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Drug Therapy for Heart Valve Diseases

Jeffrey S. Borer, MD and **Abhishek Sharma, MD**

Division of Cardiovascular Medicine, The Howard Gilman Institute for Heart Valve Diseases and the Schiavone Institute for Cardiovascular Translational Research, SUNY Downstate Medical Center, Brooklyn and New York, NY

Abstract

Valvular heart diseases (VHDs) are progressive. When not caused by acute comorbidities they are generally characterized by long asymptomatic phases during which hemodynamic severity may progress leading to morbidity and mortality. Treatment depends on VHD type and severity but when severe and symptomatic, usually involves mechanical intervention. Asymptomatic patients, and those who lack objective descriptors associated with high risk, are closely observed clinically with optimization of associated cardiovascular risk factors until surgical indications develop. Though often prescribed based on theory, no rigorous evidence supports pharmacological therapy in most chronic situations though drugs may be appropriate in acute valvular diseases, or as a bridge to surgery in severely decompensated patients. Herein, we examine evidence supporting drug use for chronic VHDs.

Keywords

valve; drug therapy; pharmacology

Valvular heart diseases (VHDs) are among the most predictable causes of heart failure and sudden cardiac death [1]. Observational studies suggest that a relatively high proportion of asymptomatic subjects manifest hemodynamically apparent VHDs varying from mild to severe[1]. VHDs comprise two overarching groups, primary, involving intrinsic abnormalities of valve structures, and secondary, or “functional”, featuring myocardial dysfunction or vascular deformation that secondarily affects valve performance. Clinically, VHDs generally are progressive. When hemodynamically severe but not caused by acute comorbidities (e.g., infection, myocardial infarction) they feature long asymptomatic phases while hemodynamic severity may progress, followed by symptoms and/or objective descriptors that predict morbidity and mortality and are considered to mandate surgery.

Treatment depends on VHD type and severity but, when severe and symptomatic, usually involves mechanical intervention. Asymptomatic patients who lack objective descriptors

Address for Correspondence: Jeffrey S, Borer, MD, SUNY Downstate Medical Center, 47 East 88th Street, New York, NY 10128-1152, Tel: 646-456-4454, Fax: 212-426-4353, jsborer1@gmail.com.

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suggesting high morbid or lethal risk are closely observed clinically (and associated cardiovascular risk factors are optimized) until surgical indications develop.

Though often prescribed based on theory, no rigorous evidence supports pharmacological therapy in most chronic situations, though drugs may be useful in acute valvular diseases, or as a bridge to surgery in severely decompensated patients. This review examines evidence supporting the use of drugs for chronic VHDs. We will focus only on drugs believed to prevent clinical, cardiac functional or valve abnormalities or to delay surgery and will avoid discussion of anticoagulants and of specific antiarrhythmics that might be appropriate in certain settings. Finally, given the volume of available clinical data and the paucity of drugs developed solely for VHD, we will present animal or experimental data only when they importantly supplement clinical information (**Table 1**).

Aortic stenosis (Table 1)

Aortic stenosis (AS) is the most common VHD in adults, increasing in prevalence with age[2]. AS presents a mechanical problem that, when hemodynamically severe, adversely affects the myocardium and ultimately requires aortic valve replacement (AVR). No pharmacological therapy has delayed progression or improved prognosis.

As in all cardiac diseases, clinical manifestations in AS result from the combined mechanical effects of the structural valve abnormality and the myocardial response to the resulting mechanical stresses. Recently, the possible impacts on clinical outcome of tissue injury, inflammation, and variations in hypertrophy and chamber remodeling have been increasingly understood[3]. Simultaneously, factors that may alter progression of valve calcification and dysfunction, such as hypertension and lipid metabolism, have been increasingly elucidated[4]. Consequently, several studies have evaluated the role of statins, angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and bisphosphonates to slow AS progression. Results have been mixed and inconsistent.

Statins

The potential of statins to retard valvular calcification initially was inferred from the similarities in risk factors and histological findings in calcific AS and coronary artery disease (CAD). Subsequent demonstration of similarity of cellular pathways leading to valve calcification and atherosclerotic plaque formation gave credence to the statin hypothesis. This was supported by several early observational studies suggesting reduction in AS progression with statin therapy, independent of changes in plasma lipids. For example, from a single center in which coronary artery calcium was assessed in 620 asymptomatic patients, the 65 patients receiving statins manifested slower AV calcification than those without statins [5]. However, study patients did not have clinically evident AS and no information about dose, statin types or lipid levels was reported[5]. Similarly, in a community-based study, progression was slower during a 3.7 years follow-up among 38 patients with moderate AS who received statins compared to those who did not[6]. Though adjusted for age, gender, cholesterol, and baseline valve area, firm conclusions about causality were not possible because the study was retrospective and non-randomized[6].

