The Pressure Is On: Implications of Blood Pressure After Aortic Valve Replacement

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Therapeutic control of blood pressure (BP) in an "all-comer" patient population is associated with a reduction in cardiovascular mortality.[1] Recent evidence and contemporary guidelines suggest that the benefit of strict therapeutic reduction in BP (systolic BP [SBP] <120 mm Hg and diastolic BP [DBP] <80 mm Hg) confers additional benefit in patients with diabetes mellitus and/or those with a prior cardiovascular event.[2] Such BP control has also been shown to be beneficial in those without diabetes mellitus and aged >75 years.[3,4] However, in patients with aortic valve disease, a large proportion of whom are elderly patients, it is unclear whether this level of intensive BP control further improves prognosis.

Guidance for BP control in patients with significant aortic stenosis has been confusing, particularly with the fear of afterload reduction causing syncope. To date, most of the evidence for BP control before aortic valve replacement (AVR) has involved alterations to the renin-angiotensin system. The renin-angiotensin system has been thought to have an influence on myocardial physiological characteristics, left ventricular hypertrophy, and extent of myocardial fibrosis. There is early evidence of potential benefits in angiotensin-converting enzyme inhibition, potentially reducing the progression of aortic stenosis without causing harm.[5] Similar prognostic benefits have been found after AVR.[6]

The observation that BP after AVR is an independent predictor of outcome was first described by Perlman et al, who made the association that postprocedural *hypertension* after transcatheter AVR (TAVR) was a predictor of a better prognosis.[7] In their study of 105 consecutive patients after TAVR, 51% had sustained increases in BP after TAVR, requiring intensification of antihypertensive treatment.[7] Patients with increased BP had an increase in stroke volume and cardiac output independent of other factors and, thereafter, a better prognosis.[7] Lindman et al, before their most recent publication, evaluated the effects of post-TAVR *hypertension* using the Edwards Balloon expandable system.[8] Analyzing the Partner I trial data, they demonstrated that postprocedural *hypertension* was independently associated with improved survival.[8] So if *hypertension* after AVR indicates a good prognosis, can we deduce that *hypotension* is a bad thing?

In this issue of the *Journal of the American Heart Association* (*JAHA*), Lindman et al demonstrate that low BP (both SBP and DBP) is linked to poorer outcomes after AVR via both surgical and transcatheter approaches.[9] Patients enrolled in the Medtronic intermediate, high- and extreme-risk trials receiving either TAVR with a self-expanding valve or surgical AVR were analyzed (Figure). They concluded that a DBP of 30 to <60 mm Hg compared with a DBP of 60 to <80 mm Hg was associated with increased all-cause (HR, 1.62; 95% CI, 1.23–2.14) and cardiovascular mortality (HR, 2.13; 95% CI, 1.52–3.00).[9] A similar association was shown for SBP, where SBP of 90 to <120 mm Hg compared with SBP of 120 to <150 mm Hg was again associated with increased all-cause (HR, 1.63; 95% CI, 1.21–2.21) and cardiovascular mortality (HR, 1.81; 95% CI, 1.25–2.61).[9] Why is this phenomenon observed and what are the biological explanations for this association?

There is no doubt that replacement of the aortic valve in the setting of long-standing and incrementally severe aortic stenosis brings about dramatic hemodynamic changes in the cardiovascular system. The abrupt relief of excess afterload causes immediate alterations in systolic and diastolic function, ventriculoarterial interactions, coronary blood flow, and, thus, cardiac output. These changes are now no longer masked by the confounding effects of cardiopulmonary bypass with the widespread introduction of TAVR as a mainstream therapy. The implications of changes in SBP and DBP early after AVR, which are crude markers of this complex hemodynamic environment, are likely to be different from those in the long-term setting. The rules governing optimal BP management, therefore, may well be different after AVR,

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J Am Heart Assoc. 2019;8:e014631. DOI: 10.1161/JAHA.119.014631.

