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CURRENT OPINION
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Management of patients with combined arterial hypertension and aortic valve stenosis: a consensus document from the Council on Hypertension and Council on Valvular Heart Disease of the European Society of Cardiology, the European Association of Cardiovascular Imaging (EACVI), and the European Association of Percutaneous Cardiovascular Interventions (EAPCI)

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Aortic valve stenosis (AS) is the third most common cardiovascular disease. The prevalence of both AS and arterial hypertension increases with age, and the conditions therefore often co-exist. Co-existence of AS and arterial hypertension is associated with higher global left ventricular (LV) pressure overload, more abnormal LV geometry and function, and more adverse cardiovascular outcome. Arterial hypertension may also influence grading of AS, leading to underestimation of the true AS severity. Current guidelines suggest re-assessing patients once arterial hypertension is controlled. Management of arterial hypertension in AS has historically been associated with prudence and concerns, mainly related to potential adverse consequences of drug-induced peripheral vasodilatation combined with reduced stroke volume due to the fixed LV outflow obstruction. Current evidence suggests that patients should be treated with antihypertensive drugs blocking the renin–angiotensin–aldosterone system, adding further drug classes when required, to achieve similar target blood pressure (BP) values as in hypertensive patients without AS. The introduction of transcatheter aortic valve implantation has revolutionized the management of patients with AS, but requires proper BP management during and following valve replacement. The purpose of this

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document is to review the recent evidence and provide practical expert advice on management of hypertension in patients with AS.

Keywords Aortic valve stenosis • Left ventricular hypertrophy • Aortic valve calcification • Arterial hypertension • Drug therapy • Cardiovascular risk • Prognosis • Aortic valve replacement

Preamble

The following document summarizes and critically evaluates available evidence on the management of hypertensive patients with aortic valve stenosis. The consensus document enrolled experts in the field of hypertension, valvular heart disease, cardiovascular imaging, invasive cardiology, representing different associations, and councils of ESC. Due to the lack of robust data coming from randomized control trials and meta-analyses, the indications reported in this Consensus document are the result of discussion and agreement among the experts participating in the task force and do not represent guideline recommendations.

Prevalence of arterial hypertension in patients with aortic stenosis

Aortic valve stenosis (AS) is the most frequent type of valvular heart disease requiring valve replacement.[1,2] While AS typically is secondary to degeneration of a tricuspid aortic valve in older patients, bicuspid aortic valve is the most common cause of AS in younger patients. In patients with bicuspid aortic valve disease, coexistence of AS is among of the main determinant of ascending aorta dilatation.[3,4] The prevalence of AS increases exponentially with age, being ~3% in subjects over the age of 75[5,6] and up to 10% in octogenarians.[7]

The prevalence of both arterial hypertension and AS increases with age and these two conditions therefore are commonly co-existing. In a study including information from 3.39 million hospital discharges in Ireland, the probability of arterial hypertension was four-fold higher in the presence of AS.[8] In the Cardiovascular Health Study, aortic valve sclerosis was present in 37% and AS in 2.6% among subjects aged >65 years. A history of arterial hypertension increases relative risk of AS by 23%.[9] In a cohort study of 5.4 million subjects without known cardiovascular disease in UK, long-term exposure to elevated BP across its whole spectrum was associated with increased risk of AS.[10] Among older patients with AS, arterial hypertension is a common comorbidity found in up to 78% of patients in population based studies.[11,12] With aging population in many countries, the combination of AS and arterial hypertension is expected to become even more frequent.