Rosuvastatin Affecting Aortic Valve Endothelium to Slow the Progression of Aortic Stenosis (RAAVE) was the first prospective study evaluating statins in AS[7]. Asymptomatic patients with moderate to severe AS and hypercholesterolemia received rosuvastatin per National Cholesterol Education Program Adult Treatment Panel III guidelines; echocardiographic progression over 18 months was compared to that of subjects whose baseline cholesterol values did not meet criteria for initiating statins. Patients who received rosuvastatin had slower echocardiographic AS progression. However, conclusions regarding causality were weakened by the non-randomized, open label study design, the intrinsic metabolic differences between the 2 groups, and the inclusion of predominately elderly patients (mean age >76 years). The Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) was the first prospective randomized double-blinded study of intensive lipid lowering therapy (atorvastatin 80mg per day) on AS progression [8]. After 25 months, statins had no significant effect. Subsequently, in the larger randomized, double-blind Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial, 1873 asymptomatic patients with mild to moderate AS and no other indication for lipid-lowering treatment received either placebo or simvastatin (40mg) plus ezetimibe (10mg)[9]. After 52.2 months (mean), lipid lowering therapy did not slow AS progression or reduce AS-related events though concomitant CAD events were significantly diminished [9].

In the Effect of Lipid Lowering With Rosuvastatin on Progression of Aortic Stenosis: Results of the Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTRONOMER) trial, the potential impact of the relatively advanced age (mean 68 years) of SEAS patients and of confounding by addition of a non-statin were addressed by placebo controlled design[10]. Of 269 patients, mean age 58years with mild to moderate AS and no clinical indications for cholesterol lowering, 40mg daily of rosuvastatin had no significant impact[10].

More recently, a relation between lipids and AS was sought in 35403 subjects by measuring genetic predisposition to abnormal plasma concentrations of LDL-C, HDL-C and triglycerides and defining the association of this measure with development of either tomographic AV calcium or overt AS [11]. The moderate association between LDL-C and the outcome variables suggested but did not prove a pathogenic relation.

Discordance between these studies may result in part from extensive mineralization in absence of smooth muscle proliferation in AS but not in CAD, suggesting different calcification pathways in the 2 diseases [12]. Hypothetically, LDL-C may be important in early stages of AS but unimportant when calcific AS is already established. However, until this hypothesis is supported with data, use of statins to limit progression of AS cannot be recommended.

Bisphosphonates

Calcification is central to AS progression and to bone formation. The calcified AV expresses proteins similar to those associated with bone formation[13,14]. Also, AS progression involves differentiation of myofibroblasts into osteoblasts. Patients with AS have higher plasma concentrations of osteogenic factors Runx2 and osteopontin than those without

AS[15, 16].These factors promote formation of calcific nodules and have a complex interaction with lipid synthetic pathways.

Since bisphosphonates inhibit vascular calcification, they may also delay progression or induce regression of AS[17]. This theory is supported by small retrospective studies reporting delay in loss of valve area[18, 19]. However, in a large retrospective analysis of 801 females (mean age 76 years) with mild to moderate AS, bisphosphonates failed to impact AS progression after >5years[20]; survival and AVR rate were unaffected over >3 years[20]. Thus, currently, bisphosphonate therapy cannot be recommended for slowing AS progression.

ACEIs/ARBs

Histopathological studies demonstrate up-regulation of ACE and angiotensin II in sclerotic AVs and suggest these factors promote AS progression[21]. ACE generates angiotensin II, facilitating degradation of antifibrotic bradykinin, thus promoting AV fibrosis[22]. Angiotensin II attracts inflammatory cells and promotes LDL uptake by macrophages[12, 23, 24], perhaps promoting AS. Also, the renin-angiotensin system is believed to modulate adverse LV remodeling and myocardial fibrosis, a response to the pressure load of AS[25].

