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Pharmacological interventions for the treatment of aortic root and heart valve disease (Protocol)

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[Intervention Protocol]

Pharmacological interventions for the treatment of aortic root and heart valve disease

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A B S T R A C T

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

The purpose of this review is to examine the benefits and harms of pharmacological intervention acting directly or indirectly on the cardiovascular system to treat aortic root and valve disease, versus placebo.

BACKGROUND

In developed countries (WESP 2019) the prevalence of valvular heart diseases in the general population is increasing, mainly because of a sharp rise in degenerative heart valve disease among older people (Nkomo 2006; Iung 2011; Coffey 2016). For instance, aortic stenosis (narrowing of the valve) is estimated to affect 7.6 million people among those age 75 and older in North America and Europe (Yadgir 2020). Degenerative aortic valve disease shares a number of risk factors with other cardiovascular (heart related) conditions and consequently, people with heart valve disease are often treated pharmacologically (with drugs) for cardiovascular comorbidities. Heart valve diseases develop slowly over many years, and patients are usually treated pharmacologically before they meet criteria for surgery (Marquis-Gravel 2016). It has been surmised that pharmacological therapy could reduce the deleterious effects of ventricular remodelling (abnormal reshaping of the heart muscle) and subsequent reduction in function. Furthermore, the progression of this disease on the tissue, cellular and molecular levels is slow, giving plenty of opportunity for therapeutic effect (Davies 1991). In this scenario, assessment of the efficacy (usefulness) and safety of different pharmacological interventions on aortic valve (and root) disease is important, to guide medical management and identify further research needs.

Description of the condition

Aortic valve disease is either the obstruction to forward blood flow (stenosis) or the presence of backward blood flow (regurgitation, also called insufficiency or incompetency) through the semilunar valve, between the left ventricle (LV) and the aorta. Although in most cases the two conditions occur in isolation, stenosis and regurgitation may also coexist (Carabello 2011; Armstrong 2018). Aortic root disease is a pathology affecting the most proximal portion of the ascending aorta, with or without the involvement of the aortic valve. Aortic root disease is rarely isolated, being more often secondary to diseases of the ascending aorta (Kirali 2018).

Aortic stenosis (AS) is the most common type of valvular disease in developed countries, together with mitral regurgitation (MR) (Iung 2011). Relatively uncommon before 65 years of age, AS prevalence increases sharply with ageing: in population-based studies, it ranges from 0.02% in groups age 18 to 44 years up to 12.4% in groups older than age 75 years (Nkomo 2006; Iung 2011; Coffey 2016). The overall prevalence of AS is similar between men and women. AS is mainly due to calcific degeneration (degeneration of the valve with formation of calcium on the valve) of a normal tricuspid (three leaflets) or a congenitally bicuspid (two leaflets) valve.

Rheumatic heart disease (RHD) remains the primary cause of AS in developing countries. Several traditional risk factors for atherosclerosis have been associated with the development and progression of calcific AS, including low-density lipoprotein (LDL) cholesterol, and lipoprotein(a) (Lp(a)) (three types of fat in the blood), as well as diabetes mellitus, smoking, chronic kidney disease, obesity and metabolic syndrome (Bäck 2020). The process of calcific degeneration determines progressive obstruction of the valve, and is responsible for the haemodynamic consequences (i.e. higher pressures in the heart) that eventually lead to symptoms. AS is considered severe when the valvular area is less than 1 cm^2 or 0.6 cm^2 persquare metre of body surface area (BSA) on echocardiography. Patients with severe AS may be considered for intervention (surgery or transcatheter). The classic clinical symptoms are shortness of breath, decreased exercise tolerance, dizziness and syncope, and chest pain (angina pectoris) (Otto 2014; Otto 2015). When AS is moderate or severe, patient survival is lower than in age- and sex-matched controls (Strange 2019). Once symptoms appear, AS progression accelerates, with half of untreated patients dying within one year (Leon 2010). In patients with symptomatic severe AS, surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVI; a minimally invasive procedure where a replacement valve is inserted through a blood vessel in the groin without open heart surgery) are associated with short-term procedural risk, but provide improved long-term survival. Symptomatic patients who do not undergo surgery have a poor prognosis, at least in part due to comorbidity precluding valve replacement (Stout 2007).

Aortic regurgitation (AR) is rarer then AS and mitral regurgitation (MR), and its prevalence in both males and females increases with ageing. The Framingham Offspring Study reported mild or more severe AR in 13% of men and 8.5% of women, with 'moderate severity' and above estimated to have a prevalence of 0.5% in the total US population (Singh 1999). Lower figures were observed in the Euro Heart Survey, with AR accounting for 5.3% of native valve disease (Iung 2011; Coffey 2016; Iung 2019).

AR may derive from a primary disease of the aortic valve leaflets, dilation of the aortic root, or both. Degeneration of aortic valve and root, with or without a bicuspid valve, is the commonest cause in developed countries, accounting for approximately two-thirds of cases (Iung 2003; Tornos 2018). RHD is the second cause of AR in developed countries, and the most prevalent in developing countries (Maganti 2010). AR may develop acutely or over a period of many years. Acute AR is a medical emergency, and its description goes beyond the purpose of the present protocol. Chronic AR evolves slowly and presents a long asymptomatic phase of haemodynamic compensation (when the heart adapts to but is slowly damaged by the large volume of blood in it); at a late stage, shortness of breath on exertion and other symptoms of heart failure may occur. When AR is suspected, diagnosis is made by echocardiography, which also is key to assessment of severity based on valve anatomy and haemodynamic consequences on LV structure and function (Gaasch 2015; Tornos 2018).

Aortic valve surgery, predominantly aortic valve replacement (AVR), is the mainstay of treatment of symptomatic severe AR or asymptomatic severe AR with LV dilatation or systolic dysfunction (poor pumping function of the heart) (Armstrong 2000). Prompt aortic valve replacement in such patients improves in-hospital and long-term survival, as long as there are no complications (such as severe embolic cerebral damage, i.e. stroke caused by the passage of a blood clot to the brain) or comorbidity that makes the prospect of recovery remote (Gaasch 2015; Nishimura 2017).

Isolated aortic root disease is much less common than aortic root pathology secondary to disease of the ascending aorta (the part of the aorta arising from the heart). Apart from acute aortic syndromes (e.g. aortic dissection), which are clinical emergencies, the remaining conditions are usually asymptomatic for a long time, and are mainly congenital or degenerative in origin. Ageing and hypertension have been linked to degenerative aortic root dilation (abnormal expansion of the part of the aorta directly connected to the heart) (Sawabe 2011; Mulè 2017). Diagnosis is

often through echocardiography and may be incidental, because of the occurrence of symptoms or during surveillance of population with risk factors (e.g. bicuspid aortic valve, and Marfan syndrome (a genetic condition affecting connective tissue where the aorta becomes dilated over time). Surgical replacement is the treatment of choice for symptomatic and/or severe aortic root disease; asymptomatic mild and moderate patients are regularly monitored and usually treated with beta-blockers and/or angiotensin receptor blockers (Vahanian 2021).

Description of the intervention

Although the definitive treatment for aortic valve and root disease is surgery, several pharmacologic interventions are used to relieve symptoms and/or to treat concomitant cardiovascular risk factors and conditions. Among these are the following.

1. Drugs modulating the renin-angiotensin-aldosterone system (RAAS) (angiotensin converting enzyme (ACE) inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs)
2. Diuretics
3. Mineralocorticoid receptor antagonists
4. Beta-blockers
5. Vasodilators (calcium channel blockers, alpha-antagonists, nitrovasodilators, and direct-acting vasodilators)
6. Lipid-lowering drugs (statins, ezetimibe)
7. Drugs acting on calcium metabolism (biphosphonates)

The role of antiplatelet therapy has been evaluated only after aortic valve replacement (AVR), for the prevention of thrombosis, and thus does not fall under the remit of this review.