Arterial hypertension, *per se*, is a risk factor for developing AS and, in small studies, has been associated with progression of stenosis and valve calcification,[13,14] and earlier development of cardinal symptoms.[15] However, in the large, prospective Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study, which followed 1873 patients with initially mild–moderate AS for a median of 4.3 years, the disease progression did not differ between normotensive and hypertensive subjects.[16]

Blood pressure measurements and aortic stenosis

Most studies addressing the association between arterial hypertension and calcific AS have reported conventional office blood pressure (BP) only, and clinical practice has entirely been based on such measurements, which should be conducted according to current recommendations.[17] However, ambulatory blood pressure monitoring (ABPM) is more accurate than office BP to confirm the diagnosis of sustained arterial hypertension (i.e. to exclude white-coat hypertension) but also allows assessing severity of arterial hypertension throughout the 24-h period and detecting nocturnal hypo- and hypertension. ABPM can therefore reveal specific BP patterns, such as nocturnal non-dipping, and alterations in short-term BP variability.[18,19] Current guidelines advocate wider use of ABPM in the management of arterial hypertension.[17] Furthermore, results of a cross sectional observational study suggests awake, asleep, and 24-h mean diastolic BP values (but not office systolic or diastolic BP) to be independently associated with more advanced aortic valve calcification.[13] Based on these data, and on the background of the solid evidence on the advantages of ABPM in the hypertensive population,[18] the opinion of the present expert panel is that ABPM should be more widely used also in the management of AS patients with arterial hypertension. However, whether improving BP control by means of ABPM might provide additional clinical benefit when compared with management based only on clinic BP measurements remains to be evaluated (*Box 1*).

Box 1 Expert panel consensus

- Blood pressure should be regularly monitored in patients with aortic valve stenosis (AS).
- Ambulatory blood pressure monitoring may be considered to confirm and refine diagnosis, and optimize management of hypertension in AS.

Impact of hypertension on left ventricular structure and function in aortic valve stenosis

Traditionally, left ventricular (LV) remodelling in AS has been considered compensatory to increased wall stress related to the severity of valve obstruction. It is, however, well documented that the presence of arterial hypertension in patients with AS substantially influences LV

remodelling and function, in addition to aortic root dimension.[16,20] When arterial hypertension coexists with AS, left ventricle is exposed to higher haemodynamic load caused by the increased outflow impedance by the valve stenosis, combined with various degrees of both volume and pressure overloads, characterizing arterial hypertension.[21] In mild-to-moderate AS, LV geometry and function are more influenced by the presence of comorbidities, such as arterial hypertension, obesity, metabolic syndrome and arterial stiffness, than by the AS itself.[22–24] Such cluster of risk factors is associated with impaired prognosis in moderate AS, compared with the general population.[25] In the SEAS study, the prevalence of abnormal LV geometry was greater in the hypertensive than in the normotensive group. Furthermore, eccentric LV hypertrophy was the most common type of LV geometry,[26] suggesting a substantial volume component of arterial hypertension participating to the haemodynamic overload (*Figure 1*).[21]

In contrast, in severe AS, LV remodelling is mainly influenced by valve obstruction, and concentric LV hypertrophy is found in the majority of patients, both in women and men.[27] The presence of arterial hypertension in AS has been associated with development of symptoms even in moderate AS, reflecting the higher global LV workload.[15]

Most AS patients have normal LV systolic function when assessed by LV ejection fraction.[5] A reduced LV ejection fraction can typically be found in AS patients with concomitant coronary artery disease or chronic kidney disease, and more often in men. However, LV systolic myocardial function may be reduced in AS, despite the presence of normal LV ejection fraction,[28] especially in the presence of concentric LV geometry. In patients with severe AS and LV hypertrophy, systolic wall stress is high and myocardial perfusion reduced, in particular in the sub-endocardium, leading to reactive and reparative fibrosis.[29,30] These myocardial changes can be diagnosed by cardiac magnetic resonance combining assessment of extracellular volume and gadolinium late enhancement imaging.[31] Furthermore, myocardial function may be assessed by tissue Doppler imaging (TDI) or by speckle tracking echocardiography to detect AS patients with more advanced myocardial disease, also when ejection fraction is normal.[32–35] Fibrosis-related myocardial dysfunction also influences LV pump performance (stroke volume) and transvalvular gradients.[36] Low-gradient severe AS is typically associated with myocardial fibrosis and reduced pump performance, and decreased myocardial function assessed by global longitudinal strain (GLS). Arterial hypertension is associated with lower longitudinal and circumferential myocardial function in moderate-to-severe AS.[37] Reduced myocardial function by GLS may also be found in non-severe AS when hypertension-associated LV hypertrophy or concentric LV geometry is present (*Box 2*).[33]

Box 2 Expert panel consensus

- Left ventricular (LV) mass and assessment of LV hypertrophy in aortic stenosis (AS) patients should be part of risk assessment
- Assessment of global longitudinal strain may be considered to identify hypertensive AS patients with reduced myocardial function, especially when decision making might be influenced.

