NCPD 2.5 CONTACT HOURS

Rx 2.0 CONTACT HOURS

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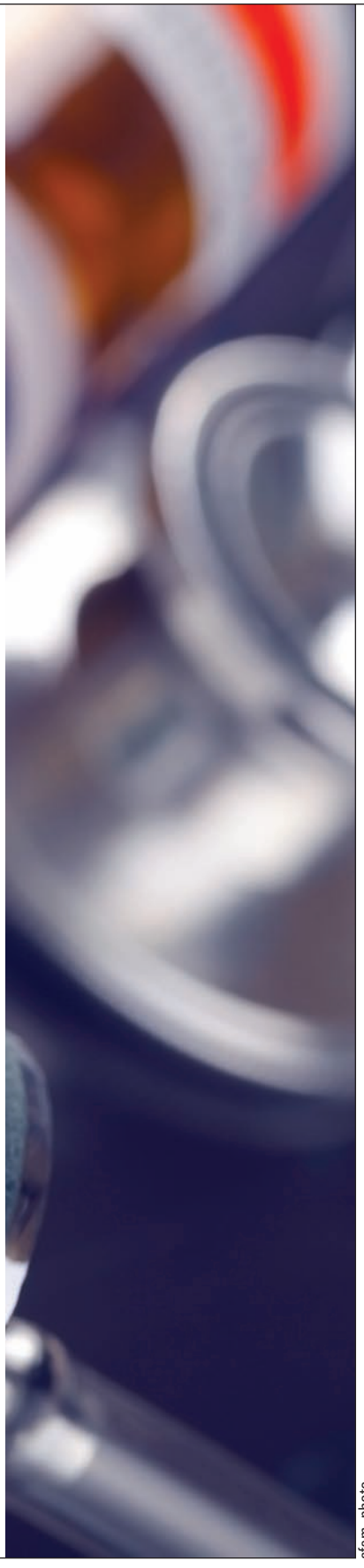

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Antihypertensive therapy in patients with moderate to severe aortic stenosis

Abstract: Patients with aortic stenosis are at risk for developing hypertension. The selection of antihypertensives is a topic of debate due to a lack of consensus regarding their safety. This article provides an overview of antihypertensives used in patients with aortic stenosis, focusing on renin-angiotensin system inhibitors, beta-blockers, diuretics, and vasodilators.

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Aortic stenosis (AS) is the narrowing of the aortic valve and the aorta.[1] Calcification, which restricts the ability of the valve to open normally, is the most common cause.[2] The implication of this calcification challenges the heart, making it work harder to pump blood into the aorta.[1]

Diagnosis of AS

Diagnosing AS may begin with identifying a systolic murmur during auscultation over the right second intercostal space, but to make a definitive diagnosis, a transthoracic echocardiogram (TTE) is needed.[2,3] The echocardiogram allows for measurement of antegrade systolic velocity (aortic jet velocity) across the stenosed aortic valve and estimation of the pressure difference between the left ventricle (LV) and aorta in systole (transvalvular aortic gradient). For example, mild AS is characterized by an aortic jet velocity of 2.0 to 2.9 m/s, whereas in moderate AS, the aortic jet velocity ranges from 3.0 to 3.9 m/s. The aortic jet velocity in severe AS is greater than or equal to 4 m/s, and in very severe AS, the aortic jet velocity reaches or exceeds 5 m/s.[3]

Staging of AS guides proper intervention timing; the American College of Cardiology and American Heart Association (ACC/AHA) classifies AS into Stages A to D.[3] Stage A includes patients at risk for AS but who are asymptomatic with no hemodynamic complications.[3] While stage B of AS is progressive, patients affected continue to be asymptomatic with some LV diastolic dysfunction.[3] Stage C is subcategorized as either C1 or C2.[3] Features of patients in C1 include asymptomatic severe AS with LV diastolic dysfunction, mild LV hypertrophy, and normal left ventricular ejection fraction (LVEF).[3] As AS progresses, patients may show features of stage C2, which is defined as asymptomatic severe AS with LV systolic dysfunction, an aortic valve area (AVA) of less than or equal to 1 cm^2, and an LVEF of less than 50%.[3] Stage D entails symptomatic severe AS and is subcategorized into D1, D2, and D3 substages.[3] Patients who have symptomatic, severe high-gradient AS, LV diastolic dysfunction, LV hypertrophy,