Medical (drug) treatment has been reported to improve symptoms, but not to affect the prognosis or natural history of severe AS. Thus, pharmacologic treatment is limited to symptomatic patients, or asymptomatic patients with LV systolic dysfunction, who may not be candidates for aortic valve surgery, or may not be in preparation for aortic valve surgery. Treatment of underlying cardiovascular risk factors and conditions is recommended (Vahanian 2021).

According to guidelines, medical treatment might be beneficial for symptomatic AR when surgery is not possible. After surgical therapy for AR, ARBs, beta-blockers and ACE-Is are considered useful in the management of heart failure, hypertension, or both. Beta-blockers, ARBs, or both, should be considered in Marfan syndrome, pre- and post-surgery, for their potential to slow aortic root dilatation. They should also be considered in cases of bicuspid aortic valve in cases of aortic root and/or ascending aorta dilation (Vahanian 2021; Otto 2021).

How the intervention might work

Several traditional risk factors for atherosclerosis have been associated with the development and progression of calcific AS, including LDL cholesterol, Lp(a), hypertension, diabetes mellitus, smoking, chronic kidney disease, obesity and metabolic syndrome. Additional factors, such as aortic jet velocity (the speed of blood through the valve) and valve area (how large the opening of the valve is for blood to flow), degree of valve calcification, older age, male gender, cause of AS, and hypercalcaemia, may be important risk factors for progression (Otto 2015).

Similarly to atherosclerosis, LDL and Lp(a) deposition occur early in the pathogenesis of AS, and the subsequent lipoprotein oxidation and inflammatory response trigger each other in a self-perpetuating loop (Otto 1994; Olsson 1999). Hypertension may increase the mechanical stress in the valve, as supported by data from cohort studies (Rahimi 2018; Nazarzadeh 2019). Furthermore, human stenotic aortic valves overexpress chymase, angiotensin receptor 1 (AT1R), and ACE, providing evidence of the involvement of the RAAS in the progression of AS, in addition to any impact on myocardial remodelling (O'Brien 2002; Helske 2004). Another key process for the progression of the disease is the calcification of the valve, mechanisms of which are similar to those involved in skeletal bone formation (Otto 1994; Freeman 2005). In light of the similarities with atherosclerosis, including the presence of common risk factors, and the role of calcification in the progression of the disease, lipid-lowering agents, vasoactive treatments and RAAS inhibition and anti-calcific drugs have been investigated as potentially useful in AS (Marquis-Gravel 2016; Donato 2020).

The similarities with atherogenesis provide the rationale for the study of lipid-lowering agents in AS. Initially, statins represented the most intriguing possibility, due to their potential to reduce the lipid deposition on the valve leaflets and for their anti-inflammatory effect; however, results from randomized controlled trials (RCTs) have so far been disappointing (Cowell 2005; Dichtl 2008; Farmer 2009; Chan 2010; Van Der Linde 2011). As an alternative, other lipid-lowering agents have also been investigated. Niacin, which has been associated with a significant although non-specific LP(a) reduction (O'Donoghue 2019; Qamar 2019), might also slow the progression of AS. The EAVaLL trial (NCT02109614) investigated its potential in patients with mild calcific AS and high Lp(a). More recently, proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors have also been considered in view of their efficacy in decreasing Lp(a) and LDL-C, and their ability to slow progression of mild to moderate calcific AS levels was evaluated in a RCT (NCT03051360).

Antihypertensives could reduce the mechanical stress on the valve and the overload on the LV. In particular, RAAS inhibition could be beneficial on the progression of AS and exert a cardioprotective effect, although available trials reported conflicting results (Andersson 2017). Additional evidence on the effect of ARBs on haemodynamic parameters and LV remodelling is expected from two RCTs on Fimasartan (NCT01589380) and Losartan (NCT03666351) in hypertensive patients with moderate to severe AS. Mineralocorticoid receptor antagonists may inhibit RAAS activation in AS, reducing LV dysfunction and hypertrophy, and also reduce inflammation and interstitial myocardial fibrosis. Eplerenone, however, did not reduce AS progression, LV dysfunction or LV mass in patients with AS (Stewart 2008). Vasodilators may have a beneficial haemodynamic effect in AS, reducing the after-load (i.e. the pressure the LV works against) and thus improving LV function and preventing remodelling. Among vasodilators, nitric oxide (NO) could be particularly useful. Similarly to atherosclerosis, oxidative stress is critical for the progression of AS (Miller 2008) and reduced NO bioavailability promotes the calcification of the valve leaflets (Kennedy 2009; Bertacco 2010). Thus, interventions that modulate the NO/soluble guanylate cyclase (sGC)/cyclic GMP (cGMP) pathway might improve LV function, and exert an anti-atherosclerotic and anti-calcific effect directly on the valve. Small RCTs evaluated the effect of

the sGC activator ataciguat (NCT02481258) in moderate calcific AS, and of the phosphodiesterase-5 (PDE5) inhibitor sildenafil (NCT01275339) in moderate to severe AS. Both agents lead to an increase in the intracellular availability of cGMP.

Aortic valve calcification may be prevented by inhibitors of pathological mineralisation. Biphosphonates may prevent ectopic calcification of the aortic valve through inhibition of bone reabsorption, but also by exerting anti-inflammatory and lipid-lowering effects (Pennanen 1995; Adami 2000; Price 2001). Several trials showed the benefits of biphosphonates on arterial and valvular calcification in patients with osteoporosis (Skolnick 2009; Elmariah 2010; Innasimuthu 2011). The SALTIRE II trial (NCT02132026) assessed the effect of alendronate in patients with AS and without osteoporosis; results are currently being analyzed. The same trial also tested the effect of Denosumab, a human monoclonal antibody that binds the receptor activator of nuclear factor kappa B ligand (RANKL) and prevents osteoclastic differentiation in the bone. Preclinical data showed inappropriate activation of the RANK/RANKL pathway in vascular and valvular calcifications, justifying the study of Denosumab for AS (Helas 2009; Lerman 2015). Vitamin K also has an anti-calcific effect, acting as a cofactor for the matrix Gla protein (MGP), a potent inhibitor of soft-tissue calcification in its active form. Recently, the potential effects of Vitamin K supplementation in AS have been evaluated in RCTs, the first of which showed an association between Vitamin K and slower progression of aortic valve calcification (Brandenburg 2017). Two ongoing trials, AVADEC (NCT03243890) and BASIK2 (NCT02917525), are evaluating vitamin K supplementation in patients without clinically significant calcific aortic stenosis or with bicuspid valve, and in mild to moderate calcific AS, respectively.

Few data are available in the literature about the association of traditional cardiovascular risk factors with ascending aorta diseases and AR. However, since it is the volume overload of regurgitant blood that leads to myocardial dysfunction in AR, drugs such as vasodilators might reduce the haemodynamic burden on the LV and prevent its remodelling. In a meta-analysis of hydralazine, calcium channel blockers (CCB), and ACE-Is in asymptomatic severe AR with normal LV function, vasodilator therapy showed favourable effects on LV remodelling (Shah 2012). Although the potential of beta-blockade in AR is controversial, since it prolongs diastole and may worsen the volume overload, preclinical and observational data suggest it may be cardioprotective in AR. Also, after AVR, beta-blockers improve LV dysfunction and reduce LV volume and mass in patients with impaired LV function (Hjalmarson 2000; Packer 2001). In a trial designed to investigate the effect of metoprolol in patients with AR, the beta-blocker was well tolerated, but did not affect LV remodelling (Broch 2016). A causal association between hypertension and AR has been postulated on the basis of early experimental data (Fowler 1975), and it is supported by the observation that long-term elevated BP is associated with increased risk of aortic valve disease, both AS and AR (Rahimi 2018). A randomized trial is currently evaluating the effect of blood pressure control with various agents (amlodipine, losartan, chlortalidone), alone or in combination, on LV hypertrophy in patients with hypertension and aortic valve disease (NCT03666351).