Nonetheless, early guidelines recommended caution in using ACEIs/ARBs in AS because of possible hemodynamic collapse. More recent studies have obviated these concerns. For example, in a randomized, double-blind, prospective study of 56 symptomatic patients with severe AS, ACEIs were well tolerated and improved exercise tolerance[26]. In parallel, among 2100 patients with varying degrees of AS studied retrospectively over 4.2 years, ACEIs/ ARBs were associated with improved survival and reduced adverse cardiovascular events [27].

In observational cohort studies (two retrospective, one prospective) ACEIs were associated with reduced calcium accumulation or AS progression[28-30] ; such an effect was suggested among the 82 patients who received statins with or without ACEI, though results were unrelated to blood cholesterol concentration[30].

Thus, though ACEI/ARB are safe in AS, their use to delay AS progression still needs evaluation in prospective randomized trials and cannot be recommended at this time. Additionally, though molecular and cellular data suggest beneficial effects of ACEI/ARB in AS, their effect on blood pressure also may be important. Hypertension is a well-established risk factor for AS progression[4,31], though the beneficial effect of hypertension amelioration, per se, has not been established in AS.

Aortic regurgitation (Table 1)

Though randomized controlled trial data do not exist, valve replacement or repair is the only generally accepted therapy to relieve symptoms in aortic regurgitation (AR). Probably, this strategy also is the only way to improve survival among symptomatic patients or those who, though aymptomatic, manifest specific indicators of myocardial dysfunction[32-36]. Nonetheless, since myocardial dysfunction in AR results directly from the abnormal wall stresses/strains of volume loading[37, 38], pharmacological unloading with vasodilators might

mitigate adverse outcomes in AR *IF* unloading magnitude is sufficient and drugs cause no unacceptable adverse effects.

Long-term outcome data are relatively sparse. Nonetheless, it appears that the effect of drugs in patients with AR may be importantly associated with comorbid systemic hypertension. Though a role in AR genesis is not rigorously established, experimental models suggest a causal association between hypertension and AR[39], AR prevalence is higher in hypertensive than in normotensive patients[40, 41] and normotensive patients with moderate AR have less longitudinal axis dysfunction than analogous hypertensive patients[42]. Also, systolic hypertension (>140mmHg) accelerates the progression of valve dysfunction, worsens cardiac function and is a risk factor for AVR indications and for adverse clinical outcomes, irrespective of AR etiology[43-46]. Thus, in a prospective assessment of outcomes among 80 consecutive asymptomatic patients with AR and normal LVEF, during a 7.2 year event-free follow-up, 24 subjects developed heart failure symptoms, subnormal LVEF at rest or death.[46] It is surprising, then, that long-term antihypertensive therapies as a group are associated with heightened risk of subsequent cardiac events, though the effect of individual drug types may vary[46]. Indeed, among the 30 subjects with systolic hypertension in the prospective study, antihypertensive therapy was associated with average annual event risk 15.5%, four-fold the risk (4%) of hypertensive subjects who did not receive such drugs ($p < 0.02$); the difference remained significant when analysis was adjusted for blood pressure at entry[46]. Most patients received ACEIs or ARBs and/or diuretics and some, direct vasodilators (none received calcium channel blockers). In contrast, as described below, long acting nifedipine appears to be beneficial in hypertensive subjects with AR.

Vasodilators

Various vasodilators have improved ventricular performance and reduced AR magnitude (nitrates, hydralazine, ACEIs) [47-50]. However, only long acting nifedipine has reduced morbidity and mortality. Reduction in LV mean wall stress and increased LVEF had been reported with long-acting nifedipine among asymptomatic patients with severe AR and normal LV systolic function[51]. Subsequently, a randomized controlled trial demonstrated that, in comparison with digoxin, long acting nifedipine delayed indications for AVR in asymptomatic patients with severe AR and normal LV systolic function[52]. Though outcomes with digoxin were similar to those previously reported in absence of therapy[35, 53], concern about the potential confounding effect of digoxin persisted until another randomized controlled trial, comparing nifedipine with no drug therapy, revealed that long-acting nifedipine delayed the need for AVR and also improved clinical/functional status long after AVR [54]. The reason for the efficacy of long-acting nifedipine (other vasodilators do not seem to have parallel effects) may be related to the blood pressure of patients in the two nifedipine trials. Individual subjects' blood pressures were not reported, but mean systolic pressure in the earlier study was 154mmHg and, in the second, 165mmHg, both substantially higher than the previously noted 140mmHg risk threshold [52, 54]. A third randomized, controlled trial found no difference in outcome between nifedipine and no therapy (hazard ratio 1.17, NS, nominally favoring no therapy) among asymptomatic patients with normal baseline LVEF[55]. However, baseline mean systolic pressures in this trial were 143mmHg in the control group and 147 mmHg in the nifedipine group, not

significantly different from one another, and substantially closer to the threshold than in the earlier trials. This trial included 95 patients in 3 groups (one group received enalapril). Therefore, despite the prolonged 7-year follow-up, power to detect statistically significant differences in clinical outcomes was modest[55]. Taken together, these results suggest that the better outcomes with nifedipine in the earlier trials related to treatment of hypertension rather than to a mechanism specifically related to AR.

