70, Group 2: 0/65
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, cardiothoracic ratio, blood pressure and left ventricular echocardiographic parameters; Blinding details: No explanation about blinding. Likely not blinded for caregivers due to different risks/adverse events from using the different drugs; Group 1 Number missing: 4, Reason: Did not return for the scheduled follow up visits; Group 2 Number missing: 4, Reason: Did not return for the scheduled follow up visits

Protocol outcome 2: Onset of symptoms or progression of NYHA class at ≥12 months
- Actual outcome for Primary aortic regurgitation : Onset of symptoms at 6 years; Group 1: 17/70, Group 2: 6/65
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, cardiothoracic ratio, blood pressure and left ventricular echocardiographic parameters; Blinding details: No explanation about blinding. Likely not blinded for caregivers due to different risks/adverse events from using the different drugs; Group 1 Number missing: 4, Reason: Did not return for the scheduled follow up visits; Group 2 Number missing: 4, Reason: Did not return for the scheduled follow up visits

Protocol outcome 3: Evidence of HVD progression on imaging (worsening of disease severity) at ≥12 months
- Actual outcome for Primary aortic regurgitation : Left ventricular ejection fraction below 50% at 6 years; Group 1: 5/70, Group 2: 0/65
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, cardiothoracic ratio, blood pressure and left ventricular echocardiographic parameters; Blinding details: No explanation about blinding. Likely not blinded for caregivers due to different risks/adverse events from using the different drugs; Group 1 Number missing: 4, Reason: Did not return for the scheduled follow up visits; Group 2 Number missing: 4, Reason: Did not return for the scheduled follow up visits

Protocol outcome 4: Need for heart valve intervention at ≥12 months
- Actual outcome for Primary aortic regurgitation : Aortic valve replacement at 6 years; Group 1: 20/70, Group 2: 6/65
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, cardiothoracic ratio, blood pressure and left ventricular echocardiographic parameters; Blinding details: No explanation about blinding. Likely not blinded for caregivers due to different risks/adverse events from using the different drugs; Group 1 Number missing: 4, Reason: Did not return for the scheduled follow up visits; Group 2 Number missing: 4, Reason: Did not return for the scheduled follow up visits

Protocol outcome 5: Withdrawal due to adverse events at ≥12 months - Actual outcome for Primary aortic regurgitation : Withdrawal due to adverse events at 6 years; Group 1: 0/70, Group 2: 0/65 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, sex, cardiothoracic ratio, blood pressure and left ventricular echocardiographic parameters; Blinding details: No explanation about blinding. Likely not blinded for caregivers due to different risks/adverse events from using the different drugs; Group 1 Number missing: 4, Reason: Did not return for the scheduled follow up visits; Group 2 Number missing: 4, Reason: Did not return for the scheduled follow up visits	
Protocol outcomes not reported by the study	Cardiac mortality at ≥12 months; Quality of life at 6 months; Quality of life at ≥12 months; Exercise tolerance at ≥12 months; Withdrawal due to adverse events at 6 months

Study (subsidiary papers)	SEAS trial: Rossebo 2008[132] (Bang 2012[14], Greve 2019[59], Greve 2018[58], Greve 2014[60], Holme 2010[71], Rossebø 2008[131])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1873)
Countries and setting	Conducted in Denmark, Finland, Germany, Norway, United Kingdom; Setting: Outpatient follow up
Line of therapy	1st line
Duration of study	Intervention + follow up: Median: 52.2 months (4.35 years)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Confirmed by echocardiography
Stratum	Primary aortic [including bicuspid] stenosis : While stating it includes mild to moderate aortic stenosis, mean aortic valve area in simvastatin-ezetimibe group = 1.29 (0.48), placebo group = 1.27 (0.46), which are of moderate severity according to British Society of Echocardiography guidance.
Subgroup analysis within study	Not applicable
Inclusion criteria	People between the ages of 45 and 85 years who had asymptomatic, mild-to-moderate aortic valve stenosis, as assessed on echocardiography with a peak aortic-jet velocity of 2.5 to 4m/s.
Exclusion criteria	Previous diagnosis or symptoms of coronary artery disease, peripheral arterial disease, cerebrovascular disease, or diabetes mellitus. If they had any other condition requiring lipid-lowering therapy.
Recruitment/selection of patients	Recruited from five countries across multiple centers.
Age, gender and ethnicity	Age - Mean (SD): 67.6 (9.6). Gender (M:F): 1150:723. Ethnicity: 99.8% of people were white
Further population details	1. Age: Mixed (Based on standard deviation and mean age). 2. Disease mechanism for aortic and mitral stenosis: Mixed (5% had bicuspid aortic valve disease. No statement regarding other aetiology.). 3. Presence vs. absence of uncontrolled systemic hypertension (140/85 mmHg) at the end of trial intervention despite medication: Not stated / Unclear (Blood pressure at the start of the trial. Simvastatin-Ezetimibe arm: 145.6/82.0 (20.4/10.6). Placebo arm: 144.0/82.0 (20.0/10.0). This is in the uncontrolled range. Unclear whether this changes during the trial.).
Indirectness of population	No indirectness

Interventions	(n=944) Intervention 1: Statins - Simvastatin . Simvastatin 40-80mg per day with Ezetimibe 10mg daily. Duration 4.35 years. Concurrent medication/care: Before starting the study, all people were given a single-blind placebo tablet and instructed to follow a lipid-lowering diet. Indirectness: Serious indirectness; Indirectness comment: Includes Ezetimibe 10mg daily combined with a statin (n=929) Intervention 2: Placebo. Placebo. Duration 4.35 years. Concurrent medication/care: Before starting the study, all people were given a single-blind placebo tablet and instructed to follow a lipid-lowering diet. Indirectness: No indirectness
Funding	Study funded by industry (Supported by Merck and Schering-Ploug Pharmaceuticals. Individuals authors supported by a variety of industry bodies.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN versus PLACEBO

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : Death from any cause at 4.35 years; Group 1: 105/944, Group 2: 100/929
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 944 people were assigned to the treatment. 943 received the study drugs. 5 discontinued the study for "other reasons". 198 discontinued study drugs and were followed per protocol. 105 died. All were included in the primary analysis.; Group 2 Number missing: 0, Reason: 929 were assigned to the placebo. All received the placebo. 11 discontinued the study (2 were lost to follow up, 9 had other reasons), 170 discontinued placebo and were followed per protocol, 100 died. All were included in the primary and safety analysis.
- Actual outcome for Primary aortic [including bicuspid] stenosis : Death from any cause at 4.35 years; Group 1: Observed events 105 n=944 ; Group 2: Observed events 100 n=929; HR 1.04; Lower CI 0.79 to Upper CI 1.36; Log rank variance: 0.80
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 944 people were assigned to the treatment. 943 received the study drugs. 5 discontinued the study for "other reasons". 198 discontinued study drugs and were followed per protocol. 105 died. All were included in the primary analysis.; Group 2 Number missing: 0, Reason: 929 were assigned to the placebo. All received the placebo. 11 discontinued the study (2 were lost to follow up, 9 had other reasons), 170 discontinued placebo and were followed per protocol, 100 died. All were included in the primary and safety analysis.
- Actual outcome for Primary aortic [including bicuspid] stenosis : Death from cardiovascular causes at 4.35 years; Group 1: Observed events 47 n=944 ; Group 2: Observed events 56 n=929; HR 0.83; Lower CI 0.56 to Upper CI 1.22; Log rank variance: 0.34
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 944 people were

assigned to the treatment. 943 received the study drugs. 5 discontinued the study for "other reasons". 198 discontinued study drugs and were followed per protocol. 105 died. All were included in the primary analysis.; Group 2 Number missing: 0, Reason: 929 were assigned to the placebo. All received the placebo. 11 discontinued the study (2 were lost to follow up, 9 had other reasons), 170 discontinued placebo and were followed per protocol, 100 died. All were included in the primary and safety analysis.

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : Death from cardiovascular causes at 4.35 years; Group 1: 47/944, Group 2: 56/929
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 944 people were assigned to the treatment. 943 received the study drugs. 5 discontinued the study for "other reasons". 198 discontinued study drugs and were followed per protocol. 105 died. All were included in the primary analysis.; Group 2 Number missing: 0, Reason: 929 were assigned to the placebo. All received the placebo. 11 discontinued the study (2 were lost to follow up, 9 had other reasons), 170 discontinued placebo and were followed per protocol, 100 died. All were included in the primary and safety analysis.

Protocol outcome 3: Onset of symptoms or progression of NYHA class at ≥12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : Congestive heart failure as a result of progression of aortic stenosis at 4.35 years; Group 1: 25/944, Group 2: 23/929
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 944 people were assigned to the treatment. 943 received the study drugs. 5 discontinued the study for "other reasons". 198 discontinued study drugs and were followed per protocol. 105 died. All were included in the primary analysis.; Group 2 Number missing: 0, Reason: 929 were assigned to the placebo. All received the placebo. 11 discontinued the study (2 were lost to follow up, 9 had other reasons), 170 discontinued placebo and were followed per protocol, 100 died. All were included in the primary and safety analysis.
- Actual outcome for Primary aortic [including bicuspid] stenosis : Congestive heart failure as a result of progression of aortic stenosis at 4.35 years; Group 1: Observed events 25 n=944 ; Group 2: Observed events 23 n=929; HR 1.09; Lower CI 0.62 to Upper CI 1.92; Log rank variance: 0.77
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 944 people were assigned to the treatment. 943 received the study drugs. 5 discontinued the study for "other reasons". 198 discontinued study drugs and were followed per protocol. 105 died. All were included in the primary analysis.; Group 2 Number missing: 0, Reason: 929 were assigned to the placebo. All received the placebo. 11 discontinued the study (2 were lost to follow up, 9 had other reasons), 170 discontinued placebo and were followed per protocol, 100 died. All were included in the primary and safety analysis.

Protocol outcome 4: Need for heart valve intervention at ≥12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : Aortic valve replacement surgery at 4.35 years; Group 1: 267/944, Group 2: 278/929
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 944 people were assigned to the treatment. 943 received the study drugs. 5 discontinued the study for "other reasons". 198 discontinued study drugs and were followed per

protocol. 105 died. All were included in the primary analysis.; Group 2 Number missing: 0, Reason: 929 were assigned to the placebo. All received the placebo. 11 discontinued the study (2 were lost to follow up, 9 had other reasons), 170 discontinued placebo and were followed per protocol, 100 died. All were included in the primary and safety analysis. - Actual outcome for Primary aortic [including bicuspid] stenosis : Aortic valve replacement surgery at 4.35 years; Group 1: Observed events 267 n=944 ; Group 2: Observed events 278 n=929; HR 1; Lower CI 0.84 to Upper CI 1.18; Log rank variance: 0.97 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 944 people were assigned to the treatment. 943 received the study drugs. 5 discontinued the study for "other reasons". 198 discontinued study drugs and were followed per protocol. 105 died. All were included in the primary analysis.; Group 2 Number missing: 0, Reason: 929 were assigned to the placebo. All received the placebo. 11 discontinued the study (2 were lost to follow up, 9 had other reasons), 170 discontinued placebo and were followed per protocol, 100 died. All were included in the primary and safety analysis. Protocol outcome 5: Withdrawal due to adverse events at ≥12 months - Actual outcome for Primary aortic [including bicuspid] stenosis : Event resulting in permanent discontinuation of study treatment at 4.35 years; Group 1: 144/943, Group 2: 122/929 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 944 people were assigned to the treatment. 943 received the study drugs. 5 discontinued the study for "other reasons". 198 discontinued study drugs and were followed per protocol. 105 died. All but one person was included in the safety analysis (the person who did not receive the medication).; Group 2 Number missing: 0, Reason: 929 were assigned to the placebo. All received the placebo. 11 discontinued the study (2 were lost to follow up, 9 had other reasons), 170 discontinued placebo and were followed per protocol, 100 died. All were included in the primary and safety analysis.	
Protocol outcomes not reported by the study	Quality of life at 6 months; Quality of life at ≥12 months; Evidence of HVD progression on imaging (worsening of disease severity) at ≥12 months; Exercise tolerance at ≥12 months; Withdrawal due to adverse events at 6 months

Study	Stewart 2008[154]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=65)
Countries and setting	Conducted in New Zealand; Setting: Outpatient follow up
Line of therapy	1st line
Duration of study	Intervention + follow up: Median: 19 months (IQR: 15-25 months)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Measured by Doppler ultrasound and echocardiography
Stratum	Primary aortic [including bicuspid] stenosis
Subgroup analysis within study	Not applicable
Inclusion criteria	Asymptomatic, moderate or severe aortic stenosis defined as a peak velocity of >3.0 m/s measured by Doppler ultrasound and normal LV systolic function by echocardiography (EF >50%).
Exclusion criteria	Angina, exertional dizziness, syncope, or dyspnoea thought to be related to aortic stenosis, previous or scheduled aortic valve replacement, another heart valve lesion of moderate or greater severity, use of potassium sparing diuretics, serum creatinine level of >0.13 mmol/L or serum potassium level of >5.0 mmol/L during the screening period, significant comorbidity, likely poor compliance, or a contraindication to magnetic resonance imaging.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 67.5 (10.1). Gender (M:F): 50:15. Ethnicity: Not stated
Further population details	1. Age: Mixed (Confidence intervals fall either side of 75 years.). 2. Disease mechanism for aortic and mitral stenosis: Not stated / Unclear 3. Presence vs. absence of uncontrolled systemic hypertension (140/85 mmHg) at the end of trial intervention despite medication: Not stated / Unclear (At the start: Blood pressure eplerenone: 145/83 (21/10). Blood pressure placebo: 144/81 (15/11). Final blood pressure not mentioned.).
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=33) Intervention 1: Diuretics - Eplerenone. Initially epleronone 50mg (1 tablet daily), increased to 100mg (2 tablets daily) after one month if serum potassium level was ≤5.0 mmol/L, serum creatinine level was ≤0.13 mmol/L, and systolic blood

	pressure was >100mmHg, and there were no adverse events of treatment. Duration 19 months. Concurrent medication/care: Other medications were at the discretions of the patient's usual doctor. Indirectness: No indirectness (n=32) Intervention 2: Placebo. Placebo. Duration 19 months. Concurrent medication/care: Other medications were at the discretions of the patient's usual doctor. Indirectness: No indirectness
Funding	Study funded by industry (The National Heart Foundation of New Zealand and Pfizer (states it was completed by the study investigators independently from sponsors). The Green Lane Research and Education fund used for salary support)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EPLERENONE versus PLACEBO

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : All-cause mortality at 19 months; Group 1: 1/30, Group 2: 2/31
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 withdrawals due to patient decision, 1 withdrawal due to gynaecomastia; Group 2 Number missing: 1, Reason: 1 withdrawal due to patient decision

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : Sudden death at 19 months; Group 1: 0/29, Group 2: 1/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 withdrawals due to patient decision, 1 withdrawal due to gynaecomastia; Group 2 Number missing: 1, Reason: 1 withdrawal due to patient decision

Protocol outcome 3: Quality of life at ≥12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : SF36 physical functioning subscale at 19 months; Group 1: mean -5 (SD 22); n=29, Group 2: mean -9 (SD 19); n=30; SF-36 physical functioning subscale 0-100 Top=High is good outcome; Comments: Baseline eplerenone: 79 (22). Baseline placebo: 87 (10).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: 2 withdrawals due to patient decision, 1 withdrawal due to gynaecomastia, 1 non-cardiac death; Group 2 Number missing: 2, Reason: 1 withdrawal due to patient decision, 1 non-cardiac death
- Actual outcome for Primary aortic [including bicuspid] stenosis : SF36 role physical subscale at 19 months; Group 1: mean -9 (SD 34); n=29, Group 2: mean -12 (SD 37); n=30; SF-36 role physical subscale 0-100 Top=High is good outcome; Comments: Baseline eplerenone: 72 (42). Baseline placebo: 82 (30).

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: 2 withdrawals due to patient decision, 1 withdrawal due to gynaecomastia, 1 non-cardiac death; Group 2 Number missing: 2, Reason: 1 withdrawal due to patient decision, 1 non-cardiac death Protocol outcome 4: Onset of symptoms or progression of NYHA class at ≥12 months - Actual outcome for Primary aortic [including bicuspid] stenosis : Symptomatic deterioration at 19 months; Group 1: 13/29, Group 2: 10/30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: 2 withdrawals due to patient decision, 1 withdrawal due to gynaecomastia, 1 non-cardiac death; Group 2 Number missing: 2, Reason: 1 withdrawal due to patient decision, 1 non-cardiac death Protocol outcome 5: Withdrawal due to adverse events at ≥12 months - Actual outcome for Primary aortic [including bicuspid] stenosis : Withdrawal due to adverse events at 19 months; Group 1: 1/32, Group 2: 0/30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 2 withdrawals due to patient decision, 1 non-cardiac death; Group 2 Number missing: 2, Reason: 1 withdrawal due to patient decision, 1 non-cardiac death	
Protocol outcomes not reported by the study	Quality of life at 6 months; Evidence of HVD progression on imaging (worsening of disease severity) at ≥12 months; Need for heart valve intervention at ≥12 months; Exercise tolerance at ≥12 months; Withdrawal due to adverse events at 6 months

Study	TASS trial: Dichtl 2008[41]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Austria; Setting: Outpatient care
Line of therapy	1st line
Duration of study	Intervention + follow up: 3-5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Transthoracic echocardiography completed throughout the study
Stratum	Primary aortic [including bicuspid] stenosis
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged >18 years with calcific aortic stenosis, mean systolic gradients of ≥18 mmHg, valvular stenotic flow velocities ≥20m/s and aortic valve calcification on echo.
Exclusion criteria	Child-bearing potential, severe liver disease, concomitant mitral valve stenosis, severe liver disease, concomitant mitral valve stenosis, severe mitral or aortic regurgitation, advanced left ventricular dysfunction (ejection fraction <40%), planned aortic valve replacement, intolerance of statins, or an indication for statin therapy according to guidelines.
Recruitment/selection of patients	Consecutively referred 120 people to their echocardiographic laboratory for evaluation of asymptomatic calcified aortic stenosis. 50 were enrolled and followed up every 12 months for 3-5 years.
Age, gender and ethnicity	Age - Mean (SD): 67.0 (11.7) years. Gender (M:F): 28:22. Ethnicity: Not stated
Further population details	1. Age: Mixed (Confidence interval falls over 75 years. Intervention: 64.2 (12.0), Control: 69.7 (10.6)). 2. Disease mechanism for aortic and mitral stenosis: Calcific 3. Presence vs. absence of uncontrolled systemic hypertension (140/85 mmHg) at the end of trial intervention despite medication: Not stated / Unclear (States that 9 in the intervention arm, and 14 in the control arm had hypertension. Antihypertensive medication was prescribed. Does not state if this was uncontrolled at the end of the trial.).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Statins - Atorvastatin . Atorvastatin 20mg once a day. Duration 3-5 years. Concurrent medication/care: 7 people were using aspirin, 6

	people were using an ACE inhibitor, 1 person was using a calcium channel blocker, 1 person with using a beta blocker, 1 person was using a vitamin K antagonist. Indirectness: No indirectness (n=25) Intervention 2: Placebo. Placebo. Duration 3-5 years. Concurrent medication/care: 14 people were using aspirin, 11 were using an ACE inhibitor, 2 were using a calcium channel blocker, 5 were using a beta blocker, 3 were using a vitamin K antagonist. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Medication provided by Pfizer Austria)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN versus PLACEBO

Protocol outcome 1: All-cause mortality at ≥12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : All-cause mortality at 5 years; Group 1: 1/24, Group 2: 1/23
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, coronary artery calcification, arterial hypertension, current smoking, renal insufficiency and medication use. Statin arm has people less medication usage, but more coronary artery disease and smoking, control arm has more people with arterial hypertension.; Group 1 Number missing: 1, Reason: 1 lost due to an intolerance to atorvastatin therapy; Group 2 Number missing: 2, Reason: 1 lost to follow up, 1 developed gastric cancer and left the trial

Protocol outcome 2: Cardiac mortality at ≥12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : Cardiac mortality at 5 years; Group 1: 1/24, Group 2: 1/23
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, coronary artery calcification, arterial hypertension, current smoking, renal insufficiency and medication use. Statin arm has people less medication usage, but more coronary artery disease and smoking, control arm has more people with arterial hypertension.; Group 1 Number missing: 1, Reason: 1 lost due to an intolerance to atorvastatin therapy; Group 2 Number missing: 2, Reason: 1 lost to follow up, 1 developed gastric cancer and left the trial

Protocol outcome 3: Need for heart valve intervention at ≥12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : Need for heart valve intervention at 5 years; Group 1: 5/24, Group 2: 1/23
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, coronary artery calcification, arterial hypertension, current smoking, renal insufficiency and medication use. Statin arm has people less medication usage, but more coronary artery disease and smoking, control arm has more people with arterial hypertension.; Group 1 Number missing: 1, Reason: 1 lost due to an intolerance to atorvastatin therapy; Group 2 Number missing: 2, Reason: 1 lost to follow up, 1 developed gastric cancer and left the trial

Protocol outcome 4: Withdrawal due to adverse events at 6 months - Actual outcome for Primary aortic [including bicuspid] stenosis : Withdrawal due to adverse events at <6 months; Group 1: 1/25, Group 2: 0/23 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Reports age, gender, coronary artery calcification, arterial hypertension, current smoking, renal insufficiency and medication use. Statin arm has people less medication usage, but more coronary artery disease and smoking, control arm has more people with arterial hypertension.; Group 1 Number missing: 0, Reason: 1 lost due to an intolerance to atorvastatin therapy; Group 2 Number missing: 2, Reason: 1 lost to follow up, 1 developed gastric cancer and left the trial	
Protocol outcomes not reported by the study	Quality of life at 6 months; Quality of life at ≥12 months; Onset of symptoms or progression of NYHA class at ≥12 months ; Evidence of HVD progression on imaging (worsening of disease severity) at ≥12 months; Exercise tolerance at ≥12 months; Withdrawal due to adverse events at ≥12 months

Study	Wisenbaugh 1994-1[177]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=32)
Countries and setting	Conducted in South Africa; Setting: Outpatient follow up
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Doppler echocardiography and clinical examination
Stratum	Primary mitral regurgitation
Subgroup analysis within study	Not applicable
Inclusion criteria	Severe isolated MR by clinical examination and Doppler echocardiographic criteria; mitral valve are >3cm² and no aortic stenosis or other significant valvular lesion; normal sinus rhythm; no clinical evidence of coronary artery disease; clear endocardial borders identifiable on echocardiographic imaging; willingness to participate in the protocol and high probability of good follow up as determined by a nurse who interviewed the person in their own language.
Exclusion criteria	More than mild symptoms (>NYHA class II).
Recruitment/selection of patients	People recruited from the cardiac clinic at Baragwanath Hospital
Age, gender and ethnicity	Age - Other: Mean age: 24.9. Gender (M:F): 5:25. Ethnicity:
Further population details	1. Age: <75 years (Mean age captopril: 26, mean age placebo: 24). 2. Disease mechanism for aortic and mitral stenosis: Not applicable 3. Presence vs. absence of uncontrolled systemic hypertension (140/85 mmHg) at the end of trial intervention despite medication: Not stated / Unclear (initial blood pressure captopril: 117/67, placebo: 110/63. From the graph it appears the value stayed under 140/85 but it is unclear.).
Extra comments	Three had myxomatous MR, the rest had rheumatic MR.
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Angiotensin-converting enzyme (ACE) inhibitors - Captopril. Captopril 25mg three times daily. Duration 6 months. Concurrent medication/care: Three had been taking enalapril (5-10mg twice daily), which was discontinued at least 2 months before entry into the study. One was taking nifedipine which was discontinued 1 month prior to entry. Other vasodilating and digitalis drugs were not

	used. People who were on furosemide were maintained on a constant dose (average captopril group: 46mg, average placebo group: 42mg). Indirectness: No indirectness (n=18) Intervention 2: Placebo. Placebo. Duration 6 months. Concurrent medication/care: Three had been taking enalapril (5-10mg twice daily), which was discontinued at least 2 months before entry into the study. One was taking nifedipine which was discontinued 1 month prior to entry. Other vasodilating and digitalis drugs were not used. People who were on furosemide were maintained on a constant dose (average captopril group: 46mg, average placebo group: 42mg). Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CAPTOPRIL versus PLACEBO Protocol outcome 1: All-cause mortality at ≥12 months - Actual outcome for Primary mitral regurgitation: Death at 6 months; Group 1: 0/12, Group 2: 1/17 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Reports that there was a randomisation error; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 excluded due to poor compliance; Group 2 Number missing: 1, Reason: 1 excluded due to poor compliance Protocol outcome 2: Cardiac mortality at ≥12 months - Actual outcome for Primary mitral regurgitation: Death at 6 months; Group 1: 0/12, Group 2: 1/17 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Reports that there was a randomisation error; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 excluded due to poor compliance; Group 2 Number missing: 1, Reason: 1 excluded due to poor compliance Protocol outcome 3: Onset of symptoms or progression of NYHA class at ≥12 months - Actual outcome for Primary mitral regurgitation: Symptom deterioration at 6 months; Group 1: 0/12, Group 2: 1/17 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Reports that there was a randomisation error; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 excluded due to poor compliance; Group 2 Number missing: 1, Reason: 1 excluded due to poor compliance	
Protocol outcomes not reported by the study	Quality of life at 6 months; Quality of life at ≥12 months; Evidence of HVD progression on imaging (worsening of disease severity) at ≥12 months; Need for

	heart valve intervention at ≥12 months; Exercise tolerance at ≥12 months; Withdrawal due to adverse events at 6 months; Withdrawal due to adverse events at ≥12 months

Study	Wisenbaugh 1994-2[177]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=23)
Countries and setting	Conducted in South Africa; Setting: Outpatient follow up
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Doppler echocardiography and clinical examination
Stratum	Primary aortic regurgitation
Subgroup analysis within study	Not applicable
Inclusion criteria	Severe isolated AR by clinical examination and Doppler echocardiographic criteria; mitral valve are >3cm² and no aortic stenosis or other significant valvular lesion; normal sinus rhythm; no clinical evidence of coronary artery disease; clear endocardial borders identifiable on echocardiographic imaging; willingness to participate in the protocol and high probability of good follow up as determined by a nurse who interviewed the person in their own language.
Exclusion criteria	More than mild symptoms (>NYHA class II)
Recruitment/selection of patients	People recruited from the cardiac clinic at Baragwanath Hospital
Age, gender and ethnicity	Age - Other: Mean age: 28.1 years. Gender (M:F): 15:5. Ethnicity: Not stated
Further population details	1. Age: <75 years (Mean age Captopril: 29, Placebo: 27). 2. Disease mechanism for aortic and mitral stenosis: Not applicable 3. Presence vs. absence of uncontrolled systemic hypertension (140/85 mmHg) at the end of trial intervention despite medication: Not stated / Unclear (Baseline captopril: 131/46, Baseline placebo: 144/57. So potentially. According to the graph there wasn't much charge at 6 months, but unclear.).
Extra comments	In most cases underlying cause of AR could not be determined (none were thought to have a rheumatic aetiology).