Why it is important to do this review

Guidance from the American Heart Association (AHA) recommends treatment of hypertension and hyperlipidemia as per guideline-directed management and therapy (GDMT). However, no data supports the use of statins for prevention of progression of AS (Van Der Linde 2011; Chan 2010). The latest AHA guidance, however, mentions that ACE-Is may be beneficial in LV fibrosis, and acknowledges that the use of a statin reduced ischemic cardiac events by 20% in mild to moderate AS (Otto 2021).

European Society of Cardiology (ESC) guidance states that "No medical therapies influence the natural history of aortic stenosis" and downplays the role of statins, ''which demonstrated favourable effects in pre-clinical studies'' without affecting disease progression (Vahanian 2021). For patients with symptoms of heart failure alongside valve disease, recommendation is limited to following the ESC guidelines on heart failure (McDonagh 2021).

With regards to aortic regurgitation, the only pharmacological treatment mentioned as useful in the ESC guidelines are ACE inhibitors and beta-blockers (Elder 2011; Zendaoui 2011). These two drug categories are specifically described in the ESC guidance as capable of slowing dilation and thus delaying surgery in Marfan's syndrome (Lacro 2014). According to the AHA, no evidence supports the use of vasodilators to reduce severity of AR or alter the disease course in the absence of systemic hypertension. Recommendations for GDMT for hypertension and heart failure apply to patients with chronic asymptomatic AR, as for the general population (Otto 2021).

With the increasing prevalence of heart valve disease and the almost invariable presence of comorbidity in the ageing population, more patients could benefit from medical management. It is therefore important to understand which interventions, if any, may influence the progression of the disease and/or improve symptoms. Alongside the benefits, potential harms of medications need to be identified. Multiple meta-analyses have been carried out in this area, such as on the role of beta-blockers in Marfan syndrome or vasodilators in AR, and more wide-ranging reviews have also been published (Mahajerin 2007; Shah 2012; Siontis 2016; Marquis-Gravel 2016). However, an up-to-date systematic review of studies involving populations with aortic valve and root disease, and treated with medication acting directly or indirectly on the cardiovascular system, may support healthcare providers when choosing pharmacologic agents in those patients for whom surgery is not (or not yet) feasible, and would be a significant addition to the literature. Last but not least, this knowledge synthesis will be useful to highlight gaps in evidence and address future research.

O B J E C T I V E S

The purpose of this review is to examine the benefits and harms of pharmacological intervention acting directly or indirectly on the cardiovascular system to treat aortic root and valve disease, versus placebo.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We will include RCTs, whether randomised at participant level or cluster level. We include studies reported as full text, those published as abstract only, and unpublished data.

We will exclude cross-over trials due to the progression of the disease over time, which makes it difficult to compare arms after cross-over.

Types of participants

We will include adult participants 18 years of age and older, with aortic root and/or aortic valve disease of any severity.

We will exclude patients who have undergone any form of aortic valve or aortic root surgery (including TAVI) prior to the study.

We will only include trials with participants under the age of 18 or with prior aortic root or aortic valve surgery if they include a subset of eligible participants, and then only if data for eligible participants are reported separately. If data for eligible participants are not reported separately, we will include such trials if more than 80% of participants are eligible participants.

Types of interventions

We will include the following pharmacological class interventions individually, as comparisons versus placebo.

1. Drugs modulating the RAAS: ACE inhibitors and ARBs as a class
2. Mineralocorticoid receptor antagonists as a class
3. Beta-blockers as a class
4. Vasodilators as a class:
   a. calcium channel blockers
   b. alpha-antagonists
   c. modulators of nitric oxide signalling pathway
   d. direct-acting vasodilators
5. Lipid-lowering drugs as a class
6. Diuretics as a class
7. Drugs acting on calcium metabolism as a class:
   a. biphosphonates as a class
   b. monoclonal antibodies as a class
8. Beta blockers and ACE inhibitors or ARBs as classes
9. Beta blockers and ACE inhibitors or ARBs and mineralocorticoid receptor antagonists as classes

For the above-named classes of agents, we will consider any preparation, route of administration, dose, duration, frequency and combination, for any period of time. We will compare pharmacological interventions versus placebo, used for secondary prevention. We will consider all standard surgical and pharmacological treatments as eligible, apart from aortic valve or aortic root surgery before enrolment, as stated above.

Drugs in these above pharmacological classes are similar. Therefore, for the purposes of this review, we will examine them as classes of drugs, rather than as individual medications.

Types of outcome measures

Reporting one or more of the outcomes listed here in the trial is not an inclusion criterion for the review. Where a published report does not appear to report one of these outcomes, we will access the trial protocol and contact the trial authors to ascertain whether the outcomes were measured but not reported. Relevant trials which measured these outcomes but did not report the data at all, or not in a usable format, will be included in the review as part of the narrative.

We aim to consider the following outcomes, at longest reported follow-up.

Primary outcomes

1. All-cause mortality
2. Aortic valve intervention (to include replacement and transcatheter implantation)
3. Aortic root surgery

Secondary outcomes

1. Cardiovascular mortality
2. Renal failure (defined as estimated glomerular filtration rate (eGFR) less than 30)
3. Hospitalisation (number of participants with at least one event)
4. 6-minute walk distance, with a minimal clinically important difference (MCID) of 45 metres (Shoemaker 2013)
5. Borg dyspnoea scale (Borg 1982), with an MCID of 1 unit (Booth 2006)
6. Quality of life measures including the 12-item Short Form-12 General Health Survey (SF-12)
7. Adverse reaction to treatment, with a "hybrid approach" to capture both anticipated and previously unrecognised adverse effects, as per the *Cochrane Handbook* (Preyer 2021); whether or not leading to its discontinuation, including:
   a. hyperkalaemia (mmol/L)
   b. cough
   c. hypotension (mmHg)
   d. gynaecomastia
   e. renal failure
   f. syncope
   g. allergic reaction
   h. dizziness
   i. liver function derangement (statins), myositis (statins), hypocalcaemia, oesophageal ulceration (bisphonates)

Search methods for identification of studies

Electronic searches

We will identify trials through systematic searches of the following bibliographic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library
- MEDLINE (Ovid, from 1946 onwards)
- Embase (Ovid, from 1980 onwards)
- Web of Science Conference Proceedings Citation Index-Science (CPCI-S) (Clarivate Analytics, from 1990 onwards)

The preliminary search strategy for MEDLINE (Ovid) (Appendix 1) will be adapted for use in the other databases. The Cochrane sensitivity- and precision- maximising RCT filter (Lefebvre 2021) will be applied to MEDLINE (Ovid) and adaptations of it to the other databases, except CENTRAL.

We will also conduct searches for ongoing or unpublished trials in the ClinicalTrials.gov trials registry of the US National Institutes of Health (www.ClinicalTrials.gov) and the International Clinical Trials Registry Platform (ICTRP) of the World Health Organization (apps.who.int/trialsearch).

We will search all databases from their inception to the present, and we will impose no restriction on language of publication or publication status.

We will not perform a separate search for adverse effects of interventions used for the treatment of the condition.

Searching other resources

We will check for additional references to trials in the reference lists of all included studies and of any relevant systematic reviews that we identify. We will also examine any relevant retraction statements and errata for included studies. We will contact authors by email for missing data and contact authors of ongoing trials for data.

Data collection and analysis

Selection of studies

Two review authors (RM, RT) will independently screen titles and abstracts for inclusion of all the potential studies we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there are any disagreements, a third review author (FM) will be asked to arbitrate. We will retrieve the full-text study reports. Two review authors (RM, RT) will independently screen the full-text articles to identify studies for inclusion, and will identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third review author (MA). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Liberati 2009) and a 'Characteristics of excluded studies' table.