Keywords: ACEIs, antihypertensives, aortic stenosis, aortic valve stenosis, ARBs, beta-blockers

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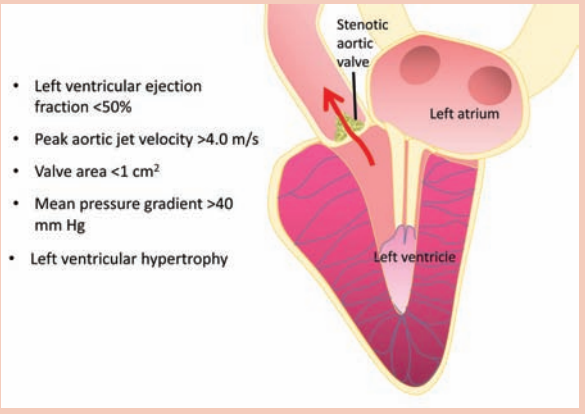
Common Features of Severe Aortic Stenosis



and potentially pulmonary hypertension are categorized as stage D1.[3] Exertional dyspnea, angina, syncope or presyncope, decreased exercise tolerance, and heart failure (HF) are symptoms present in Stage D1.[3] Stage D2 is defined as symptomatic, severe, low-flow, low-gradient AS with reduced LVEF.[3] Finally, stage D3 is symptomatic, severe, low-gradient AS with normal LVEF or paradoxical low-flow severe AS.[3] Symptoms of stages D2 and D3 include HF, angina, and syncope or presyncope.[3] The TTE is also used to determine AVA, reflecting the valve size compared with the area of the patient's outflow tract.[3] The AVA demonstrates the degree of obstruction and valve dysfunction (see *Common features of severe aortic stenosis*).[3]

In AS, the aortic orifice is usually narrowed to half or less of its usual 3 cm^2 size, causing an increase in the pressure gradient across the valve (see *Aortic orifice in AS*).[4] Mild AS is graded based on an AVA of >1.5 cm^2, moderate as 1.0-1.5 cm^2, and severe as less than 1.0 cm^2.[5] AS most commonly presents in individuals 65 years of age and older but can develop in younger people who have a congenital heart defect or have experienced rheumatic fever.[1] Patients with AS are not always symptomatic, but when symptoms do arise, they can include chest pressure, light-headedness, dyspnea, fatigue, and possibly syncope, which requires immediate investigation.[1]

Diagnosing AS requires using echocardiography to determine the speed of blood traveling through the valve and visualize the heart's structure and function. Because of its association with decreased arterial compliance and increased vascular resistance, hypertension impacts the severity of AS.[6] Hypertension adds to the already increased afterload by increasing systolic stress.[6] Increasing the afterload causes further deleterious hypertrophic remodeling of the left ventricle.[7] Hypertension has a 50% prevalence in patients with AS.[7] Due to the calcified aortic valve, which causes a high afterload, the ventricle must generate a higher pressure.[7] While hypertension has been associated with progression of AS and increased risk for cardiovascular disease, excessive lowering of BP can impair tissue perfusion and result in organ dysfunction or failure in patients with AS.[6] The fixed mechanical obstruction of AS impedes the ability of the heart to increase cardiac output in case of hypotension. Administration of vasodilators often falls short of dilating a fixed obstruction in the aortic valve.[6,7] The NP should ensure careful titration of vasodilators to avoid excessive peripheral vasodilation, which can potentially reduce coronary blood flow and cause further hypotension and hemodynamic instability.

Therefore, administering antihypertensives in patients with AS must be based on evidence-based guidelines to limit unnecessary variation in clinical practice and improve patient outcomes.[7] Optimal diastolic BP values can range from 70 to 90 mm Hg, whereas the recommended target systolic BP must be between 130 and 140 mm Hg.[7,8] Given that the ultimate treatment of AS is surgical correction, the purpose of this article is to provide NPs with an overview of the common antihypertensives used in AS while awaiting surgery.