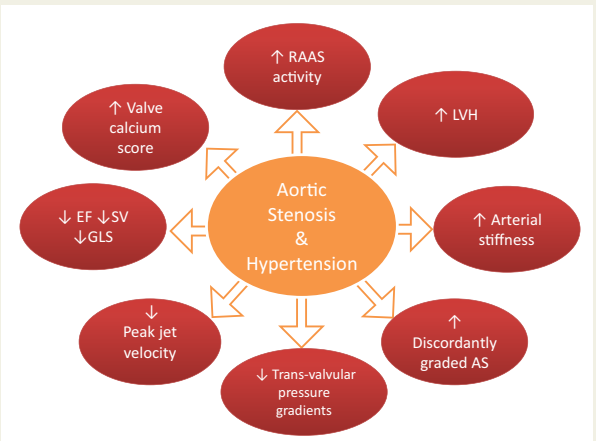

Figure 1 Main features of patients with combined arterial hypertension and aortic stenosis.

Grading aortic stenosis in patients with concomitant arterial hypertension

Current guidelines acknowledge the high prevalence of arterial hypertension especially in the elderly and recommend avoiding AS severity evaluation in the presence of uncontrolled BP at the time of echocardiography.[5] Furthermore, current guidelines recommend to record BP at the time of the echocardiographic examination to facilitate comparison with earlier examinations and to repeat assessment of AS severity in patients with arterial hypertension when BP is controlled.[5] These recommendations are based on the evidence that high BP affects measures of AS severity.

In a cohort study of patients with moderate or severe AS, those with increased systemic vascular resistance had higher systemic BP, lower stroke index, lower transvalvular flow rate, and lower cardiac index, when stratified by effective orifice area and other measures of AS severity.[38]

In an animal experiment, fixed supra-aortic stenosis was created and thereafter systemic BP was augmented by thoracic banding or phenylephrine infusion. Pressure gradient across the fixed supra-aortic stenosis decreased during hypertension, while calculated stenotic area did not. Mean transvalvular flow rate also decreased, although stroke volume did not. There was a strong effect of systemic hypertension on peak-to-peak catheter gradients, which decreased massively in the presence of severely elevated BP in spite of the continuing presence of severe AS.[39] Thus, in this experimental model, severe arterial hypertension masked identification of severe AS when assessed based upon transvalvular pressure gradient.

In a small study of 22 patients with AS, handgrip or phenylephrine infusion was used to increase systemic BP.[40] While stroke volume and mean transvalvular pressure gradient did not change substantially, mean transvalvular flow rate decreased, and calculated valve area

slightly decreased. The latter observation is difficult to explain and a plot of change in valve area vs. change in mean BP showed only a weak correlation, suggesting that the influence of BP on grading of AS may vary.

In hypertensive patients with low gradient severe AS (area <1 cm^2) with acute lowering of BP with sodium nitroprusside to low-normal range values, Gorlin formula-calculated aortic valve area increased[41]; also stroke volume, cardiac index, and transvalvular gradients increased slightly. Accordingly, in the presence of elevated BP, AS severity assessment should be done also using flow-dependent indices and estimation of aortic valve area in patients with discordantly graded AS (*Figure 1*). The presence of tachycardia may impact echocardiographic assessment of AS, particularly in case of atrial fibrillation, more common among hypertensive patients. Heart rate should be recorded and preferably controlled before echocardiographic assessment of AS (*Box 3*).