Data extraction and management

We will use a data collection form for study characteristics and outcome data which has been piloted on at least one study in the review. Two review authors (LN, HK) will extract study characteristics from included studies. We will extract the following study characteristics.

1. Methods: study design, total duration of study, number of study centres and location, study setting, and date of study.
2. Participants: N randomized, N lost to follow-up/withdrawn, N analyzed, mean age, age range, gender, days in hospital per patient, LV dimensions, LVEF, NYHA class[1], diabetes mellitus, hypertension, smoking status, type and severity of aortic root or valve disease including bicuspid/tricuspid nature), mean gradient, peak velocity AV, aortic valve area, stroke volume, peak velocity tricuspid regurgitation or assessment of pulmonary

pressure, aortic root diameter (mean), diagnostic criteria, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (LN, HK) will independently extract outcome data from included studies. We will resolve disagreements by consensus or by involving a third person (FM). One review author (AS) will transfer data into RevMan Web. We will double-check that data is entered correctly by comparing the data presented in the systematic review with the data extraction form. A second review author (BL) will spot-check study characteristics for accuracy against the trial report.

[1]New York Heart Association Functional Classification for the symptoms of heart failure. Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath). Class II: Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath). Class III: Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea. Class IV: Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases (American Heart Association 2021).

Assessment of risk of bias in included studies

Two review authors (RT, HK) will independently assess the risk of bias in each study using version two of the Cochrane 'Risk of bias' tool (RoB 2), outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a). We will resolve any disagreements by discussion or by involving another review author (MA). We will assess the risk of bias of specific results of each trial, according to the following domains:

1. bias arising from the randomization process;
2. bias due to deviations from intended interventions;
3. bias due to missing outcome data;
4. bias in measurement of the outcome;
5. bias in selection of the reported result.

We will assess the risk of bias in each domain for all outcomes. We will use the effect of assignment to the interventions using ITT (Higgins 2021a).

We will use the signalling questions in the RoB 2 tool and rate each domain as 'low risk of bias', 'some concerns' or 'high risk of bias'. We will prepare 'Risk of bias' tables that will provide the rationale for our judgements. Where appropriate, we will provide relevant verbatim quotes from studies to support our judgements.

We will summarise the 'Risk of bias' judgements across different studies for each outcome, for each of the domains listed. The

'overall risk of bias' for the result is the least favourable assessment across the domains of bias.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

We will be using the RoB 2 Excel tool to carry out our assessment (www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2). Due to the large amount of data generated by the RoB 2 tool, we will be unable to list all of this in the full review. We will, however, list our consensus decisions for the signalling questions in supplemental appendices.

For cluster-RCTs we will use a version of the RoB 2 specifically intended for use with cluster-RCTs (www.riskofbias.info/welcome/rob-2-0-tool/rob-2-for-cluster-randomized-trials). We will use the guidance in the *Cochrane Handbook* (Higgins 2021b).

Measures of treatment effect

We will analyze dichotomous data in terms of risk ratios (RRs) with 95% confidence intervals (CIs). We will analyze continuous data in terms of the mean difference (MD) with 95% CIs, provided the studies have all used the same tool to measure the outcome. If studies have used different tools to measure an outcome (such as quality of life), we will instead use the standardized mean difference (SMD) with 95% CIs. For SMDs, we will use Hedges' (adjusted) 'g' statistic, which uses a pooled standard deviation (SD) in the denominator of its calculation (Higgins 2021c). This pooled SD is an estimate of the SD using outcome data from the intervention groups, based on the assumption that the SDs in the two groups are similar. An SMD less than 0.2 will be interpreted as trivial, between 0.2 and 0.5 as small, between 0.5 and 0.8 as medium, and greater than 0.8 as large (Cohen 1988; Farivar 2004).

In the case of continuous data provided as a MD or change from baseline, data will be extracted on both change from baseline and post-intervention outcomes if the required means and SDs are available; but mean difference will be preferred. The advantage of using an MD is that it allows the possibility of combining end of follow-up data with change from baseline data, if reported by different studies. This contrasts with the SMD, where this cannot be done. Skewed data will be narratively reported as medians and interquartile ranges (Deeks 2021).

Unit of analysis issues

Multi-arm RCTs and cluster-RCTs will be eligible for inclusion. We will overcome unit of analysis error in cluster-RCTs by conducting the analysis at the same level as the allocation. The data will be analyzed considering each cluster as a unit of analysis. However, in cluster-RCTs where the unit of analysis is not reported, we will use an intracluster correlation coefficient (ICC) to calculate the effective sample size (Higgins 2021b).

If we identify trials that could contribute multiple correlated comparisons with multiple treatment arms, we will combine groups to create a single pair-wise comparison for analysis. For continuous outcomes, we will carry out multiple pair-wise comparisons, where we split the control group accordingly to avoid double-counting.

Regarding multiple observations on patients, we will select the longest reported follow-up from each study.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data, as indicated (e.g. when a study is identified as abstract only). When possible, we will use the RevMan calculator to calculate missing standard deviations (RevMan Web 2021), using other data from the trial, such as confidence intervals, based on methods outlined in the *Cochrane Handbook (*Higgins 2019a). When this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results, with a sensitivity analysis.

Assessment of heterogeneity

We will assess heterogeneity among the studies using the Chi² test from the forest plot. Heterogeneity may be indicated if there is a statistically significant result (P < 0.10). However, if the studies included in the review have small sample sizes, then careful interpretation of the Chi² test is needed. In this situation, we will use the I² statistic, which measures the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error/chance. The inconsistency among the studies will be quantified as follows:

• 0% to 40%: might not be important;
• 30% to 60%: may represent moderate heterogeneity;
• 50% to 90%: may represent substantial heterogeneity;
• 75% to 100%: considerable heterogeneity (Deeks 2021).

 If we identify substantial or considerable heterogeneity, we will report it and explore possible causes by pre-specified subgroup analysis.

Assessment of reporting biases

If we are able to pool data from 10 or more trials, we will create and examine a funnel plot to explore potential small study biases for the primary outcomes. We will perform a formal statistical test for asymmetry (Egger 1997).

Data synthesis

All studies will be included in the primary analysis. To assess the potential effects of studies at high risk of bias, or with some concerns about risk of bias, we will carry out sensitivity analyses. We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense. We will use a random effects model, due to the high probability of heterogeneity in the RCTs that we will identify.

If a meta-analysis is not possible, we will present our data narratively, using the nine-point checklist in the new 'Synthesis without meta-analysis' (SWiM) guidance (Campbell 2020). We will group studies by intervention. We will use vote counting based on the direction of effect and we will present characteristics, such as study design, sample sizes, and risk of bias. We will describe synthesis findings, clarifying which studies contribute to each synthesis and will also explain the limitations of the synthesis (Campbell 2020).

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses where we detect substantial or considerable heterogeneity to attempt to explore it:

1. Absence versus presence of LV dysfunction (ejection fraction (EF) 35% or less) (Ponikowski 2016)
2. NYHA class I/II versus III/IV
3. Aortic stenosis vs aortic regurgitation (both AR alone and with root involvement)
4. Aortic regurgitation alone vs aortic regurgitation with aortic root involvement

We will use the formal test for subgroup differences in Revman Web (RevMan Web 2021), and will base our interpretation on this.

Sensitivity analysis

We plan to carry out the following sensitivity analyses, to test whether key methodological factors or decisions have affected the main result.

1. We would exclude randomized studies with high risk of bias and some concerns.
2. We would repeat the analysis using a fixed effect model.
3. We plan to explore the impact of missing data. If we identify studies with more than 20% of participants have missing data that were unobtainable, we will repeat the analyses, excluding them to find their impact on the primary analyses.

