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Therapeutic Controversies in the Medical Management of Valvular Heart Disease

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Abstract

Objective: To evaluate the evidence for common therapeutic controversies in the medical management of valvular heart disease (VHD). **Data Sources:** A literature search of PubMed (inception to December 2020) was performed using the terms *angiotensin-converting enzyme* (ACE) *inhibitors* or *angiotensin receptor blockers* (ARBs) and *aortic stenosis* (AS); and *adrenergic β-antagonists* and *aortic valve regurgitation* (AR) or *mitral stenosis* (MS). **Study Selection and Data Extraction:** Randomized controlled trials (RCTs) and meta-analyses conducted in humans and published in English that reported ≥1 clinical outcome were included. **Data Synthesis:** Nine articles were included: 3 RCTs and 1 meta-analysis for ACE inhibitors/ARBs in AS, 1 RCT for β-blockers in AR, and 4 RCTs for β-blockers in MS. Evidence suggests that ACE inhibitors/ARBs do not increase the risk of adverse outcomes in patients with AS but may delay valve replacement. β-Blockers do not appear to worsen outcomes in patients with chronic AR and may improve left-ventricular function in patients with a reduced ejection fraction. β-Blockers do not improve and may actually worsen exercise tolerance in patients with MS in sinus rhythm. **Relevance to Patient Care and Clinical Practice:** ACE inhibitors/ARBs and β-blockers can likely be safely used in patients with AS or AR, respectively, who have a compelling indication. There is insufficient evidence to recommend routine use of β-blockers in patients with MS without atrial fibrillation. **Conclusions:** Common beliefs about the medical treatment of VHD are not supported by high-quality data. There remains a need for larger-scale RCTs in the medical management of VHD.

Keywords

adrenergic β-antagonists, aortic valve insufficiency, aortic valve stenosis, angiotensin receptor antagonists, angiotensin-converting enzyme inhibitors, drug therapy, heart valve diseases, mitral valve stenosis

Introduction

Valvular heart disease (VHD) has an estimated prevalence of 2% to 3% in the United States adult population and can be categorized as either acquired or congenital.[1] The most prevalent etiology of acquired VHD in North America is aging—the incidence increases from <1% in those aged 18 to 44 years to 12% to 13% in those aged ≥75 years.[1] The prevalence of VHD is likely to increase as the overall population ages. For example, the number of patients with aortic stenosis (AS) secondary to calcific degeneration is estimated to double in the United States by 2050.[1] In contrast, rheumatic fever is the most common cause of VHD worldwide.[1] Mild VHD is pervasive in the population, and a prospective cohort study in the United Kingdom identified previously undiagnosed VHD in approximately half of individuals aged ≥65 years.[2]

The definitive treatment for VHD is surgical intervention. Further, less-invasive interventions, such as transcatheter valve replacement techniques, are becoming more routinely adopted as viable alternatives to open heart surgery. However, medical management is still necessary in patients who are waiting for or deemed to be unsuitable for surgery. Currently, no pharmacological therapies have been shown to improve survival or prevent disease progression in persons with VHD.[3] Thus, the goal of medical management of VHD is to improve cardiac hemodynamics, reduce symptoms, and prevent adverse myocardial remodeling. Some pharmacological interventions have been adequately studied in patients with VHD, such as the lack of benefit

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with statins in patients with AS.[3] However, in practice, there are a number of controversial therapeutic beliefs that are still widely disseminated among clinicians in the medical management of VHD. The objective of this review was to evaluate the literature to support or refute 3 commonly encountered controversies relating to the treatment of VHD.

Data Sources

Literature searches were conducted with PubMed (inception to December 18, 2020) using the following Medical Subject Headings: "angiotensin-converting enzyme inhibitors" (ACE inhibitors) or "angiotensin receptor blockers" (ARBs) and "aortic valve stenosis" (146 citations), "adrenergic beta-antagonists" and "aortic valve insufficiency" or "aortic valve regurgitation" (AR; 59 citations), and "adrenergic beta-antagonists" and "mitral valve stenosis" (76 citations after 8 duplicates removed) for a total of 281 citations. The searches were limited to studies conducted in humans and published in English. Studies included were randomized controlled trials (RCTs) or meta-analyses that reported ≥1 clinically relevant outcome, defined as quality of life using a validated assessment tool, an objective measure of exercise capacity (eg, 6-minute walk distance, maximum oxygen consumption [VO_{2max}]), need for valve replacement surgery, or death. The primary outcome of the individual trials was also considered as well as any potential adverse events (eg, hypotension). Also, trials that included <15 patients were excluded. Two authors independently screened the citations, identified relevant articles, and extracted the data. In total, 8 RCTs and 1 meta-analysis were included.[4-12] A summary of the RCTs is included in Table 1. Of note, observational studies of the medical management of patients with VHD have been published[3]; however, only RCTs were included as the highest level of evidence with the least amount of confounding and bias.

