Drug Therapy for Heart Valve Diseases

Jeffrey S. Borer, MD; Abhishek Sharma, MD

Valvular heart diseases (VHDs) are among the most predictable causes of heart failure and sudden cardiac death. Observational studies suggest that a relatively high proportion of asymptomatic subjects manifest hemodynamically apparent VHDs varying from mild to severe. VHDs comprise 2 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 (eg, infection, myocardial infarction) they feature long asymptomatic phases while hemodynamic severity may progress, followed by symptoms 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 suggesting high morbidity or lethal risk are closely observed clinically (and associated cardiovascular risk factors are optimized) until surgical indications develop.

Although often prescribed based on theory, no rigorous evidence supports pharmacological therapy in most chronic situations, although 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 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).

Aortic Stenosis

Aortic stenosis (AS) is the most common VHD in adults, increasing in prevalence with age. 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. Simultaneously, factors that may alter the progression of valve calcification and dysfunction, such as hypertension and lipid metabolism, have been increasingly elucidated. 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 historical findings in calcific AS and coronary artery disease. Subsequent demonstration of the 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 aortic valve (AV) calcification than those without statins. However, study patients did not have clinically evident AS and no information about dose, statin types, or lipid levels was reported. Similarly, in a community-based study, progression was slower during a 3.7-year follow-up among 38 patients with moderate AS who received statins in comparison with those who did not. Although adjusted for age, sex, cholesterol, and baseline valve area, firm conclusions about causality were not possible because the study was retrospective and nonrandomized.

Rosuvasatin Affecting Aortic Valve Endothelium to Slow the Progression of Aortic Stenosis (RAAVE) was the first prospective study evaluating statins in AS. Asymptomatic patients with moderate to severe AS and hypercholesterolemia received rosuvasatin per National Cholesterol Education Program Adult Treatment Panel III guidelines; echocardiographic progression over 18 months was compared with that of subjects whose baseline cholesterol values did not meet criteria for initiating statins. Patients who received rosuvasatin had slower echocardiographic AS progression. However, conclusions regarding causality were weakened by the nonrandomized, 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 80 mg per day) on AS progression. 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 (40 mg) plus ezetimibe (10 mg). After 52.2 months (mean), lipid-lowering therapy did not slow progression or reduce AS-related events, although concomitant coronary artery disease events were significantly diminished.

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 nonstatin were addressed by placebo-controlled design. In 269 patients, with a mean age of 58 years with mild to moderate AS and no clinical indications for cholesterol lowering, 40 mg daily of rosvastatin had no significant impact.

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

Discordance between these studies may result in part from extensive mineralization in the absence of smooth muscle proliferation in AS but not in coronary artery disease, suggesting different calcification pathways in the 2 diseases. Hypothetically, low-density lipoprotein cholesterol may be important in the early stages of AS, but unimportant when calcific AS is already established. However, until this hypothesis is supported with data, the use of statins to limit the 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. 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. Bisphosphonates fail to impact AS progression after >5 years; survival and AVR rate were unaffected over >3 years. Thus, currently, bisphosphonate therapy cannot be recommended for slowing AS progression.

**Angiotensin-Converting Enzyme Inhibitors/ Angiotensin Receptor Blockers**
Histopathologic studies demonstrate upregulation of ACE and angiotensin II in sclerotic AVs and suggest these factors promote AS progression. ACE generates angiotensin II, facilitating the degradation of antifibrotic bradykinin, thus promoting AV fibrosis. Angiotensin II attracts inflammatory cells and promotes low-density lipoprotein uptake by macrophages, perhaps promoting AS. Also, the renin-angiotensin system is believed to modulate adverse left ventricular (LV) remodeling and myocardial fibrosis, a response to the pressure load of AS.