Summary of findings and assessment of the certainty of the evidence

We will create 'Summary of findings' tables for each comparison using the following primary outcomes and any patient-relevant secondary outcomes, at longest reported follow-up.

1. All-cause mortality
2. Aortic valve intervention (to include replacement and transcatheter implantation)
3. Aortic root surgery
4. Cardiovascular mortality

5. Hospitalisation (number of participants with at least one event)
6. 6-minute walk distance, with an MCID of 45 metres (Shoemaker 2013)
7. Borg dyspnoea scale (Borg 1982), with an MCID of 1 unit (Oxberry 2012)

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of evidence as it relates to the studies contributing data to the meta-analyses. We will display our assessments of the evidence certainty for each prespecified outcome in 'Summary of findings' tables. We will use our RoB 2 judgements of overall risk of bias to inform our GRADE assessments. We will use GRADEpro GDT software to create the 'Summary of findings' tables (GRADEpro GDT 2015). We will use footnotes to justify all decisions to downgrade the certainty of evidence, and where necessary, we will make comments to aid readers' understanding of the review (Schünemann 2021).

Judgements about evidence certainty will be made by two review authors (RM, MA) working independently, with disagreements resolved by discussion or by involving a third review author (FM). Judgements will be justified, documented and incorporated into the reporting of results for each outcome.

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice and our implications for research will suggest priorities for future research and outline the remaining uncertainties are in the field.

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REFERENCES

Additional references

Adami 2000

Adami S, Braga V, Guidi G, Gatti G, Gerardi D, Fracassi E. Chronic intravenous aminobisphosphonate therapy increases high-density lipoprotein cholesterol and decreases low-density lipoprotein cholesterol. *Journal of Bone and Mineral Research* 2000;**15**(3):599-604. [DOI: 10.1359/jbmr.2000.15.3.599]

American Heart Association 2021

Classes of heart failure. www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure (accessed prior to 2 December 2021).

Andersson 2017

Andersson C, Abdulla J. Is the use of renin-angiotensin systeminhibitors in patients with aortic valve stenosis safe and of prognostic benefit? A systematic review and meta-analysis. *European Heart Journal - Cardiovascular Pharmacotherapy* 2017;**3**(1):21-7. [DOI: 10.1093/ehjcvp/pvw027]

Armstrong 2000

Armstrong P. Left ventricular dysfunction: causes, natural history, and hopes for reversal. *Heart* 2000;**84**(Suppl 1):i15-7. [DOI: 10.1136/heart.84.suppl_1.i15]

Armstrong 2018

Armstrong G. Aortic regurgitation (Aortic Insufficiency). In: MSD Manual Professional. Merck & Co., Inc., Kenilworth, NJ, USA, 2018. [AVAILABLE AT: https://www.msdmanuals.com/professional/cardiovascular-disorders/valvular-disorders/aortic-regurgitation]

Bäck 2020

Bäck M, Larsson SC. Risk factors for aortic stenosis. E-Journal of Cardiology Practice 2020;**18**:11-9. [AVAILABLE AT: escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-18/risk-factors-for-aortic-stenosis]

Bertacco 2010

Bertacco E, Millioni R, Arrigoni G, Faggin E, Iop L, Puato M, et al. Proteomic analysis of clonal interstitial aortic valve cells acquiring a pro-calcific profile. *Journal of Proteome Research* 2010;**9**(11):5913-21. [DOI: 10.1021/pr100682g]

Borg 1982

Borg GA. Psychophysical bases of perceived exertion. *Medical Science Sports Exercise* 1982;**14**(5):377-81. [PMID: 7154893]

Brandenburg 2017

Brandenburg VM, Reinartz S, Kaesler N, Krüger T, Dirrichs T, Kramann R, et al. Slower progress of aortic valve calcification with Vitamin K supplementation: Results from a prospective interventional proof-of-concept study. *Circulation* 2017;**135**(21):2081-3. [DOI: 10.1161/CIRCULATIONAHA.116.027011]

Broch 2016

Broch K, Urheim S, Lønnebakken MT, Stueflotten W, Massey R, Fosså K, et al. Controlled release metoprolol for aortic regurgitation: a randomised clinical trial. *Heart* 2016;**102**(3):191-7. [DOI: 10.1136/heartjnl-2015-308416]

Campbell 2020

Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al . Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline . *British Medical Journal* 2020;**368**:6890 . [DOI: 10.1136/bmj.l6890]

Carabello 2011

Carabello BA. Valvular Heart Disease. 1 edition. Elsevier Inc., 2011.

Chan 2010

Chan KL, Teo K, Dumesnil JG, Ni A, Tam J. Effect of lipid lowering with rosuvastatin on progression of aortic stenosis: results of the aortic stenosis progression observation: measuring effects of rosuvastatin (Astronomer) trial. *Circulation* 2010;**121**(2):306-14. [DOI: 10.1161/CIRCULATIONAHA.109.900027]

Coffey 2016

Coffey S, Cairns BJ, Iung B. The modern epidemiology of heart valve disease. *Heart* 2016;**102**(1):75-85. [DOI: 10.1136/heartjnl-2014-307020]

Cohen 1988

Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd edition. Hillsdale, NJ, USA: Erlbaum, 1988.

Cowell 2005

Cowell SJ, Newby DE, Prescott RJ, Bloomfield P, Reid J, Northridge DB, et al. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. *New England Journal of Medicine* 2005;**352**(23):2389-97. [DOI: 10.1056/NEJMoa043876]

Davies 1991

Davies SW, Gershlick AH, Balcon R. Progression of valvar aortic stenosis: a long-term retrospective study. *European Heart Journal* 1991;**12**:10–4. [DOI: 10.1093/oxfordjournals.eurheartj.a059815]

Deeks 2021

Deeks JJ, Higgins JP, Altman DG (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Dichtl 2008

Dichtl W, Alber HF, Feuchtner GM, Hintringer F, Reinthaler M, Bartel T, et al. Prognosis and risk factors in patients with asymptomatic aortic stenosis and their modulation by

atorvastatin (20 mg). *American Journal of Cardiology* 2008;**102**(6):743-8. [DOI: 10.1016/j.amjcard.2008.04.060]

Donato 2020

Donato M, Ferri N, Lupo MG, Faggin E, Rattazzi M. Current evidence and future perspectives on pharmacological treatment of calcific aortic valve stenosis. *International Journal of Molecular Sciences* 2020;**21**(21):1-28. [DOI: 10.3390/ijms21218263]

Elder 2011

Elder DH, Wei L, Szwejkowski BR, Libianto R, Nadir A, Pauriah M, et al. The impact of renin-angiotensin-aldosterone system blockade on heart failure outcomes and mortality in patients identified to have aortic regurgitation: a large population cohort study. *Journal of the American College of Cardiology* 2011;**58**:2084–91. [DOI: 10.1016/j.jacc.2011.07.043.]

Elmariah 2010

Elmariah S, Delaney JA, O'Brien KD, Budoff MJ, Vogel-Claussen J, Fuster V, et al. Bisphosphonate use and prevalence of valvular and vascular calcification in women: MESA (The Multi-Ethnic Study of Atherosclerosis). *Journal of the American College of Cardiology* 2010;**56**(21):1752-9. [DOI: 10.1016/j.jacc.2010.05.050]

Farivar 2004

Farivar SS, Liu H, Hays RD. Half standard deviation estimate of the minimally important difference in HRQOL scores? *Expert Review of Pharmacoeconomics & Outcomes Research* 2004;**4**(5):515-23. [DOI: 10.1586/14737167.4.5.515]

Farmer 2009

Farmer JA. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis (the SEAS trial). *Current Atherosclerosis Reports* 2009;**11**(2):82-3. [PMID: 19228479]

Fowler 1975

Fowler NO, Holmes JC, Spitz H. Influence of acute hypertension on aortic valve competence. *Journal of Applied Physiology* 1975;**39**(6):879-84. [DOI: 10.1152/jappl.1975.39.6.879]

Freeman 2005

Freeman RV, Otto CM. Spectrum of calcific aortic valve disease: Pathogenesis, disease progression, and treatment strategies. *Circulation* 2005;**111**(24):3316-26. [DOI: 10.1161/CIRCULATIONAHA.104.486738]

Gaasch 2015

Gaasch WH. Clinical manifestations and diagnosis of chronic aortic regurgitation in adults. UpToDate 2015;**Last updated: Oct 04, 2019**:1-22. [AVAILABLE AT: http://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-chronic-aortic-regurgitation-in-adults]

GRADEpro GDT 2015 [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015. Available at gradepro.org.