Common antihypertensive therapy in AS

Renin-angiotensin system blockers

The renin-angiotensin system (RAS) is speculated to be involved in the pathogenesis of aortic valve lesions because of the presence of angiotensin II receptors in stenosed aortic valves. Angiotensin II receptors do not exist in healthy valve tissue.[9] Based on the presence of angiotensin II receptors in sclerotic valves, RAS inhibition has the potential to be beneficial in targeting the progression of valvular stenosis as well as LV remodeling.[9] Angiotensin II stimulates inflammation and furthers stenosis due to the presence of the angiotensin II receptors in the sclerotic valves.[10] Pharmacologic therapy that targets the angiotensin-converting enzyme pathway, such as renin-angiotensin system blockers (RASBs), could have the ability to slow the progression of AS by inhibiting the promotion of the inflammatory process and fibrosis.[10]

Natorska et al., Goh et al., and Magne et al. conducted retrospective cohort studies focusing on RASB

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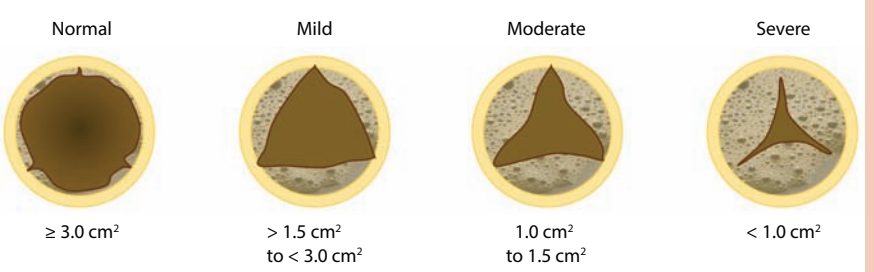
Aortic orifice in AS



therapy in AS.[9,11,12] Natorska et al. focused on the use of angiotensin-converting enzyme inhibitors (ACEis), whereas Goh et al. and Magne et al. studied both ACEis and angiotensin receptor blockers (ARBs).[9,11,12] Natorska et al. aimed to determine the association between ACEis and inflammatory and coagulation proteins in AS valves.[9] Goh et al. aimed to determine the effectiveness of RASB use on LV remodeling in patients with severe AS and preserved LVEF focusing on the effects on low-flow compared with normal-flow AS.[11] Magne et al. focused on mortality.[12] In patients with severe AS, ACEi use is associated with lower expression of tissue factor, prothrombin, C-reactive protein, and interleukin-6 within aortic valves at both the protein and messenger ribonucleic acid (mRNA) levels within diseased valve cusps.[9] Natorska et al.[9] concluded that the use of ACEi in patients with AS could alter the atherosclerotic process in aortic valves and slow the progression of the disease (see *Studies of pharmacotherapy methods for AS*).

Chen et al. and Andersson and Abdulla conducted analyses of the literature focusing on the effects of ACEis and ARBs on patients with AS.[13,14] Specifically, Andersson and Abdulla aimed to determine whether RASB therapy is safe and of prognostic benefit for individuals with AS.[14] Chen et al. concluded from the results of the Placement of AoRTic TraNscathetER Valves II trials and registries that patients who received ACEis or ARBs experienced lower 2-year all-cause mortality, decreased cardiovascular mortality, and reduced noncardiovascular mortality.[11,13] Goh et al. concluded that groups receiving RASB therapy in studies demonstrated significantly lower left ventricular mass index (LVMI) with a correspondingly lower incidence of concentric LV hypertrophy.[11] Patients with mild to moderate AS tolerated ARBs and ACEis without orthostatic hypotension or syncope.[15] Administration of RASB therapy before transcatheter aortic valve replacement (TAVR) led to improved outcomes post-TAVR.[13] Goh et al., Magne et al., and Chen et al. concluded that RASB therapy was associated with delaying cardiovascular complications associated with AS, decreasing morbidity and mortality.[11-13] Additionally, Andersson and Abdulla found that the use of RASB therapy also lowered the risk of aortic valve replacement (AVR) surgery.[14] RASB therapy appears to be a beneficial treatment strategy as it combines antihypertensive action with possible additional beneficial effects on the pathogenesis and progression of AS.[6] Treatment with ARBs and ACEis was not associated with sudden cardiac death, cardiovascular mortality, or all-cause mortality, and additionally led to slower progression of LV mass.[6] RASB therapy has been established to act on the adverse LV remodeling that occurs with AS, and is seen to reduce myocardial hypertrophy and fibrosis. These actions of RASB therapy prove both its safety and benefit to those with HF and those with AS.[10] To avoid hypotension in patients with severe AS and hypertension, RASB therapy should be prescribed with half the usual dose and then carefully titrated upwards to therapeutic levels.[7]