Indirectness of population	No indirectness
Interventions	(n=13) Intervention 1: Angiotensin-converting enzyme (ACE) inhibitors - Captopril. Captopril 25mg three times a day. Duration 6 months. Concurrent medication/care: In the placebo group, one person had been taken enalapril, which was discontinued for two months before entry. One was taking hydralazine which was discontinued for one month. In the captopril group, two had been enalapril which was discontinued for two and three months respectively. Three were taking hydralazine, which was discontinued for 2-3 months before entry. People who were on chronic furosemide were maintained at a constant dose (captopril group average daily dose = 47mg, placebo group average daily dose = 31mg) (n=10) Intervention 2: Placebo. Placebo. Duration 6 months. Concurrent medication/care: In the placebo group, one person had been taken enalapril, which was discontinued for two months before entry. One was taking hydralazine which was discontinued for one month. In the captopril group, two had been enalapril which was discontinued for two and three months respectively. Three were taking hydralazine, which was discontinued for 2-3 months before entry. People who were on chronic furosemide were maintained at a constant dose (captopril group average daily dose = 47mg, placebo group average daily dose = 31mg). Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CAPTOPRIL versus PLACEBO Protocol outcome 1: Onset of symptoms or progression of NYHA class at ≥12 months - Actual outcome for Primary aortic regurgitation : Symptom deterioration at 6 months; Group 1: 0/11, Group 2: 0/9 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 lost to follow up after 3 months; Group 2 Number missing: 1, Reason: 1 lost to follow up after 3 months	
Protocol outcomes not reported by the study	All-cause mortality at ≥12 months; Cardiac mortality at ≥12 months; Quality of life at 6 months; Quality of life at ≥12 months; Evidence of HVD progression on imaging (worsening of disease severity) at ≥12 months; Need for heart valve intervention at ≥12 months; Exercise tolerance at ≥12 months; Withdrawal due to adverse events at 6 months; Withdrawal due to adverse events at ≥12 months

D.2 Valve disease with heart failure

Study	Alan 2002[6]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=80)
Countries and setting	Conducted in Turkey; Setting: Initiated and followed up in secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months (received an IV dose of diltiazem for induction, then 3 months of oral diltiazem)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Noted previous diagnosis of mitral stenosis as assessment method for HVD (However, go on to do echocardiography confirming this). Congestive heart failure assessed by NYHA status.
Stratum	Primary mitral stenosis: Noted previous diagnosis of mitral stenosis as assessment method for HVD (However, go on to do echocardiography confirming this).
Subgroup analysis within study	Not applicable: N/A
Inclusion criteria	People with a diagnosis of mitral stenosis of mild-to-moderate severity
Exclusion criteria	People with moderate-to-severe degrees of aortic insufficiency and aortic stenosis, and patients with severe pulmonary hypertension or right-sided heart failure.
Recruitment/selection of patients	No additional information available.
Age, gender and ethnicity	Age - Mean (SD): 38±6.8 years. Gender (M:F): 28:52 (35/65%). Ethnicity: Not stated
Further population details	1. Age: <75 years (Range: 33-45 years). 2. Heart rate: Normal (82±10 per minute). 3. Presence vs. absence of uncontrolled systemic hypertension: Absence of uncontrolled systemic hypertension (Mean 112/71 and 115/78 in diltiazem and metoprolol groups). 4. Severe vs non-severe HVD: Non-severe (Mild-to-moderate). 5. Symptomatic vs asymptomatic: Symptomatic (NYHA II or III).
Extra comments	Age range = 33-45 years; Functional capacities of all patients included in the study were NYHA class II and class III.
Indirectness of population	No indirectness: Population fits guideline condition (adults aged 18 years and over diagnosed with mitral stenosis with congestive heart failure).
Interventions	(n=40) Intervention 1: Beta blockers - Metoprolol. Initially: 5mg intravenous, followed by 50mg orally twice daily. Duration 3 months. Concurrent medication/care: Not stated. Indirectness: No indirectness Comments: Initial intravenous loading dose. Not necessarily standard treatment. (n=40) Intervention 2: Calcium-channel blockers (CCB) - Diltiazem. Initially 25mg intravenously followed by 60mg orally three times daily. Duration 3 months. Concurrent medication/care: Not stated. Indirectness: No

	indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METOPROLOL versus DILTIAZEM Protocol outcome 1: Exercise tolerance at 12 months - Actual outcome for Primary mitral stenosis: Total effort time (sec) - treadmill exercise test (Bruce protocol) at 3 months; Group 1: mean 520 Seconds (SD 90); n=40, Group 2: mean 570 Seconds (SD 126); n=40; Comments: Initial values (at beginning of treatment): Metoprolol: 452±120 Diltiazem: 534±120 Note: Results are from 3 months, outside of that required for inclusion in the outcome. Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - Outcome follow up is at 3 months rather than the 6 or greater required for inclusion.; Indirectness of outcome: No indirectness, Comments: Bruce protocol is widely used in clinical practice.; Baseline details: Difference in baseline effort time greater than difference in final values. Full baseline characteristics not reported. The age and sex is reported, and appears similar.; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Withdrawal due to adverse events at 6 months - Actual outcome for Primary mitral stenosis: Adverse events that interrupted treatment at 3 months; Group 1: 0/40, Group 2: 0/40; Comments: Note: Outcome assessed at 3 months. Outside of the value accepted for follow up in this protocol. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - Outcome follow up is at 3 months rather than the 6 or greater required for inclusion.; Indirectness of outcome: No indirectness; Baseline details: Full baseline characteristics not reported. The age and sex is reported, and appears similar.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at 6 months; Hospitalisation due to heart failure at 12 months; Cardiac mortality at 12 months; Quality of life at 12 months; Need for valve intervention at 6 months; Need for valve intervention at 12 months; Withdrawal due to adverse events at 12 months; All-cause mortality at 12 months; Cardiac mortality at 6 months

Study	Bassan 1987[15]
Study type	RCT (Patient randomised; Crossover: 1 week (washout period), except for week 3 (when patients were given half doses of propranolol - during this period patients could have had propranolol or placebo during the week before with no washout))
Number of studies (number of participants)	N/A (n=10)
Countries and setting	Conducted in Israel; Setting: Not stated - likely secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 weeks, follow up for at least 24 months after the intervention
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Well explained. Diagnosis established by typical auscultatory, electrocardiographic, radiographic, and echocardiographic findings.
Stratum	Primary mitral stenosis: Patients with isolated mitral stenosis.
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with isolated mitral stenosis.
Exclusion criteria	No patient had echocardiographic evidence of left ventricular hypertrophy or abnormal left ventricular function. No evidence of right heart failure. No obstructive lung disease or contraindication to beta-blockade.
Recruitment/selection of patients	No information stated
Age, gender and ethnicity	Age - Other: Individual values given. The mean is 38.7 (Range: 19-56). Gender (M:F): 4:6. Ethnicity: Not stated
Further population details	1. Age: <75 years (Mean = 38.7). 2. Heart rate: Not stated / Unclear (No pre-treatment values given; comparison between placebo and treatment group shows bradycardiac-normal rates). 3. Presence vs. absence of uncontrolled systemic hypertension: Not stated / Unclear 4. Severe vs non-severe HVD: Not stated / Unclear (At least 2 with "severe stenosis". Others not clearly stated.). 5. Symptomatic vs asymptomatic: Symptomatic (NYHA class II or III.).
Extra comments	NYHA class II or III. They determine the mitral valve area post-hoc for some cases (after surgery).
Indirectness of population	No indirectness: All patients are older than 18 years. The range is fairly last, but not indirect.
Interventions	(n=10) Intervention 1: Beta blockers - Propranolol . Full dose (dependent on weight) - 40mg orally (two or three times a day dependent on weight). Patients were trained according to an individual exercise protocol to reach a reproducible degree of near maximal dyspnoea. Five patients performed bicycle exercise and five exercised on a treadmill. In the training phase the patients learnt to recognise their dyspnoea end point. Achievement of stable performance (less than a 30 second variation in exercise duration) usually required 8-12 exercise bouts over several weeks with 2-3 bouts per session. The starting level for the study phase was chosen so that endpoint dyspnoea

	was reached after 3-6 minutes of exercise. At the final training session the patient was given a test dose of 40mg of propranolol and was observed for several hours for possible adverse effects as well as for the degree of induced bradycardia. Duration 1 week. Concurrent medication/care: None stated. Indirectness: No indirectness; Indirectness comment: Is only for a short duration, but is not indirect in itself. (n=10) Intervention 2: Placebo. Matching placebo. Duration 1 week. Concurrent medication/care: None stated. Indirectness: No indirectness; Indirectness comment: Is only for a short duration, but is not indirect in itself.
Funding	Academic or government funding (MacRamer Heart Research Scholarship Fund, Flushing, New York)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROPRANOLOL (FULL DOSE) versus PLACEBO Protocol outcome 1: Exercise tolerance at 12 months - Actual outcome for Primary mitral stenosis: Time to near maximal dyspnoea at 1 week; Group 1: mean 274 seconds (SD 79); n=10, Group 2: mean 283 seconds (SD 82); n=10; Comments: SD calculated from SE in paper Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Crossover study; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at 6 months; Hospitalisation due to heart failure at 12 months; Cardiac mortality at 12 months; Quality of life at 12 months; Need for valve intervention at 6 months; Need for valve intervention at 12 months; Withdrawal due to adverse events at 6 months; Withdrawal due to adverse events at 12 months; All-cause mortality at 12 months; Cardiac mortality at 6 months

Study	Chockalingam 2004[29]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=56)
Countries and setting	Conducted in India; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Referral from a cardiology service and states specific parameters that needed to be met for inclusion.
Stratum	Primary aortic [including bicuspid] stenosis: Unclear how defined/diagnosed
Subgroup analysis within study	Post-hoc subgroup analysis: They reported completing subgroup analysis for age, sex, baseline walk distance and LV dysfunction for the outcome of effort tolerance - they showed no difference. They found that patients with associated regurgitant lesions had a trend toward more improvement in exercise capacity and symptoms in another analysis.
Inclusion criteria	Severe AS (aortic valve area <0.75 cm2, mean aortic gradient >50 mm Hg, or aortic valve Doppler jet >4.5 m/s) and symptomatic New York Heart Association class III or IV dyspnoea or angina.
Exclusion criteria	Persistent hypotension (systolic BP <90 or mean BP <60), severe mitral stenosis (mitral valve orifice <1.0 cm2), known intolerance for ACEI, and renal dysfunction (serum creatinine >2.5 mg/dL).
Recruitment/selection of patients	Recruitment from a cardiology service of a medical college hospital.
Age, gender and ethnicity	Age - Mean (SD): Intervention arm: 43±11, Control arm: 46±12. Gender (M:F): 39:13. Ethnicity: Not reported
Further population details	1. Age: <75 years (Mean in Enalapril arm = 43 +/-11, Mean in Placebo arm = 46 +/-12). 2. Heart rate: Normal (Mean in Enalapril arm = 83 +/-8, Mean in Placebo arm = 83 +/-8). 3. Presence vs. absence of uncontrolled systemic hypertension: Absence of uncontrolled systemic hypertension (mean blood pressure for both arms given. Doesn't state whether this is systolic or diastolic. However, for both arms this is less than or equal to 90mmHg). 4. Severe vs non-severe HVD: Severe 5. Symptomatic vs asymptomatic : Symptomatic
Extra comments	Patients were waiting for surgery or unwilling to have surgery.
Indirectness of population	No indirectness: Fits our guideline criteria.
Interventions	(n=37) Intervention 1: Angiotensin-converting enzyme (ACE) inhibitors - Enalapril. 2.5mg BD gradually titrated up to 10mg BD over 2 weeks (in 5 patients this was not achievable and they remained at 2.5-5mg BD during the study).

	All were initially stabilised in hospital (5 ± 3 days) with diuretics, digoxin, and intravenous dobutamine infusion before initiating the study medication. Duration 3 months (in the majority). Concurrent medication/care: Prior treatment was continued (apart from potassium replacement for which the dose was decreased). All had frusemide, 94% had digoxin, 48% had spironalactone and 9.6% had dobutamine. Indirectness: No indirectness (n=19) Intervention 2: Placebo. All were initially stabilised in hospital (5 ± 3 days) with diuretics, digoxin, and intravenous dobutamine infusion before initiating the study medication. Duration 3 months. Concurrent medication/care: Prior treatment was continued. All had frusemide, 94% had digoxin, 48% had spironalactone and 9.6% had dobutamine. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENALAPRIL versus PLACEBO Protocol outcome 1: Exercise tolerance at 12 months - Actual outcome for Primary aortic [including bicuspid] stenosis : 6-minute walk distance (meters) at 4 weeks; Group 1: mean 402 Meters (SD 150); n=34, Group 2: mean 376 Meters (SD 174); n=18; Comments: Values at baseline were reported: Enalapril arm: 330±157 Control arm: 349±147 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: 2:1 ratio of intervention to placebo. However, proportions were maintained.; Group 1 Number missing: 3, Reason: Patients withdrew due to adverse events; Group 2 Number missing: 1, Reason: Patient withdrew due to adverse events Protocol outcome 3: Withdrawal due to adverse events at 6 months - Actual outcome for Primary aortic [including bicuspid] stenosis : Withdrawal due to intolerance to study medication at 3 months ; Group 1: 3/37, Group 2: 1/19; Comments: Enalapril: 3 had significant hypotension; placebo: unclear Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: 2:1 ratio of intervention to placebo. However, proportions were maintained.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at 6 and 12 months; Hospitalisation due to heart failure at 12 months; Cardiac mortality at 6 and 12 months; Need for valve intervention at 6 or 12 months; Withdrawal due to adverse events at 12 months; All-cause mortality at 12 months.

Study	Dalsgaard 2014[38]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=44)
Countries and setting	Conducted in Denmark; Setting: Secondary care
Line of therapy	1st line
Duration of study	Follow up (post intervention): Median of 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Aortic valve area <1cm², in sinus rhythm and without symptoms at rest = severe AS. Independently assessed for NYHA class.
Stratum	Primary aortic [including bicuspid] stenosis
Subgroup analysis within study	Not applicable
Inclusion criteria	Severe AS. Symptomatic and asymptomatic patients (32 were symptomatic, 12 were asymptomatic).
Exclusion criteria	Mitral regurgitation, unable to perform exercise testing, resting systolic BP <100 mmHg, known renal artery stenosis or creatinine >200 umol/l, prior treatment with ACE-I or ARBs in the last month.
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): 69.9±8.3 (range of 55-85 years). Gender (M:F): 4:7. Ethnicity: Not stated
Further population details	1. Age: Mixed 2. Heart rate: Not stated / Unclear 3. Presence vs. absence of uncontrolled systemic hypertension: Not stated / Unclear 4. Severe vs non-severe HVD: Severe 5. Symptomatic vs asymptomatic: Mixed
Extra comments	Severe aortic stenosis - 32 patients were symptomatic, 12 were asymptomatic. 30 had another comorbidity (hypertension, IHD, diabetes mellitus).
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Angiotensin-converting enzyme (ACE) inhibitors - Trandolapril. Daily increasing doses of trandolapril, 0.5 mg on day 1; 1 mg on day 2 and 2 mg in day 3. At discharge on day 3 patients were given the maximum tolerated dose for the rest of the study. Duration 8 weeks. Concurrent medication/care: Calcium antagonists (14%); beta-blockers (27%); diuretics (50%). Indirectness: No indirectness (n=22) Intervention 2: Placebo. Matched placebo. Duration 8 weeks. Concurrent

	medication/care: Calcium antagonists (18%); beta-blockers (45%); diuretics (32%). Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANDOLAPRIL versus PLACEBO Protocol outcome 1: Exercise tolerance at 12 months - Actual outcome for Primary aortic [including bicuspid] stenosis : Exercise duration to exhaustion (minutes) at 3 days; Group 1: mean 0.2 minutes (SD 0.6); n=21, Group 2: mean 0.2 minutes (SD 0.4); n=22; Comments: Baseline : ACE-I: 5.9 (1.9); placebo: 6.1 (2.1) minutes Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Follow-up period 3 days; Group 1 Number missing: 1, Reason: Ischaemic stroke; Group 2 Number missing: 0 Protocol outcome 3: Withdrawal due to adverse events at 6 months - Actual outcome for Primary aortic [including bicuspid] stenosis : Withdrawal due to adverse events at 8 weeks; Group 1: 1/22, Group 2: 0/22; Comments: 1 cerebral ischaemic stroke (not thought to be due to the study drug) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Follow-up period 8 weeks; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at 6 months; Hospitalisation due to heart failure at 12 months; Cardiac mortality at 12 months; Quality of life at 12 months; Need for valve intervention at 6 or 12 months; Withdrawal due to adverse events at 12 months; All-cause mortality at 12 months; Cardiac mortality at 6 months

Study	Helske-Suihko 2015[67]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=51)
Countries and setting	Conducted in Finland; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 46 to 310 days. Mean = 164 +/- 67 days for intervention arm, 151 +/- 72 days for control arm (a little under 6 months).
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Previous diagnosis of AS (have been referred to them for consideration for surgery). However, they have an echo as a part of the intervention, which would assess this. The paper states the majority of patients had symptoms equivalent to NYHA class II, but selectively reports proportion in classes I-II vs. III. No clear assessment of NYHA reported.
Stratum	Primary aortic [including bicuspid] stenosis
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients (aged >18 years) with symptomatic AS referred to hospital for consideration of valve surgery.
Exclusion criteria	Past myocardial infarction, more than mild mitral valve disease, previous cardiac surgery, patients in urgent need for surgery due to severe symptoms or heart failure, hypotension (systolic <110mmHg), current use of ACE inhibitors or ARBs, complicated diabetes, primary cardiomyopathy, potential pregnancy or breast-feeding, recent history of malignancy, history of alcohol or drug abuse, elevated serum creatinine (>176 micromol/L), and participation in another investigational drug study.
Recruitment/selection of patients	May 2009 - August 2012; consecutive patients screened
Age, gender and ethnicity	Age - Mean (SD): Intervention: 73±9, control: 70±12. Gender (M:F): 22:27. Ethnicity: Not stated
Further population details	1. Age: Mixed (Candesartan mean: 73+/-9, Placebo mean: 70+/-12). 2. Heart rate: Normal (Candesartan mean: 68+/-15, Placebo mean: 67+/-13). 3. Presence vs. absence of uncontrolled systemic hypertension: Mixed (Candesartan mean: 134/78+/-14/12 (could be classified as hypertensive towards the higher values). Placebo mean: 137/80+/-21/13). 4. Severe vs non-severe HVD: Severe 5. Symptomatic vs asymptomatic : Symptomatic
Extra comments	Severity: aortic valve area index (cm^2/m^2) - 0.42 (0.13) and 0.41 (0.11); mean LV-AO pressure gradient (mmHg): 52 (14) and 49 (14). Patients who did not meet the exclusion criteria and could be put on the hospital's normal waiting list for invasive investigations and surgery were included
Indirectness of population	No indirectness: Possible that the NYHA classes could not be completely applicable (possible selective reporting).