Box 3 Expert panel consensus

- Blood pressure (BP) and heart rate should be taken at the time of echocardiographic examination
- A well-controlled BP and heart rate is critical for reliable assessment of aortic stenosis (AS) severity.
- High cuff BP values are associated with frequent underestimation of AS severity based on transaortic gradients, whereas aortic valve area is less affected. Continuity equation should be always used together with gradient assessment.

Impact of hypertension on decision making for aortic valve replacement and prognosis in patients with aortic valve stenosis

Concomitant arterial hypertension in AS is associated with a two-fold higher mortality even in patients with non-severe AS.[16] The risk for concomitant coronary artery disease and hospitalization for heart failure is also higher in AS patients when arterial hypertension coexists.[16] Patients with combined arterial hypertension and AS develop symptoms earlier during AS progression.[15] Arterial hypertension and uncontrolled BP can impact the timing of intervention in AS, mainly due to underestimation of its severity and, consequently delayed referral for valve replacement.[5,39–42] The increased LV pressure overload in uncontrolled hypertension,[38,43] contributes to excessive concentric LV geometry and hypertrophy and the consequent reduction in cavity size and in diastolic function, impairs LV filling. Therefore, the consequences of systemic hypertension in AS increases the likelihood of development of low-flow low-gradient AS with preserved ejection fraction (paradoxical low-flow low-gradient aortic stenosis). The low-flow status results in low transvalvular gradients further contributing to underestimation of AS severity and to the consequent potential delay in treatment. However, patients are usually symptomatic, with shortness of breath occurring early in the course of the disease because of high LV filling pressures, resulting in high left atrial pressures and pulmonary congestion. Symptoms will prompt detailed full evaluation of AS severity in order to determine the need for intervention. In this regard, natriuretic peptides can also be useful to determine optimal timing for intervention.[5]

Arterial hypertension associated with AS can impact prognosis[42] by further promoting LV hypertrophy with consequent irreversible myocardial fibrosis. The presence of LV hypertrophy in mild-to-moderate AS and presence of inappropriately high LV mass in severe AS have been associated with higher mortality and development of heart failure.[44,45] The systolic LV overload from combined AS and arterial impedance due to arterial hypertension is estimated by calculating the valvulo-arterial impedance. High valvulo-arterial impedance was found to be associated with increased mortality in a retrospective study of patients with asymptomatic, moderate-to-severe AS.[36] It was also found to predict a higher rate of major non-fatal cardiovascular events and aortic valve events (but not mortality) in patients with only mild-to-moderate AS, independent of arterial hypertension, LV ejection fraction, female gender, age, abnormal LV geometry, and AS severity.[46] Concomitant arterial hypertension possibly contributed to the poor long-term prognosis in moderate AS recently reported from the National Echocardiography Database Australia.[47] However, neither BP nor history of arterial hypertension was included in their analysis (*Box 4*).

Box 4 Expert panel consensus

- Patients with low flow—low gradient aortic stenosis (AS) should be referred to Heart Valve Clinics for expert evaluation
- Symptomatic hypertensive AS patients also should be promptly referred to Heart Valve Clinics

Treatment of arterial hypertension in aortic valve stenosis

Current guidelines on the management of valvular heart disease emphasize the need for treatment of concomitant arterial hypertension in patients with AS, ensuring frequent assessment of patients aimed at implementing tailored drug choice and titration to avoid hypotension.[5,17,48] However, BP control in elderly subjects with AS is often challenging in real life, and many patients remain uncontrolled with deleterious consequences for LV function and outcome, whereas hypotension is rarely seen. A *post hoc* analysis from the SEAS study reported a systolic BP of 130–139 mmHg and a diastolic BP of 70–90 mmHg to be associated with the lowest rate of cardiovascular morbidity and all-cause mortality across all age groups during 4 years of follow-up,[49] consistent with the general indications from the 2018 ESC/ESH Guidelines on arterial hypertension.[15] Of note, the SEAS study did not include patients with known cardiovascular disease or diabetes.