ACEIs, indirect vasodilators, act primarily by decreasing production of angiotensin II, supernormal in chronic AR[56]. In experimental severe AR, ACEIs improved myocardial metabolism and survival in association with reduction of LV hypertrophy and other structural changes[57]. In patients with chronic AR, ACEI diminished regurgitant volume[49]. Also, in a 12 month randomized double blind trial of asymptomatic patients with non-rheumatic mild to moderate AR, LV end diastolic and systolic volumes and mass indices improved with enalapril compared with hydralazine[58]. In a retrospective observational study of 876 patients (median systolic blood pressure 140mmHg) with moderate to severe AR, clinical outcomes were related to use of ACEIs/ARBs[59], with significantly lower all-cause mortality and adverse cardiovascular events among those receiving renin-angiotensin system blockade. However, the severity of AR varied widely within the cohort, cardiac (and other) comorbidities were not reported or incorporated in the analysis, and echocardiographic progression of AR was not assessed[59]. Thus, study design limitations preclude firm conclusions from these retrospective data.

Moreover, in the previously noted randomized outcomes trial[55], enalapril nominally was associated with worse outcomes than no therapy (hazard ratio 1.77, NS, after 7 years, favoring no therapy; systolic blood pressure at baseline was 142 before enalapril, 143 before control); nifedipine also was nominally better than enalapril (hazard ratio 0.71, NS)[55].

The apparent lack of efficacy of ACEI/ARB may relate to their non-vasodilating pharmacological effects, specifically prevention of angiotensin-induced production of TNF-α, which stimulates interstitial fibroblast collagen production, or, alternatively, to relative increase in antifibrotic bradykinin, which mitigates collagen synthesis[60]. Collagen synthesis may be important in slowing the LV dilatation caused by AR, thus retarding the increase in wall stress that is transduced to myocyte dysfunction and heart failure[61].

Beta blockers

Chronic volume overload due to AR results in substantial alterations of adrenergic activity and adrenergic receptor density/function [62-64]. However, benefits of beta blockade would be surprising: slowing heart rate in AR should increase regurgitant volume, stroke volume and afterload. Nonetheless, few empirical data support this concern. Indeed, in an animal model of AR with experimentally maintained bradycardia, maximal cardiac minute work increased[65]. In another animal model of severe AR, long-term beta blockade preserved LV filling parameters and LVEF and prevented cardiac hypertrophy and dilatation, apparently by modulating extracellular remodeling[66]. However, presumably because of the relatively low doses employed, heart rate was only minimally affected, unexpected given the association of heart rate reduction with improved survival in systolic heart failure[67]. In

patients with impaired LV function after AVR[68] beta blocker therapy ameliorates LV dysfunction and reduces LV volume and mass, paralleling its actions in systolic heart failure[69-71].

The utility of beta blockers in unoperated patients with AR remains to be studied.

Mineralocorticoid receptor antagonists (MRA)

The MRA, spironolactone, reduces myocardial fibrosis and LV mass among rodents with chronic AR[72]. However, the impact of the drug on the specific components of fibrosis that are most likely important pathophysiologically (glycoproteins, rather than collagen[61]) has not been defined. A role for such therapy in humans remains to be demonstrated.

Mitral regurgitation (Table 1)

MR differs from AR in that, while both feature LV volume overload, regurgitation into the left atrium in MR commonly leads to pulmonary hypertension with pressure overload of the right ventricle (RV). Indeed, RV dysfunction appears to occur earlier and to have greater prognostic impact than LV changes[73]. (Pulmonary vasodilators have not been assessed in MR.) Because of the low outflow impedance into the left atrium, afterload abnormalities of the LV occur less frequently and later in MR than in AR[74], but nonetheless ultimately lead to impairment of myocardial contractility[75].