Controversy 1: ACE Inhibitors and ARBs Should Be Avoided in Patients With AS

AS is primarily a disease of older persons secondary to calcific degeneration. Moderate to severe disease occurs in roughly 3% of those aged ≥75 years.[1] In younger persons, AS is typically secondary to a congenital bicuspid aortic valve—the most common type of congenital valvular disease—with a prevalence of 1% to 2%.[1] Symptoms of AS include syncope, angina, and heart failure, with an event-free survival of 30% to 50% at 2 years in patients with severe AS.[3] A commonly held belief in the medical community is that therapies that reduce afterload, such as ACE inhibitors or ARBs, should be avoided in patients with AS. This is based on the theory that an acute decrease in afterload (ie, reduced systemic vascular resistance) in the presence of a fixed obstruction (ie, a stenotic aortic valve) in patients with low cardiac output could increase the risk of death via severe hypotension because of inability to compensate through increased cardiac output; however, AS does not typically have a fixed obstruction until the late stages of the disease. To date, 3 RCTs have evaluated the use of ACE inhibitors in patients with AS.[4-6]

The Symptomatic Cardiac Obstruction—Pilot Study of Enalapril in Aortic Stenosis (SCOPE-AS) trial enrolled 56 patients with severe symptomatic (New York Heart Association [NYHA] class III to IV) AS who were randomized in a double-blind fashion to enalapril (n = 37) or placebo (n = 19).[4] All patients were either awaiting or unwilling to undergo open heart surgery because the trial was conducted prior to the routine use of transcatheter aortic valve replacement (TAVR). The mean age was 43 to 46 years, and 8 patients (14%) had a left-ventricular ejection fraction (LVEF) of <50%. The proportion of patients with hypertension was not reported. Patients were initiated on enalapril 2.5 mg twice daily (titrated to 10 mg twice daily over 2 weeks) or placebo. Three patients in the enalapril group (8%) discontinued therapy because of hypotension. After 4 weeks, there was a modest but significant improvement in the primary outcome of 6-minute walk distance (72 m with enalapril vs 27 m with placebo; $P = 0.003$), with a similar improvement in Borg dyspnea index. After 1 month, 6 patients in the enalapril group (18%) and 3 patients in the placebo group (17%) underwent elective aortic valve replacement (AVR).

Dalsgaard et al[5] investigated trandolapril versus placebo in a double-blind randomized trial of 44 patients with severe AS who were referred for AVR surgery.[5] Patients were recruited between 2005 and 2009 prior to the routine use of TAVR. The mean age was 70 years; 23 patients had hypertension (52%), and 5 patients (11%) had an LVEF of <50%. Among patients with hypertension, the mean systolic blood pressure (SBP) was 158 ± 23 mm Hg versus 136 ± 15 mm Hg in those without hypertension. Trandolapril was started at 0.5 mg daily and titrated to 2 mg daily on day 3. Outcomes were evaluated through invasive measurement with a Swann-Ganz catheter. On day 3, there was a significant decrease in the primary outcome of SBP with trandolapril (−14 vs −5 mm Hg; $P = 0.02$) but no significant reduction in left-ventricular end systolic volume. After a median follow-up of 49 days, change in left-ventricular end systolic volume was significantly greater with trandolapril (−8 vs −0.5 mL; $P = 0.04$), and there were no episodes of symptomatic hypotension. Planned AVR before 8 weeks was similar between groups (11/22 vs 8/22; $P = 0.37$).

The Ramipril in Aortic Stenosis (RIAS) trial was the largest to date and included 100 patients with asymptomatic moderate to severe AS.[6] In all, 80 patients had moderate AS, and 20 patients had severe AS; all patients did not have an indication for surgical or transcatheter AVR. The approximate mean age was 69 years, 29% had hypertension, and

Table 1. Summary of Included Randomized Controlled Trials.