The risk for hypotension is increased in patients with symptomatic, severe AS and systolic LV dysfunction.[49,50] Also, there is circumstantial evidence that an achieved systolic BP below 120 mmHg or a

diastolic BP below 70 mmHg in high-risk cardiovascular patients (including diabetes and coronary artery disease) is associated with an increased risk for adverse cardiovascular events.[51–54] Thus, although antihypertensive treatment in AS patients in general should follow the guideline recommendations for management of arterial hypertension,[15,53] care should be taken to avoid hypotension. Furthermore, in patients with severe AS, symptomatic AS or known heart failure or LV systolic dysfunction, antihypertensive treatment should follow expert evaluation at Heart Valve Clinics in the individual patient.

Initiating drug treatment for arterial hypertension in asymptomatic patients with AS with a BP of ≥140/90 mmHg (≥160/90 mmHg in patients >80 years) is reasonable. Treatment should be started with low doses followed by a personalized titration. A target BP <140/90 mmHg is recommended for most patients, if tolerated (with no age restriction), while aiming at a BP target <120/70 mmHg is not recommended. Although a target BP <130/80 mmHg has been suggested for some patients with arterial hypertension (including patients with concomitant cardiovascular disease),[55,56] this remains to be demonstrated in patients with AS. ABPM might be particularly useful to ensure smooth BP control over 24 h (*Figure 2*).

Neuroendocrine activation is well demonstrated in AS, although the molecular mechanisms in combined hypertension and AS are incompletely studied. Sympathetic nervous system activation and increased expression of angiotensin II and angiotensin-converting enzyme (ACE) have been documented in AS.[57,58] In particular, angiotensin II was demonstrated to induce aortic valves thickening, endothelial disruption and accumulation of myofibroblasts in an experimental animal model.[59] In humans, activation of the renin–angiotensin–aldosterone system (RAAS) in patients with AS is related to the development of LV hypertrophy and myocardial fibrosis[60] (*Figure 1*). Reducing LV hypertrophy in the treatment of arterial hypertension has important prognostic implications, and drugs blocking the RAAS may be a preferred therapeutic option.[61] These drugs are the best studied antihypertensive medications in patients with AS, although randomized controlled studies in this context are limited and small. In patients with symptomatic severe AS, the ACE inhibitor enalapril was well tolerated compared with placebo and improved exercise tolerance and dyspnoea level; however hypotension was more common in patients with congestive heart failure with LV dysfunction.[50] Compared with placebo, in patients with severe AS, the ACE inhibitor trandolapril was safe and improved haemodynamic LV load.[62] Bull *et al.*[63] reported positive effects of the ACE inhibitor ramipril over placebo on the regression of LV hypertrophy in moderate-to-severe AS. In another small study, the angiotensin receptor blockers (ARB) candesartan failed to show a beneficial effect on LV geometry, function, or symptoms compared with placebo in patients with severe symptomatic AS, despite being well-tolerated.[64]

These findings are supported by observational data showing that blocking RAAS is safe and effective in reducing BP and LV mass, and is associated with lower CV events and all-cause mortality, independent of the severity of valve disease.[65,66] Thus, ACE-inhibitors or ARB should be the preferred antihypertensive treatment in patients with AS and concomitant arterial hypertension.

Hypertension in AS augments myocardial oxygen consumption, due to increased heart rate and BP, predisposing to myocardial ischemia and heart failure. Theoretically, reducing sympathetic activation may improve the coupling of stroke work and oxygen consumption at myocardial level.[67] Small retrospective studies have demonstrated