Beta-blockers

The use of beta-blockers (Bbl) in patients with AS has previously been avoided because of the concern that Bbl may cause LV dysfunction; however, recent research concluded that Bbls may be safe for treatment of hypertension in patients with AS.[7] Hansson et al. and Bang et al. both aimed to determine the effectiveness and safety of Bbl in patients with AS.[15,16] Specifically, Hansson et al. performed a double-blinded quantitative study to investigate whether metoprolol could reduce the hemodynamic and metabolic burden brought on by AS, whereas, Bang et al. performed a post hoc analysis of patients with mild to moderate AS and preserved LVEF to assess risk ratios for all-cause mortality, sudden cardiac death, and cardiovascular death.[16,17] Both research groups determined that metoprolol can improve outcomes in asymptomatic AS because of the

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Studies of pharmacotherapy methods for AS

Study, sample, pharmacotherapy	Results
Natorska et al.[9] • Pharmacotherapy studied: ACEi • N = 111 n = 37 (treated with ACEi) n = 74 (control group)	• Decreased immunoreactive areas for valvular TF ($P = .03$), TFPI ($P < .001$), prothrombin ($P < .001$), CRP ($P = .009$), and IL-6 ($P < .001$) among patients treated with ACEi. • In patients with severe AS, ACEi use is associated with lower expression of TF, prothrombin, CRP, and IL-6 within aortic valves on both protein and mRNA levels within diseased valve cusps. • Retrospective cohort study
Goh et al.[11] • Pharmacotherapy studied: RASB (ACEi and ARB) • N = 428 patients n = 242 with low-flow severe AS (64 treated with RASB) (178 comparison group) n = 186 with normal-flow severe AS (49 treated with RASB) (137 comparison group)	• Patients receiving RASB demonstrated significantly lower LVMI with a correspondingly lower incidence of concentric LV hypertrophy. • Of the low-flow group, despite length of RASB treatment, the patients who were treated with RASB were associated with lower LVMI compared with those without the therapy. • Subjects in the normal-flow subgroup did not demonstrate any significant differences between those who received RASB therapy and those who did not receive this intervention. • Retrospective cohort study
Magne et al.[12] • Pharmacotherapy studied: RASB (ACEi and ARB) • N = 508 n = 268 receiving RASB therapy at baseline (before surgery)–125 receiving ACEi and 143 receiving ARB	• The 30-day mortality rate after surgical aortic valve replacement was lower under ARB than ACEi ($P = .017$). • Patients receiving RASB had a better 8-year survival rate than those without ($P < .0001$). Patients receiving ARB had lower mortality than those receiving ACEi ($P = .028$). • Retrospective cohort study
Chen et al.[13] • Pharmacotherapy studied: RASB (ACEi and ARB) • N = 3,979 n = 1,736 (treated with ACEi/ARB) n = 2,243 (comparison group)	• Study included results of the PARTNER II trials and registries. • Patients who received ACEis or ARBs experienced lower 2-year all-cause mortality ($P < .0001$), decreased cardiovascular mortality ($P < .0001$), and reduced noncardiovascular mortality ($P < .0001$). • Retrospective meta-analysis
Andersson and Abdulla[14] • Pharmacotherapy studied: RASB (ACEi and ARB) • N = 8,763 n = 3,869 (receiving RASB therapy) n = 4,894 (control group)	• Eight studies in total reviewed • Overall, found that RASBs could be used safely in patients with AS with no observed increase in mortality risk: ○ 576/3,389 patients receiving RASB therapy versus 1,118/4,384 patients in the control group died ($P = .44$). • The use of RASBs was also found to lower the risk of aortic valve replacement surgery ($P = .01$). • Treatment with ARBs and ACEis was not associated with sudden cardiac death, cardiovascular mortality, or all-cause mortality. • Systematic review and meta-analysis
Hansson et al.[16] • Pharmacotherapy studied: Bbl (metoprolol) • N = 38 n = 19 (receiving metoprolol) n = 19 (placebo group)	• Compared with the placebo group, the trial group experienced decreased heart rate ($P = .003$), increased ejection time ($P = .03$), reduction in the progression of the aortic valve gradients, both peak ($P = .05$) and mean ($P = .03$), with no effect on stroke volume with the administration of metoprolol. • Patients receiving metoprolol experienced a reduction in myocardial oxygen consumption ($P = .01$) and valvuloarterial impedance ($P = .03$), both cardioprotective factors. • Randomized, double-blind, placebo-controlled study