In acute severe MR, drug therapy can stabilize patients preparing for surgery. In normotensive patients, intravenous nitroprusside reduces pulmonary congestion and regurgitant volume, increases forward flow and reduces MR severity[76, 77]. In hypotensive patients, management is more complex: intravenous nitroprusside plus inotropic agents, or intraaortic balloon counterpulsation, have been useful[32].

In chronic primary MR (leaflet dysfunction), current consensus favors surgery for symptoms and when certain objective descriptors develop indicating “high risk”. No role for pharmacological therapy has been demonstrated. When MR is “functional” (secondary to myocardial dysfunction) treatment proceeds according to algorithms for heart failure though here, too, no rigorous demonstration of benefit has been shown.

ACEIs/ARB

Valve surgery is the treatment of choice for primary MR though clinicians commonly employ ACEIs/ARBs in asymptomatic patients to delay disease progression[78]. There is absolutely no evidence to support this strategy. In absence of hypertension and/or clinical decompensation, ACEIs/ARBs are not recommended by AHA/ACC for primary MR[32]. In fact, animal models[79, 80, 81] (and limited clinical trial data[82]) have shown detrimental effects of these drugs on LV contractility and volumes. Most recently, in a prospective observational cohort, ACEI/ARB were not associated with benefit on outcomes, though benefit was suggested among those with hypertension[83].

Nonetheless, in a prospective, placebo controlled, double-blind study of 23 patients with chronic moderate MR and normal LV function, lisinopril reduced MR severity[84] and, in

another trial, ACEIs reduced LV mass and volumes after 6 months of therapy in asymptomatic patients[85]. However, studies reporting hemodynamic/functional benefits of ACEIs in chronic MR have been limited by small sample sizes, withdrawal of therapy from substantial numbers of subjects because of drug intolerance, and failure to relate observations to pretherapy LV size and function or MR severity. Moreover, benefits of ACEIs/ARBs are not consistent: several studies reported no improvement in systolic function[82, 83] and none has demonstrated reduction in clinical events. In a randomized controlled trial of enalapril for exercise tolerance, after 1 year, enalapril produced worse oxidative threshold than no therapy [82].

Nonetheless, these drugs may be useful in secondary (functional) MR, for which current published guidelines suggest pharmacological management as if for systolic heart failure[32].

Beta blockers

Beta blockade for MR was first suggested by the relation between sympathetic traffic and loss of contractility in both animal models and patients with MR[86, 87]. Volume overload due to MR leads to a heightened β-adrenergic state, decreased myocyte protein synthesis and extracellular matrix degradation, similar to that in systolic heart failure. In animal models of chronic MR, beta blockade improves intrinsic contractile function of isolated cardiomyocytes and increases contractile elements[88, 89]. However, disturbingly, in a recent study of rodents with surgically-induced MR, carvedilol-mediated reduction in heart rate resulted in significant decrease in LVEF, increase in LV volumes and, most importantly, increase in mortality compared with no therapy[90, 91].

In a retrospective cohort study, survival apparently was better among those who received beta blockers than those who did not, even after adjustment for important baseline variables[92]. A 2 year randomized, double-blind study of metoprolol among 38 asymptomatic patients with moderate to severe, isolated MR and normal LV ejection fraction revealed increased LVEF and early diastolic filling rate but no effect on LV volumes, strain rate, wall thicknesses or mass [93]. This study was too small to meaningfully assess clinical outcomes[93]. In the absence of rigorous data from randomized controlled trials, benefit cannot be firmly inferred.

Acuity and severity of surgically created MR in animal models versus response to chronic and possibly gradually worsening MR in humans, along with differences in heart rate response and use of different beta blockers in different studies, precludes rigorous extrapolations from experimental studies to clinical practice. Consequently, currently, beta blockade cannot be recommended to prevent progression of myocardial dysfunction or to reduce clinical events in chronic primary MR. The situation may differ in secondary (“functional”) MR, most commonly resulting from coronary artery disease with myocardial infarction, which, as noted above, may respond relatively well to standard pharmacological therapy for systolic heart failure.