Interventions	(n=25) Intervention 1: Angiotensin-II receptor blockers (ARBs) - Candesartan. 8mg per day for 2 weeks, and then 16mg per day until 3 days before they have valve surgery. Duration Mean = 5.4 months, with some higher (up to 1 year) and some lower (2 months). Concurrent medication/care: Not reported. Indirectness: No indirectness (n=26) Intervention 2: Placebo. Placebo. Duration Mean = 5.4 months, with some higher (up to 1 year) and some lower (2 months). Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Also academic support (Finnish Foundation for Cardiovascular Research, EVO research funds of the Helsinki University Central Hospital, the Jenny and Antti Wihuri Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CANDESARTAN versus PLACEBO

Protocol outcome 1: Hospitalisation due to heart failure at 12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis : Acute heart failure and anaemia at Mean: 5.4 months. Range: 2-12 months; Group 1: 1/25, Group 2: 0/26; Comments: Defined as acute decompensated heart failure, so hospitalisation is assumed
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Possible indirectness dependent on whether the anaemia caused the heart failure; Baseline details: More people taking statins in the candesartan group. Higher proportion NYHA class III in placebo group (27% vs 12% in candesartan group).; Group 1 Number missing: 3, Reason: 2 due to adverse events, 1 due to being denied valve surgery; Group 2 Number missing: 5, Reason: 2 due to adverse events, 2 significant coronary artery disease, 1 preoperative exitus

Protocol outcome 2: Exercise tolerance at 12 months
- Actual outcome for Primary aortic [including bicuspid] stenosis: 6 minute walk test at Mean: 5.4 months. Range: 2-12 months; Group 1: mean -20 meters (SD 42); n=22, Group 2: mean -2 meters (SD 59); n=21; Comments: Baseline values:
Candesartan: 390 (99), Placebo: 380 (197). Final values are not reported separately.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: More people taking statins in the candesartan group. Higher proportion NYHA class III in placebo group (27% vs 12% in candesartan group). Group 1 Number missing: 3, Reason: 2 due to adverse events, 1 due to being denied valve surgery; Group 2 Number missing: 5, Reason: 2 due to adverse events, 2 due to significant coronary artery disease, 1 had preoperative exitus

Protocol outcome 3: Withdrawal due to adverse events at 6 months
- Actual outcome for Primary aortic [including bicuspid] stenosis: Withdrawal due to adverse events at Mean: 5.4 months. Range: 2-12 months; Group 1: 2/25, Group 2: 2/26; Comments: All due to dizziness
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: More people taking statins in the candesartan group. It doesn't trigger their significant P value, but the NYHA class looks like the placebo group has more severe cases. Group 1 Number missing: 1, Reason: Denied valve surgery; Group 2 Number missing: 3, Reason: Significant coronary artery disease (2); preoperative exits (1) Protocol outcome 4: All-cause mortality at 12 months - Actual outcome for Primary aortic [including bicuspid] stenosis : All-cause mortality at Mean: 5.4 months. Range: 2-12 months; Group 1: 0/25, Group 2: 1/26; Comments: Sudden death while awaiting surgery Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: More people taking statins in the candesartan group. Higher proportion NYHA class III in placebo group (27% vs 12% in candesartan group). Group 1 Number missing: 3, Reason: 2 due to adverse events, 1 due to being denied valve surgery; Group 2 Number missing: 5, Reason: 2 due to adverse events, 2 due to significant coronary artery disease, 1 had preoperative exitus	
Protocol outcomes not reported by the study	Quality of life at 6 months; Cardiac mortality at 12 months; Quality of life at 12 months; Need for valve intervention at 6 months; Need for valve intervention at 12 months; Withdrawal due to adverse events at 12 months; Cardiac mortality at 6 months

Study	**Klein 1985[87]**
Study type	RCT (Patient randomised; Crossover: Not reported)
Number of studies (number of participants)	1 (n=13)
Countries and setting	Conducted in South Africa; Setting: Unclear
Line of therapy	1st line
Duration of study	Intervention time: Two phases consisting of 2 weeks each (atenolol and placebo phases)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of mitral stenosis made clinically and confirmed by echocardiography. Mitral stenosis was considered 'significant' in every patient based on an echocardiographic finding of a mitral valve orifice area <1.5 cm.
Stratum	Primary mitral stenosis: All patients with mitral stenosis
Subgroup analysis within study	Not applicable
Inclusion criteria	Significant isolated mitral stenosis and sinus rhythm
Exclusion criteria	Not reported
Recruitment/selection of patients	Consecutive patients

Age, gender and ethnicity	Age - Range: 15-35 years. Gender (M:F): 2:11. Ethnicity: Not reported
Further population details	1. Age: <75 years (Age range of those included was 15-35 years). 2. Heart rate: Not stated / Unclear (States post-treatment values only). 3. Presence vs. absence of uncontrolled systemic hypertension: Not stated / Unclear (States post-treatment values only). 4. Severe vs non-severe HVD: Not stated / Unclear (Significant mitral stenosis defined as mitral valve orifice area <1.5 cm). 5. Symptomatic vs asymptomatic: Symptomatic (NYHA class II or III - corresponds to mild or moderate symptoms of heart failure).
Extra comments	Patients with isolated mitral stenosis and in sinus rhythm. Functional class II or III of the New York Heart Association classification. All had evidence of pulmonary arterial hypertension (based on palpable right ventricular impulse and a loud pulmonic component of the second heart sound).
Indirectness of population	Serious indirectness: Includes some patients under 18 years of age but the proportion is unclear. Mean age not reported. Also unclear severity of heart valve disease.
Interventions	(n=13) Intervention 1: Beta blockers - Atenolol. 100 mg oral atenolol taken in the morning for 2 weeks. Duration 2 weeks. Concurrent medication/care: All patients received oral diuretic therapy throughout the study period. Indirectness: Serious indirectness; Indirectness comment: Unclear whether the treatment was first line Comments: 6 patients had atenolol during first phase of crossover study and 7 patients had atenolol during second phase of crossover study (n=13) Intervention 2: Placebo. Placebo taken in the morning for 2 weeks. Placebo tablet was identical in appearance to the atenolol tablet. Duration 2 weeks. Concurrent medication/care: All patients received oral diuretic therapy throughout the study period. Indirectness: Serious indirectness; Indirectness comment: Unclear whether treatment was first line Comments: 7 patients had placebo during first phase of crossover study and 6 patients had placebo during second phase of crossover study
Funding	Equipment / drugs provided by industry (Atenolol and placebo tablets were provided by Imperial Chemical Industries, Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATENOLOL versus PLACEBO

Protocol outcome 1: Exercise tolerance at 12 months
- Actual outcome for Primary mitral stenosis: Total duration of exercise (during modified Bruce protocol) at End of 2-week treatment period; Group 1: mean 11 minutes (SD 2); n=13, Group 2: mean 9 minutes (SD 2); n=13; Comments: Exercise testing was performed on commercial treadmills according to a modified Bruce protocol until the point of exhaustion, dizziness or severe dyspnoea was reached
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Follow-up is end of study rather than 12 month follow-up; Baseline details: Crossover study - same participants in both groups; Blinding details: Statement that atenolol and placebo tablets were

identical in appearance; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Primary mitral stenosis: Maximal exercise capacity (during modified Bruce protocol) at End of 2-week treatment period; Group 1: mean 84 work units (SD 47); n=13, Group 2: mean 45 work units (SD 29); n=13; Comments: Exercise testing was performed on commercial treadmills according to a modified Bruce protocol until the point of exhaustion, dizziness or severe dyspnoea was reached. Maximal exercise capacity derived from following equation, which was calculated for each stage of exercise and then summated: [time (min) x speed (km/h) x incline (degrees)/3 minutes]. The index takes into account the time spent exercising as well as the increasing difficulty of exercise with each successive stage. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: Serious indirectness, Comments: Follow-up is end of study rather than 12 month follow-up; Baseline details: Crossover study - same participants in both groups; Blinding details: Statement that atenolol and placebo tablets were identical in appearance; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at 6 months; Hospitalisation due to heart failure at 12 months; Cardiac mortality at 12 months; Quality of life at 12 months; Need for valve intervention at 6 months; Need for valve intervention at 12 months; Withdrawal due to adverse events at 6 months; Withdrawal due to adverse events at 12 months; All-cause mortality at 12 months; Cardiac mortality at 6 months

Study	Kumar 1994[90]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=31)
Countries and setting	Conducted in India; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Previously seen in clinic. Have an echo during the procedure to verify it. Baseline NYHA class recorded.
Stratum	Primary mitral stenosis
Subgroup analysis within study	Not applicable
Inclusion criteria	Isolated symptomatic rheumatic mitral stenosis in sinus rhythm
Exclusion criteria	Mitral valve area <0.8cm²; haemoglobin <12gm%; obstructive lung disease; >grade I mitral or aortic regurgitation on 2D echocardiogram and colour doppler
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): Intervention: 23.6±7.7; Placebo: 22.8±8.2. Gender (M:F): 15:11. Ethnicity: Not stated
Further population details	1. Age: <75 years (Metoprolol mean: 23.6+/-7.7; Placebo mean: 22.8+/-8.2). 2. Heart rate: Mixed (Metoprolol mean: 88.3+/-16.7, Placebo mean: 91.8+/-10.8. At the extreme high would be tachycardic). 3. Presence vs. absence of uncontrolled systemic hypertension: Absence of uncontrolled systemic hypertension (states that no one was recruited who had a systemic blood pressure >140/90mmHg). 4. Severe vs non-severe HVD: Not stated / Unclear 5. Symptomatic vs asymptomatic : Symptomatic
Extra comments	All had been advised surgery or balloon valvotomy and were awaiting intervention or had declined. The exclusion criteria are not very well defined (not prespecified, just noted in response to the patients they had)
Indirectness of population	Serious indirectness: Includes some patients under 18 years of age but the proportion is unclear.
Interventions	(n=13) Intervention 1: Beta blockers - Metoprolol. 25mg BD increasing up to 50mg BD dependent on patient preference. Duration 6 months. Concurrent medication/care: Not stated - it does state that digoxin was not given. Indirectness: No indirectness (n=13) Intervention 2: Placebo. Placebo. Duration 6 months. Concurrent medication/care: As previously - not stated. However, no patients were given digoxin. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METOPROLOL versus PLACEBO Protocol outcome 1: Exercise tolerance at 12 months - Actual outcome for Primary mitral stenosis: Pulmonary capillary wedge pressure after exercise at 6 months; Group 1: mean 35.7 mmHg (SD 7.3); n=13, Group 2: mean 50.5 mmHg (SD 10.4); n=13; Comments: Baseline values: metoprolol - 40.3±10.8; placebo 34.1±10.6 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Surrogate outcome measure; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Hospitalisation due to heart failure at 12 months; Cardiac mortality at 12 months; Quality of life at 12 months; Need for valve intervention at 6 months; Need for valve intervention at 12 months; Withdrawal due to adverse events at 6 months; Withdrawal due to adverse events at 12 months; All-cause mortality at 12 months; Cardiac mortality at 6 months

Study	Patel 1995[123]
Study type	RCT (Patient randomised; Crossover: 1 week)
Number of studies (number of participants)	1 (n=19)
Countries and setting	Conducted in South Africa; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 4 weeks
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Not stated.
Stratum	Primary mitral stenosis:
Subgroup analysis within study	Not applicable
Inclusion criteria	People with symptomatic isolated tight pliable mitral stenosis admitted for percutaneous mitral valvotomy with NYHA class II-III heart failure, four of whom had a previous surgical closed mitral valvotomy.
Exclusion criteria	Presence of atrial fibrillation, right heart failure, obstructive or embolic lung disease, and any contraindication to beta-blocker therapy.
Recruitment/selection of patients	From their patients admitted to hospital
Age, gender and ethnicity	Age - Mean (range): 28 (17-51). Gender (M:F): 3:16. Ethnicity: Not stated
Further population details	1. Age: <75 years (Range = 17-51). 2. Heart rate: Normal (82+/-11). 3. Presence vs. absence of uncontrolled systemic hypertension: Not stated / Unclear 4. Severe vs non-severe HVD: Not stated / Unclear 5. Symptomatic vs asymptomatic: Symptomatic
Extra comments	All medication except maintenance diuretic therapy was discontinued for at least 7 days prior to enrolment.
Indirectness of population	Serious indirectness: May include some patients under 18 years of age but the proportion is unclear. Also unclear severity of heart valve disease.
Interventions	(n=19) Intervention 1: Beta blockers - Acebutolol. Acebutolol 400mg daily or Atenolol 100mg daily. Duration 1 week. Concurrent medication/care: Background diuretic therapy, but all others were stopped at least 7 days before the study protocol started. Indirectness: Serious indirectness; Indirectness comment: See atenolol - people in the intervention were given either acebutalol or atenolol with no way to tell which patient received which in the reported data. (n=19) Intervention 2: Placebo. Placebo. Duration 1 week. Concurrent medication/care: Background diuretic therapy, but all others were stopped at least 7 days before the study protocol started. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACEBUTOLOL/ATENOLOL versus PLACEBO Protocol outcome 1: Exercise tolerance at 12 months - Actual outcome for Primary mitral stenosis: Treadmill exercise time to exhaustion (using Weber's protocol) at 4 weeks; Group 1: mean 8.8 min (SD 1.7); n=19, Group 2: mean 9.4 min (SD 1.8); n=19; Comments: Baseline value = 9.2±1.8 Risk of bias: All domain - High, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Reports baseline only for the parameters they are measuring; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Primary mitral stenosis: Heart rate at peak exercise at 4 weeks; Group 1: mean 63 beats per minute (SD 10); n=19, Group 2: mean 78 beats per minute (SD 9); n=19 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Time period is only 4 weeks rather than 12 months; Baseline details: Reports baseline only for the parameters they are measuring but crossover trial so will be matched; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at 6 months; Hospitalisation due to heart failure at 12 months; Cardiac mortality at 12 months; Quality of life at 12 months; Need for valve intervention at 6 months; Need for valve intervention at 12 months; Withdrawal due to adverse events at 6 months; Withdrawal due to adverse events at 12 months; All-cause mortality at 12 months; Cardiac mortality at 6 months

Study	Seneviratne 1994[147]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=28)
Countries and setting	Conducted in Australia; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Echocardiography and clinical assessment
Stratum	Secondary heart valve disease – mitral regurgitation or tricuspid regurgitation: Mitral regurgitation secondary to dilated heart failure
Subgroup analysis within study	Not applicable
Inclusion criteria	NYHA grade II-III with dilated left ventricles, ejection fraction <40% and a functional mitral regurgitant area of >5cm².
Exclusion criteria	Myocardial infarction within the preceding three months; unstable or severe angina pectoris; valvar (?valvular) heart disease; serum creatinine >0.18mmol/L, a history of alcohol misuse, and ACE inhibitor treatment of either >25mg of captopril or >5mg of enalapril a day.
Age, gender and ethnicity	Age - Mean (range): 71.6 (57-80). Gender (M:F): 27:1. Ethnicity: Not stated
Further population details	1. Age: Mixed (Captopril mean = 72.3+/-5.4, Placebo mean = 71.5+/-7.2 - Fall under 75 for the mean, but confidence intervals cross. Therefore, mixed?). 2. Heart rate: Not stated / Unclear 3. Presence vs. absence of uncontrolled systemic hypertension: Absence of uncontrolled systemic hypertension (arterial pressure reported (rather than systolic/diastolic). Captopril mean = 99+/-13.8, Placebo mean = 93+/-9.8). 4. Severe vs non-severe HVD: Not stated / Unclear (No severity mentioned). 5. Symptomatic vs asymptomatic: Symptomatic (NYHA class II or III).
Extra comments	Severity of regurgitation not stated
Indirectness of population	Serious indirectness: unclear severity of heart valve disease.
Interventions	(n=14) Intervention 1: Angiotensin-converting enzyme (ACE) inhibitors - Captopril. 6.25mg twice daily, increasing to 12.5mg twice daily after 4 weeks, increasing to 25mg twice daily after 8 weeks, increasing to 50mg twice daily at 12 weeks. Duration 6 months. Concurrent medication/care: Randomisation occurred after a 2 week placebo washout period and a test dose of 6.25 mg oral captopril. Digoxin, diuretics and nitrates were continued. Indirectness: No indirectness (n=14) Intervention 2: Placebo. Placebo. Duration 6 months. Concurrent medication/care: Randomisation

	occurred after a 2 week placebo washout period and a test dose of 6.25 mg oral captopril. Digoxin, diuretics and nitrates were continued. Indirectness: No indirectness
Funding	Study funded by industry (Aid of a grant from Bristol-Squibb-Myers who played no part in the analysis and interpretation of the data.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CAPTOPRIL versus PLACEBO

Protocol outcome 1: Quality of life at 6 months
- Actual outcome for Secondary heart valve disease – mitral regurgitation or tricuspid regurgitation: Duke activity index score at 12 weeks; Group 1: mean 29 No units (SD 8.9); n=10, Group 2: mean 22.3 No units (SD 9.8); n=13; Comments: Baseline characteristics:
Captopril Duke activity status index: 21.5 (7.8)
Placebo Duke activity status index: 22.6 (11)
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Only measures physical activity rather than other aspects of quality of life; Group 1 Number missing: 4; Group 2 Number missing: 1

Protocol outcome 2: Cardiac mortality at 6 months
- Actual outcome for Secondary heart valve disease – mitral regurgitation or tricuspid regurgitation: Cardiac mortality at 12 weeks; Group 1: 0/14, Group 2: 1/14; Comments: Acute MI
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Withdrawal due to adverse events at 6 months
- Actual outcome for Secondary heart valve disease – mitral regurgitation or tricuspid regurgitation: Withdrawals due to adverse events at 12 weeks; Group 1: 0/14, Group 2: 0/13
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Cardiac mortality at 12 months; Quality of life at 12 months; Exercise tolerance at 12 months; Need for valve intervention at 6 months; Need for valve intervention at 12 months; Withdrawal due to adverse events at 12 months; All-cause mortality at 12 months; Hospitalisation due to heart failure at 12 months

Study	Shu 2005[150]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=88)
Countries and setting	Conducted in China; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical assessment and echocardiographic evidence
Stratum	Primary mitral stenosis: Significant mitral stenosis with or without accompanying mitral valve regurgitation or aortic lesions (as a result of rheumatic heart disease)
Subgroup analysis within study	Not applicable
Inclusion criteria	1) History of uncorrected rheumatic heart valvular disease or NYHA class III or IV disease necessitating hospitalisation; 2) cardiothoracic ratio of less than 65%; 3) AF with a resting ventricular rate of 70 beats/minute or more for at least 3 months, as depicted by ECG; 4) An echocardiogram showing a significant mitral stenosis or aortic lesions and mitral valve regurgitation
Exclusion criteria	Uncorrected congenital heart disease; sustained ventricular tachycardia; severe liver and kidney dysfunction; chronic obstructive pulmonary disease; bronchial asthma; obstructive or restrictive cardiomyopathy or myocarditis; myocardial infarction; or unstable angina within the past three months. Additionally if they required intensive care or concurrent IV therapy; or were using calcium channel blockers, class I or III antiarrhythmic drugs, MAO-inhibitors or beta2-agonists.
Recruitment/selection of patients	Recruitment from their patients. No obvious consecutive patients.
Age, gender and ethnicity	Age - Mean (SD): Intervention = 40.6±6.8; Control = 43.5±7.4. Gender (M:F): 24:43. Ethnicity: Not stated
Further population details	1. Age: <75 years (Control mean = 43.5+/-7.4, Treatment mean = 40.6+/-6.8). 2. Heart rate: Mixed (Gives ventricular rate (which would indicate mixed between normal and tachycardic). Is this equivalent to heart rate? Control mean = 105+/-19, Treated mean = 110+/-21). 3. Presence vs. absence of uncontrolled systemic hypertension: Absence of uncontrolled systemic hypertension (systolic BP given. Control mean = 121+/-14, Treated mean = 115+/-12). 4. Severe vs non-severe HVD: Not stated / Unclear (Severity not mentioned). 5. Symptomatic vs asymptomatic: Symptomatic (NYHA class III or IV during admission to hospital).
Indirectness of population	No indirectness: Patients have multiple types of valve lesion at the same time. All patients had atrial fibrillation.

Interventions	(n=44) Intervention 1: Beta blockers - Bisoprolol. Initial dose of 1.25mg/day. Recommended maximum dose of 10mg/day. Gradual titration over 3 to 5 days by 2 to 3 weeks. Duration 6 to 12 months. Concurrent medication/care: All patients received basic therapy using one of the following: a diuretic, digoxin (extracted from Digitalis lanata), ACE-inhibitors (or ARBs if ACE-inhibitors were not tolerated) or nitrates. All received warfarin. Indirectness: No indirectness (n=44) Intervention 2: Usual care. All patients received basic therapy using one of the following: a diuretic, digoxin (extracted from Digitalis lanata), ACE-inhibitors (or ARBs if ACE-inhibitors were not tolerated) or nitrates. All received warfarin. Duration 6 to 12 months. Concurrent medication/care: N/A. Indirectness: No indirectness
Funding	Academic or government funding (One of the doctors was supported by a fellowship from the Departments of Cardiology and Ultrasound diagnosis in Southwest Hospital)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BISOPROLOL versus USUAL CARE

Protocol outcome 1: Hospitalisation due to heart failure at 12 months
- Actual outcome: Hospitalisation due to exacerbated heart failure at 12 months; Group 1: 3/33, Group 2: 10/34
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Even though the measures are objective, there is still a large risk of care being different due to the intervention not being blinded; Group 1 Number missing: 11, Reason: Adverse drug reactions in 5. Then they provide overall information - 14 excluded from evaluation at follow up with 7 having insufficient quality ECG/echo data, and 7 having poor telephone-connection difficulties. From the bits reported, the numbers don't add up so there is not full reporting; Group 2 Number missing: 10, Reason: See experimental group.

Protocol outcome 2: Exercise tolerance at 12 months
- Actual outcome: 6-minute walking distance at 6-12 months; Group 1: mean 423 meters (SD 25); n=33, Group 2: mean 290 meters (SD 23); n=34; Comments: Values at hospital discharge:
Treated = 391±32
Control = 309±28
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Blinding details: Even though the measures are objective, there is still a large risk of care being different due to the intervention not being blinded; Group 1 Number missing: 11, Reason: Adverse drug reactions in 5. Then they provide overall information - 14 excluded from evaluation at follow up with 7 having insufficient quality ECG/echo data, and 7 having poor telephone-connection difficulties. From the bits reported, the numbers don't add up so there is not full reporting; Group 2 Number missing: 10, Reason: See experimental group.

Protocol outcome 3: Withdrawal due to adverse events at 12 months
- Actual outcome: Withdrawal due to adverse events at 12 months; Group 1: 5/44, Group 2: 0/44; Comments: They don't report all of the withdrawal

reasons for each patient (the figures don't add up) - a little dubious. Also don't report if any withdrawals due to drug effects in control group. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Even though the measures are objective, there is still a large risk of care being different due to the intervention not being blinded; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at 6 months; Cardiac mortality at 12 months; Quality of life at 12 months; Need for valve intervention at 6 months; Need for valve intervention at 12 months; Withdrawal due to adverse events at 6 months; All-cause mortality at 12 months; Cardiac mortality at 6 months

Appendix E: Forest plots

E.1 Valve disease without heart failure

E.1.1 Primary aortic [including bicuspid] stenosis

E.1.1.1 ACE inhibitors compared to placebo

Figure 3: Need for heart valve intervention at 12 months

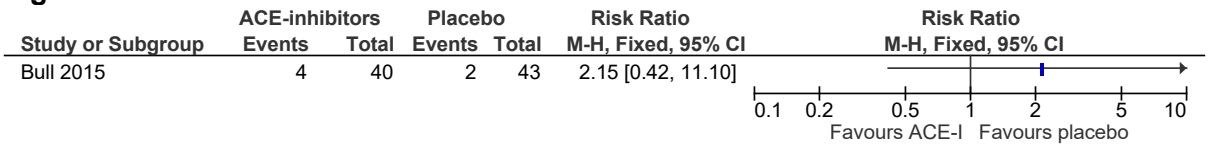
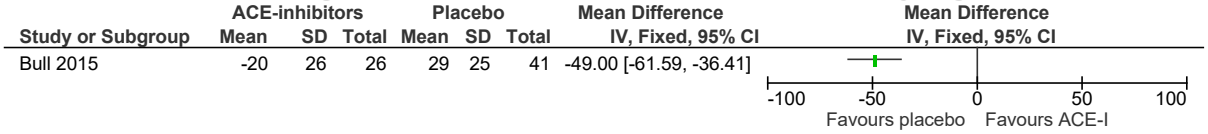
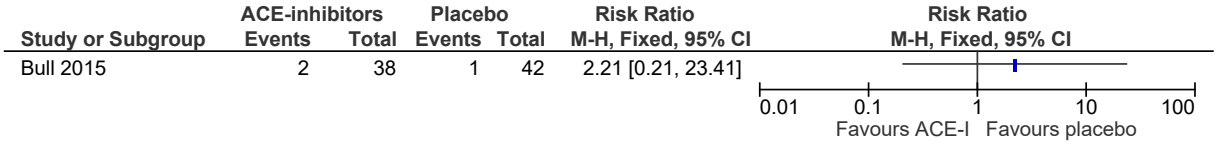


Figure 4: Exercise tolerance (exercise distance measured with treadmill exercise test, meters, change score) at 12 months (better indicated by higher values)



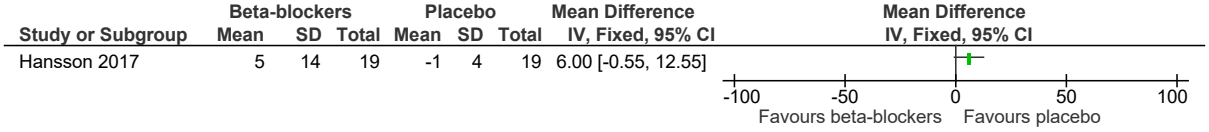
MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (373) by 0.5 and were ±187.0.

Figure 5: Withdrawal due to adverse events at 12 months



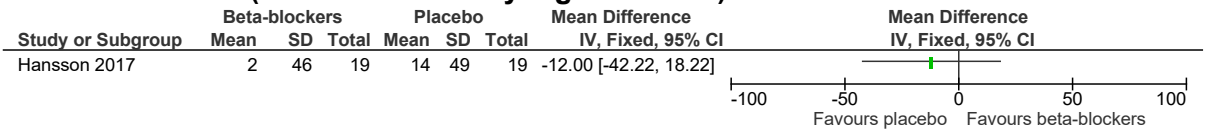
E.1.1.2 Beta blockers compared to placebo

Figure 6: Quality of life (Minnesota living with heart failure questionnaire, scale 0-105, change score, better indicated by lower values) at 5 months



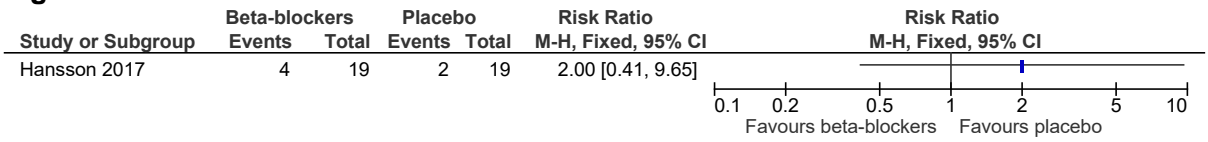
Published MIDs of ±5.0 were used to assess imprecision for MLWHF questionnaire.

Figure 7: Exercise tolerance (6 minute walk test distance, meters, change score) at 5 months (better indicated by higher values)



MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (41) by 0.5 and were ±21.0.