Helas 2009

Helas S, Goettsch C, Schoppet M, Zeitz U, Hempel U, Morawietz H, et al. Inhibition of receptor activator of NF-κB ligand by denosumab attenuates vascular calcium deposition in mice. *American Journal of Pathology* 2009;**175**(2):473-8. [DOI: 10.2353/ajpath.2009.080957]

Helske 2004

Helske S, Lindstedt KA, Laine M, Mäyränpää M, Werkkala K, Lommi J, et al. Induction of local angiotensin II-producing systems in stenotic aortic valves. *Journal of the American College of Cardiology* 2004;**44**(9):1859-66. [DOI: 10.1016/j.jacc.2004.07.054]

Higgins 2019a

Higgins JP, Li T, Deeks JJ, editor(s). Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Higgins 2021a

Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Availablefrom www.training.cochrane.org/handbook.

Higgins 2021b

Higgins JP, Eldridge S, Li T (editors). Chapter 23: Including variants on randomized trials. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021.

Hjalmarson 2000

Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF). *JAMA* 2000;**283**(10):1295-302. [DOI: 10.1001/jama.283.10.1295]

Innasimuthu 2011

Innasimuthu AL, Katz WE. Effect of bisphosphonates on the progression of degenerative aortic stenosis. *Echocardiography* 2011;**28**(1):1-7. [DOI: 10.1111/j.1540-8175.2010.01256.x]

Iung 2003

Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, et al. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. *European Heart Journal* 2003;**24**(13):1231-43. [DOI: 10.1016/s0195-668x(03)00201-x]

Iung 2011

Iung B, Vahanian A. Epidemiology of valvular heart disease in the adult. *Nature Reviews Cardiology* 2011;**8**(3):162-72. [DOI: 10.1038/nrcardio.2010.202]

Iung 2019

Iung B, Delgado V, Rosenhek R, Price S, Prendergast B, Wendler O, et al. Contemporary presentation and management of valvular heart disease: the EURObservational Research Programme Valvular Heart Disease II Survey. *Circulation* 2019;**140**(14):1156-69. [DOI: 10.1161/CIRCULATIONAHA.119.041080]

Kennedy 2009

Kennedy JA, Hua X, Mishra K, Murphy GA, Rosenkranz AC, Horowitz JD. Inhibition of calcifying nodule formation in cultured porcine aortic valve cells by nitric oxide donors. *European Journal of Pharmacology* 2009;**602**(1):28-35. [DOI: 10.1016/j.ejphar.2008.11.029]

Kirali 2018

Kirali K, Kahveci G. Aortic root pathologies. In: New Approaches to Aortic Diseases from Valve to Abdominal Bifurcation. Elsevier Inc., 2018. [DOI: 10.1016/B978-0-12-809979-7.00005-5]

Lacro 2014

Lacro RV, Dietz HC, Sleeper LA, Yetman AT, Bradley TJ, Colan SD, et al. Atenolol versus losartan in children and young adults with Marfan's syndrome. *New England Journal of Medicine* 2014;**371**:2061–71. [DOI: 10.1056/NEJMoa1404731]

Lefebvre 2021

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf MI, et al. Chapter 4: Searching for and selecting studies. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Leon 2010

Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *New England Journal of Medicine* 2010;**363**(17):1597-607. [DOI: 10.1056/NEJMoa1008232]

Lerman 2015

Lerman DA, Prasad S, Alotti N. Denosumab could be a potential inhibitor of valvular interstitial cells calcification in vitro. *International Journal of Cardiovascular Research* 2016;**5**(1):1-19. [DOI: 10.4172/2324-8602.1000249]

Liberati 2009

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;**6**(7):e1000100. [DOI: 10.1371/journal.pmed.1000100]

Maganti 2010

Maganti K, Rigolin VH, Sarano ME, Bonow RO. Valvular heart disease: diagnosis and management. *Mayo Clinic Proceedings* 2010;**85**(5):483-500. [DOI: 10.4065/mcp.2009.0706]

Mahajerin 2007

Mahajerin A, Gurm HS, Tsai TT, Chan PS, Nallamothu BK. Vasodilator therapy in patients with aortic insufficiency: a systematic review. *American Heart Journal* 2007;**153**(4):454-61. [DOI: 10.1016/j.ahj.2007.01.006]

Marquis-Gravel 2016

Marquis-Gravel G, Redfors B, Leon MB, Généreux P. Medical treatment of aortic stenosis. *Circulation* 2016;**134**:1766-84. [DOI: 10.1161/CIRCULATIONAHA.116.023997]

McDonagh 2021

McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *European Heart Journal* 2021;**42**(36):3599-726. [DOI: 10.1093/eurheartj/ehab368]

Miller 2008

Miller JD, Chu Y, Brooks RM, Richenbacher WE, Peña-Silva R, Heistad DD. Dysregulation of antioxidant mechanisms contributes to increased oxidative stress in calcific aortic valvular stenosis in humans. *Journal of the American College of Cardiology* 2008;**52**(10):843-50. [DOI: 10.1016/j.jacc.2008.05.043]

Mulè 2017

Mulè G, Nardi E, Morreale M, Castiglia A, Geraci Giulio, Altieri D, et al. The relationship between aortic root size and hypertension: an unsolved conundrum. In: Islam, Md Shahidul, editors(s). Hypertension: from basic research to clinical practice. Cham: Springer International Publishing, 2017:427-45.

Nazarzadeh 2019

Nazarzadeh M, Pinho-Gomes AC, Smith BK, Canoy D, Raimondi F, Ayala SJ, et al. Systolic blood pressure and risk of valvular heart disease: a mendelian randomization study. *JAMA Cardiology* 2019;**4**(8):788-95. [DOI: 10.1001/jamacardio.2019.2202]

NCT01275339

NCT01275339. Aortic stenosis and phosphodiesterase type 5 inhibition (ASPEN): a pilot study. clinicaltrials.gov/ct2/show/NCT01275339 (first posted 12 January 2011).

NCT01589380

NCT01589380. A randomized trial of angiotensin receptor blocker, fimasartan, in aortic stenosis (ALFA Trial) (ALFA). clinicaltrials.gov/ct2/show/NCT01589380 (first posted 1 May 2012).

NCT02109614

NCT02109614. Early aortic valve lipoprotein(a) lowering trial (EAVaLL). clinicaltrials.gov/ct2/show/study/NCT02109614 (first posted 10 April 2014).

NCT02132026

NCT02132026. Study investigating the effect of drugs used to treat osteoporosis on the progression of calcific aortic stenosis (SALTIRE II). clinicaltrials.gov/ct2/show/NCT02132026 (first posted 6 May 2014).

NCT02481258

NCT02481258. A study evaluating the effects of ataciguat (HMR1766) on aortic valve calcification (CAVS). clinicaltrials.gov/ct2/show/NCT02481258 (first posted 25 January 2015).

NCT02917525

NCT02917525. Bicuspid aortic valve stenosis and the effect of vItamin K2 on calciummetabolism on 18F-NaF PET/MRI (BASIK2). clinicaltrials.gov/ct2/show/NCT02917525 (first posted 28 September 2016).