Topic	Author (year)	Number and population	Exclusion criteria	Intervention and comparator	Follow-up	Outcomes
ACE inhibitor/ ARB in AS	Chockalingam et al[4] (2004)	n = 56; Patients with severe AS and NYHA class III-IV symptoms	SBP <90 mm Hg or mean BP <60 mm Hg, severe MS, ACE inhibitor intolerance, or serum creatinine >2.5 mg/dL	Enalapril 2.5 mg po twice daily (titrated to 10 mg po twice daily) vs placebo	4 Weeks	6MWD: 72 vs 27 m, $P = 0.003$ Δ in Borg dyspnea index: −1.4 vs −0.7; $P = 0.03$ AVR: 18% vs 17%; P = NR
	Dalsgaard et al[5] (2014)	n = 44; Patients with severe AS referred for AVR surgery	Resting SBP <100 mm Hg, MR, renal artery stenosis or serum creatinine >2.3 mg/dL, treatment with ACE inhibitor or ARB in the previous month, or inability to perform exercise testing	Trandolapril 0.5 mg po daily (titrated to 2 mg po daily) vs placebo	49 Days	SBP at day 3: −14 vs −5 mm Hg; $P = 0.02$ Planned AVR <8 weeks: 50% vs 36%; P = NS
	Bull et al[6] (2015)	n = 100; Patients with asymptomatic moderate to severe AS	LVEF ≤50%, other moderate-to-severe valvular disease, BP <100/40 or >200/110 mm Hg, ACE inhibitor or ARB intolerance, or treatment with ACE inhibitor or ARB in the previous 3 months	Ramipril 2.5 mg po daily (titrated to 10 mg po daily) vs placebo	1 Year	Δ in LV mass: −3.9 vs +4.5 g, $P = 0.006$ Δ in SBP: −5.5 vs −2.9 mm Hg, P = NS AVR: 8% vs 4%, P = NS
BB in AR	Broch et al[8] (2016)	n = 75; Patients with asymptomatic AR, LVEF >50%, and LV end-diastolic internal diameter >5.0 cm	Symptomatic HF or CHD, history of MI or AF, significant AS or indication for AV surgery, other hemodynamically significant valvular or congenital heart disease, 2° or 3° heart block, intracardiac device, serum creatinine >2.8 mg/dL, elevated liver enzymes, any illness or disorder limiting survival or adherence, or metoprolol intolerance	Metoprolol succinate CR/XL 25 mg po daily (titrated to 200 mg po daily) vs placebo	175 Days	LV end diastolic volume: 267 versus 256 mL; P = NS

(continued)

Table 1. (continued)

Topic	Author (year)	Number and population	Exclusion criteria	Intervention and comparator	Follow-up	Outcomes
BB in MS	Stoll et al[9] (1995)	n = 15; Patients with MS in sinus rhythm and NYHA class II-III symptoms	Moderate to severe AR, AS, or MR, or clinically significant atherosclerotic heart disease	Atenolol 50 or 100 mg po daily vs placebo	1 Week	VO_{2max}: 1020 mL/min/m^2 (atenolol 50 mg daily) and 1050 mL/min/m^2 (atenolol 100 mg daily) vs 1150 mL/min/m^2 (placebo); $P < 0.02$
	Patel et al[10] (1995)	n = 19; Patients with MS in sinus rhythm and NYHA class II-III symptoms	AF, right HF, obstructive or thromboembolic lung disease, or contraindication to BB therapy	Acebutolol 400 mg po daily or atenolol 100 mg po daily vs placebo	1 Week	Peak VO_2: 15.6 mL/min/kg (β-blocker) vs 17.8 mL/min/kg (placebo); P = NS
	Menadas et al[11] (2002)	n = 17; Patients with MS in sinus rhythm and NYHA class I-II symptoms	LV dysfunction, AF, IHD, uncontrolled hypertension, significant MR or other significant valvular disease, or inability to perform exercise testing	Atenolol 50 mg po daily (before and after)	1 Week	VO_{2max}: 16.8 mL/min/kg (baseline) vs 15.0 mL/min/kg (1 week); P = NS
	Alan et al[12] (2002)	n = 40; Patients with mild to moderate MS in sinus rhythm and NYHA class II-III symptoms	Moderate to severe AR or AS, severe pulmonary hypertension, or right HF	Metoprolol 5 mg IV, then 50 mg po twice daily (before and after)	3 Months	Mean VO_2 during exercise: 283 mL/min/m^2 (baseline) vs 267 mL/min/m^2 (3 months); $P < 0.05$ Mean VO_2 during recovery: 183 mL/min/m^2 (baseline) vs 178 mL/min/m^2 (3 months); $P < 0.05$