Figure 8: Withdrawal or dose reduction due to adverse events at 5 months



E.1.1.3 Diuretics compared to placebo

Figure 9: All-cause mortality at 19 months

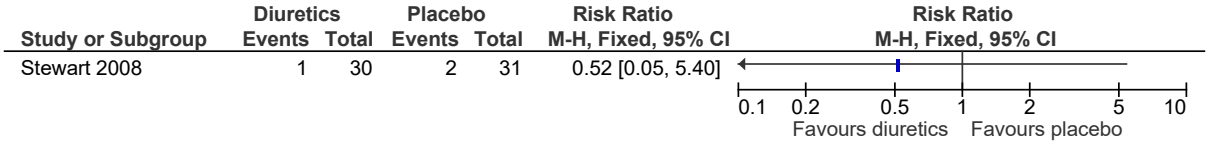


Figure 10: Cardiac mortality at 19 months

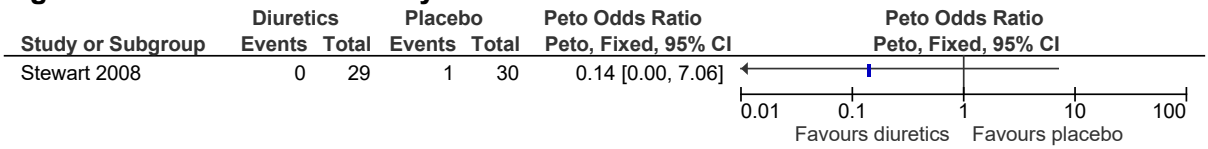
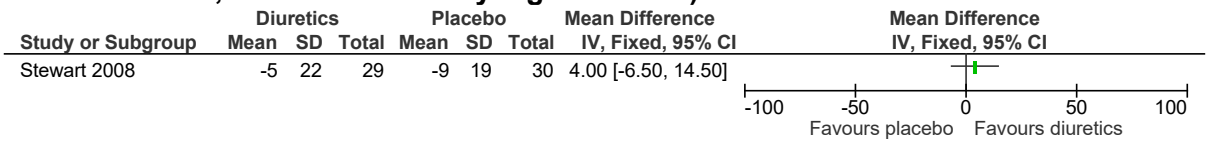
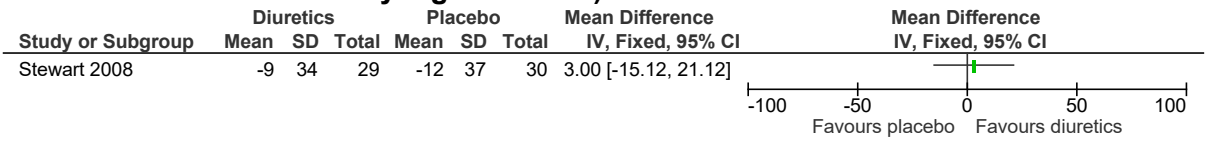


Figure 11: Quality of life (SF-36 physical functioning subscale, scale 0-100, change score, better indicated by higher values) at 12 months



Published MIDs of ±3.0 were used to assess imprecision for SF-36 physical functioning subscale.

Figure 12: Quality of life (SF-36 role physical subscale, scale 0-100, change score, better indicated by higher values) at 12 months



Published MIDs of ±3.0 were used to assess imprecision for SF-36 role physical subscale.

Figure 13: Onset of symptoms or progression of NYHA class at 19 months

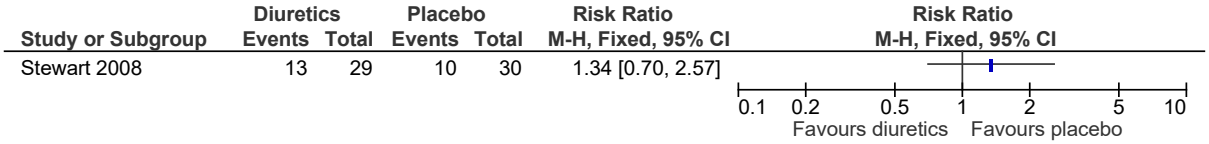
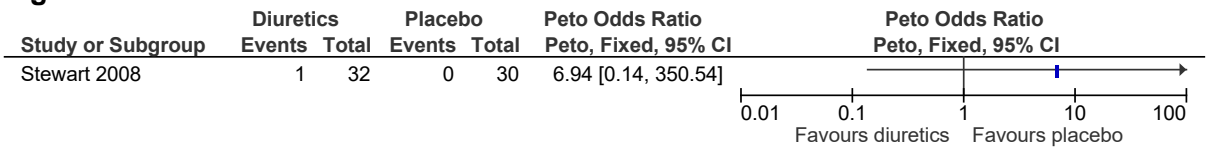


Figure 14: Withdrawal due to adverse events at 19 months



E.1.1.4 Statins compared to placebo

Figure 15: All-cause mortality at 4.3 years

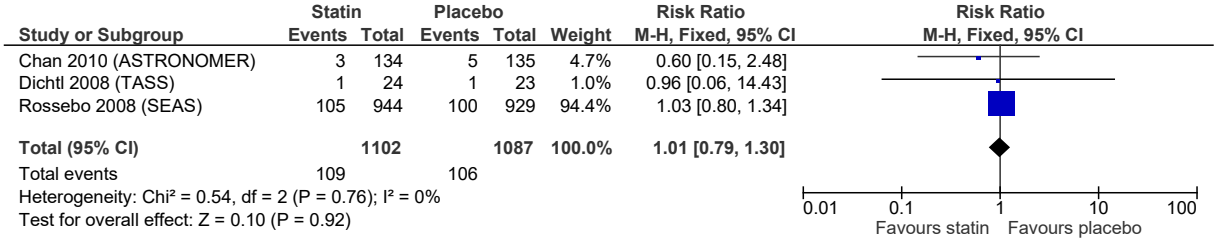


Figure 16: All-cause mortality at 4.4 years (time-to-event data)

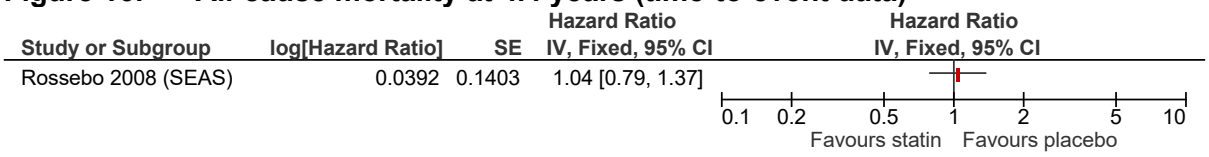


Figure 17: Cardiac mortality at 3.7 years

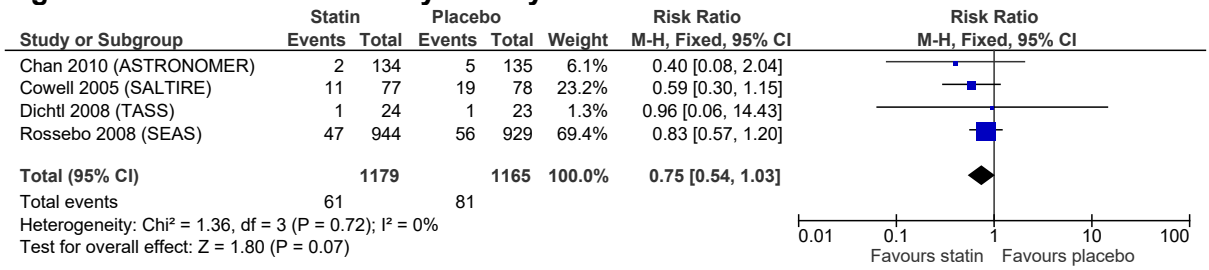


Figure 18: Cardiac mortality at 4.4 years (time-to-event data)

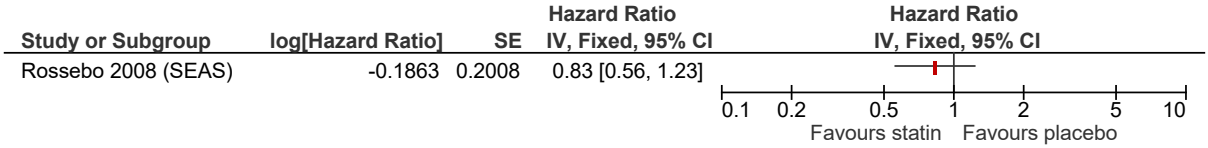


Figure 19: Onset of symptoms or progression of NYHA class at 3.2 years

Figure 20: Onset of symptoms of progression of NYHA class at 4.4 years (time-to-event data)

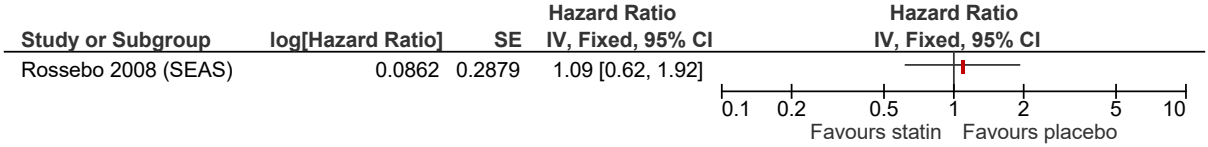


Figure 21: Need for heart valve intervention at 3.7 years

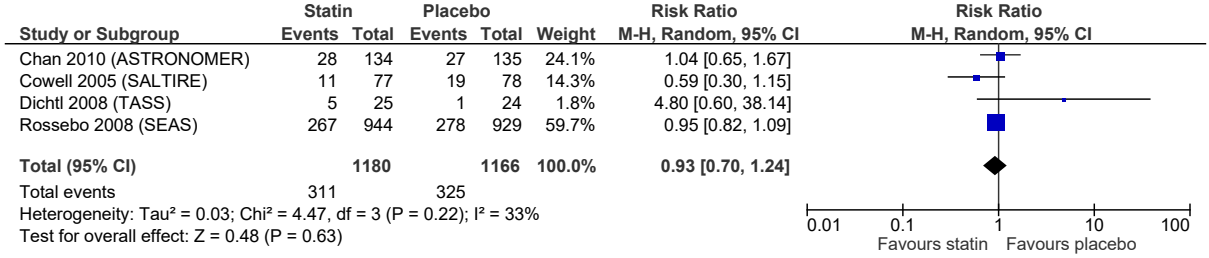


Figure 22: Need for heart valve intervention at 4.4 years (time-to-event data)

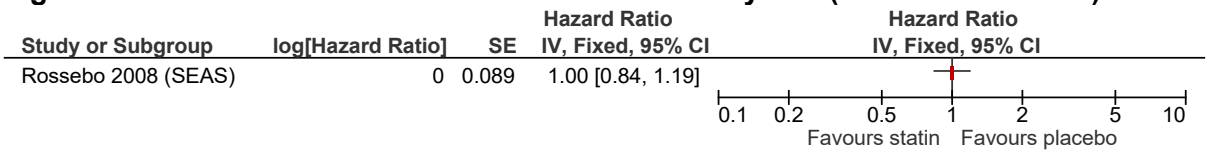


Figure 23: Withdrawal due to adverse events at 6 months

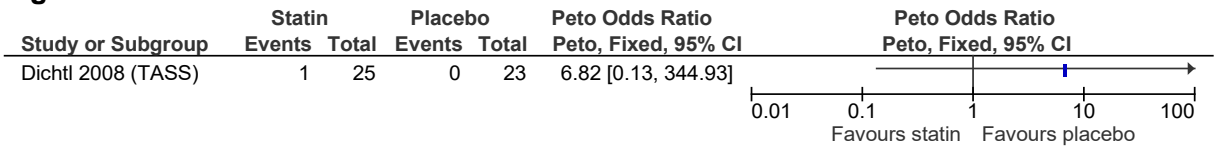
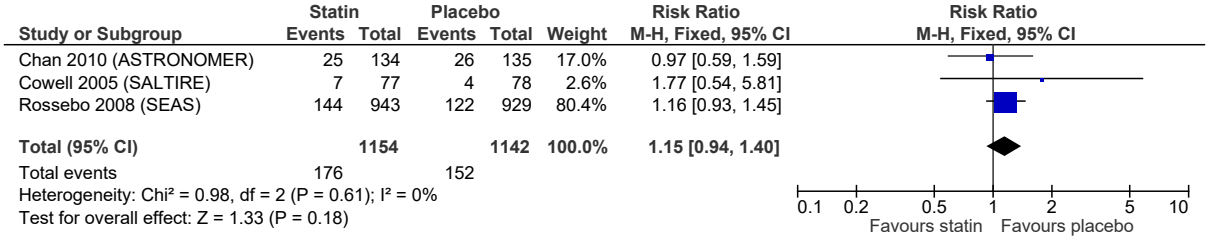


Figure 24: Withdrawal due to adverse events at 3.3 years



E.1.2 Primary aortic regurgitation

E.1.2.1 ACE inhibitors compared to placebo/no treatment

Figure 25: All-cause mortality at 7 years

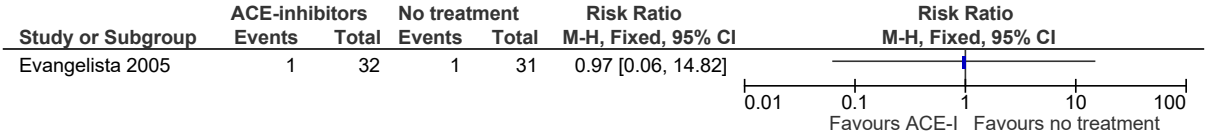


Figure 26: Cardiac mortality at 7 years

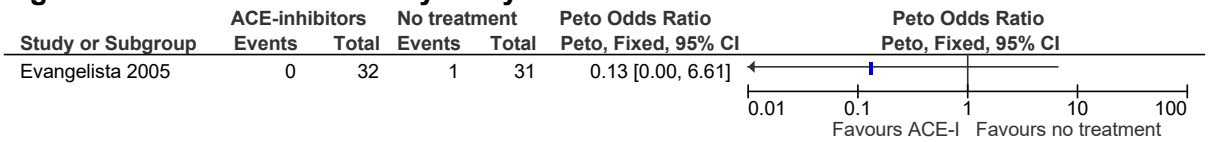


Figure 27: Onset of symptoms or progression of NYHA class at 0.5-7 years

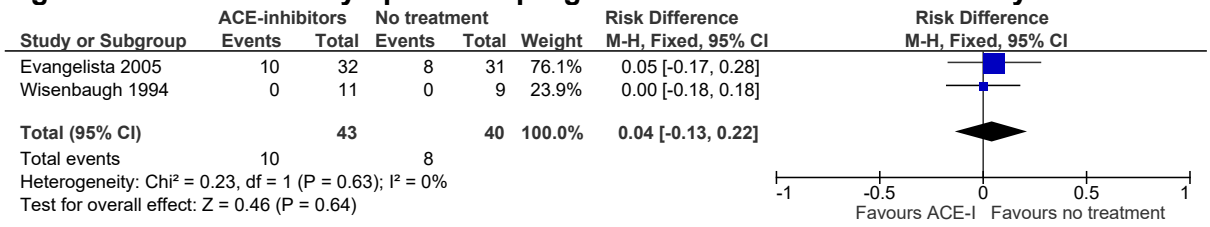


Figure 28: Evidence of HVD progression on imaging (worsening of disease severity) at 7 years

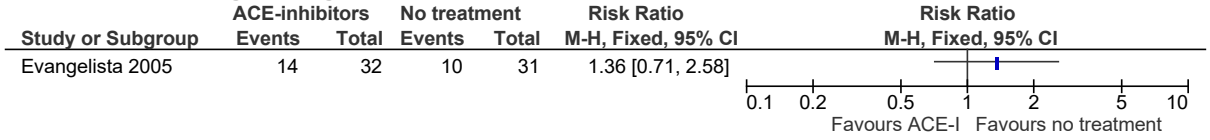


Figure 29: Need for heart valve intervention at 7 years

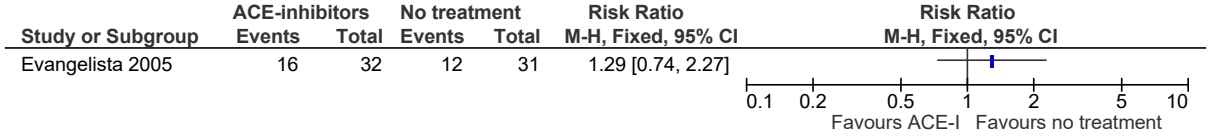
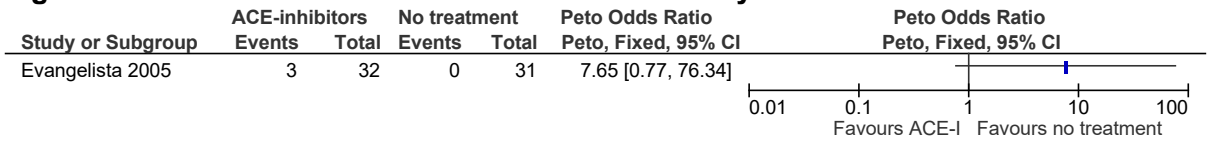


Figure 30: Withdrawal due to adverse events at 7 years



E.1.2.2 ACE inhibitors compared to calcium channel blockers

Figure 31: All-cause mortality at 7 years

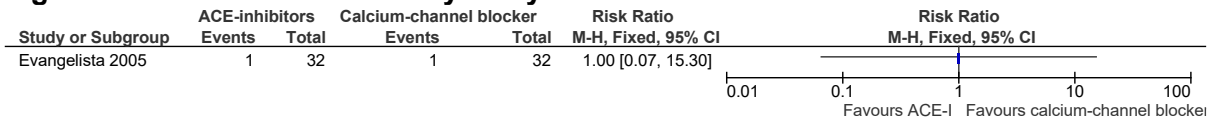


Figure 32: Cardiac mortality at 7 years

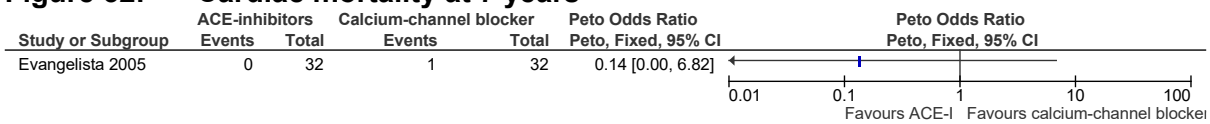


Figure 33: Onset of symptoms or progression of NYHA class at 4.8 years

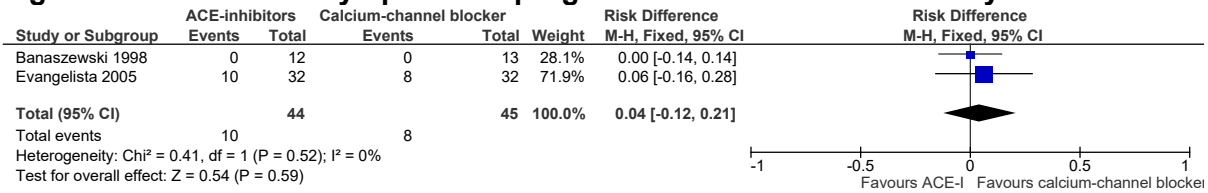


Figure 34: Evidence of HVD progression on imaging (worsening of disease severity) at 4.8 years

Figure 35: Need for heart valve intervention at 7 years

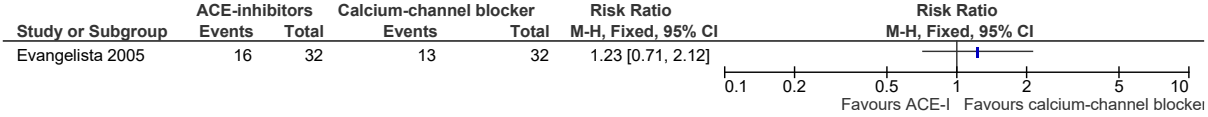
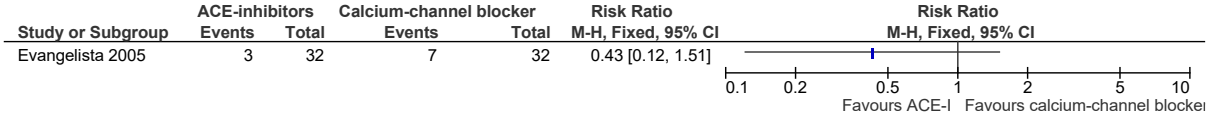
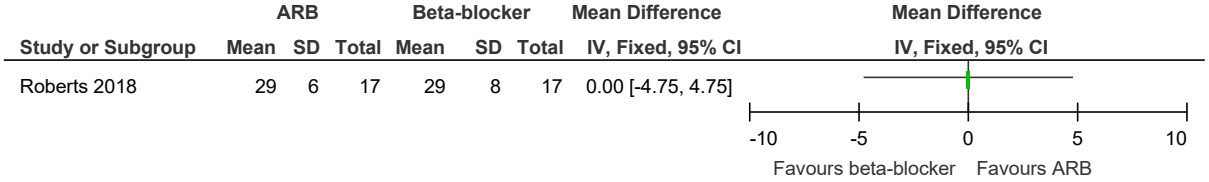


Figure 36: Withdrawal due to adverse events at 7 years



E.1.2.3 ARBs compared to beta blockers

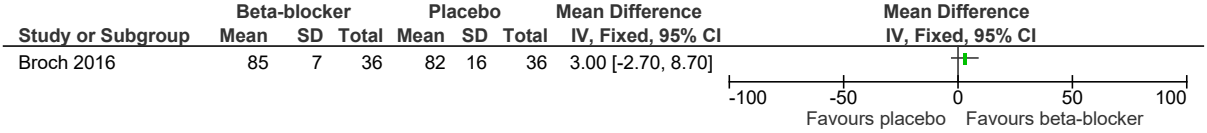
Figure 37: Exercise tolerance (exercise work rate using an ergometer, Watts, final value) at 3 weeks (better indicated by higher values)



MIDs used to assess imprecision were calculated by multiplying the median control group final value SD across studies (8.0) by 0.5 and were ±4.0.

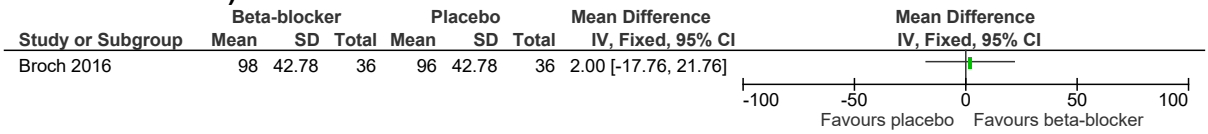
E.1.2.4 Beta blockers compared to placebo

Figure 38: Quality of life (EuroQol visual analogue scale, scale 0-100, final value, better indicated by higher values) at 6 months



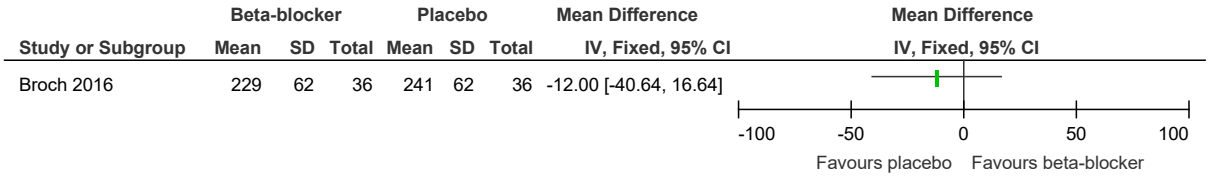
MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (10.0) by 0.5 and were ±5.0.

Figure 39: Quality of life (KCCQ, scale 0-100, final value, better indicated by higher values) at 6 months



MIDs used to assess imprecision were calculated by multiplying the median control group final value SD across studies (42.78) by 0.5 and were ±21.39.

Figure 40: Exercise tolerance (peak work, watts, final value) at 6 months (better indicated by higher values)



MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (63.0) by 0.5 and were ±31.5.