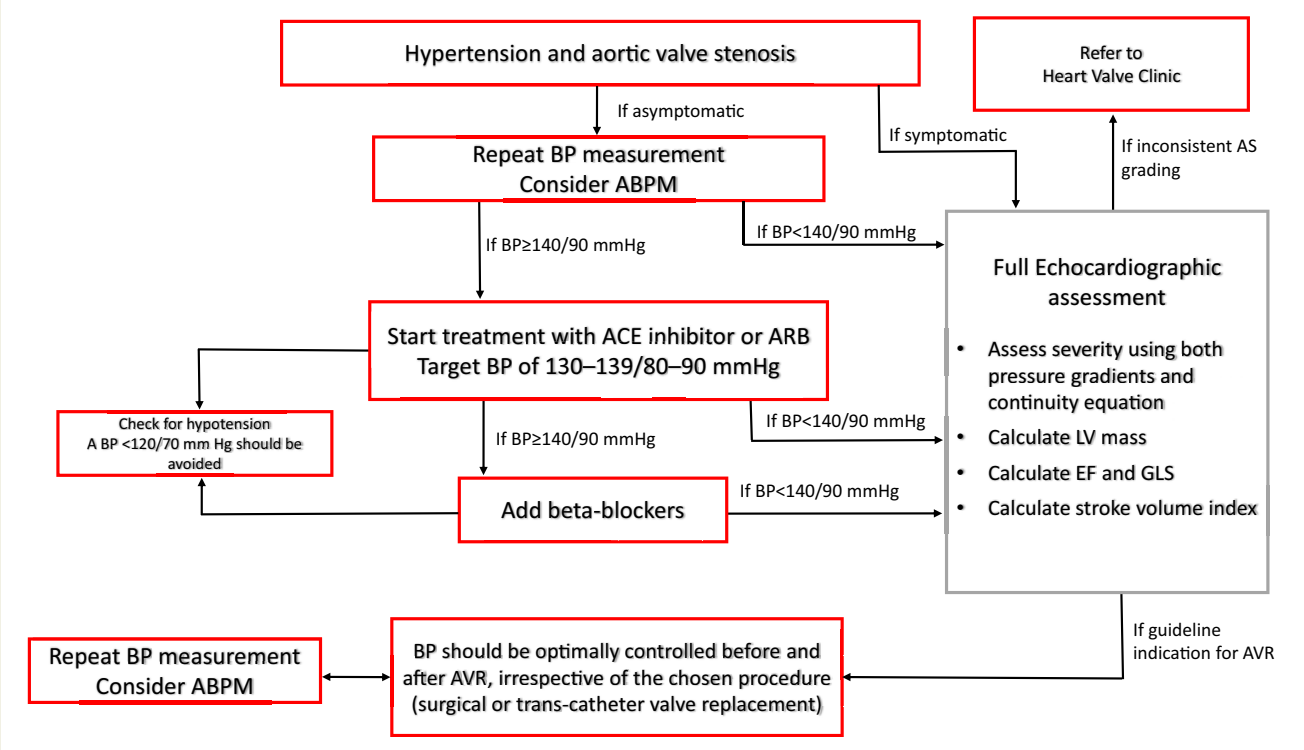

Figure 2 Flowchart for management of patients with combined arterial hypertension and aortic stenosis.

that also use of β-blockers is associated with improved survival in patients with severe symptomatic AS.[68] In addition, in a small randomized controlled trial in asymptomatic patients with moderate AS,[69] treatment with metoprolol was related to improved LV haemodynamics, lowering afterload, and oxygen consumption. Also, a *post hoc* analysis from the SEAS study suggests that use of β-blockers in patients with asymptomatic mild-to-moderate AS is safe and associated with improved survival.[70] Thus, β-blockers may be indicated in hypertensive patients with AS, especially when concomitant compelling indications exist, such as coronary artery disease or arrhythmias.

Treatment with vasodilators has been a concern in patients with AS. The outdated view that antihypertensive drug treatment might result in reduced cardiac output (because valvular obstruction is the dominant cause of increased LV load) has not been corroborated in studies of medical therapy in AS patients. In the acute setting, small studies, mainly involving patients with low gradient AS, have demonstrated safety and improved haemodynamics with sodium nitroprusside infusion.[41,71] However, no studies are available on long-term antihypertensive therapy with vasodilators (such as calcium channel blockers or nitrates) and outcome in patients with AS, and these drug classes should therefore not be considered first line choices in AS patients with arterial hypertension. Noteworthy, alpha-blockers were the only antihypertensive treatment in the SEAS study associated with higher risk of ischaemic cardiovascular events.[16] We advise that antihypertensive treatment with diuretics should be used carefully in patients with concentric geometry and small LV cavity, because decreased volumes can result in a fall in cardiac output.