Abbreviations: 6MWD, 6-minute walk distance; Δ, change; ACE, angiotensin-converting enzyme; AF, atrial fibrillation; AR, aortic regurgitation; ARB, angiotensin receptor blocker; AS, aortic stenosis; AV, aortic valve; AVR, aortic valve replacement; BB, β-blocker; BP, blood pressure; CHD, coronary heart disease; HF, heart failure; IHD, ischemic heart disease; IV, intravenously; LV, left ventricular; LVEF, left-ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; MS, mitral stenosis; NR, not reported; NS, not significant; NYHA, New York Heart Association; SBP, systolic blood pressure; VO_{2max}, maximum oxygen consumption.

mean LVEF was 72% (number of patients with a reduced LVEF was not reported). Patients were randomized to ramipril 2.5 mg daily (titrated to 10 mg daily over 12 weeks) or placebo. At 1 year, the primary outcome of left-ventricular mass was lower in the ramipril group (difference of 8.4 g; $P = 0.006$), whereas SBP was similar between groups (−5.5 mm Hg with ramipril vs −2.9 mm Hg with placebo; $P = 0.37$). The rate of AVR and major adverse cardiac events (death, AVR, or hospital admission with cardiac symptoms) was similar between groups. The authors did not report the rate of hypotension or syncope.

A meta-analysis by Andersson and Abdulla[7] that evaluated the use of ACE inhibitors/ARBs in patients with AS included 8 studies (n = 8763), with the 3 previously discussed RCTs[4-6] and 5 observational trials.[7] Follow-up ranged from 49 days to 4.3 years. There was no significant difference in the rate of all-cause death between groups (relative risk [RR] = 0.93; 95% confidence interval [CI] = 0.78-1.11), whereas the rate of AVR was lower with ACE inhibitor/ARB therapy (RR = 0.68; 95% CI = 0.51-0.91). Weighted mean difference in SBP was lower with ACE inhibitors/ARBs (−2.0 mm Hg; 95% CI = −0.5 to −4.0 mm Hg), but this outcome was associated with high statistical heterogeneity ($I^2 = 89\%$). There were no reported adverse events of hypotension.

The available literature seems to support that ACE inhibitors/ARBs are safe in patients with AS who have a compelling indication (eg, hypertension), although most patients did not have a reduced LVEF. However, all 3 RCTs[4-6] were limited by low enrollment and short duration of follow-up as well as a general lack of details regarding blinding and allocation concealment. Furthermore, all trials utilized a low starting dose with a deliberate titration based on the patient's tolerance. The lower rate of AVR observed in the meta-analysis by Andersson and Abdulla[7] is intriguing. However, this finding needs to be confirmed by an adequately powered RCT because most of the data in this analysis were observational and, thus, at risk of unmeasured confounding. Additionally, it is not known whether the increasing use of TAVR in recent years will affect this outcome. Overall, these data are insufficient to suggest that all patients with AS should be routinely started on ACE inhibitor/ARB therapy.

Controversy 2: β-Blockers Should Be Avoided in Patients With AR

The prevalence of AR in the US population is approximately 0.5%, with moderate to severe AR prevailing in about 3% of those aged ≥70 years.[1] Acute AR is typically secondary to blunt force trauma or Stanford type A (or DeBakey types I and II) aortic dissection, which requires urgent surgical intervention.[3] Chronic AR may be the result of a variety of etiologies, including rheumatic disease, hypertension, or Marfan's syndrome, and patients may be asymptomatic for decades. Those with mild to moderate AR with a normal LVEF are not recommended medical therapy.[3] It is often purported that negative chronotropic agents, such as β-blockers, worsen the regurgitant volume by prolonging diastole. However, in patients with impaired left-ventricular function, β-blockers have been shown to reduce adverse cardiac remodeling and improve LVEF. Therefore, it is unclear whether β-blockers have a role in patients with chronic AR.