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Bang et al.[17] • Pharmacotherapy studied: Bbl • N = 1,873 (ages 45-85) n = 932 receiving Bbl at baseline	• Patients receiving Bbls showed a 2% larger decrease in systolic BP ($P = .006$) and a 2% greater reduction in LV ejection fraction ($P = .04$). • Change values of LV mass, aortic valve area index, aortic peak jet velocity, and heart rate did not differ between patients who received Bbl therapy and the comparison group ($P > .38$). • Bbl use was associated with a lower risk of all-cause mortality ($P < .001$), cardiovascular death ($P < .001$), and sudden cardiac death ($P = .004$). • Post hoc analysis study
Saeed et al.[18] • Pharmacotherapy studied: CCB • N = 314 n = 80 (receiving CCB therapy) n = 234 (not receiving CCB therapy)	• Patients who received CCBs showed a lower peak heart rate, a shorter exercise time, and were more likely to have a blunted BP response compared with patients who were not receiving CCBs during an exercise treadmill test ($P < .05$) and were at higher risk for adverse events. • In a multivariable Cox regression model, the use of CCBs in patients with AS was associated with a sevenfold increased hazard ratio for all-cause mortality ($P = .001$). • Retrospective cohort analysis
Mitsui et al.[19] • Pharmacotherapy studied: diuretic (tolvaptan) • N = 56 n = 16 with low-flow severe AS n = 40 with normal-flow severe AS	• The results indicated that the combination of tolvaptan and furosemide did not result in adverse clinical events in those with severe AS, but actually reduced total fluid balance ($P < .05$) and increased urinary output ($P < .01$) compared with baseline. • Retrospective observational study
Claveau et al.[23] • Pharmacotherapy studied: nitrate (nitroglycerin) • N = 195 episodes of acute pulmonary edema n = 65 episodes among 49 patients with severe AS n = 65 episodes among 61 patients with moderate AS n = 65 episodes among 64 patients without AS	• There was no association between moderate or severe AS and development of clinically relevant hypotension after administration of nitroglycerin for acute pulmonary edema (occurrence of 26.2% among those with moderate and severe AS and 23.1% among those without AS). • Retrospective cohort study

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AS, aortic stenosis; Bbl, beta-blocker; CCB, calcium channel blocker; CRP, C-reactive protein; IL-6, interleukin-6; LV, left ventricular; LVMI, left ventricular mass index; mRNA, messenger ribonucleic acid; PARTNER II, Placement of AoRTic TraNscathetER Valves II; RASB, renin-angiotensin system blocker; TF, tissue factor; TFPI, tissue factor pathway inhibitor.