E.1.2.5 Calcium channel blockers compared to placebo/no treatment

Figure 41: All-cause mortality at 7 years

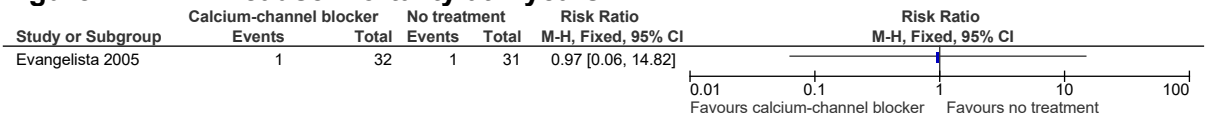


Figure 42: Cardiac mortality at 7 years

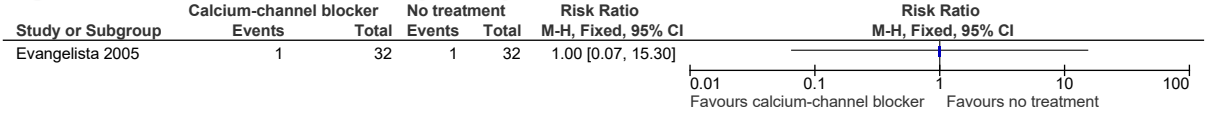


Figure 43: Onset of symptoms or progression of NYHA class at 7 years

Study or Subgroup	Calcium-channel blocker Events	Total	No treatment Events	Total	Risk Ratio M-H, Fixed, 95% CI
Evangelista 2005	8	32	8	31	0.97 [0.42, 2.26]

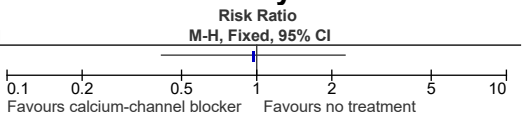


Figure 44: Evidence of HVD progression on imaging (worsening of disease severity) at 7 years

Study or Subgroup	Calcium-channel blocker Events	Total	No treatment Events	Total	Risk Ratio M-H, Fixed, 95% CI
Evangelista 2005	10	32	10	31	0.97 [0.47, 2.00]

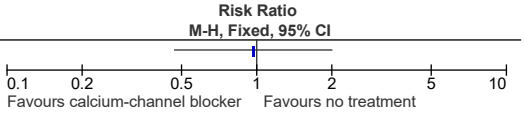


Figure 45: Need for heart valve intervention at 1-7 years

Study or Subgroup	Calcium-channel blocker Events	Total	No treatment Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Evangelista 2005	13	32	12	31	46.7%	0.02 [-0.22, 0.26]
Scognamiglio 1990	0	36	0	36	53.3%	0.00 [-0.05, 0.05]
Total (95% CI)		**68**		**67**	**100.0%**	**0.01 [-0.11, 0.13]**
Total events	13		12			

Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.88)

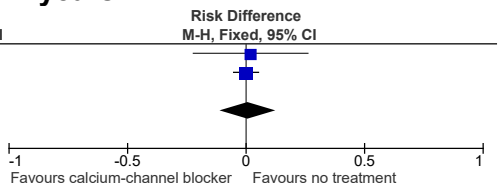
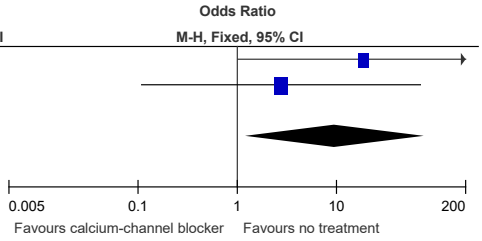


Figure 46: Withdrawal due to adverse events at 1-7 years

Study or Subgroup	Favours calcium-channel blocker Events	Total	No treatment Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Evangelista 2005	7	32	0	31	43.6%	18.53 [1.01, 340.12]
Scognamiglio 1990	1	38	0	34	56.4%	2.76 [0.11, 70.04]
Total (95% CI)		**70**		**65**	**100.0%**	**9.64 [1.22, 76.04]**
Total events	8		0			

Heterogeneity: Chi² = 0.77, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 2.15 (P = 0.03)



E.1.2.6 Digoxin compared to calcium channel blockers

Figure 47: All-cause mortality at 6 years

Study or Subgroup	Digoxin Events	Total	Calcium channel blocker Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Scognamiglio 1994	1	70	0	65	6.88 [0.14, 347.65]

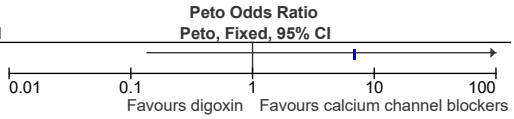


Figure 48: Onset of symptoms or progression of NYHA class at 6 years

Study or Subgroup	Digoxin Events	Total	Calcium channel blocker Events	Total	Risk Ratio M-H, Fixed, 95% CI
Scognamiglio 1994	17	70	6	65	2.63 [1.11, 6.26]

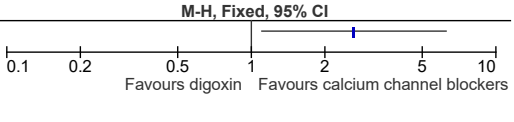


Figure 49: Evidence of HVD progression on imaging (worsening of disease severity) at 6 years

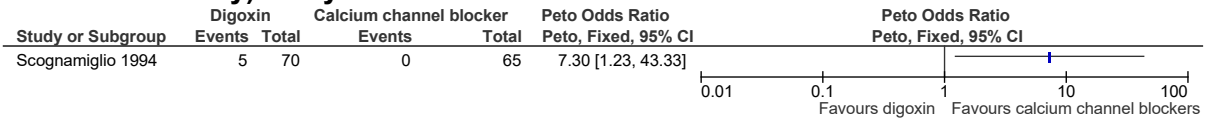


Figure 50: Need for heart valve intervention at 6 years

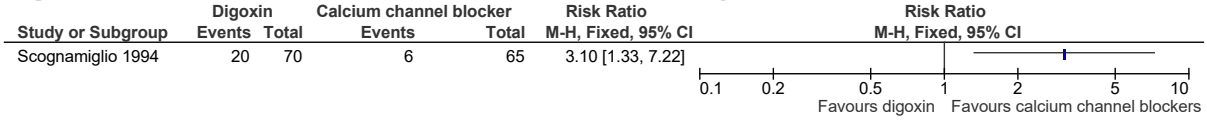
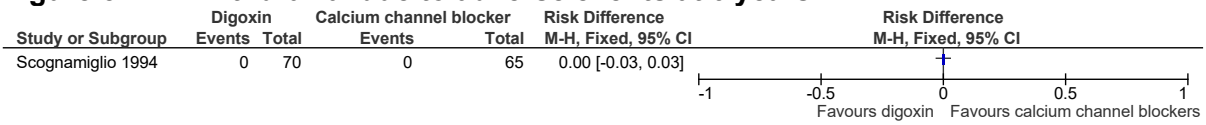


Figure 51: Withdrawal due to adverse events at 6 years



E.1.3 Primary mitral stenosis

No studies identified.

E.1.4 Primary mitral regurgitation

E.1.4.1 ACE inhibitors compared to placebo

Figure 52: All-cause mortality at 6-12 months

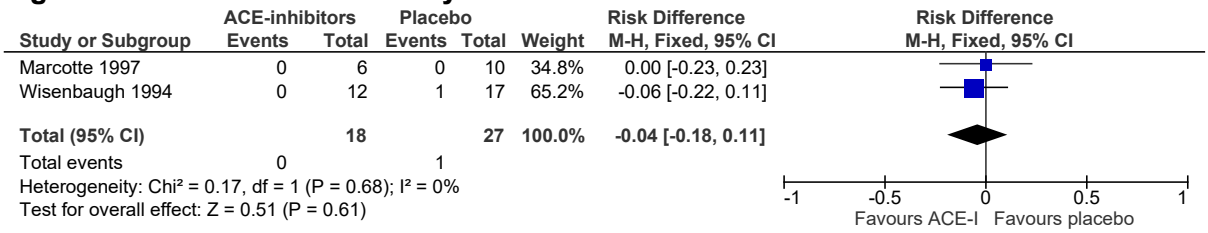


Figure 53: Cardiac mortality at 6-12 months

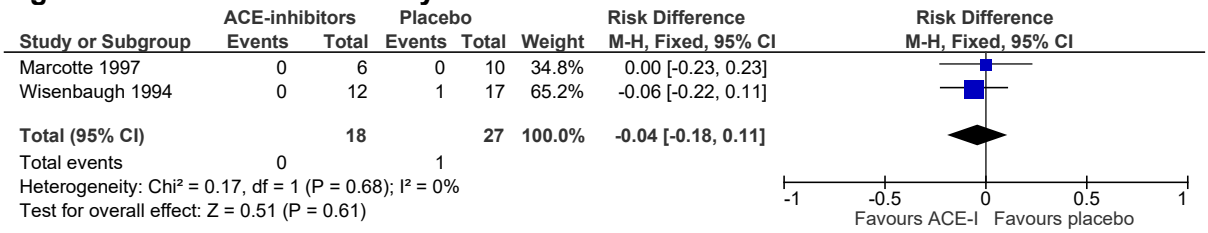
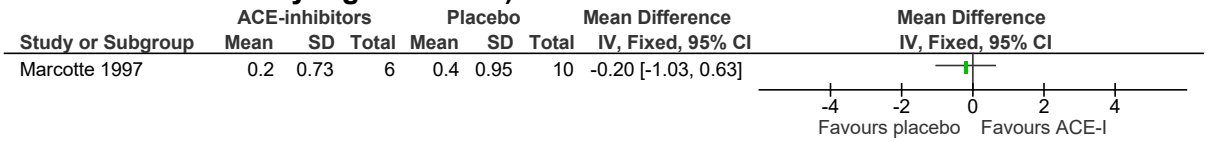
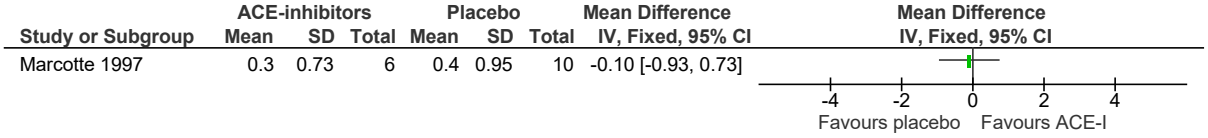


Figure 54: Quality of life (life quality index, scale 1-6, change score, better indicated by higher values) at 6 months



MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (2.24) by 0.5 and were ±1.12.

Figure 55: Quality of life (life quality index, scale 1-6, change score, better indicated by higher values) at 1 year



MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (2.24) by 0.5 and were ±1.12.

Figure 56: Onset of symptoms or progression of NYHA class at 6-12 months

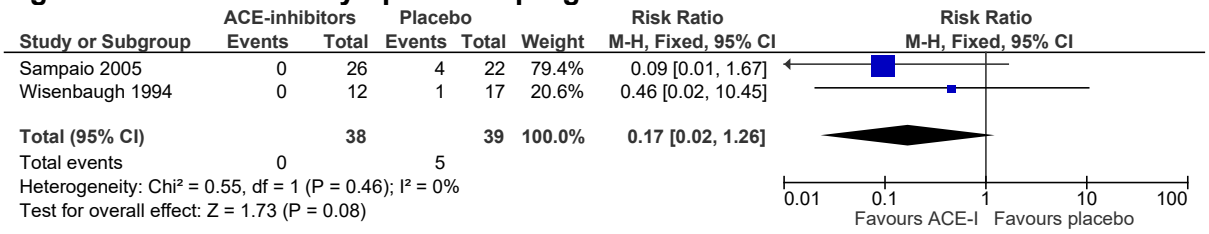


Figure 57: Need for heart valve intervention at 1 year

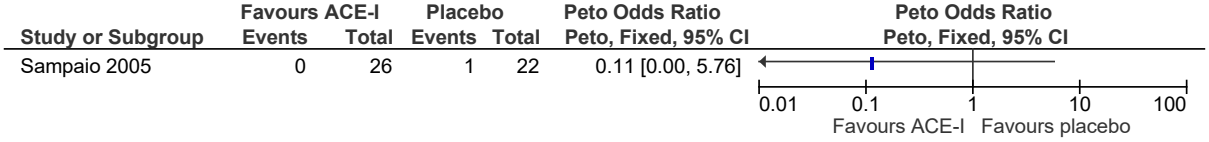
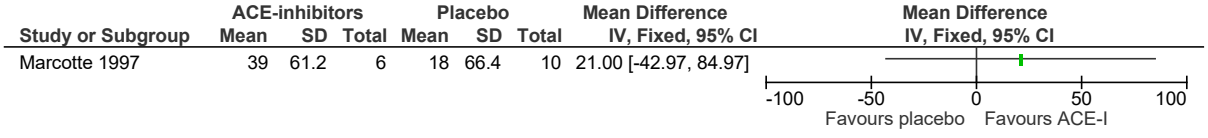
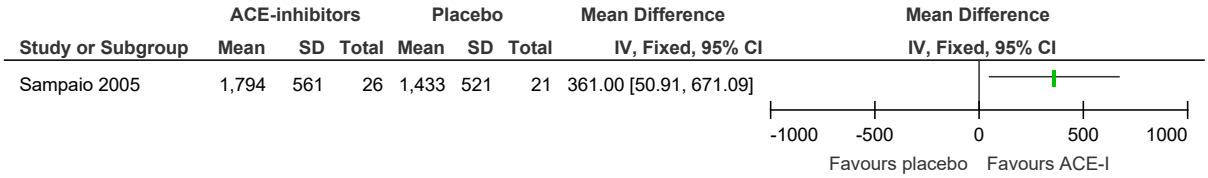


Figure 58: Exercise tolerance (Bruce Protocol treadmill exercise time, seconds, change score) at 1 year (better indicated by higher values)



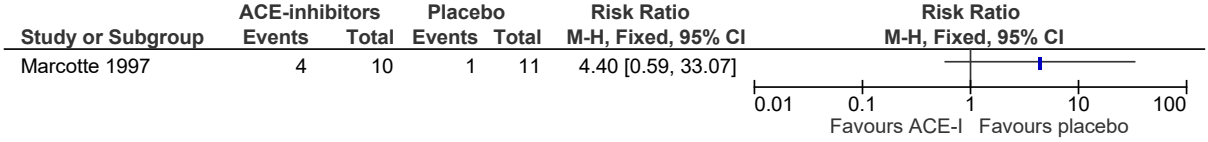
MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (133.85) by 0.5 and were ±66.9.

Figure 59: Exercise tolerance (oxygen uptake at peak exercise, mL/min, final value) at 1 year (better indicated by higher values)



MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (541.0) by 0.5 and were ±270.5.

Figure 60: Withdrawal due to adverse events at 1 year



E.1.4.2 Beta blockers compared to placebo

Figure 61: All-cause mortality at 2 years

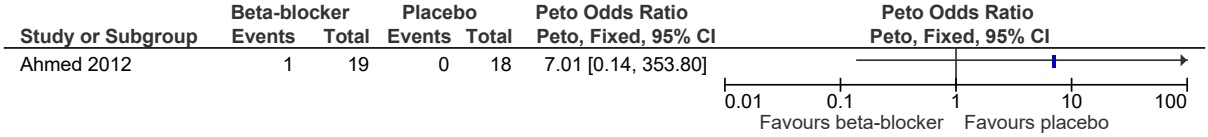


Figure 62: Cardiac mortality at 2 years

Figure 63: Need for heart value intervention at 2 years

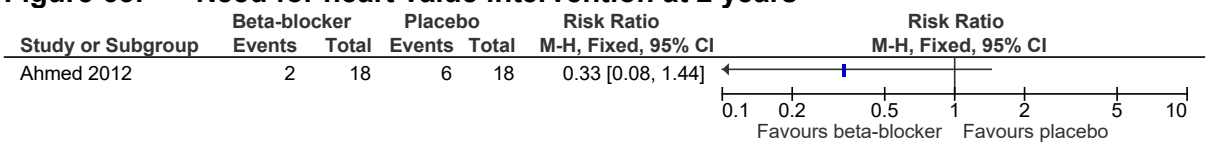
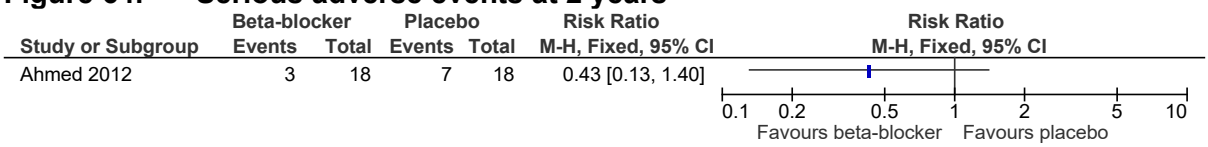


Figure 64: Serious adverse events at 2 years



E.1.5 Primary tricuspid regurgitation

No studies identified.

E.1.6 Secondary heart valve disease – mitral regurgitation or tricuspid regurgitation

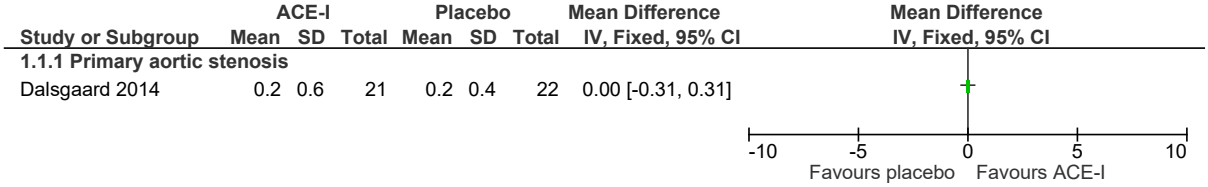
No studies identified.

E.2 Valve disease with heart failure

E.2.1 Primary aortic stenosis

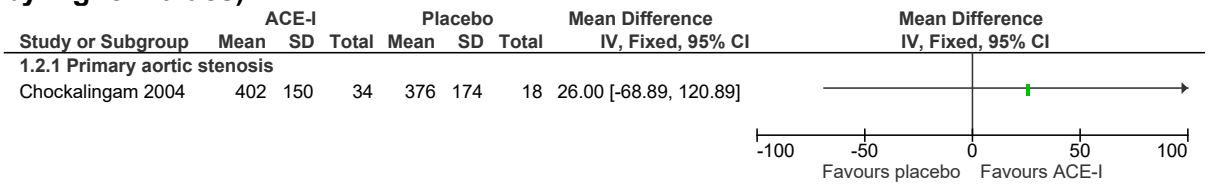
E.2.1.1 ACE-I versus placebo

Figure 65: Exercise tolerance: change in exercise duration (minutes) at 3 days (better indicated by higher values)



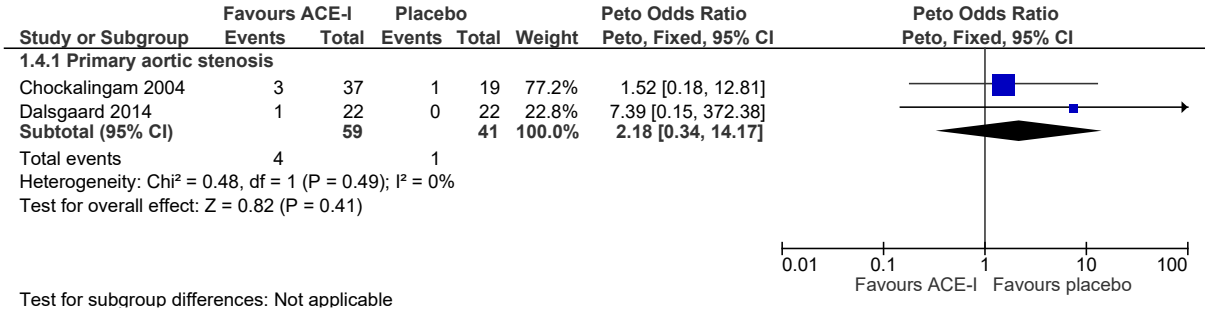
MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (2.0) by 0.5 and were ±1.0.

Figure 66: Exercise tolerance: 6-minute walk distance at 4 weeks (better indicated by higher values)



MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (152.0) by 0.5 and were ±76.0.

Figure 67: Withdrawal due to adverse events at 2-3 months



E.2.1.2 ARB versus placebo

Figure 68: All-cause mortality at 2-12 months

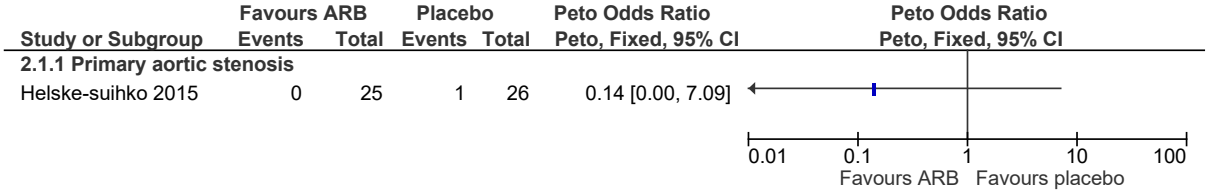


Figure 69: Incidence of acute heart failure at 2-12 months

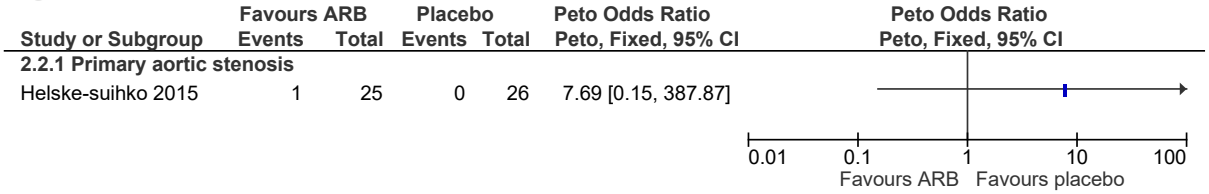
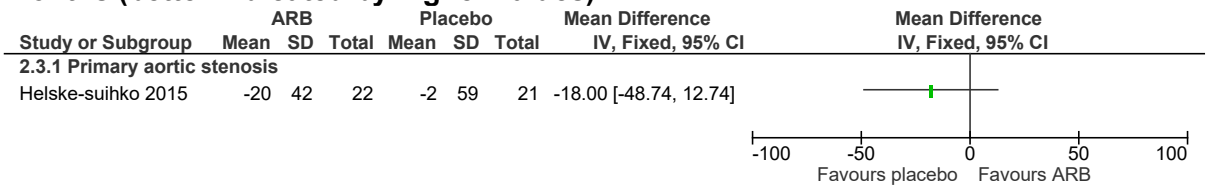
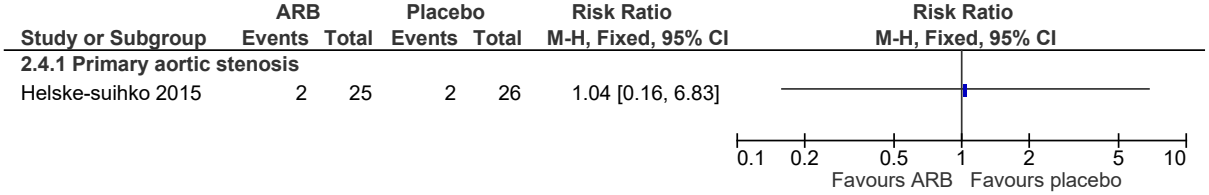


Figure 70: Exercise tolerance: change from baseline 6-minute walking distance at 2-12 months (better indicated by higher values)



MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (148) by 0.5 and were ±74.0.

Figure 71: Withdrawal due to adverse events at 2-12 months



E.2.2 Primary mitral stenosis

E.2.2.1 Beta-blocker versus usual care

Figure 72: Hospitalisation due to heart failure at 12 months

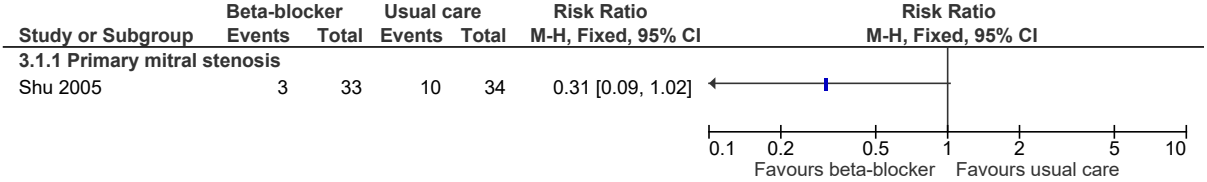
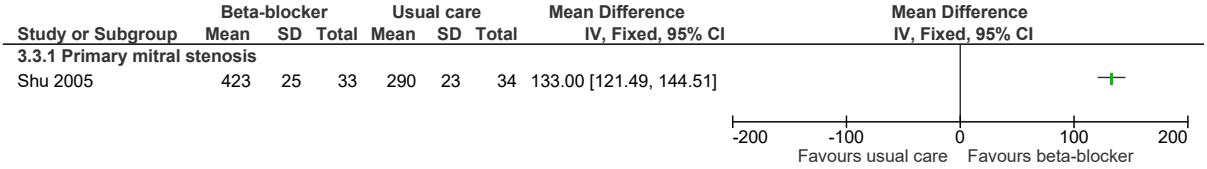
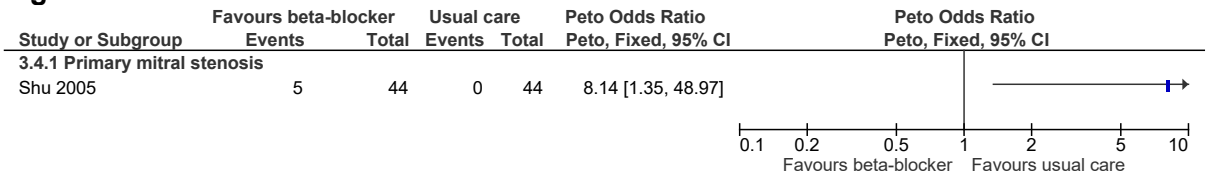


Figure 73: Exercise tolerance: 6-minute walking distance at 6-12 months (better indicated by higher values)



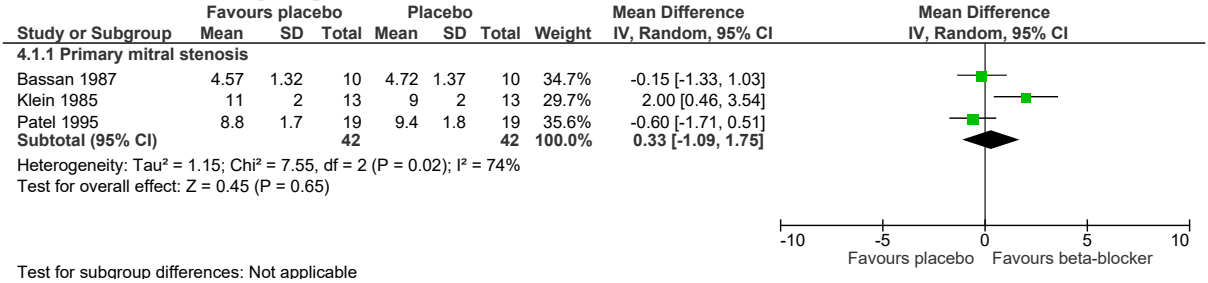
MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (30.0) by 0.5 and were ±15.0.