To date, only 1 RCT by Broch et al[8] has evaluated the use of β-blockers in AR.[8] In this double-blind trial, 75 patients with asymptomatic AR, an LVEF >50%, and left-ventricular end diastolic internal diameter >5.0 cm were randomized to metoprolol succinate (long acting) 25 mg daily (titrated up to 200 mg daily, as tolerated) or placebo. Mean age was 44 years, and mean LVEF was 55%. The primary outcome of left-ventricular end diastolic volume as per cardiac magnetic resonance imaging at approximately 6 months was not significantly different between groups (267 vs 256 mL; adjusted difference between groups = 8 mL; 95% CI = −8 to +25 mL). Additionally, there was no significant difference in AR fraction, peak oxygen consumption, quality of life, or adverse effects between groups.

Based on this singular trial of relatively low enrollment, β-blockers appear to neither benefit nor harm patients with chronic AR and an LVEF >50%; however, this trial excluded patients with a reduced LVEF and did not report other clinically relevant outcomes (eg, AVR). The overall risk of bias was low.

Controversy 3: Patients With Mitral Stenosis in Normal Sinus Rhythm Should Be on a β-Blocker

Mitral stenosis (MS) is most often secondary to rheumatic disease, which accounts for 60% of lone MS cases.[1] About 30% to 40% of patients with severe MS develop atrial fibrillation (AF), which is by definition valvular AF.[1] The rationale for β-blocker therapy in patients with MS is to improve exercise tolerance by reducing exercise-induced tachycardia because negative chronotropic agents prolong diastole and may decrease the mean gradient across the mitral valve. Exercise tolerance is often assessed via VO_{2max}, which is a measure of the maximum rate of oxygen consumption during incremental exercise. β-Blockers have been studied in 4 small RCTs[9-12] that each reported an objective measure of exercise tolerance. All included patients were in sinus rhythm, and the incidence rate of new AF was not reported in any of the RCTs.

A double-blind crossover study by Stoll et al[9] randomized 15 patients (mean age 46 years) with MS in normal sinus rhythm and NYHA class II to III symptoms to atenolol 50 or 100 mg daily, or placebo, for 1 week.[9] Despite significant improvements in mean peak transvalvular

gradient and heart rate, VO_{2max} was actually significantly lower in patients on atenolol therapy compared with those on placebo (1150 mL/min/m^2 with placebo vs 1020 mL/min/m^2 with atenolol 50 mg daily and 1050 mL/min/m^2 with atenolol 100 mg daily; analysis of variance $P < 0.02$).

A similar double-blind trial by Patel et al[10] included 19 patients (mean age 28 years) with symptomatic MS in normal sinus rhythm and NYHA class II to III symptoms.[10] In a crossover design, patients were randomized to a β-blocker (acebutolol 400 mg daily or atenolol 100 mg daily) or placebo for 1 week. Mean heart rate at peak exercise was significantly lower with β-blocker therapy, but there was no significant difference in peak VO_2 between groups (17.8 mL/min/kg with placebo vs 15.6 mL/min/kg with β-blocker). However, peak VO_2 was significantly lower from baseline with β-blocker therapy in the subgroup of patients with a peak heart rate of ≤130 beats/min (17.5 mL/min/kg at baseline vs 14.0 mL/min/kg at peak exercise; $P < 0.05$).

A study by Menadas et al[11] evaluated exercise tolerance before and after 1 week of atenolol 50 mg daily in 17 patients with MS in normal sinus rhythm and NYHA class I to II symptoms.[11] The investigator who evaluated patients after 1 week was blinded. Again, median heart rate was significantly lower during peak exercise compared with baseline in the atenolol group, but there was no significant difference in median VO_{2max} from baseline to after 1 week of atenolol therapy (16.8 vs 15.0 mL/min/kg; P value not significant).

Finally, a trial by Alan et al[12] randomized 80 patients with mild to moderate MS (NYHA class II to III) in sinus rhythm to diltiazem or metoprolol. A total of 40 patients (mean age 38 years) in the metoprolol group received 5 mg intravenously followed by 50 mg twice daily for 3 months. At the end of treatment, patients in the metoprolol group had a lower maximum heart rate during an exercise treadmill test from baseline (173 vs 161 beats/min; $P < 0.05$), and total exercise time improved by approximately 1 minute (452 vs 520 s; $P < 0.05$). However, as compared with before treatment, patients' mean oxygen consumption was significantly lower during exercise (283 vs 267 mL/min/m^2; $P < 0.05$) and during recovery (183 vs 178 mL/min/m^2; $P < 0.05$).