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

| Table. Effects of Drugs on Functional Measures, Progression, and Clinical Outcomes of VHD |
|---------------------------------|--------|--------|--------|--------|--------|
| **ACEI/ARB**                    | **AS** | **AR** | **MS** | **MR** | **TR** |
| β-Blockers                     | RCT: +; OS: +; DNR | RCT: –; OS: +; DNR | N | RCT: N; OS: +; DNR | N |
| Bisphosphonates                | RCTs: N; OS: ±; DNR | N | N | N | N |
| Hydralazine                    | N | F | DNR | N | N |
| MRAs                            | N | N | N | N |
| Nitrates                       | F | F | DNR | N | F | DNR | N |
| Nifedipine                     | N | + † | N | N | N |
| Statin                         | RCTs: –; DNR | N | N | N | N |

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

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

†RCT benefit for progression/natural history apparently only for hypertensive patients.
study of 56 symptomatic patients with severe AS, ACEIs were well tolerated and improved exercise tolerance. 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. Nonetheless, since myocardial dysfunction in AR results from the abnormal wall stresses/strains of volume concentration. ACEIs, although results were unrelated to blood cholesterol concentration.

In observational cohort studies (2 retrospective, 1 prospective), ACEIs were associated with reduced calcium accumulation or AS progression, such an effect was suggested among the 82 patients who received statins with or without ACEI, although results were unrelated to blood cholesterol concentration.

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

**Aortic Regurgitation**

Although randomized, controlled trial data do not exist, valve replacement or repair is the only generally accepted therapy to relieve symptoms in aortic regurgitation (AR). This strategy probably is also the only way to improve survival among symptomatic patients or those who, although asymptomatic, manifest specific indicators of myocardial dysfunction. Nonetheless, since myocardial dysfunction in AR results directly from the abnormal wall stresses/strains of volume loading, 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 (Table). Nonetheless, it appears that the effect of drugs in patients with AR may be importantly associated with comorbid systemic hypertension. Although a role in AR genesis is not rigorously established, experimental models suggest a causal association between hypertension and AR. AR prevalence is higher in hypertensive than in normotensive patients, and normotensive patients with moderate AR have less longitudinal axis dysfunction than analogous hypertensive patients. Also, systolic hypertension (>140 mmHg) 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. Thus, in a prospective assessment of outcomes among 80 consecutive asymptomatic patients with AR and normal LV ejection fraction (LVEF), during a 7.2-year event-free follow-up, 24 subjects developed heart failure symptoms, subnormal LVEF at rest, or death. It is surprising, then, that long-term antihypertensive therapies as a group are associated with heightened risk of subsequent cardiac events, although the effect of individual drug types may vary. Indeed, among the 30 subjects with systolic hypertension in the prospective study, antihypertensive therapy was associated with average annual event risk 15.5%, 4-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. Most patients received ACEIs or ARBs with or without diuretics and some received 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). 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. 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. Although outcomes with digoxin were similar to those previously reported in the absence of therapy, 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. 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 2 nifedipine trials. Individual subjects’ blood pressures were not reported, but mean systolic pressure in the earlier study was 154 mmHg and, in the second, 165 mmHg, both substantially higher than the previously noted 140 mmHg risk threshold. A third randomized, controlled trial found no difference in outcome between nifedipine and no therapy (hazard ratio, 1.17; not significant, nominally favoring no therapy) among asymptomatic patients with normal baseline LVEF. However, baseline mean systolic pressures in this trial were 143 mmHg 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 (1 group received enalapril). Therefore, despite the prolonged 7-year follow-up, the power to detect statistically significant differences in clinical outcomes was modest. Taken together, these results suggest that the better outcomes with nifedipine in the earlier trials related to the treatment of hypertension rather than to a mechanism specifically related to AR.