Figure 74: Withdrawal due to adverse events at 12 months



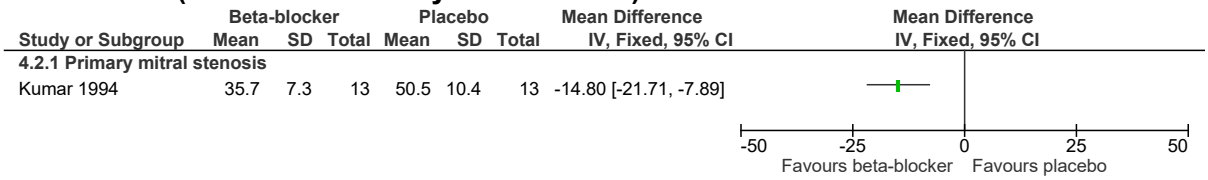
E.2.2.2 Beta-blocker versus placebo

Figure 75: Exercise tolerance: treadmill exercise time to exhaustion at 1-4 weeks (better indicated by higher values)



MIDs used to assess imprecision were calculated by multiplying the median final value control group SD across studies (1.8) by 0.5 and were ±0.9.

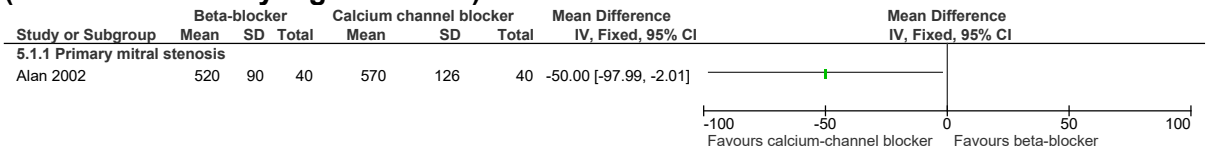
Figure 76: Exercise tolerance: pulmonary capillary wedge pressure after exercise at 6 months (better indicated by lower values)



MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (10.7) by 0.5 and were ±5.35.

E.2.2.3 Beta-blocker versus calcium channel blocker

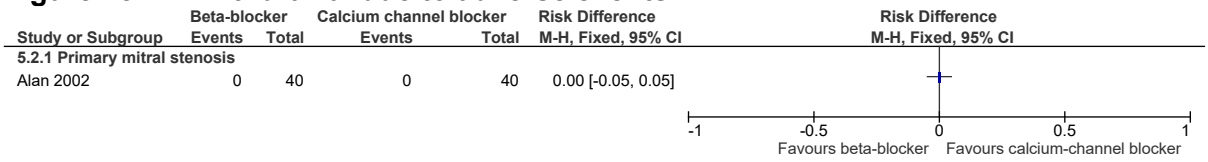
Figure 77: Exercise tolerance: total effort time on treadmill exercise test at 3 months (better indicated by higher values)



MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (120) by 0.5 and were ±60.0.

Note: baseline total effort time not matched – beta-blocker: 452±120; calcium-channel blocker: 534±120

Figure 78: Withdrawal due to adverse events



E.2.3 Secondary heart valve disease (mitral regurgitation and tricuspid regurgitation)

Figure 79: Cardiac mortality at 12 weeks

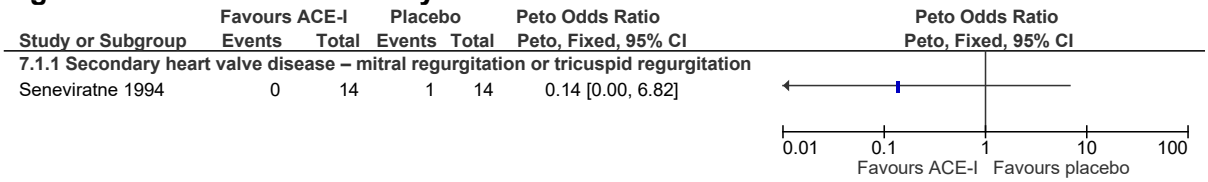
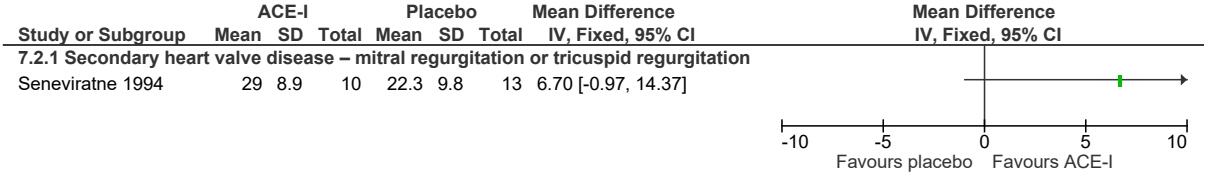
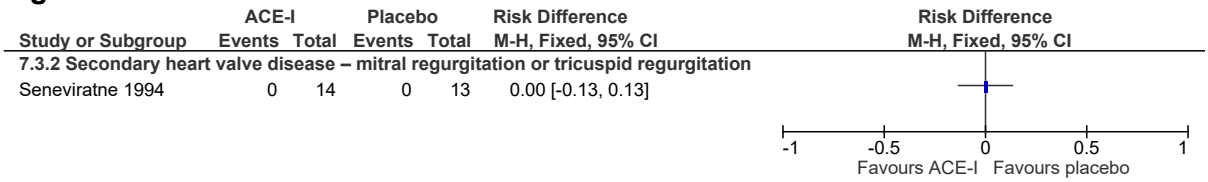


Figure 80: Quality of life: Duke activity index score at 12 weeks – scale ranges from 2.75 to 58.2 points (better indicated by higher values)



MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (9.4) by 0.5 and were ±4.7.

Figure 81: Withdrawal due to adverse events at 3 months



Appendix F: GRADE tables

F.1 Valve disease without heart failure

F.1.1 Primary aortic [including bicuspid] stenosis

Table 32: Clinical evidence profile: ACE inhibitors compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACE-inhibitors	Placebo	Relative (95% CI)	Absolute		
All-cause mortality - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Cardiac mortality - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Health-related quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Health-related quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Onset of symptoms or progression in NYHA class - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Evidence of HVD progression on imaging (worsening of disease severity) - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Need for heart valve intervention (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/40 (10%)	4.7%	RR 2.15 (0.42 to 11.1)	54 more per 1000 (from 27 fewer to 475 more)	⊕OOO VERY LOW	CRITICAL
Exercise tolerance (change score) (follow-up 12 months; measured with: Exercise distance measured with treadmill exercise test; Better indicated by higher values)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	26	41	-	MD 49 lower (61.59 to 36.41 lower)	⊕⊕OO LOW	IMPORTANT
Withdrawal due to adverse events (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/38 (5.3%)	2.4%	RR 2.21 (0.21 to 23.41)	29 more per 1000 (from 19 fewer to 538 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] MIDs used to assess imprecision were ±187.0

Table 33: Clinical evidence profile: beta blockers compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Beta-blockers**	**Placebo**	**Relative (95% CI)**	**Absolute**		
All-cause mortality - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Cardiac mortality - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Health-related quality of life (change score) (follow-up 5 months; measured with: Minnesota living with heart failure questionnaire; range of scores: 0-105; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	19	19	-	MD 6 higher (0.55 lower to 12.55 higher)	⊕OOO VERY LOW	CRITICAL
Health-related quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Onset of symptoms or progression in NYHA class - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Evidence of HVD progression on imaging (worsening of disease severity) - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Need for heart valve intervention - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Exercise tolerance (change score) (follow-up 5 months; measured with: 6 minute walk test distance; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2,4]	none	19	19	-	MD 12 lower (42.22 lower to 18.22 higher)	⊕OOO VERY LOW	IMPORTANT
Withdrawal or dose reduction due to adverse events (follow-up 5 months)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[5]	very serious[2]	none	4/19 (21.1%)	10.5%	RR 2 (0.41 to 9.65)	105 more per 1000 (from 62 fewer to 908 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] MIDs used to assess imprecision were ±5.0
[4] MIDs used to assess imprecision were 21.0
[5] Downgraded by 1 increment as the outcome includes people who had dose reductions or withdrawal due to adverse events

Table 34: Clinical evidence profile: diuretics compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Diuretics**	**Placebo**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 19 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/30 (3.3%)	6.5%	RR 0.52 (0.05 to 5.4)	31 fewer per 1000 (from 62 fewer to 286 more)	⊕OOO VERY LOW	CRITICAL
Cardiac mortality (follow-up 19 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/29 (0%)	3.3%	OR 0.14 (0 to 7.06)	30 fewer per 1000 (from 120 fewer to 60 more)[3]	⊕OOO VERY LOW	CRITICAL
Health-related quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Health-related quality of life (change score) (follow-up 12 months; measured with: SF-36 physical functioning subscale; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,4]	none	29	30	-	MD 4 higher (6.5 lower to 14.5 higher)	⊕OOO VERY LOW	CRITICAL
Health-related quality of life (change score) (follow-up 12 months; measured with: SF-36 role physical subscale; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,4]	none	29	30	-	MD 3 higher (15.12 lower to 21.12 higher)	⊕OOO VERY LOW	CRITICAL
Onset of symptoms or progression of NYHA class (follow-up 19 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13/29 (44.8%)	33.3%	RR 1.34 (0.7 to 2.57)	113 more per 1000 (from 100 fewer to 523 more)	⊕OOO VERY LOW	CRITICAL
Evidence of HVD progression on imaging (worsening of disease severity) - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL

Need for heart valve intervention - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Withdrawal due to adverse events (follow-up 19 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/32 (3.1%)	0%	OR 6.94 (0.14 to 350.54)	30 more per 1000 (from 50 fewer to 120 more)[3]	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect calculated manually using risk difference as zero events in one arm of the study
[4] MIDs used to assess imprecision were ±3.0

Table 35: Clinical evidence profile: statins compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Statins**	**Placebo**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up mean 4.3 years)												
3	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	109/1102 (9.9%)	4.4%	RR 1.01 (0.79 to 1.3)	0 more per 1000 (from 9 fewer to 13 more)	⊕OOO VERY LOW	CRITICAL
All-cause mortality (time to event) (follow-up 4.4 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	105/944 (11.1%)	100/929 (10.8%)	HR 1.04 (0.79 to 1.37)	4 more per 1000 (from 22 fewer to 37 more)	⊕OOO VERY LOW	CRITICAL
Cardiac mortality (follow-up mean 3.7 years)												
4	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	61/1179 (5.2%)	5.2%	RR 0.75 (0.54 to 1.03)	13 fewer per 1000 (from 24 fewer to 2 more)	⊕⊕OO LOW	CRITICAL
Cardiac mortality (time to event) (follow-up 4.4 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	47/944 (5%)	56/929 (6%)	HR 0.83 (0.56 to 1.23)	10 fewer per 1000 (from 26 fewer to 13 more)	⊕OOO VERY LOW	CRITICAL
Health-related quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Health-related quality of life - not reported												

0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Onset of symptoms or progression of NYHA class (follow-up mean 3.2 years)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3]	none	28/1021 (2.7%)	4.4%	RR 0.99 (0.59 to 1.66)	0 fewer per 1000 (from 18 fewer to 29 more)	⊕OOO VERY LOW	CRITICAL
Onset of symptoms or progression of NYHA class (time to event) (follow-up 4.4 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	25/944 (2.6%)	23/929 (2.5%)	HR 1.09 (0.62 to 1.92)	2 more per 1000 (from 9 fewer to 22 more)	⊕OOO VERY LOW	CRITICAL
Evidence of HVD progression on imaging (worsening of disease severity) - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Need for heart valve intervention at 3.7 years (follow-up mean 3.7 years)												
4	randomised trials	no serious risk of bias	serious[4]	serious[2]	serious[3]	none	311/1180 (26.4%)	22.2%	RR 0.93 (0.7 to 1.24)	16 fewer per 1000 (from 67 fewer to 53 more)	⊕OOO VERY LOW	CRITICAL
Need for heart valve intervention (time to event) (follow-up 4.4 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	267/944 (28.3%)	278/929 (29.9%)	HR 1 (0.84 to 1.19)	0 fewer per 1000 (from 41 fewer to 46 more)	⊕⊕OO LOW	CRITICAL
Withdrawal due to adverse events (follow-up 6 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/25 (4%)	0%	OR 6.82 (0.13 to 344.93)	40 more per 1000 (from 70 fewer to 150 more)[5]	⊕OOO VERY LOW	IMPORTANT
Withdrawal due to adverse events (follow-up mean 3.3 years)												
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	176/1154 (15.3%)	13.1%	RR 1.15 (0.94 to 1.4)	20 more per 1000 (from 8 fewer to 52 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment as one study included a statin and ezetimibe in the intervention group
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Downgraded by 1 as the point estimate varies widely across studies, with subgroup analysis not being possible due to the difference being seen in one study
[5] Absolute effect calculated manually using risk difference as zero events in one arm of the study

F.1.2 Primary aortic regurgitation

Table 36: Clinical evidence profile: ACE inhibitors compared to placebo/no treatment

Quality assessment						No of patients	Effect		Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ACE-inhibitors**	**Placebo/no treatment**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 7 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/32 (3.1%)	3.2%	RR 0.97 (0.06 to 14.82)	1 fewer per 1000 (from 30 fewer to 442 more)	⊕OOO VERY LOW	CRITICAL
Cardiac mortality (follow-up 7 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/32 (0%)	3.2%	OR 0.13 (0 to 6.61)	30 fewer per 1000 (from 120 fewer to 50 more)[3]	⊕OOO VERY LOW	CRITICAL
Health-related quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Health-related quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Onset of symptoms or progression of NYHA class (follow-up 7 years)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	10/43 (23.3%)	8/40 (20%)	RD 0 (-0.13 to 0.22)	40 more per 1000 (from 130 fewer to 220 more)[5]	⊕OOO VERY LOW	CRITICAL
Evidence of HVD progression on imaging (worsening of disease severity) (follow-up 7 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	14/32 (43.8%)	32.3%	RR 1.36 (0.71 to 2.58)	116 more per 1000 (from 94 fewer to 510 more)	⊕OOO VERY LOW	CRITICAL
Need for heart valve intervention (follow-up 7 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16/32 (50%)	38.7%	RR 1.29 (0.74 to 2.27)	112 more per 1000 (from 101 fewer to 491 more)	⊕OOO VERY LOW	CRITICAL
Withdrawal due to adverse events (follow-up 7 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/32 (9.4%)	0%	OR 7.65 (0.77 to 76.34)	90 more per 1000 (from 20 fewer to 210 more)[3]	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect calculated manually using risk difference as zero events in one arm of the study
[4] Imprecision was assessed based on OIS value as there were zero events in both arms of one of the studies. Downgraded by 2 increments as the OIS was <80%.
[5] Absolute effect calculated manually using risk difference as zero events in both arms of a study

Table 37: Clinical evidence profile: ACE inhibitors compared to calcium channel blockers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACE-inhibitors	Calcium channel blockers	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 7 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/32 (3.1%)	1/32 (3.1%)	RR 1 (0.07 to 15.3)	0 fewer per 1000 (from 29 fewer to 447 more)	⊕OOO VERY LOW	CRITICAL
Cardiac mortality (follow-up 7 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/32 (0%)	1/32 (3.1%)	OR 0.14 (0 to 6.82)	30 fewer per 1000 (from 110 fewer to 50 more)[3]	⊕OOO VERY LOW	CRITICAL
Health-related quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Health-related quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Onset of symptoms or progression of NYHA class (follow-up mean 4.8 years)												
2	randomised trials	very serious[1]	serious	no serious indirectness	very serious[4]	none	10/44 (22.7%)	12.5%	-RD 0.04 (-0.12 to 0.21)	40 more per 1000 (from 120 fewer to 210 more)[5]	⊕OOO VERY LOW	CRITICAL
Evidence of HVD progression on imaging (worsening of disease severity) (follow-up mean 4.8 years)												
2	randomised trials	very serious[1]	serious[6]	no serious indirectness	very serious[2]	none	14/45 (31.1%)	24%	RR 0.84 (0.14 to 4.94)	20 fewer per 1000 (from 330 fewer to 290 more)[7]	⊕OOO VERY LOW	CRITICAL
Need for heart valve intervention (follow-up 7 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16/32 (50%)	40.6%	RR 1.23 (0.71 to 2.12)	93 more per 1000 (from 118 fewer to 455 more)	⊕OOO VERY LOW	CRITICAL
Withdrawal due to adverse events (follow-up 7 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/32 (9.4%)	21.9%	RR 0.43 (0.12 to 1.51)	125 fewer per 1000 (from 193 fewer to 112 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

[3] Absolute effect calculated manually using risk difference as zero events in one arm of the study
[4] Imprecision was assessed based on OIS value as there were zero events in both arms of one of the studies. Downgraded by 2 increments as the OIS was <80%.
[5] Absolute effect calculated manually using risk difference as zero events in both arms of one study
[6] Downgraded by 1 increment as the point estimates varied widely between the two studies

[7] Absolute effect calculated manually using risk difference as zero events in one arm of one study

Table 38: Clinical evidence profile: ARBs compared to beta blockers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARB	Beta-blocker	Relative (95% CI)	Absolute		
All-cause mortality - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Cardiac mortality - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Health-related quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Health-related quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Onset of symptoms or progression in NYHA class - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Evidence of HVD progression on imaging (worsening of disease severity) - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Need for heart valve intervention - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Exercise tolerance (final value) (follow-up 3 weeks; measured with: exercise work rate using an ergometer; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3,4]	none	17	17	-	MD 0 higher (4.75 lower to 4.75 higher)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment as follow up less than 1 month
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] MIDs used to assess imprecision were ±4.0

Table 39: Clinical evidence profile: beta blockers compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-blocker	Placebo	Relative (95% CI)	Absolute		
All-cause mortality - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Cardiac mortality - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Onset of symptoms or progression in NYHA class - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Quality of life (final value) (follow-up 6 months; measured with: EuroQol visual analogue scale; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	36	36	-	MD 3 higher (2.7 lower to 8.7 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (final value) (follow-up 6 months; measured with: KCCQ; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,4]	none	36	36	-	MD 2 higher (17.76 lower to 21.76 higher)	⊕⊕OO LOW	CRITICAL
Evidence of HVD progression on imaging (worsening of disease severity) - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Need for heart valve intervention - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Exercise tolerance (follow-up 6 months; measured with: Peak work (bicycle ergometer); Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,5]	none	36	36	-	MD 12 lower (40.64 lower to 16.64 higher)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] MIDs used to assess imprecision were ±5.00
[4] MIDs used to assess imprecision were ±21.39
[5] MIDs used to assess imprecision were ±31.50

Table 40: Clinical evidence profile: calcium channel blockers compared to placebo/no treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Calcium channel blockers	Placebo/no treatment	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 7 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/32 (3.1%)	3.2%	RR 0.97 (0.06 to 14.82)	1 fewer per 1000 (from 30 fewer to 442 more)	⊕OOO VERY LOW	CRITICAL
Cardiac mortality (follow-up 7 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/32 (3.1%)	3.1%	RR 1 (0.07 to 15.3)	0 fewer per 1000 (from 29 fewer to 443 more)	⊕OOO VERY LOW	CRITICAL
Health-related quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Health-related quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Onset of symptoms or progression of NYHA class (follow-up 7 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/32 (25%)	25.8%	RR 0.97 (0.42 to 2.26)	8 fewer per 1000 (from 150 fewer to 325 more)	⊕OOO VERY LOW	CRITICAL
Evidence of HVD progression on imaging (worsening of disease severity) (follow-up 7 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/32 (31.3%)	32.3%	RR 0.97 (0.47 to 2)	10 fewer per 1000 (from 171 fewer to 323 more)	⊕OOO VERY LOW	CRITICAL
Need for heart valve intervention (follow-up 7 years)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	13/68 (19.1%)	12/67 (17.9%)	RD 0.01 (-0.11 to 0.13)	10 more per 1000 (from 110 fewer to 130 more)[4]	⊕OOO VERY LOW	CRITICAL
Withdrawal due to adverse events (follow-up 7 years)												

2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/70 (11.4%)	0%	OR 9.64 (1.22 to 76.04)	120 more per 1000 (from 30 more to 200 more)[5]	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

[3] Imprecision was assessed based on OIS value as there were zero events in both arms of one of the studies. Downgraded by 2 increments as the OIS was <80%.
[4] Absolute effect calculated manually using risk difference as zero events in both arms of a study
[5] Absolute effect calculated manually using risk difference as zero events in one arm of both studies

Table 41: Clinical evidence profile: digoxin compared to calcium channel blockers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Digoxin	Calcium channel blockers	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 6 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/70 (1.4%)	0/65 (0%)	OR 6.88 (0.14 to 347.65)	10 more per 1000 (from 30 fewer to 50 more)[3]	⊕OOO VERY LOW	CRITICAL
Cardiac mortality - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Health-related quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Health-related quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Onset of symptoms of progression of NYHA class (follow-up 6 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17/70 (24.3%)	6/65 (9.2%)	RR 2.63 (1.11 to 6.26)	150 more per 1000 (from 10 more to 486 more)	⊕⊕OO LOW	CRITICAL
Evidence of HVD progression on imaging (worsening of disease severity) (follow-up 6 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5/70 (7.1%)	0/65 (0%)	OR 7.30 (1.23 to 43.33)	70 more per 1000 (from 10 more to 140 more)[3]	⊕⊕OO LOW	CRITICAL
Need for heart valve intervention (follow-up 6 years)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/70 (28.6%)	6/65 (9.2%)	RR 3.10 (1.33 to 7.22)	194 more per 1000 (from 30 more to 574 more)	⊕⊕⊕O MODERATE	CRITICAL
Withdrawal due to adverse events (follow-up 6 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	0/70 (0%)	0/65 (0%)	RD 0 (-0.03 to 0.03)	0 fewer per 1000 (from 30 fewer to 30 more)[5]	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect calculated from risk difference due to zero events in one study arm
[4] Imprecision assessed based on sample size as zero events in both arms of single study. Downgraded by 1 increment as sample size is between 75 and 350
[5] Absolute effect calculated from risk difference due to zero events in both study arms

F.1.3 Primary mitral stenosis

No studies identified.

F.1.4 Primary mitral regurgitation

Table 42: Clinical evidence profile: ACE inhibitors compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ACE-inhibitors**	**Placebo**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 6-12 months)												
2	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/18 (0%)	2.9%	-RD -0.04 (-0.18 to 0.11)	40 fewer per 1000 (from 180 fewer to 110 more)[4]	⊕OOO VERY LOW	CRITICAL
Cardiac mortality (follow-up 6-12 months)												
2	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/18 (0%)	2.9%	RD -0.04 (-0.18 to 0.11)-	40 fewer per 1000 (from 180 fewer to 110 more)[4]	⊕OOO VERY LOW	CRITICAL

Quality of life (change score) (follow-up 6 months; measured with: Life quality index; range of scores: 1-6; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision[5]	none	6	10	-	MD 0.2 lower (1.03 lower to 0.63 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (change score) (follow-up 1 years; measured with: Life quality index; range of scores: 1-6; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision[5]	none	6	10	-	MD 0.1 lower (0.93 lower to 0.73 higher)	⊕OOO VERY LOW	CRITICAL
Onset of symptoms or progression of NYHA class (follow-up 6-12 months)												
2	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[6]	none	0/38 (0%)	12%	RR 0.17 (0.02 to 1.26)	140 fewer per 1000 (from 270 fewer to 10 fewer)[4]	⊕OOO VERY LOW	CRITICAL
Evidence of HVD progression on imaging (worsening of disease severity) - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Need for heart valve intervention (follow-up 1 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[6]	none	0/26 (0%)	4.6%	OR 0.11 (0 to 5.76)	50 fewer per 1000 (from 160 fewer to 70 more)[4]	⊕OOO VERY LOW	CRITICAL
Exercise tolerance (change score) (follow-up 1 years; measured with: Bruce Protocol treadmill exercise time; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[6,7]	none	6	10	-	MD 21 higher (42.97 lower to 84.97 higher)	⊕OOO VERY LOW	IMPORTANT
Exercise tolerance (final value) (follow-up 1 years; measured with: oxygen uptake at peak exercise; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[6,8]	none	26	21	-	MD 361 higher (50.91 to 671.09 higher)	⊕OOO VERY LOW	IMPORTANT
Withdrawal due to adverse events (follow-up 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[6]	none	4/10 (40%)	9.1%	RR 4.4 (0.59 to 33.07)	309 more per 1000 (from 37 fewer to 1000 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[2] Downgraded by 1 increment as some of the participants in one study may have had congenital valvular heart disease
[3] Imprecision was assessed based on OIS value as there were zero events in both arms of one of the studies. Downgraded by 2 increments as the OIS was <80%.
[4] Absolute effect calculated manually using risk difference as zero events in the studies
[5] MIDs used to assess imprecision were ±1.12

[6] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[7] MIDs used to assess imprecision were ±66.90
[8] MIDs used to assess imprecision were ±270.50

Table 43: Clinical evidence profile: beta blockers compared to placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-blocker	Placebo	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 2 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/19 (5.3%)	0%	OR 7.01 (0.14 to 353.8)	50 more per 1000 (from 80 fewer to 190 more)[3]	⊕OOO VERY LOW	CRITICAL
Cardiac mortality (follow-up 2 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/19 (5.3%)	0%	OR 7.01 (0.14 to 353.8)	50 more per 1000 (from 80 fewer to 190 more)[3]	⊕OOO VERY LOW	CRITICAL
Health-related quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Health-related quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Onset of symptoms or progression in NYHA class - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Evidence of HVD progression on imaging (worsening of disease severity) - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Need for heart valve intervention (follow-up 2 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/18 (11.1%)	33.3%	RR 0.33 (0.08 to 1.44)	223 fewer per 1000 (from 306 fewer to 147 more)	⊕OOO VERY LOW	CRITICAL
Serious adverse events (follow-up 2 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	3/18 (16.7%)	38.9%	RR 0.43 (0.13 to 1.4)	222 fewer per 1000 (from 338 fewer to 156 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect calculated manually using risk difference as zero events in the studies
[4] Downgraded by 1 increment as the study does not report withdrawal due to adverse events

F.1.5 Primary tricuspid regurgitation

No studies identified.