Despite objectively measuring exercise capacity, these data are limited by a small number of participants and short follow-up. Three of the 4 trials enrolled between 15 and 19 patients and only evaluated β-blocker therapy for 1 week, which offers little generalizability to clinical practice. The observed improvements in heart rate during exercise did not translate into improved exercise tolerance, and the significantly lower VO_{2max} observed with treatment in 3 of the trials also suggest that β-blockers may actually be harmful in patients with MS in sinus rhythm.[9,10,12] However, because of the short follow-up, the reduction in VO_2 may be reflective of the initial negative inotropic effects of β-blockers, and thus the long-term effects remain unknown. Furthermore, in the trial by Stoll et al,[9] stroke volume was not increased despite prolonged diastole from β-blocker therapy because of the fixed obstruction of the mitral valve.

Relevance to Patient Care and Clinical Practice

Use of ACE inhibitor/ARBs appear to be safe in most patients with AS who have a valid indication (eg, hypertension), but they should be started at a low dose with frequent monitoring and gradual titration based on the patient's response. Of note, few patients with a reduced LVEF were included in these trials. The 2020 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of patients with VHD make reference to the controversy surrounding ACE inhibitors/ARBs and AS, but the authors did not make any explicit recommendations.[3] Because many patients with calcific AS also have concurrent hypertension, the guideline authors recommended that the treatment of hypertension in patients with AS follow guideline-directed medical therapy (class 1; level of evidence B, nonrandomized).

β-Blockers do not appear to have a role in patients with chronic AR and an LVEF >50%. Authors of the 2020 ACC/AHA VHD guidelines did not make any specific recommendations for or against the use of β-blockers in patients with chronic AR, though they stated that β-blockers may cause an apparent paradoxical increase in blood pressure because of an increase in transaortic stroke volume.[3] In the 2014 guidelines, the authors weakly recommended that β-blockers were reasonable in patients with severe AR and reduced LVEF when surgery is not possible (class IIa, level of evidence B).[13] This recommendation was based on a retrospective cohort study of 756 patients with chronic AR, where, over 4.4 years, β-blocker use was associated with improved survival in a multivariate regression model (adjusted hazard ratio = 0.74; 95% CI = 0.58-0.93).[14] However, patients had a mean LVEF of 54% ± 19% (adjusted for in the regression analysis), so it is unclear why the recommendation was specific to patients with left-ventricular dysfunction. Use of β-blocker therapy could be considered in patients with chronic AR and a reduced LVEF, though an RCT is needed to confirm this recommendation.

Although limited, current evidence is suggestive that routine use of β-blockers in patients with MS in normal sinus rhythm should not be recommended. Based on these data, authors of the 2020 ACC/AHA VHD guidelines provided a weak recommendation that heart rate control may be beneficial in patients with MS in sinus rhythm if they have symptoms associated with resting or exertional tachycardia (class 2a, level of evidence A).[3] However, the authors also state that the "routine use of heart rate control for patients with rheumatic MS in normal sinus rhythm in the absence of

tachycardia may result in chronotropic incompetence, preventing an adequate cardiac output response to exercise."[3(p e44)] Therefore, β-blockers should generally be avoided in patients with MS without AF.

Conclusion

Despite advances in surgical and minimally invasive valve replacement or repair techniques, the medical management of VHD remains necessary in patients awaiting or ineligible for these procedures. No pharmacological therapy has been demonstrated to improve survival or abate disease progression in patients with VHD. Notwithstanding, misconceptions continue to be propagated among practitioners regarding drug therapy in patients with valvular dysfunction despite a paucity of high-quality clinical data. Currently, there is no evidence to support that ACE inhibitors/ARBs increase the risk of death in patients with AS, and contemporary evidence actually suggests that these drugs may reduce the rate of AVR. Also, present data suggest that β-blockers are not harmful in patients with chronic AR and may be considered in patients with left-ventricular dysfunction. Finally, limited evidence has demonstrated that, in the short term, β-blockers do not improve, and actually may worsen, exercise tolerance in patients with MS who are in sinus rhythm. There remains a need for additional RCT data to further corroborate these findings. In the interim, clinicians should base their management of VHD not on historical and theoretical beliefs, but rather contemporary RCT evidence.

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