ACEIs, indirect vasodilators, act primarily by decreasing the production of angiotensin II, supernormal in chronic AR. In experimental severe AR, ACEIs improved myocardial metabolism and survival in association with the reduction of LV hypertrophy and other structural changes. In patients with chronic AR, ACEI diminished regurgitant volume. Also, in a 12-month randomized, double-blind trial of asymptomatic patients with nonrheumatic mild to moderate AR, LV end-diastolic and systolic volumes and mass indices improved with enalapril in comparison with hydralazine. In a retrospective observational study of 876 patients (median systolic blood pressure, 140 mmHg) with moderate to severe AR, clinical outcomes were related to the use of ACEIs/ARBs,
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.66 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; not significant, 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, not significant).55

The apparent lack of efficacy of ACEI/ARB may relate to their nonvasodilating pharmacological effects, specifically prevention of angiotensin-induced production of tumor necrosis factor-α, which stimulates interstitial fibroblast collagen production, or, alternatively, to relative increase in anti-fibrotic 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

**β-Blockers**

Chronic volume overload attributable to AR results in substantial alterations of adrenergic activity and adrenergic receptor density/function.62–64 However, benefits of β-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 β-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 used, heart rate was only minimally affected, which was 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 β-blocker therapy ameliorates LV dysfunction and reduces LV volume and mass, paralleling its actions in systolic heart failure.69–71

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

**Mineralocorticoid Receptor Antagonists**

The mineralocorticoid receptor antagonist, 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 pathophysologically (glycoproteins, rather than collagen)63 has not been defined. A role for such therapy in humans remains to be demonstrated.

**Mitra Regurgitation**

Mitrval regurgitation (MR) differs from AR in that, whereas 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 intra-aortic 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, although here, too, no rigorous demonstration of benefit has been presented.

**Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers**

Valve surgery is the treatment of choice for primary MR though clinicians commonly use ACEIs/ARBs in asymptomatic patients to delay disease progression.78 There is absolutely no evidence to support this strategy. In the absence of hypertension or clinical decompensation, ACEIs/ARBs are not recommended by American Heart Association/American College of Cardiology for primary MR.32 In fact, animal models79–81 (and limited clinical trial data82) have shown detrimental effects of these drugs on LV contractility and volumes. Most recently, in a prospective observational cohort, ACEIs/ARBs were not associated with benefit on outcomes, although 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 severity84 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, the benefits of ACEIs/ARBs are not consistent: several studies reported no improvement in systolic function82,83 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
β-Blockers

β-Blockade for MR was first suggested by the relation between sympathetic traffic and the loss of contractility in both animal models and patients with MR.90,91 Volume overload attributable 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, β-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 a significant decrease in LVEF, an increase in LV volumes, and, most importantly, an increase in mortality compared with no therapy.90,91

In a retrospective cohort study, survival apparently was better among those who received β-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 clinical outcomes.33 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 β-blockers in different studies, precludes rigorous extrapolations from experimental studies to clinical practice. Consequently, currently, β-blockade cannot be recommended to prevent the 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.

Mitrail Stenosis

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, ie, RV dysfunction and, ultimately, right heart failure. Although drugs cannot affect the valve obstruction, lengthening diastole by reducing heart rate can ameliorate hemodynamic abnormalities and symptoms. This can be achieved with β-blockers or, less well, with nondihydropyridine 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, although there is no evidence that any drug therapy prolongs survival (Table). However, when symptoms or pulmonary hypertension become severe, mitral balloon dilatation or surgery are necessary.32

The impedance to LV inflow in MS is directly transmitted to the 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.95,96 Atrial fibrillation increases the risk of systemic embolization and, when ventricular rate is relatively high and diastolic duration is limited, the arrhythmia minimizes forward stroke volume, increasing left atrial pressure and worsening pulmonary congestion.90,97 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

Severe tricuspid regurgitation (TR) is associated with adverse clinical outcomes, independent of age, RV or LV systolic function, RV size, and inferior vena cava dilation. 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 used. However, because 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 phosphodiesterase type 5. This is particularly prominent in patients with ischemic cardiomyopathy.98 Phosphodiesterase type 5 inhibitors can increase RV inotropy independent of concurrent reduction of RV outflow impedance.99 However, when TR is complicated by RV failure, the clinical benefit of phosphodiesterase type 5 inhibitors remains to be demonstrated.