F.1.6 Secondary heart valve disease – mitral regurgitation or tricuspid regurgitation

No studies identified.

F.2 Valve disease with heart failure

F.2.1 Primary aortic stenosis

Table 44: Clinical evidence profile: ACE-I versus placebo in aortic stenosis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACE-I	Placebo: primary aortic stenosis	Relative (95% CI)	Absolute		
Exercise tolerance: change in exercise duration (minutes) (follow-up mean 3 days; measured with: semisupine cycle exercise test; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision[3]	none	21	22	-	MD 0 higher (0.31 lower to 0.31 higher)	⊕⊕OO LOW	IMPORTANT

Exercise tolerance: 6-minute walk distance (meters) (follow-up mean 4 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4,5]	none	34	18	-	MD 26 higher (68.89 lower to 120.89 higher)	⊕⊕OO LOW	IMPORTANT
Withdrawal due to adverse events (follow-up 2-3 months)												
2	randomised trials	serious[6]	no serious inconsistency	serious[7]	very serious[8]	none	4/59 (6.8%)	2.6%	OR 2.18 (0.34 to 14.17)	29 more per 1000 (from 17 fewer to 248 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment because the evidence was at high risk of bias
[2] Downgraded by 1 increment because the mean follow-up period was less than 1 month
[3] MIDs used to assess imprecision were ±1.0
[4] Downgraded by 1 increment because the confidence interval crossed one MID
[5] MIDs used to assess imprecision were ±76.0
[6] Downgraded by 1 increment because the majority of evidence was at high risk of bias
[7] Downgraded by 1 increment because the mean follow-up period was less than 3 months
[8] Downgraded by 2 increments because the confidence interval crossed both MIDs

Table 45: Clinical evidence profile: ARB versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ARB**	**Placebo**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 2-12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/25 (0%)	3.9%	OR 0.14 (0 to 7.09)	39 fewer per 1000 (from 140 fewer to 63 more)[3]	⊕OOO VERY LOW	CRITICAL
Acute heart failure (follow-up 2-12 months)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	1/25 (4%)	0%	OR 7.69 (0.15 to 387.87)	40 more per 1000 (from 63 fewer to 143 more)[3]	⊕OOO VERY LOW	CRITICAL
Exercise tolerance: change from baseline 6-minute walking distance (follow-up 2-12 months; Better indicated by higher values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision[6]	none	22	21	-	MD 18 lower (48.74 lower to 12.74 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Withdrawal due to adverse events (follow-up 2-12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/25 (8%)	7.7%	RR 1.04 (0.16 to 6.83)	3 more per 1000 (from 65 fewer to 449 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 2 increments because the evidence was at very high risk of bias
[2]
Downgraded by 2 increments because the confidence interval crossed both MIDs

[3] Absolute effect calculated manually using risk difference as zero events in one arm of the study
[4] Downgraded by 1 increment because of uncertainty as to the aetiology of reported acute heart failure
[5] Downgraded by 1 increment because the evidence was at high risk of bias
[6] MIDs used to assess imprecision were ±74.0

F.2.2 Primary mitral stenosis

Table 46: Clinical evidence profile: Beta-blocker versus usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Beta-blocker**	**Usual care**	**Relative (95% CI)**	**Absolute**		
Hospitalisation due to heart failure (follow-up mean 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/33 (9.1%)	29.4%	RR 0.31 (0.09 to 1.02)	203 fewer per 1000 (from 268 fewer to 6 more)	⊕OOO VERY LOW	CRITICAL
Exercise tolerance: 6-minute walking distance (follow-up 6-12 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	33	34	-	MD 133 higher (121.49 to 144.51 higher)	⊕⊕OO LOW	IMPORTANT

Withdrawal due to adverse events (follow-up mean 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/44 (11.4%)	0%	OR 8.14 (1.35 to 48.97)	114 more per 1000 (from 13 more to 214 more)[4]	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 2 increments because the evidence was at very high risk of bias
[2] Downgraded by 1 increment because the confidence interval crossed one MID
[3] MIDs used to assess imprecision were ±15.0
[4] Absolute effect calculated manually as zero events in one arm of the study

Table 47: Clinical evidence profile: Beta-blocker versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta blocker	Placebo	Relative (95% CI)	Absolute		
Exercise tolerance: treadmill exercise time (minutes) to exhaustion (follow-up 1-4 weeks; Better indicated by higher values)												
3	randomised trials	very serious[1]	serious[2]	very serious[3]	very serious[4,5]	none	42	42	-	MD 0.33 higher (1.09 lower to 1.75higher)	⊕OOO VERY LOW	IMPORTANT
Exercise tolerance: Pulmonary capillary wedge pressure after exercise (follow-up mean 6 months; Better indicated by lower values)												
1	randomised trials	serious[6]	no serious inconsistency	serious[7]	no serious imprecision[8]	none	13	13	-	MD 14.8 lower (21.71 to 7.89 lower)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 2 increments because the majority of the evidence was at very high risk of bias
[2] Downgraded by one increment because the I2 = 74% and heterogeneity was not explained by subgroup analyses.
[3] Downgraded by 1 increment because the mean follow-up period is less than 1 month and the majority of the studies appear to have included people under 18 years of age and do not specify the severity of mitral stenosis
[4] Downgraded by 2 increments because the confidence interval crossed both MIDs
[5] MIDs used to assess imprecision were ±0.9
[6] Downgraded by 1 increment because the evidence was at high risk of bias
[7] Downgraded by 1 increment because the outcome is a surrogate measure and the study appears to have included people under 18 years of age
[8] MIDs used to assess imprecision were ±5.35

Table 48: Clinical evidence profile: Beta-blocker versus calcium channel blocker

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta blocker	Calcium channel blocker	Relative (95% CI)	Absolute		
Exercise tolerance: total effort time on treadmill exercise test (follow-up mean 3 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	40	40	-	MD 50 lower (97.99 to 2.01 lower)[4]	⊕OOO VERY LOW	IMPORTANT
Withdrawal due to adverse events (follow-up mean 3 months)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	0/40 (0%)	0%	-RD 0 (-0.048 to 0.048)	0 fewer per 1000 (from 48 fewer to 48 more)[7]	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 2 increments because the evidence was at very high risk of bias
[2] Downgraded by 1 increment because the confidence interval crossed one MID
[3] MIDs used to assess imprecision were ±60.0
[4] Baseline total effort time not matched
[5] Downgraded by 1 increment because the evidence was at high risk of bias
[6] Downgraded by 1 increments because sample size was >70 and <350 (imprecision was assessed based on sample size as zero events in both arms of the study)
[7] Absolute effect calculated manually as zero events in both arms of the study

F.2.3 Secondary heart valve disease (mitral regurgitation and tricuspid regurgitation)

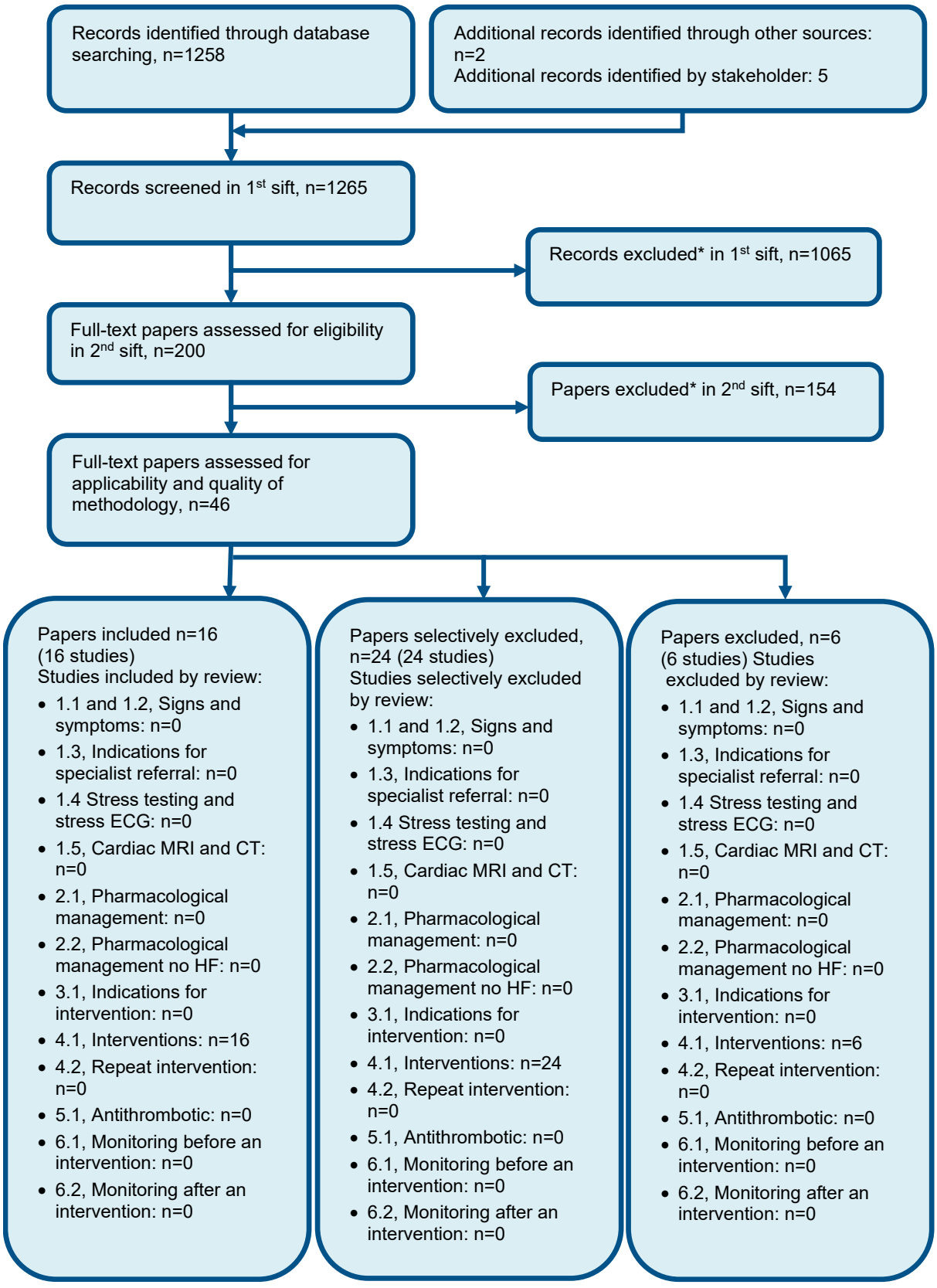
Table 49: Clinical evidence profile: ACE-I versus placebo in secondary heart valve disease

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACE-I	Placebo	Relative (95% CI)	Absolute		
Cardiac mortality (follow-up mean 12 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/14 (0%)	7.1%	OR 0.14 (0 to 6.82)	71 fewer per 1000 (from 248 fewer to 106 more)[4]	⊕⊕OO LOW	CRITICAL

Quality of life: Duke activity index score (follow-up mean 12 weeks; range of scores: 2.75-58.2; Better indicated by higher values)												
1	randomised trials	very serious[5]	no serious inconsistency	serious[6]	serious[7,8]	none	10	13	-	MD 6.7 higher (0.97 lower to 14.37 higher)	⊕OOO VERY LOW	CRITICAL
Withdrawal due to adverse events (follow-up mean 3 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[9]	none	0/14 (0%)	0%	-RD 0 (-0.133 to 0.133)	0 fewer per 1000 (from 133 fewer to 133 more)[10]	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment because the evidence was at high risk of bias
[2] Downgraded by 1 increment as the severity of heart valve disease was unclear
[3] Downgraded by 2 increments as the confidence interval crossed both MIDs
[4] Absolute effect calculated manually using risk difference as zero events in one arm of the study
[5] Downgraded by 2 increments because the evidence was at very high risk of bias
[6] Downgraded by 1 increment because the reported measure only reports physical activity rather than other aspects of quality of life and the severity of heart valve disease is unclear
[7] Downgraded by 1 increment because the confidence interval crossed one MID
[8] MIDs used to assess imprecision were ±4.7
[9] Downgraded by 2 increments because sample size was <70 (imprecision was assessed based on sample size as zero events in both arms of the study)
[10] Absolute effect calculated manually as zero events in both arms of the study

Appendix G: Health economic evidence selection



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

Appendix H: Health economic evidence tables

H.1 Valve disease without heart failure

None.

H.2 Valve disease with heart failure

None.

Appendix I: Excluded studies

I.1 Valve disease without heart failure

I.1.1 Excluded clinical studies

Table 51: Studies excluded from the clinical review

Study	Exclusion reason
Agnihotri 2017[1]	Could not be retrieved
Agrawal 2016[2]	Incorrect interventions. Uses Ivabradine that is not included in our scope. Included patients with mild valve disease
Ahmed 2002[3]	Incorrect study design. Mixed population <75% HVD
Ahuja 1989[5]	Incorrect study design
Alan 2002[6]	Not review population
Andersson 2002[7]	Incorrect study design. Not guideline condition. Not review population. Mixed population <75% HVD
Andersson 2017[8]	Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Inappropriate comparison. References checked and extracted
Andrus 2007[9]	Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Systematic review: literature search not sufficiently rigorous. Systematic review: study designs inappropriate. Not review population. Inappropriate comparison. Incorrect interventions
Antonini-Canterin 2006[10]	Protocol only
Aumont 1990[11]	Not in English language
Bassan 1987[15]	Not review population
Bechler-lisińska 1990[16]	Not in English language
Bergstrom 2004[17]	Not guideline condition. Not review population
Borer 1978[18]	Incorrect study design. Inappropriate comparison. Incorrect interventions
Bornheimer 1982[19]	Incorrect study design. Inappropriate comparison. No control group. Severity not mentioned
Butrous 1986[22]	Incorrect study design. Not review population.
Capucci 1981[23]	Not in English language
Carabello 2010[24]	Correspondence only
Chockalingam 2004P[29]	Not review population
Choi 2015[30]	Systematic review: study designs inappropriate. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Chua 2006[31]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Cicoira 2002[32]	Not guideline condition. Not review population

Clark 1983[33]	Not guideline condition
Cleland 2006[34]	Not guideline condition. Not review population
Cohen 1968[35]	Not guideline condition. Not review population. Inappropriate comparison
Crawford 1989[37]	Incorrect study design. Incorrect interventions
Dalsgaard 2014[38]	Not review population
De Vicchis 2013[39]	Systematic review; quality assessment is inadequate
Demirbag 2003[40]	Not in English language
De vecchis 2013[39]	Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate
Eichhorn 2001[42]	Not guideline condition. Not review population
Eleid 2013[43]	Incorrect study design. Inappropriate comparison. Incorrect interventions
Ennis 2010[44]	No appropriate outcomes reported
Erbel 1978[45]	Not in English language
Erbel 1979[46]	No appropriate outcomes reported
Ergun 2016[47]	Incorrect study design. Letter
Eskandr 2018[48]	Not review population. Medical management in the intra- or post-operative period. Incorrect line of therapy. Incorrect interventions
Ge 2010[50]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Ghadimi 2019[51]	Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Incorrect line of therapy
Ghiringhelli 1990[52]	Incorrect study design. Incorrect interventions
Giles 1988[53]	Not guideline condition. Not review population. Mixed population <75% HVD
Giunta 1993[54]	Not guideline condition. Not review population
Gottlieb 2018[55]	Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Inappropriate comparison. Incorrect line of therapy
Grayburn 2000[56]	Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Inappropriate comparison. Incorrect line of therapy
Greenberg 1994[57]	Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Incorrect line of therapy
Greve 2008[61]	Systematic review: study designs inappropriate. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Gupta 2001[62]	Incorrect interventions
Hachenberg 1997[63]	Incorrect interventions
Hamilton-craig 2009[64]	Correspondence only
Han 2018[65]	Systematic review: methods are not adequate/unclear. Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate.

	Inappropriate comparison. Incorrect line of therapy. Incorrect interventions
Helske-Suihko 2015[67]	Not review population
Henriquez 2009[68]	Systematic review is not relevant to review question or unclear PICO. Incorrect interventions
Hjalmarson 1991[69]	Not guideline condition. Not review population. Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Inappropriate comparison
Hjalmarson 1994[70]	Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Not guideline condition. Not review population. Inappropriate comparison
Hongning 2014[72]	No appropriate outcomes reported
Host 1997[73]	Incorrect outcomes
Hung 2002[75]	Incorrect study design. Not guideline condition. Not review population
Ibragimova 2018[76]	Not available in English language
Inano 2007[77]	Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Jirasirirojanakorn 1998[78]	Incorrect population: combines different types of heart valve disease
Kang 2019[80]	Incorrect interventions
Kasama 2007[81]	Mixed population <75% HVD
Kelbaek 1996[82]	Not review population
Keren 1992[83]	Not review population
Keren 1994[84]	Not guideline condition. Not review population
Kesaniemi 2007[85]	Commentary only
Kleaveland 1986[86]	Not review population. Mixed population <75% heart failure. Incorrect interventions
Klein 1985[87]	Not review population
Klugmann 1983[88]	Not guideline condition. Not review population. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Inappropriate comparison
Korewicki 1990[89]	Not available in English language
Kumar 1994[90]	Not review population
Lanas 1995[91]	Not available in English language
Lanas 1996[93]	Not available in English language
Lanas 1998[92]	Not available in English language
Leenen 1991[94]	Incorrect study design
Legault 1996[95]	Not review population. Medical management in the intra- or post-operative period
Levine 1998[96]	Not review population. Incorrect study design. Inappropriate comparison
Lin 1994[98]	Not guideline condition. Not review population. Incorrect interventions

Lin 1994[99]	Not review population. Incorrect interventions
Lin 2011[97]	Not review population. Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Littler 1995[100]	Not guideline condition. Not review population
Loomba 2010[101]	Systematic review: study designs inappropriate. Systematic review: methods are not adequate/unclear. Systematic review: quality assessment is inadequate
Lowes 1999[102]	Not guideline condition. Not review population
Mahajerin 2007[103]	Not review population
Mardikar 1995[105]	Incorrect study design
Memon 2016[106]	Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate
Misra 1989[107]	Incorrect study design. Severity of heart disease not mentioned
Mizuno 2002[108]	Not guideline condition. Not review population
Moura 2007[109]	Incorrect study design
Muhammad 2016[110]	Incorrect interventions. Mild-to-moderate heart valve disease
Nagatomo 2007[111]	Not review population. Not guideline condition
Nikitin 1998[113]	Not guideline condition. Not review population. Inappropriate comparison
Novo 2011[114]	Systematic review: study designs inappropriate. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Nyolczas 2017[115]	Not review population. Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Inappropriate comparison
Olsen 2004[116]	Not review population
Olsson 2009[117]	Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Packer 1983[118]	Not guideline condition. Not review population. Systematic review: methods are not adequate/unclear. Systematic review: quality assessment is inadequate. Systematic review: literature search not sufficiently rigorous. Systematic review is not relevant to review question or unclear PICO. Inappropriate comparison
Panahi 2013[119]	Not review population
Parakh 2012[120]	Not review population. Incorrect interventions. Mild to moderate mitral stenosis
Park 2016[121]	Medical management in the intra- or post-operative period
Parolari 2011[122]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Patel 1995[123]	Not review population
Pedersen 2008[124]	Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Systematic review: study designs inappropriate. Systematic review: literature search not sufficiently rigorous
Quinn 2005[125]	Correspondence only

Rajesh 2016[126]	Incorrect interventions
Ramos 2018[127]	Incorrect interventions. Systematic review: methods are not adequate/unclear. Systematic review: quality assessment is inadequate. Systematic review: literature search not sufficiently rigorous
Rivera 2003[128]	Not review population. Mixed population <75% heart failure. Mild mitral regurgitation
Rosenhek 2008[130]	Systematic review: study designs inappropriate. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Roth 1993[133]	Medical management in the intra- or post-operative period. Incorrect interventions
Rothlisberger 1993[134]	Not review population
Rothlisberger 1994[135]	Not review population
Ruiz Ros 1999[136]	Medical management in the intra- or post-operative period. Not review population
Saeed 2020[137]	Incorrect study design
Saggu 2015[138]	Incorrect interventions. Mild-to-moderate mitral stenosis
Sahebkar 2012[139]	Conference abstract only
Sahoo 2016[140]	No protocol outcomes
Salas 2012[141]	Not review population. Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Inappropriate comparison
Saltissi 1983[142]	Not review population. Mitral valve prolapse without regurgitation
Sanada 2007[144]	Not guideline condition. Not review population. Incorrect interventions
Seneviratne 1994[147]	Not review population
Shah 2012[148]	Not review population. Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Shen 1995[149]	Not available in English language
Shu 2005[150]	Not review population
Slipczuk 2016[151]	Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Sondergaard 2000[152]	Not review population
Stewart 2008[155]	No appropriate outcomes reported
Stewart 2009[153]	Systematic review is not relevant to review question or unclear PICO. Systematic review: study designs inappropriate. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Stoll 1995[156]	Mild heart valve disease
Strauss 2012[157]	Not review population. Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Takagi 2009[159]	Letter only

Takagi 2019[158]	Not review population
Takahama 2018[160]	Not guideline condition. Not review population. Inappropriate comparison
Tan 1998[161]	Not available in English language
Tendera 1987[162]	Not available in English language
Teo 2011[163]	Systematic review: quality assessment is inadequate
Thilly 2003[164]	Not guideline condition. Not review population. Inappropriate comparison
Tjon 1990[165]	Not available in English language
Tourmousoglou 2008[166]	Systematic review: methods are not adequate/unclear. Systematic review: quality assessment is inadequate. Systematic review: literature search not sufficiently rigorous. Systematic review: study designs inappropriate
Tschirkov 1992[167]	Medical management in the intra- or post-operative period
Van der Linde 2011[168]	Not review population
Venegas 1992[169]	Not available in English language
Venegas 1992[170]	Not available in English language
Vizzardi 2010[171]	Not guideline condition. Not review population
Vonder Muhll 2004[172]	Not review population. Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Waagstein 2003[173]	Not guideline condition. Not review population
Wagner 2003[174]	Medical management in the intra- or post-operative period. Incorrect study design. Incorrect interventions
Wenaweser 2011[175]	Incorrect study design. Incorrect interventions
Wisenbaugh 1991[176]	Incorrect study design. Incorrect interventions
Witczak 2008[178]	Medical management in the intra- or post-operative period. Mixed population <75% HVD
Yurpolskaya 1996[179]	Not available in English language
Zhao 2016[180]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Zhao 2016[181]	Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate
Zhou 2008[182]	Not available in English language

I.1.2 Excluded 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 Valve disease with heart failure