favorable hemodynamic effects and improvement in myocardial efficiency. Hansson et al. specifically described a decreased heart rate, increased ejection time, and reduction in aortic valve gradients—both peak and mean—with no adverse cardiovascular reactions with the administration of metoprolol.[16] They also established that patients receiving metoprolol experienced a reduction in myocardial oxygen consumption and valvuloarterial impedance, both cardioprotective factors.[16] Because of these positive outcomes, Hansson et al. determined that metoprolol may postpone or prevent the need for an AVR.[16] Bang et al. emphasized that patients treated with Bbl showed more significant decreases in systolic BP and greater reductions in LVEF.[17] They concluded that Bbl use was associated with a lower risk of all-cause mortality, cardiovascular death, and sudden cardiac death. Although Bbls have been proven to be beneficial in treating AS, a disadvantage of this class of medications is that they may increase the severity of valve regurgitation.[6] Although this has been a safety concern in patients with AS in the past, Bbls have proven to be safe in the management of AS.[7]

Calcium channel blockers

The use of calcium channel blockers (CCBs) has been widely studied in the management of hypertension; however, their use has not been covered in depth in patients with AS.[18] To determine their safety and effectiveness in patients with AS, Saeed et al. performed

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a retrospective analysis on the use of CCBs in patients with moderate to severe asymptomatic AS.[18] The use of CCBs was associated with adverse reactions on treadmill exercise and reduced survival in asymptomatic patients with moderate or severe AS.[18] Saeed et al. found that patients who received CCBs showed lower peak heart rate, a shorter exercise time, and were more likely to have a blunted BP response than patients on placebo.[18] They concluded that the use of CCB in patients with AS was associated with an increased hazard ratio for all-cause mortality.[18] Further research is required to determine the safety of CCBs; therefore, CCBs are currently not recommended as pharmacotherapy in patients with moderate to severe AS.[18]

Diuretics

AS commonly leads to acute decompensated HF due to progressive obstruction of the aortic valve, at which time prompt management is required to manage symptoms, maintain cardiac output, and improve prognosis.[19,20] The use of loop diuretics in the management of HF is extremely common. However, there is controversy surrounding their use in HF and hypertension in patients with AS.[19] The caution stems from the likelihood that diuretics will induce cardiogenic shock secondary to hypovolemia.[19] Kanwar et al. established that the use of diuretics in patients with AS has the potential to cause hypotension with deleterious effects because diuretic use may lead to a decrease in cardiac output, thus worsening or resulting in failure of the compensatory mechanisms to maintain perfusion in patients with AS.[21]

Mitsui et al. performed a retrospective observational study and found that tolvaptan, a vasopressin receptor blocker, added to furosemide in patients with low-flow and normal-flow AS is safe and effective without consequences of hypotension or renal dysfunction.[19] Mitsui et al. trialed conventional diuretic therapy alone and conventional diuretic therapy in combination with tolvaptan to determine the effectiveness of diuretics in managing fluid overload and hypertension in individuals with AS and acute decompensated HF.[19] The results indicated that the combined use of tolvaptan and furosemide had no adverse clinical events in those with severe AS but actually reduced fluid volume and increased urinary output compared with furosemide alone.[19] Despite these findings, Mitsui et al. recommended that further research needs to be done to address the use of diuretics in patients with AS.[19]

Nitrates

Treatment of angina and acute pulmonary edema with nitrates in patients with AS has been controversial because of safety concerns. Marquis-Gravel et al. determined through their literature analysis that hypotension rates following nitroglycerin administration were similar between patients with moderate or severe AS and no AS.[22] There are challenges in determining if patients with AS can maintain an adequate BP after the administration of nitrates due to their inability to increase stroke volume.[23] To investigate the safety of nitrates in patients with AS, Claveau et al. performed a retrospective cohort study where nitroglycerin was administered as a treatment for acute pulmonary edema.[23] Overall, Claveau et al. reported no association between administration of nitroglycerin for acute pulmonary edema in those with moderate and severe AS and development of clinically relevant hypotension and no increase in rate of adverse events occurring during or after the administration of nitroglycerin.[23] They determined that the use of nitroglycerin in patients with AS is safer than once thought but emphasized caution in administration until safety is further assessed.[23] Nitroglycerin is not recommended as a treatment modality due to Claveau et al.'s small sample size and design limitations prohibiting a complete safety assessment.[23]