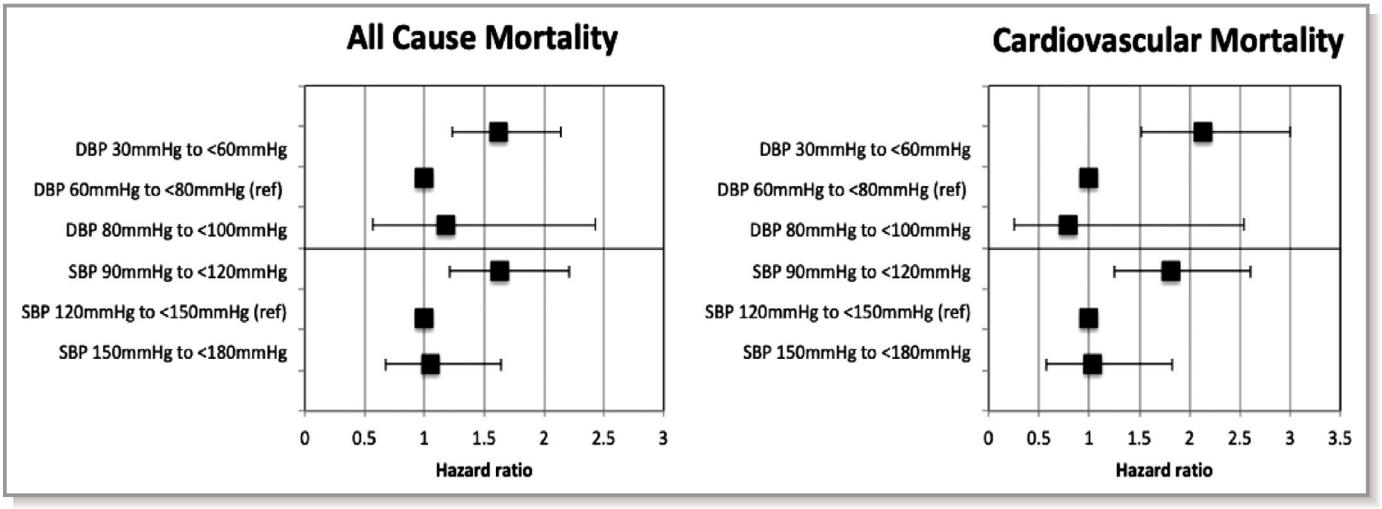

Figure. Forest plot of adjusted hazard ratio of 1-year all-cause mortality and cardiovascular mortality, according to early post–aortic valve replacement (AVR) diastolic blood pressure (DBP) and systolic blood pressure (SBP) (all patients with transcatheter AVR and surgical AVR).[9]

compared with those in a stable outpatient without severe valve disease.

The observations of Lindman and colleagues suggest that low BP either *causes* an adverse outcome or is *associated* with a clinical scenario with a less favorable prognosis.[9] There are several potential explanations as to why low BP may be *associated* with a poor outcome, the first of which is variation in the complex ventriculo-aortic-arterial interaction and the changes that occur when aortic valve stenosis is suddenly relieved. Arterial stiffness has been repeatedly associated with adverse left ventricular remodeling and a poor outcome.[10–12] The crude echocardiographic index of *ejection fraction* is a poor marker of myocardial contractility, which is often depressed at the time of AVR.[13] It is, therefore, conceivable that those patients with a stiffer vasculature and more pronounced ventriculoaortic interaction have lower DBP, and a consequent adverse outcome as the heart attempts to equilibrate to the new norm after AVR.

The second *association* is the possibility of low DBP being a marker of paravalvular leak (PVL). In the literature, the measurement of post-TAVR PVL has been hugely variable, with the use of echocardiography, aortography, and hemodynamics all giving slightly different information.[14] Such assessment has become less uniform with the decline in peri-TAVR transesophageal echo, which is perhaps the most accurate imaging modality in assessing PVL.[15] Moreover, many of those involved in these studies, both the device companies and enthusiastic physicians alike, have been keen to underplay its severity, particularly now that we know that *more than mild* aortic regurgitation after TAVR confers a poorer prognosis.[16] Transthoracic echocardiography on table is notoriously difficult in obtaining an accurate quantification of PVL, and many TAVR operators use hemodynamics to identify significant aortic regurgitation immediately after valve deployment.[17] The findings of Lindman et al[9] of an association between post-AVR hypotension and poor outcome hold true, even when the analysis excluded those reported to have "moderate to severe PVL," but it remains possible/likely that in a population after AVR of patients with low DBP, there will be a higher prevalence of unappreciated or poorly imaged PVL, thus explaining the worse prognosis in this group. However, although this mechanism may account for the DBP *association*, it is more difficult to account for the relationship with SBP, although the systolic association was weaker.