I.2.1 Excluded clinical studies

Table 52: Studies excluded from the clinical review

Study	Exclusion reason
Agnihotri 2017[1]	Could not be retrieved
Agrawal 2016[2]	Incorrect interventions. Uses Ivabradine that is not included in our scope. Included patients with mild valve disease
Ahmed 2002[3]	Incorrect study design. Mixed population <75% HVD
Ahmed 2012[4]	Mixed population <75% heart failure
Ahuja 1989[5]	Incorrect study design
Andersson 2002[7]	Incorrect study design. Not guideline condition. Not review population. Mixed population <75% HVD
Andersson 2017[8]	Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Inappropriate comparison. References checked and extracted
Andrus 2007[9]	Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Systematic review: literature search not sufficiently rigorous. Systematic review: study designs inappropriate. Not review population. Inappropriate comparison. Incorrect interventions
Aumont 1990[11]	Not in English
Balmforth 2019[12]	Not review population. Incorrect interventions.
Banaszewski 1998[13]	Incorrect study design. Not review population. Mixed population <75% heart failure
Bechler-Lisińska 1990[16]	Not in English language
Bergstrom 2004[17]	Not guideline condition. Not review population
Borer 1978[18]	Incorrect study design. Inappropriate comparison. Incorrect interventions
Bornheimer 1982[19]	Incorrect study design. Inappropriate comparison. No control group. Severity not mentioned
Broch 2016[20]	Not review population. No patients with heart failure
Bull 2015[21]	Not review population. No participants with heart failure
Butrous 1986[22]	Incorrect study design. Not review population. No participants with heart failure. No mention of severity
Capucci 1981[23]	Not in English language
Cicoira 2002[32]	Not guideline condition. Not review population
Clark 1983[33]	Not guideline condition
Cleland 2006[34]	Not guideline condition. Not review population
Cohen 1968[35]	Not guideline condition. Not review population. Inappropriate comparison
Crawford 1989[37]	Incorrect study design. Incorrect interventions

Demirbag 2003[40]	Not in English language
Eichhorn 2001[42]	Not guideline condition. Not review population
Eleid 2013[43]	Incorrect study design. Inappropriate comparison. Incorrect interventions
Ennis 2010[44]	Mixed population <75% heart failure
Erbel 1978[45]	Not available in English language
Erbel 1979[46]	Not review population. No mention of severity
Ergun 2016[47]	Incorrect study design. Letter
Eskandr 2018[48]	Not review population. Medical management in the intra- or post-operative period. Incorrect line of therapy. Incorrect interventions
Evangelista 2005[49]	Not review population
Ghadimi 2019[51]	Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Incorrect line of therapy
Ghiringhelli 1990[52]	Incorrect study design. Incorrect interventions
Giles 1988[53]	Not guideline condition. Not review population. Mixed population <75% HVD
Giunta 1993[54]	Not guideline condition. Not review population
Gottlieb 2018[55]	Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Inappropriate comparison. Incorrect line of therapy
Grayburn 2000[56]	Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Inappropriate comparison. Incorrect line of therapy
Greenberg 1994[57]	Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Incorrect line of therapy
Gupta 2001[62]	Incorrect interventions
Hachenberg 1997[63]	Incorrect interventions
Han 2018[65]	Systematic review: methods are not adequate/unclear. Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Inappropriate comparison. Incorrect line of therapy. Incorrect interventions
Hansson 2017[66]	Not review population. Incorrect line of therapy
Henriquez 2009[68]	Systematic review is not relevant to review question or unclear PICO. Incorrect interventions
Hjalmarson 1991[69]	Not guideline condition. Not review population. Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Inappropriate comparison
Hjalmarson 1994[70]	Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Not guideline condition. Not review population. Inappropriate comparison

Hongning 2014[72]	Mixed population <75% heart failure
Host 1997[73]	Incorrect outcomes
Hung 2002[75]	Incorrect study design. Not guideline condition. Not review population
Ibragimova 2018[76]	Not available in English language
Inano 2007[77]	Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Jirasirirojanakorn 1998[78]	Incorrect population: combines different types of heart valve disease
Kang 2019[80]	Incorrect interventions
Kasama 2007[81]	Mixed population <75% HVD
Kelbaek 1996[82]	Incorrect outcomes
Keren 1992[83]	Majority of participants had mild valve disease
Keren 1994[84]	Not guideline condition. Not review population
Kleaveland 1986[86]	Not review population. Mixed population <75% heart failure. Incorrect interventions
Klugmann 1983[88]	Not guideline condition. Not review population. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Inappropriate comparison
Korewicki 1990[89]	Not available in English language
Lanas 1995[91]	Not available in English language
Lanas 1996[93]	Not available in English language
Lanas 1998[92]	Not available in English language
Legault 1996[95]	Not review population. Medical management in the intra- or post-operative period
Levine 1998[96]	Not review population. Incorrect study design. Inappropriate comparison
Lin 1994[98]	Not guideline condition. Not review population. Incorrect interventions
Lin 1994[99]	Not review population. Incorrect interventions
Lin 2011[97]	Not review population. Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Littler 1995[100]	Not guideline condition. Not review population
Lowes 1999[102]	Not guideline condition. Not review population
Mahajerin 2007[103]	Not review population
Marcotte 1997[104]	Not review population
Mardikar 1995[105]	Incorrect study design
Misra 1989[107]	Incorrect study design. Severity of heart disease not mentioned
Mizuno 2002[108]	Not guideline condition. Not review population
Muhammad 2016[110]	Incorrect interventions. Mild-to-moderate heart valve disease
Nagatomo 2007[111]	Not review population. Not guideline condition

Nikitin 1998[113]	Not guideline condition. Not review population. Inappropriate comparison
Nyolczas 2017[115]	Not review population. Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Inappropriate comparison
Olsen 2004[116]	Not review population
Packer 1983[118]	Not guideline condition. Not review population. Systematic review: methods are not adequate/unclear. Systematic review: quality assessment is inadequate. Systematic review: literature search not sufficiently rigorous. Systematic review is not relevant to review question or unclear PICO. Inappropriate comparison
Parakh 2012[120]	Not review population. Incorrect interventions. Mild to moderate mitral stenosis
Rajesh 2016[126]	Incorrect interventions
Ramos 2018[127]	Incorrect interventions. Systematic review: methods are not adequate/unclear. Systematic review: quality assessment is inadequate. Systematic review: literature search not sufficiently rigorous
Rivera 2003[128]	Not review population. Mixed population <75% heart failure. Mild mitral regurgitation
Roberts 2018[129]	Not review population
Roth 1993[133]	Medical management in the intra- or post-operative period. Incorrect interventions
Rothlisberger 1993[134]	Not review population
Rothlisberger 1994[135]	Not review population
Ruiz Ros 1999[136]	Medical management in the intra- or post-operative period. Not review population
Saeed 2020[137]	Incorrect study design
Saggu 2015[138]	Incorrect interventions. Mild-to-moderate mitral stenosis
Sahoo 2016[140]	No protocol outcomes
Salas 2012[141]	Not review population. Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Inappropriate comparison
Saltissi 1983[142]	Not review population. Mitral valve prolapse without regurgitation
Sampaio 2005[143]	Mixed population <75% heart failure
Sanada 2007[144]	Not guideline condition. Not review population. Incorrect interventions
Scognamiglio 1990[145]	Not review population
Scognamiglio 1994[146]	Not review population
Shah 2012[148]	Not review population. Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Shen 1995[149]	Not available in English language

Slipczuk 2016[151]	Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Sondergaard 2000[152]	Not review population
Stewart 2008[154]	Not review population
Stewart 2008[155]	Mixed population <75% heart failure
Stoll 1995[156]	Mild heart valve disease
Strauss 2012[157]	Not review population. Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Takahama 2018[160]	Not guideline condition. Not review population. Inappropriate comparison
Tan 1998[161]	Not available in English language
Tendera 1987[162]	Not available in English language
Thilly 2003[164]	Not guideline condition. Not review population. Inappropriate comparison
Tjon 1990[165]	Not available in English language
Tschirkov 1992[167]	Medical management in the intra- or post-operative period
Venegas 1992[169]	Not available in English language
Venegas 1992[170]	Not available in English language
Vizzardi 2010[171]	Not guideline condition. Not review population
Vonder Muhll 2004[172]	Not review population. Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Waagstein 2003[173]	Not guideline condition. Not review population
Wagner 2003[174]	Medical management in the intra- or post-operative period. Incorrect study design. Incorrect interventions
Wenaweser 2011[175]	Incorrect study design. Incorrect interventions
Wisenbaugh 1991[176]	Incorrect study design. Incorrect interventions
Wisenbaugh 1994[177]	Mixed population <75% heart failure. Mean NYHA class 1.3
Witczak 2008[178]	Medical management in the intra- or post-operative period. Mixed population <75% HVD
Yurpolskaya 1996[179]	Not available in English language
Zhou 2008[182]	Not available in English language

I.2.2 Excluded 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

J.1 Heart valve disease without concomitant heart failure: aortic regurgitation

J.1.1 Research recommendation

What is the clinical and cost-effectiveness of ACE inhibitors, angiotensin-II receptor antagonists, beta-blockers and calcium channel blockers, including compared with placebo, for adults with aortic regurgitation?

J.1.2 Why this is important

There are two aspects to this:

1. The tolerability and secondary effect on aortic regurgitation of these drugs when taken for other purposes as for example for systemic hypertension or for angina or arrhythmia
2. The perceived by some potential role of these drugs in delaying progression of aortic regurgitation or the consequences of it on symptoms and on the left ventricle.

J.1.3 Rationale for research recommendation

Importance to 'patients' or the population	This is a key area of concern in current UK practice as there is uncertainty about whether pharmacological management is required for people with heart valve disease to prevent progression or delay consequences of the disease and the effect of pharmacological treatment given for other conditions in those that also have heart valve disease. More specifically, there is uncertainty as to whether medications for the management of systemic hypertensions are more poorly tolerated in the presence of valve disease. In addition, there is uncertainty as to whether medications will delay the consequences of valve disease, for example symptoms.
Relevance to NICE guidance	There was very limited evidence on ACE-Is, ARBs, beta-blockers and calcium channel blockers for aortic regurgitation. Additional evidence would enable recommendations to be made.
Relevance to the NHS	New research would allow standardisation of care. In addition, if the pharmacologic approach will be found to be effective in managing aortic regurgitation, this will reduce the cost for the NHS by reducing the number of people in need of an intervention and delaying the offset of serious symptoms requiring hospitalsiation.

National priorities	None known
Current evidence base	There was insufficient evidence to draw conclusions about the relative benefits and harms of ACE-I, ARB, beta-blockers and calcium channel blockers based on the evidence available. The evidence was based on a small number of studies with a small number of participants. A lot of the studies were historical and so may not reflect current practice.
Equality considerations	None identified

J.1.4 Modified PICO table

Population	Inclusion Adults aged 18 years and over with diagnosed at least moderate aortic regurgitation and no current indication for intervention Exclusion Pharmacological management in children (17 years and under) People with congenital heart valve disease, except bicuspid aortic valve disease. Known contraindication for the assessed drug
Intervention	• Angiotensin-converting enzyme (ACE) inhibitors • Angiotensin-II receptor blockers (ARBs) • Beta-blockers • Calcium channel blockers • Any combination of 2 or more of the above
Comparator	• Placebo or no treatment (usual care) • Other active comparator listed above, including combinations
Outcome	Primary outcomes: All-cause mortality at ≥12 months; Cardiac mortality at ≥12 months; Health-related quality of life at 6 months and ≥12 months; Onset of symptoms or progression in NYHA class at ≥12 months; Evidence of HVD progression on imaging (worsening of disease severity) at ≥ 12 months and Need for heart valve intervention (surgical or transcatheter) at ≥12 months Secondary outcomes: Exercise tolerance and withdrawal from the trial due to adverse events at 6 and 12 months

Study design	Adequately powered randomised controlled trial
Timeframe	Long term
Additional information	None

J.2 Heart valve disease without concomitant heart failure: aortic stenosis

J.2.1 Research recommendation

What is the clinical and cost-effectiveness of ACE inhibitors, angiotensin II receptor antagonists, beta-blockers and diuretics for adults with severe aortic stenosis?

J.2.2 Why this is important

To assess the tolerability and secondary effects on patients with severe aortic stenosis of these drugs when taken for other purposes as for example for systemic hypertension, angina, arrhythmia or heart failure symptoms and signs. To assess the potential role of ACE inhibitors in delaying progression of consequences of aortic stenosis on the left ventricle, consequences that lead to heart failure with preserved ejection fraction, particularly in case of coexistence of aortic stenosis and systemic hypertension.

J.2.3 Rationale for research recommendation

Importance to 'patients' or the population	Robust evidence covering this area would allow improved management of coexistent conditions in those with aortic stenosis.
Relevance to NICE guidance	Only very limited evidence was available on ACE inhibitors, beta-blockers and diuretics, with studies having small numbers of participants and low event rates across the study periods. No evidence was available for angiotensin II receptor antagonists. It was therefore not possible to draw conclusions about the relative benefits and harms. Additional evidence may enable recommendations to be made in the future.
Relevance to the NHS	ACE inhibitors, angiotensin II receptor antagonists, beta-blockers and diuretics are widely used in clinical practice for several conditions that can coexist with aortic stenosis. Robust evidence in this population may inform future recommendations about whether these drugs are appropriate in those that have severe aortic stenosis. If new evidence will find these drugs to be effective in delaying the progression of symptoms of aortic stenosis, a recommendation may lead to cost savings for the NHS as less people will be required to receive the intervention and will develop serious symptoms of the disease requiring hospitalsation.

	This is a key area of concern in current UK practice as there is uncertainty about whether pharmacological management is required for people with heart valve disease to prevent progression or delay consequences of the disease and the effect of pharmacological treatment given for other conditions in those that also have heart valve disease. More specifically, there is uncertainty as to whether medications for the management of systemic hypertensions are more poorly tolerated in the presence of valve disease. In addition, there is uncertainty as to whether medications will delay the consequences of valve disease, for example symptoms.
National priorities	None known
Current evidence base	There was insufficient evidence to draw conclusions about the relative benefits and harms of ACE-I, angiotensin II receptor antagonists, beta-blockers and diuretics based on the evidence available. While ACE-I and beta-blockers showed clinically important harms, the evidence was collected from small studies that did not show a large enough difference in effect for recommendations to be made.
Equality considerations	None identified

J.2.4 Modified PICO table

Population	Adults aged 18 years and over with diagnosed with severe aortic stenosis, including bicuspid
Intervention	• Angiotensin-converting enzyme (ACE) inhibitors • Angiotensin II receptor antagonists • Beta blockers • Diuretics • Any combination of 2 or more of the above
Comparator	• Placebo or no treatment (usual care) • Other active comparator listed above, including combinations
Outcome	Primary outcomes: All-cause mortality at ≥12 months; cardiac mortality at ≥12 months; health-related quality of life at 6 months and ≥12 months; onset of symptoms or progression in NYHA class at ≥12 months; and need for heart valve intervention (surgical or transcatheter) at ≥12 months Secondary outcomes: Exercise tolerance and withdrawal from the trial due to adverse events at 6 and 12 months
Study design	Adequately powered randomised controlled trial

Timeframe	Long-term
Additional information	None

J.3 Heart valve disease without concomitant heart failure: mitral regurgitation

J.3.1 Research recommendation

What is the clinical and cost-effectiveness of ACE inhibitors, angiotensin II receptor antagonists, beta-blockers and diuretics for adults with primary severe mitral regurgitation?

J.3.2 Why this is important

Patients with primary severe mitral regurgitation may develop symptoms of heart failure and may be unsuitable for an intervention or waiting for it to be performed. Whilst ACE inhibitors, beta-blockers and diuretics have proven benefit in patients with heart failure due to reduced left ventricular systolic function, there is no robust evidence for their effectiveness in patients with primary severe mitral regurgitation.

Perceived benefit in delaying the need for intervention in patients with primary severe mitral regurgitation has not been demonstrated and there has been some evidence of harm.

J.3.3 Rationale for research recommendation

Importance to 'patients' or the population	Robust evidence covering this area would allow improved management of those with primary severe mitral regurgitation.
Relevance to NICE guidance	There was very limited evidence on ACE inhibitors, angiotensin II receptor antagonists, beta-blockers and diuretics for mitral regurgitation. Additional evidence may enable recommendations to be made in the future.
Relevance to the NHS	Robust evidence may inform the use of ACE inhibitors, angiotensin II receptor antagonists, beta-blockers and diuretics in the primary severe mitral regurgitation population as there is currently limited evidence to support this. If new evidence will find these drugs to be effective in delaying the progression of symptoms of aortic stenosis, a recommendation may lead to cost savings for the NHS as less people will be required to receive the intervention and will develop serious symptoms of the disease requiring hospitalisation.
National priorities	None known

Current evidence base	There was insufficient evidence to draw conclusions about the relative benefits and harms of ACE-I, angiotensin II receptor antagonists, beta-blockers and diuretics based on the evidence available. The evidence was based on a small number of studies with a small number of participants. The populations in these studies was younger than that which would be seen on average in the UK, and so may not be representative.
Equality considerations	Patients with primary severe mitral regurgitation and heart failure symptoms that are unsuitable for intervention are a subgroup of patients with primary severe mitral regurgitation that needs to be addressed. They also have certain differences compared to the general heart failure population.

J.3.4 Modified PICO table

Population	Inclusion Adults aged 18 years and over with diagnosed primary severe mitral regurgitation (asymptomatic with no indication for intervention or symptomatic and unsuitable for intervention)
Intervention	• Angiotensin-converting enzyme (ACE) inhibitors • Angiotensin II receptor antagonists • Beta blockers • Diuretics • Any combination of 2 or more of the above
Comparator	• Placebo or no treatment (usual care) • Other active comparator listed above, including combinations
Outcome	Primary outcomes: All-cause mortality at ≥12 months; cardiac mortality at ≥12 months; health-related quality of life at 6 months and ≥12 months; onset of symptoms or progression in NYHA class at ≥12 months; and need for heart valve intervention (surgical or transcatheter) at ≥12 months Secondary outcomes: Exercise tolerance and withdrawal from the trial due to adverse events at 6 and 12 months
Study design	Adequately powered randomised controlled trial
Timeframe	Long-term
Additional information	None

J.4 Heart failure and concomitant heart valve disease: mitral stenosis

J.4.1 Research recommendation

What is the clinical and cost effectiveness of beta-blockers for adults ≥75 years with non-rheumatic/calcific mitral stenosis, in both sinus rhythm and atrial fibrillation?

J.4.2 Why this is important

Calcific mitral stenosis is an increasing in prevalence heart valve disease in the UK with ageing of the population. Surgical mitral valve replacement in these patients carries a higher risk than other heart valve procedures for the same individual because of technical particularities of the procedure and morphologic aspects of the disease. Furthermore, current evidence on transcatheter valve implantation in mitral annular calcification is limited and suggests that this procedure has only a compassionate role. Consequently, it is important to provide pharmacological management of symptoms, classically offered for several decades in individuals with rheumatic mitral stenosis. Slowing down the heart rate reduces the pressure gradient through the stenotic mitral valve, as demonstrated in classic studies of heart catheterisation and known from clinical practice on echocardiography. This was always thought to result in an improvement in symptoms and was the base of pharmacological management of mitral stenosis. Most patients with mitral stenosis significant enough to provoke symptoms are in atrial fibrillations, however occasionally patients may have preserved sinus rhythm.

J.4.3 Rationale for research recommendation

Importance to 'patients' or the population	Satisfactory management of symptoms may help delay or avoid need for intervention on the valve.
Relevance to NICE guidance	Only 3 out of 6 of the studies in the evidence review specified whether the participants were in sinus rhythm or atrial fibrillation and none included older adults with calcific heart valve disease. Therefore, to inform future updates of this guidance further research is needed on beta blockers, the key drug intervention in this group, for older adults with non-rheumatic/calcific mitral stenosis, in both sinus rhythm and atrial fibrillation. This is to encourage research to clarify whether this form of pharmacological management is safe and effective in the population most relevant to UK clinical practice and for those in both sinus rhythm and atrial fibrillation as there is currently no randomised evidence to answer these important clinical questions.
Relevance to the NHS	If new evidence will find beta-blockers to avoid the cost and the risk related to intervention in these patients, improve their quality of life and

	reduce their need for hospitalisation, a recommendation may lead to important cost savings for the NHS
National priorities	None known
Current evidence base	Only 3 out of 6 of the studies in the evidence review specified whether the participants were in sinus rhythm or atrial fibrillation and none included older adults with calcific heart valve disease. It was also noted that a study showing a benefit included only people in sinus rhythm, while the others did not report the numbers in sinus rhythm or atrial fibrillation. This highlights the need to address whether beta blockers are effective in both sinus rhythm and atrial fibrillation.
Equality considerations	Standardisation of care

J.4.4 Modified PICO table

Population	<u>Inclusion</u> Adults ≥75 years with non-rheumatic/calcific mitral stenosis, in both sinus rhythm and atrial fibrillation <u>Exclusion</u> • • People with congenital heart valve disease, except bicuspid aortic valve disease.Patients with contraindication to beta-blockers
Intervention	Beta blockers
Comparator	• Placebo or no treatment • Usual care (e.g. following standard heart failure guidelines)
Outcome	<u>Primary outcomes</u> All-cause mortality at 12 months; Cardiac mortality at 12 months; Hospital admission due to heart failure at 12 months; Health-related quality of life at 6 months and 12 months <u>Secondary outcomes</u> Exercise tolerance; Need for heart valve intervention (surgical or transcatheter) within 12 months; Withdrawal from the study due to adverse events at 6 months and 12 months
Study design	Adequately powered randomised controlled trial
Timeframe	Long term
Additional information	None

J.5 Heart failure and concomitant heart valve disease: aortic regurgitation or mitral regurgitation

J.5.1 Research recommendation

What is the clinical and cost effectiveness of pharmacological management of heart failure for adults with concomitant severe aortic stenosis, severe aortic regurgitation or severe mitral regurgitation?

J.5.2 Why this is important

Pharmacological management of heart failure may have particularities in patients with aortic stenosis or aortic regurgitation or mitral regurgitation, because of particularities of the valve disease impact on haemodynamics. For example, in aortic regurgitation, betablockers are thought to have a negative impact if they reduce the heart rate significantly, because slower heart rate is associated with longer diastole so longer time for a diastolic phenomenon like aortic regurgitation to occur and consequently higher regurgitant volume worsening rather than improvement heart failure in these patients. Also for example in aortic stenosis, peripheral vasodilation for example with new introduction of an ACE-inhibitor in a patient with decompensated aortic stenosis and consequent heart failure may worsen haemodynamics and lead to cardiogenic shock. Regarding mitral regurgitation, is it more likely that standard heart failure management established for heart failure due to reduced left ventricular systolic function has no contraindication, but it not known if it has the same beneficial effect as in heart failure due to reduced left ventricular systolic function.

J.5.3 Rationale for research recommendation

Importance to ‘patients’ or the population	Establish indication and contraindication for pharmacological management agents in order to maximise the benefit to patients and minimise harms
Relevance to NICE guidance	For aortic stenosis evidence was available for the ACE-I versus placebo and ARB versus placebo only but was not considered sufficient to base recommendations on. No relevant randomised controlled trials for aortic or primary mitral regurgitation were identified. This meant that there was only limited evidence to determine whether pharmacological interventions improve outcomes for these people. Therefore, evidence is required to be able to make strong recommendations.
Relevance to the NHS	New evidence will improve standardisation of care, as current practice varies due to uncertainties and lack of evidence. In addition, if the pharmacological management will be found to reduce symptoms and the need of repeat hospitalisations for adults with concomitant

	health diseases, a recommendation may lead to important NHS savings.
National priorities	Not known
Current evidence base	There was insufficient evidence to draw conclusions about the relative benefits and harms of ACE-I or ARB compared with placebo and no other comparisons were available for this stratum. Further evidence is needed in order to consider making strong recommendations. No randomised control trials were identified on pharmacological interventions for people with aortic or mitral regurgitation.
Equality considerations	None identified

J.5.4 Modified PICO table

Population	Inclusion Adults aged 18 years and over with diagnosed heart failure and severe heart valve disease stratified by type: • aortic [including bicuspid] stenosis • aortic [including bicuspid] regurgitation • Primary mitral regurgitation Exclusion • Pharmacological management in children (17 years and under) • People with congenital heart valve disease, except bicuspid aortic valve disease. • Patients that can have valve intervention immediately after the diagnosis of their condition rather than be treated medically for a period of time.
Intervention	• Angiotensin-converting enzyme (ACE) inhibitors • Angiotensin-II receptor blockers (ARBs) • Beta blockers • Digoxin • Diuretics • Nitrates (including nitroprusside) • Any combination of 2 or more of the above
Comparator	• Placebo or no treatment • Usual care (e.g. following standard heart failure guidelines: ACE + beta-blocker + diuretic) • Other active comparator listed above, including combinations
Outcome	Primary outcomes:

	All-cause mortality at 12 months; Cardiac mortality at 12 months; Hospital admission due to heart failure at 12 months; Health-related quality of life at 6 months and 12 months and Exercise tolerance Secondary outcomes: Need for heart valve intervention (surgical or transcatheter) within 12 months; and withdrawal from the study due to adverse events at 6 months and 12 months
Study design	Adequately powered randomised controlled trial
Timeframe	Long term
Additional information	None