Medical management of AS patients with bicuspid aortic valve and ascending aorta dilatation requires aggressive BP control with β-blockers and either ACE inhibitors or ARB as first-line agents (*Box 5*).[72]

Box 5 Expert panel consensus

- Antihypertensive drug treatment should be initiated in patients with aortic stenosis (AS) at a blood pressure (BP) ≥140/90 mmHg (≥160/90 mmHg in patients >80 years).
- A target BP of 130–139/80–90 mmHg is advisable in most patients, if well tolerated.
- A BP target <120/70 mmHg should be avoided.
- Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be considered as first line therapy for antihypertensive treatment.
- β-Blockers may be considered in hypertensive patients with AS and concomitant compelling indications such as coronary artery disease or arrhythmias.

Peri-operative management of hypertension in patients with aortic valve stenosis

The risk profile of patients undergoing aortic valve replacement (AVR) has worsened over time. Patients are older and present with higher prevalence of arterial hypertension.[73,74] Pre-procedural arterial hypertension is a predictor of increased mortality after surgical AVR.[75] In patients with severe AS presenting severe pre-intervention BP elevation, BP control should be pursued using RAAS blockers and β-blockers, if indicated. In patients presenting with severe BP elevation and acute decompensated HF treatment should be promptly pursuit according to current guidelines.[76,77]

Also, post-procedural uncontrolled arterial hypertension is detrimental. AVR often causes haemodynamic changes with increased BP that can challenge post-procedural care,[78,79]. Similarly, systolic BP can rise immediately after transcatheter aortic valve implantation (TAVI).[80] About half of the patients have a rise in systolic BP, necessitating immediate and long-term antihypertensive treatment.[81] Peri- and post-procedural care are challenging in these patients, as TAVI is generally performed under conscious sedation that does not allow the tight haemodynamic control achievable under general anaesthesia.[82–84] The rise in BP after TAVI is associated with greater increase in both stroke volume and cardiac output, and better myocardial contractile reserve than in case of conventional surgery, even in patients with reduced LV function at baseline.[67,81] Systemic arterial load changes rapidly after TAVI.[85] These acute changes include an immediate increase in forward and reflecting pressure waves in the aorta, an increase in central aortic systolic BP and vascular impedance, leading to augmented arterial load. In addition, the abrupt pressure rise, immediately after valve deployment, might result in severe pulmonary oedema. In patients who underwent surgical AVR BP control is obtained under general anaesthesia, using parenteral drugs.

BP response and prognostic implications following AVR can differ among patients. In the PARTNER I trial, a combined post-procedural systolic BP <130 mmHg and high arterial load 30 days after TAVI, was associated with more symptoms of heart failure and angina pectoris, and higher 1-year mortality.[86] This could be explained, because lack of increase in BP after TAVI is possibly a proxy of compromised LV function (e.g. lack of contractile reserve), vascular stiffness, and/or incident vascular complications (bleedings).[81] A *post hoc* analysis from the Placement of AoRTic TraNscathetER Valve (PARTNER) Trial 2 study and registries including 3979 patient with severe, symptomatic AS treated with TAVI, baseline treatment with ACE inhibitors or ARB was associated with a 32% lower risk of 2-year all-cause and cardiovascular mortality.[87] Once severe AS is resolved following surgical AVR or TAVI, guideline-recommended BP control should be pursuit.[17] Treatment with RAAS inhibition, following surgical AVR or TAVI is associated with reduction of LV mass and lower CV mortality (*Box 6*).[88,89]

Box 6 Expert panel consensus

- Blood pressure (BP) should be optimally controlled before aortic valve replacement (AVR), irrespective of the chosen procedure (surgical or transcatheter valve replacement).
- BP should be carefully managed in the early post-operative phase, because the increase in systolic BP after AVR may induce pulmonary oedema and acute heart failure.
- Arterial hypertension in stabilized patients after AVR should be managed according to guidelines to reduce morbidity and mortality.

Conflict of interest: No conflict of interest to declare.

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