Other possible associations between low BP early after AVR and a poorer long-term outcome include impairment of left ventricular function, although the study by Lindman et al[9] showed no such correlation, which is rather surprising. The final conceivable *association* would be a systemic inflammatory response, particularly in the surgical AVR group, which would lower early BP values and has previously been associated with a poor long-term outcome.[18] Again, the most recent study of Lindman et al[9] found no such relationship, with either surgical AVR or changes in systemic vascular resistance.

How could low BP early after AVR *cause* an adverse outcome? The first potential hypothetical mechanism involves changes in coronary flow and myocardial perfusion that occur after AVR. Low diastolic pressure may be a marker of less adequate coronary perfusion, which, in turn, would lead to subendocardial ischemia, particularly in the setting of diffuse coronary atheroma. On-table studies after TAVR have demonstrated *increases* in coronary flow, most likely related to changes in systemic hemodynamics.[19] However, it is conceivable that the aortic valve prosthesis may disturb normal

aortic root flow patterns and alter the blood flow impairing coronary perfusion, thus making lower diastolic perfusion pressure more deleterious.[8]

The second potential causative mechanism is overtreatment. After the results of the SPRINT (Systolic Blood Pressure Intervention) trial, efforts have intensified to control systemic pressure, in particular with evidence of the benefit of angiotensin-converting enzyme inhibitors.[3,5] It is possible that overmedication in the early postprocedure period will lead to systemic hypotension and reduced coronary flow, as well as renal underperfusion, which, in turn, would lead to increased adverse events.

In the spirit of Goldilocks and the 3 bears, if too high is bad and too low is bad, what then is just right? There is no doubt that hemodynamics after AVR are complex and at present not well understood. The management of BP in the post-AVR period should, therefore, be separated from conventional BP treatment in the stable setting and tailored to the individual patient. Establishing the optimal BP range in this growing patient group is the most important clinical goal and will form a platform for further research into the mechanistic association to help us understand the most appropriate post-AVR management. In patients after AVR, it may be reasonable to accept a more relaxed level of BP in the early postoperative period, then adopt a more intensified longer-term approach. Clinical considerations in the management of BP early after AVR are summarized in Table.

Lindman et al[9] have demonstrated an intriguing association of post-AVR low SBP and DBP with a poor outcome. The authors acknowledge limitations of their study, including using post hoc data from previous studies designed to answer a different question and only a crude *snapshot* measure (2 readings) of BP early after AVR. As such, the study has potentially raised more questions than it has answered, but it has exposed our lack of understanding of the complex hemodynamics that occur after this increasingly common intervention. It is intriguing that although the study demonstrated an increase in all-cause and cardiovascular mortality, there was no increase in myocardial infarction or stroke, raising the question: what are these patients dying of? There are several hypothesized mechanistic reasons for the association that need to be further explored, and randomized trials of "liberal" versus "intensive" BP control in the post-AVR cohort are needed to translate these theories into clinical practice and ultimately patient benefit.

Table. Procedural and Postprocedural Considerations Related to Blood Pressure Management After AVR

Avoidance of excessively low systolic (<120 mm Hg) or diastolic (<60 mm Hg) BP within 30 d after AVR
Avoidance of negatively chronotropic drugs early after AVR
Caution with early reintroduction of ACE inhibitors (particularly in patients with significant renal impairment)
Avoidance of overmedication in the early postprocedural period
Low diastolic pressure should prompt detailed assessment to diagnose and subsequently manage paravalvular leak, particularly in patients with TAVR

ACE indicates angiotensin-converting enzyme; AVR, aortic valve replacement; BP, blood pressure; TAVR, transcatheter AVR.

Disclosures

Prof MacCarthy is a procedural proctor for Edwards LifeSciences, has received an educational grant from Edwards LifeSciences and research support from Boston Scientific.

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Key Words: Editorials • aortic stenosis • aortic valve replacement • blood pressure