Mitral stenosis (Table 1)

No pharmacological therapy can relieve the fixed mechanical obstruction of mitral stenosis (MS) or the pulmonary vascular congestion and pulmonary hypertension that eventually occur when MS is severe. As pulmonary hypertension worsens, the consequences are similar to those in MR, i.e., RV dysfunction and, ultimately, right heart failure. Though drugs cannot affect the valve obstruction, lengthening diastole by reducing heart rate can ameliorate hemodynamic abnormalities and symptoms. This can be achieved with beta blockers or, less well, with non-dihydropyridine calcium channel blockers[94], but not with digoxin[95]. As long as pulmonary hypertension and symptoms are mild, such treatment is reasonable and can be beneficially supplemented with diuretics. Survival is quite good in this situation, though there is no evidence that any drug therapy prolongs survival. However, when symptoms and/or pulmonary hypertension become severe, mitral balloon dilatation or surgery are necessary[32].

The impedance to LV inflow in MS is directly transmitted to left atrium as volume and pressure loading[96]. Left atrial overload alters atrial electrophysiological properties and predisposes to atrial fibrillation, present in one third of symptomatic patients with MS. Atrial fibrillation impacts negatively on clinical outcome[96, 97]. Atrial fibrillation increases risk of systemic embolization and, when ventricular rate is relatively high and diastolic duration limited, the arrhythmia minimizes forward stroke volume, increasing left atrial pressure and worsening pulmonary congestion[96, 97]. In MS atrial fibrillation often initially is paroxysmal, then persistent and eventually therapy resistant/ permanent[96]. When paroxysmal, antiarrhythmic drugs may maintain sinus rhythm. However such therapy usually is not durable. Arrhythmia persistence may be an indication for mechanical therapy.

Tricuspid regurgitation (Table 1)

Severe tricuspid regurgitation (TR) is associated with adverse clinical outcomes, independent of age, RV or LV systolic function, RV size, and inferior vena cava dilatation. Severe TR results in progressive RV pressure and volume overload and progressive RV failure. Most TR is secondary to left heart disease. Repair or replacement of mechanically defective left heart structures, with repair or replacement of an irreversibly misshapen tricuspid valve, is the therapy of choice. If left heart surgery is not feasible, drugs for left heart problems should be employed. However, since the primary effect of TR is to limit forward cardiac output, symptom relief can be difficult. Diuretics may be useful but can further limit forward output. Primary tricuspid regurgitation is now recognized as a clinically debilitating problem. Appropriate criteria for tricuspid valve surgery currently are under study. No drugs are clearly effective for primary TR. The failing RV undergoes remodeling marked by alterations in expression of a fetal gene program including increased expression of PDE-5. This is particularly prominent in patients with ischemic cardiomyopathy[98]. PDE5 inhibitors can increase RV inotropy independent of concurrent reduction of RV outflow impedance[99]. However, when TR is complicated by RV failure, clinical benefit of PDE5 inhibitors remains to be demonstrated.

Conclusions

No drug ever has been developed specially for use in chronic VHD. Efforts to apply drug therapy have employed agents developed for other purposes. Moreover, despite theoretical considerations and some promising experimental studies, no drug therapy has been rigorously demonstrated to improve clinical outcomes in patients with chronic VHD except in treatment for some specific comorbidities. As in all areas of VHD, randomized controlled trial experience is sorely lacking to inform decisions about drug use. Such trials should be the primary focus of future activities in the area.

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Table

Effects of drugs on functional measures, progression and clinical outcomes of VHD.

	AS	AR	MS	MR	TR
ACEi/ARB	RCT: +*; OS: + ; DNR	RCT: −; OS: + ; DNR	N	RCT: N; OS: +; DNR	N
Beta-blockers	N	BA, F; DNR	F	BA, F; DNR	N
Bisphosphonates	RCTs: N; OS:±; DNR	N	N	N	N
Hydralazine	N	F, DNR	N	N	N
MRAs	N	N	N	N	N
Nitrates	F	F; DNR	N	F; DNR	N
Nifedipine	N	+**	N	N	N
Statin	RCTs: −; DNR	N	N	N	N

VHD: valvular heart diseases; AS: aortic stenosis; AR: aortic regurgitation; MS: mitral stenosis; MR: mitral regurgitation; TR: tricuspid regurgitation; ACEi: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; MRA: mineralocorticoid receptor antagonists; RCT: randomized controlled trials; OS: observational studies; N: not studied/insufficient data; +: benefit; −: no benefit; ±: mixed/inconsistent results on clinical natural history; BA : beneficial effects in animal models only; F: short-term hemodynamic/functional benefits in humans, no long-term data DNR: do not recommend

* RCT benefit for exercise tolerance only; no natural history outcome data

** RCT benefit for progression/natural history apparently only for hypertensive patients