NCT03051360

NCT03051360. PCSK9 inhibitors in the progression of aortic stenosis. clinicaltrials.gov/ct2/show/NCT03051360 (first posted 13 February 2017).

NCT03243890

NCT03243890. The aortic valve decalcification (AVADEC) trial (AVADEC). clinicaltrials.gov/ct2/show/NCT03243890 (first posted 9 August 2017).

NCT03666351

NCT03666351. Study to evaluate the effect on improvement of LVH by the control of BP in hypertension patients with AV disease. clinicaltrials.gov/ct2/show/NCT03666351 (first posted 11 September 2018).

Nishimura 2017

Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology* 2017;**70**(2):252-89. [DOI: 10.1016/j.jacc.2017.03.011]

Nkomo 2006

Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;**368**(9540):1005-11. [DOI: 10.1016/S0140-6736(06)69208-8]

O'Brien 2002

O'Brien KD, Shavelle DM, Caulfield MT, McDonald TO, Olin-Lewis K, Otto CM, et al. Association of angiotensin-converting enzyme with low-density lipoprotein in aortic valvular lesions and in human plasma. *Circulation* 2002;**106**(17):2224-30. [DOI: 10.1161/01.cir.0000035655.45453.d2]

Olsson 1999

Olsson M, Thyberg J, Nilsson J. Presence of oxidized low density lipoprotein in nonrheumatic stenotic aortic valves. *Arteriosclerosis, Thrombosis, and Vascular Biology* 1999;**19**(5):1218-22. [DOI: 10.1161/01.atv.19.5.1218]

Otto 1994

Otto CM, Kuusisto J, Reichenbach DD, Gown AM, O'Brien KD. Characterization of the early lesion of 'degenerative' valvular aortic stenosis: Histological and immunohistochemical studies. *Circulation* 1994;**90**(2):844-53. [DOI: 10.1161/01.cir.90.2.844]

Otto 2014

Otto CM, Nishimura RA. New ACC/AHA valve guidelines: Aligning definitions of aortic stenosis severity with treatment recommendations. *Heart* 2014;**100**(12):902-4. [DOI: 10.1136/heartjnl-2013-305134]

Otto 2015

Otto CM. Clinical manifestations and diagnosis of aortic stenosis in adults. Uptodate.com 2015:1-27. [AVAILABLE AT: http://www.uptodate.com.ezproxy.is.ed.ac.uk/contents/clinical-manifestations-and-diagnosis-of-aortic-stenosis-in-adults?source=search_result&search=aortic+stenosis&selectedTitle=1~150]

Otto 2021

Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2021;**143**:e72–e227. [DOI: 10.1161/CIR.0000000000000923]

Oxberry 2012

Oxberry SG, Bland JM, Clark AL, Cleland JG, Johnson MJ. Minimally clinically important difference in chronic breathlessness: Every little helps. *American Heart Journal* 2012;**164**(2):229-35. [DOI: 10.1016/j.ahj.2012.05.003]

O'Donoghue 2019

O'Donoghue ML, Fazio S, Giugliano RP, Stroes ESG, Kanevsky E, Gouni-Berthold I et al. Lipoprotein(a), PCSK9 inhibition, and cardiovascular risk. *Circulation* 2019;**139**(12):1483-92. [DOI: 10.1161/CIRCULATIONAHA.118.037184]

Packer 2001

Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. *New England Journal of Medicine* 2001;**344**(22):1651-8. [DOI: 10.1056/NEJM200105313442201]

Pennanen 1995

Pennanen N, Lapinjoki S, Urtti A, Mönkkönen J. Effect of liposomal and free bisphosphonate on the IL-1B, IL-6 and TNFalfa secretion from RAW 264 cells in vitro. *Pharmaceutical Research* 1995;**12**:916-22. [DOI: 10.1023/a:1016281608773]

Ponikowski 2016

Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC guidelines for the diagnosis and

treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). *European Heart Journal* 2016;**37**:2129–200.

Preyer 2021

Preyer G, Golder S, Junqueira D, Vohra S, Loke YK. Chapter 19: Adverse effects. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Price 2001

Price PA, Faus SA, Williamson MK. Bisphosphonates alendronate and ibandronate inhibit artery calcification at doses comparable to those that inhibit bone resorption. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2001;**21**(5):817-24. [DOI: 10.1161/01.atv.21.5.817]

Qamar 2019

Qamar A, Giugliano RP, Keech AC, Kuder JF, Murphy SA, Kurtz CE, et al. Interindividual variation in low-density lipoprotein cholesterol level reduction with evolocumab: an analysis of FOURIER trial data. *JAMA Cardiology* 2019;**4**(1):59-63. [DOI: 10.1001/jamacardio.2018.4178]

Rahimi 2018

Rahimi K, Mohseni H, Kiran A, Tran J, Nazarzadeh M, Rahimian F, et al. Elevated blood pressure and risk of aortic valve disease: a cohort analysis of 5.4 million UK adults. *European Heart Journal* 2018;**39**(39):3596-603. [DOI: 10.1093/eurheartj/ehy486]

RevMan Web 2021 [Computer program]

The Cochrane Collaboration Review Manager Web (RevMan Web). Version 3.11.1. The Cochrane Collaboration, 2021. available at revman.cochrane.org.

Sawabe 2011

Sawabe M, Hamamatsu A, Chida K, Mieno MN, Ozawa T. Age is a major pathobiological determinant of aortic dilatation: a large autopsy study of community deaths. *Journal of Atherosclerosis and Thrombosis* 2011;**18**(2):157-65. [DOI: doi:10.5551/jat.6528]

Schünemann 2021

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, Guyatt GH. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Shah 2012

Shah RM, Singh M, Bhuriya R, Molnar J, Arora RR, Khosla S. Favorable effects of vasodilators on left ventricular remodeling in asymptomatic patients with chronic moderate-severe aortic regurgitation and normal ejection fraction: a meta-analysis of clinical trials. *Clinical Cardiology* 2012;**35**:619-25. [PMID: 10.1002/clc.22019]

Shoemaker 2013

Shoemaker MJ, Curtis AB, Vangsnes E, Dickinson MG. Clinically meaningful change estimates for the six-minute walk test and daily activity in individuals with chronic heart failure. *Cardiopulmonary Physical Therapy Journal* 2013;**24**(3):21-9. [PMID: 23997688]

Singh 1999

Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller D, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *American Journal of Cardiology* 1999;**83**(6):897-902. [DOI: 10.1016/s0002-9149(98)01064-9]

Siontis 2016

Siontis GC, Praz F, Pilgrim T, Mavridis D, Verma S, Salanti G, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of severe aortic stenosis: a meta-analysis of randomized trials. *European Heart J ournal* 2016;**37**(47):3503-12. [DOI: 10.1093/eurheartj/ehw225]

Skolnick 2009

Skolnick AH, Osranek M, Formica P, Kronzon I. Osteoporosis treatment and progression of aortic stenosis. *American Journal of Cardiology* 2009;**104**(1):122-4. [DOI: 10.1016/j.amjcard.2009.02.051]

Stewart 2008

Stewart RA, Kerr AJ, Cowan BR, Young AA, Occleshaw C, Richards AM, et al. A randomized trial of the aldosterone-receptor antagonist eplerenone in asymptomatic moderate-severe aortic stenosis. *American Heart Journal* 2008;**156**(2):348-55. [DOI: 10.1016/j.ahj.2008.03.012]

Stout 2007

Stout K, Otto C. Indication for aortic valve replacement in aortic stenosis. *Journal of Intensive Care Medicine* 2007;**22**(1):14-25. [DOI: 10.1177/0885066606295298]

Strange 2019

Strange G, Stewart S, Celermajer D, Prior D, Scalia GM, Marwick T, et al. Poor long-term survival in patients with moderate aortic stenosis. *Journal of the American College of Cardiology* 2019;**74**(15):1851-63. [DOI: 10.1016/j.jacc.2019.08.004]