Nitroprusside

Vasodilator therapy is highly used in the treatment of LV dysfunction, however, avoided in those with AS because of the possible consequence of causing life-threatening hypotension.[7]

Vasodilator therapy results in a reduction in LV afterload and filling pressures with improvement in pulmonary hypertension in patients with low-gradient, severe AS.[21] Kanwar et al. determined based on their literature search of various treatment strategies for AS that nitroprusside I.V. may be used as a bridge in patients who require prompt stabilization due to severe AS and severe HF prior to a valve replacement or transition to oral vasodilators for patients who choose not to undergo surgery, but these patients require extensive monitoring because of the risk of sudden decline in cardiac output due to the obstructed valve.[21] Vasodilators must be administered I.V. to manage AS-associated emergencies until the patient is stable then oral vasodilator therapy can be initiated.[21]

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Implications for practice, nursing education, research, and policy

Pharmacologic therapy for patients with AS in the setting of hypertension must follow guideline-directed medical therapy. Given the fixed obstruction in AS, hemodynamic stability is both preload- and afterload-dependent. Therefore, NPs prescribing antihypertensives to patients with AS require the knowledge and expertise to strike a *delicate* balance between preload and afterload to boost the forward blood flow and sustain adequate cardiac output. The lack of randomized clinical trials addressing specific antihypertensive medications in patients with AS creates a challenge for NPs to choose the right therapy to avoid causing hemodynamic compromise. NPs must be aware that patients with AS are permitted to have a relatively higher target BP than the general population. Future clinical trials are needed to establish the ideal target BP in patients with AS. Stringent approaches and preoccupation with keeping the BP within arbitrary ranges can result in adverse clinical outcomes. Therefore, NPs must individualize treatment based on the patient's medical context, always guided by clinical judgment. Subtherapeutic response to antihypertensive drugs requires immediate attention and collaboration with the cardiologist to avoid deterioration in clinical status. For example, if afterload reduction strategies do not produce adequate reduction in systemic vascular resistance or BP, the NP should consider the up-titration of vasodilators. Understanding the patterns of AS progression and the associated hemodynamic challenges is likely to support the NP's decision-making process to avoid causing hemodynamic instability or collapse as a consequence of subtherapeutic or supratherapeutic dosages of the prescribed antihypertensives. Nurse educators must be intentional about discussing the potential adverse reactions of antihypertensives when used in patients with AS. Finally, early diagnosis of AS is of paramount importance to allow for early initiation of drug therapy to slow disease progression. Considering that the ultimate treatment for AS is surgical correction, centers with the right surgical expertise must be established and made accessible to allow for timely surgical intervention that will limit possible comorbidities resulting from AS. Governments should allocate more resources to establish centers of excellence for the management of AS.

Conclusion

This article offers healthcare providers such as NPs evidence to consider in decisions related to pharmacotherapy for individuals diagnosed with AS. Antihypertensive treatment has proven to be effective overall and not dangerous in treating and managing patients with AS. Although some antihypertensive treatments are safe and beneficial for patients with AS, surgical management is the only definitive treatment and will eventually be required.[21] When selecting and prescribing antihypertensives, it is best practice to follow antihypertensive guidelines by starting at a low dose and titrating upwards as needed to keep the BP within the recommended ranges.[3,7] The guidelines do not recommend a specific antihypertensive for AS patients, but given the theoretical assumptions that RASBs reduce LV fibrosis and control BP, NPs are encouraged to try RASBs as the first line of medication.[3] The NP must also ensure that the patient does not have other comorbidities and individual factors that may contravene the initiation of RASBs. If RASBs fail to control BP, then Bbl therapy can be added to lower BP to the goal.[7] The use of ARBs may be more effective than ACEis when administering RASBs.[9,11-14] CCBs have proven to be dangerous for those with AS and are not recommended in treatment guidelines.[18] Diuretics are controversial based on their ability to cause deleterious effects; however, the diuretic furosemide when paired with tolvaptan proved to be safe in those with normal-flow or low-flow severe AS and acute decompensated HF.[19] Further research is required to determine the safety of these medications before they can be recommended as part of treatment guidelines.

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