Conclusions

No drug ever has been developed specially for use in chronic VHD. Efforts to apply drug therapy have used 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 the 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.

Sources of Funding

Work performed by Dr Borer that was critical to the creation of this review was supported at various times by The Howard Gilman Foundation (New York, NY), The Schiavone Family Foundation (White House Station, NJ), The Gladys and Roland Harriman
Disclosures

Dr Borer has consulting relationships with Servier Laboratoires, Amgen, Takeda USA, Novartis, Pfizer, ARMGO, and Celladon; he also owns stock in BioMARIN. Dr Sharma reports no conflicts.

References


improve left ventricular function and remodeling in subacute mitral regur-
treatment in dogs.

Volume-overload cardiac hypertrophy is unaffected by ACE inhibitor
magnetic heart disease.
diameters and exercise capacity in asymptomatic or mildly symptomatic
Sampaio R
Cardiol

Mechanism of reduction of mitral regurgitation with vasodilator therapy.
J Am Coll Cardiol
1993;88:2700–2704. doi: 10.1161/JAHA.88.6.2700.

Starling MR. Emerging biology of mitral regurgitation: implications for

Tsutsui H, Spinaile FG, Nagatsu M, Schmid PG, Ishihara K, DeFreyte G,
Cooper G 4th, Carabello BA. Effects of chronic beta-adrenergic block-
ade on the left ventricular and cardiocyte abnormalities of chronic canine
JC117277.

Pu M, Gao Z, Pu DK, Davidson WR Jr. Effects of early, late, and long-
term nonselective beta-blockade on left ventricular remodeling, function,
and survival in chronic organic mitral regurgitation. Circ Heart Fail.

Borer JS. Mitral regurgitation: has another magic bullet bitten the dust? Circ Heart Fail. 2013;6:624–626. doi: 10.1161/CIRC Heart Fail.113.000409.

Varadarajan P, Joshi N, Appel D, Duvvuri L, Pui RG. Effect of Beta-
blocker therapy on survival in patients with severe mitral regurgitation
and normal left ventricular ejection fraction. Am J Cardiol. 2008;102:611–

Ahmed MI, Aban I, Lloyd SG, Gupta H, Howard G, Iusah S, Peri K,
Robinson J, Smith P, McGiffin DC, Schiros CG, Denney T Jr, Dell’Italia
LJ. A randomized controlled phase IIb trial of beta(1)-receptor blockade

Alam S, Ugen MS, Ozdemir K, Keles T, Toprak N. Reliability and effi-
cacy of metoprolol and diiltiazem in patients having mild to moderate
mitral stenosis with sinus rhythm. Angiology. 2002;53:575–581. doi:

Beiser GD, Epstein SE, Stampfer M, Robinson B, Braunwald E. Studies on
digitalis. XVII. Effects of ouabain on the hemodynamic response to


Olesen KH. The natural history of 271 patients with mitral stenosis under

Shan X, Quaile MP, Monk JK, French B, Cappola TP. Margulies
KB. Differential expression of PDEs in failing and nonfailing human myocardium. Circ Heart Fail. 2012;5:79–86. doi: 10.1161/
CIRC Heart Fail.111.961706.

A, St Aubin C, Webster L, Rebeyka IM, Ross DB, Light PE, Dyck J,
Michelakis ED. Phosphodiesterase type 5 is highly expressed in the
hypertrophied human right ventricle, and acute inhibition of phosphodies-

KEY WORDS: drug therapy ● heart valve diseases ● pharmacology
Drug Therapy for Heart Valve Diseases
Jeffrey S. Borer and Abhishek Sharma

Circulation. 2015;132:1038-1045
doi: 10.1161/CIRCULATIONAHA.115.016006
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/132/11/1038

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/