Tornos 2018

Mas PT, Lansac E. Aortic regurgitation. In: Camm AJ, Luscher TF, Maurer G, Serruys PW, editors(s). ESC CardioMed (3 edn). Oxford University Press, 2018:1-25. [DOI: 10.1093/med/9780198784906.001.0001]

Vahanian 2021

Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease: developed by the Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *European Heart Journal* 2021;**ehab395**:1-72. [DOI: 10.1093/eurheartj/ehab395]

Van Der Linde 2011

Van Der Linde D, Yap SC, Van Dijk AP, Budts W, Pieper PG, Van Der Burgh PH, et al. Effects of rosuvastatin on progression of stenosis in adult patients with congenital aortic stenosis (PROCAS Trial). *American Journal of Cardiology* 2011;**108**(2):265-71. [DOI: 10.1016/j.amjcard.2011.03.032]

WESP 2019

World Economic Situation and Prospect 2019. Available from www.un.org/development/desa/dpad/wp-content/uploads/sites/45/WESP2019_BOOK-ANNEX-en.pdf (accessed prior to 12 October 2021).

Yadgir 2020

Yadgir S, Johnson CO, Aboyans V, Adebayo OM, Adedoyin RA, Afarideh M, et al. Global Burden of Disease Study 2017 Nonrheumatic Valve Disease Collaborators. Global, regional, and national burden of calcific aortic valve and degenerative mitral valve diseases, 1990-2017. *Circulation* 2020;**141**(21):1670-80. [DOI: 10.1161/CIRCULATIONAHA.119.043391]

Zendaoui 2011

Zendaoui A, Lachance D, Roussel E, Couet J, Arsenault M. Usefulness of carvedilol in the treatment of chronic aortic valve regurgitation. *Circulation: Heart Failure* 2011;**4**(2):207–13. [DOI: 10.1161/CIRCHEARTFAILURE.110.958512]

APPENDICES

Appendix 1. Preliminary MEDLINE (Ovid) search strategy

1 Heart Valve Diseases/ (24122)

2 heart valv* disease*.tw. (1056)

3 Aortic Valve Insufficiency/ (14771)

4 (aortic adj2 (incompetence or insufficiency)).tw. (4689)

5 aortic root.tw. (9758)

6 aortic valve disease*.tw. (3009)

7 exp Aortic Valve Stenosis/ (42808)

8 (aortic adj2 stenos*).tw. (20145)

9 ascending aorta.tw. (13365)

10 (aortic adj2 regurgitation).tw. (8849)

11 "Sinus of Valsalva"/ (3206)

12 aortic sinus.tw. (1322)

13 (sinus adj2 valsalva).tw. (3350)

14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (104084)

15 exp Angiotensin-Converting Enzyme Inhibitors/ (43995)

16 Ace inhibitor*.tw. (17507)

17 angiotensin converting enzyme antagonist*.tw. (11)

18 angiotensin converting enzyme inhibitor*.tw. (18989)

19 kininase ii inhibitor*.tw. (74)

20 exp Angiotensin Receptor Antagonists/ (24050)

21 angiotensin receptor antagonist*.tw. (715)

22 angiotensin receptor blocker*.tw. (6797)

23 angiotensin ii receptor antagonist*.tw. (2047)

24 angiotensin ii receptor blocker*.tw. (3520)

25   Spironolactone/ (6776)

26   Spironolactone.tw. (5866)

27   Eplerenone/ (885)

28   Eplerenone.tw. (1243)

29   exp Mineralocorticoid Receptor Antagonists/ (9545)

30   (mineralocorticoid adj2 antagonist*).tw. (1532)

31   (aldosterone adj2 antagonist*).tw. (1850)

32   exp Adrenergic beta-Antagonists/ (84411)

33   (beta adj2 antagonist*).tw. (8927)

34   (beta adj2 block*).tw. (49228)

35   exp Vasodilator Agents/ (427979)

36   (vasodilator adj1 (agents or drugs)).tw. (1034)

37   Vasorelaxant*.tw. (2648)

38   exp Diuretics/ (79907)

39   diuretic*.tw. (38219)

40   exp Calcium Channel Blockers/ (87185)

41   (calcium channel adj1 (antagonist* or blocker*)).tw. (18107)

42   exp Hypolipidemic Agents/ (142799)

43   (Antihyperlipemics or antihyperlipidemics or antilipemics).tw. (82)

44   (antilipemic adj1 (agents or drugs)).tw. (108)

45   (hypolipidemic adj1 (agents or drugs)).tw. (920)

46   exp Antihypertensive Agents/ (259002)

47   ((anti hypertensive or antihypertensive) adj1 (agents or drugs)).tw. (14434)

48   (anti hypertensives or antihypertensives).tw. (3345)

49   Hydroxymethylglutaryl-CoA Reductase Inhibitors/ (30275)

50   HMG-CoA reductase inhibitor*.tw. (4087)

51   (statin or statins).tw. (39190)

52   Enalapril/ (6124)

53   Enalapril.tw. (6537)

54   Ramipril/ (2044)

55   Ramipril.tw. (2242)

56   Captopril/ (10025)

57   Captopril.tw. (11427)

58   Trandolapril.tw. (637)

59   Candesartan.tw. (2683)

60   Losartan/ (6765)

61   Losartan.tw. (8652)

62   Fimasartan.tw. (104)

63   Eplerenone/ (885)

64   Eplerenone.tw. (1243)

65   Metoprolol/ (5469)

66   Metoprolol.tw. (7149)

67   Nebivolol/ (798)

68   Nebivolol.tw. (987)

69   Nifedipine/ (15585)

70   Nifedipine.tw. (19504)

71   Felodipine/ (1226)

72   Felodipine.tw. (1567)

73   Hydralazine/ (4455)

74   Hydralazine.tw. (4176)

75   Atorvastatin/ (6625)

76   Atorvastatin.tw. (8705)

77   Fluvastatin/ (1392)

78   Fluvastatin.tw. (1879)

79   Rosuvastatin Calcium/ (2516)

80   Rosuvastatin.tw. (3531)

81   Simvastatin/ (7749)

82   Simvastatin.tw. (9569)

83   Ezetimibe/ (2044)

84   Ezetimibe.tw. (3133)

85   Niacin/ (10787)

86   Niacin.tw. (4877)

87   Alendronic acid.tw. (117)

88   Denusomab.tw. (9)

89   or/15-88 (895014)

90   14 and 89 (4523)

91   randomized controlled trial.pt. (516343)

92   controlled clinical trial.pt. (93912)

93   randomized.ab. (497574)

94   placebo.ab. (212224)

95   clinical trials as topic.sh. (193550)

96   randomly.ab. (344066)

97   trial.ti. (227980)

98   91 or 92 or 93 or 94 or 95 or 96 or 97 (1323403)

99   exp animals/ not humans.sh. (4752348)

100   98 not 99 (1218444)

101   90 and 100 (501)

CONTRIBUTIONS OF AUTHORS

Franca Morselli and Mahmood Ahmad drafted the protocol.

Ross J Thomson, Richard Steeds, Ryan McNally, Lorenzo Nesti, Boyang Liu, Haris Khan, Alex Stevenson, Amitava Banerjee, Moghees Hanif and Mansoor Khan revised and amended the protocol.

All authors contributed to the conception and design of the protocol, and approved the final version.

DECLARATIONS OF INTEREST

Franca Morselli (FM): nothing to disclose.

Ryan McNally (RN): nothing to disclose.

Lorenzo Nesti (LN): nothing to disclose.

Boyang Liu (BL): nothing to disclose.

Haris Khan (HK): nothing to disclose.

Ross J Thomson (RT): nothing to disclose.

Alex Stevenson (AS): nothing to disclose.

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