

The development or worsening of hypertension after transcatheter aortic valve replacement (TAVR) improves short-term and long-term patient outcomes

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ABSTRACT

Objectives In patients with symptomatic aortic valve disease who are at intermediate to high risk for open surgical aortic valve replacement, transcatheter aortic valve replacement (TAVR) decreases overall mortality and improves quality of life. Hypertension (HTN) after TAVR has been associated with improved cardiac function and short-term survival but its effect on survival over 1 year is unclear. Our study aims to evaluate the effect of HTN following TAVR on short-term and long-term clinical and echocardiographic outcomes

Methods A retrospective chart review case–control study of 343 consecutive patients who underwent TAVR between August 2012 and November 2016 was performed to elucidate the relationship between HTN and post-TAVR outcomes.

Results 193 patients who underwent TAVR (56.2%) developed or had a worsening of their HTN after TAVR. The development of post-TAVR HTN was associated with a significantly better overall survival at 1 year (89% vs 67%, $p<0.001$) and 2 years (72% vs 46%, $p=0.002$). Patients with increased blood pressure also had a significant lower in hospital cardiovascular mortality (1% vs 12%, $p<0.001$). However, the development or worsening of their HTN after TAVR was associated with an increase in heart failure (HF) exacerbations and diuretic use.

Conclusions The development or worsening of HTN after TAVR is associated with improved overall survival despite an increase in postprocedural HF exacerbations and antihypertensive medication utilisation. The outcomes of this study could be important in postoperative management of patients who underwent TAVR.

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has been a major advancement in the treatment of symptomatic aortic valve disease in patients at intermediate or high risk for surgical complications. In this population, outcomes after TAVR have consistently shown benefit over non-surgical medical treatment, as well as improvements in hospitalisation rate, patient symptoms and overall quality of life.^{1,2} Despite the 44% improvement in overall survival versus medical management, the 1-year and 2-year overall mortality remains elevated at 24.2% and 43.3%, respectively, in the highest risk patients.^{1,3}

There has been little published data on validated postprocedural prognostic factors that could be easily applied to tailor post-TAVR management based on the patient's clinical and haemodynamic response to TAVR. Postoperative factors associated

with an increased risk of death after TAVR include acute kidney injury, major bleeding complications, postprocedural cardiac tamponade, elevated creatine kinase-myocardial band (CK-MB), post-TAVR paravalvular leak, left-ventricular stroke volume index at discharge, severe pulmonary HTN, postinterventional myocardial infarction, stroke, pulmonary embolism or systemic inflammatory response syndrome (SIRS).^{4–14} New onset atrial fibrillation following TAVR and post-TAVR permanent pacemaker implantation have been associated with a poor prognosis, but not consistently with overall mortality.^{15,16}

In 2013, Perlman *et al* published a study of 105 patients who underwent TAVR which demonstrated improved postprocedural outcomes, but not mortality in patients who developed new onset HTN or had increased blood pressure (BP) during the first five postprocedural days.¹⁷ Perlman *et al* concluded that increased BP after TAVR indicates a relative improvement of cardiac function and suggests a better overall haemodynamic response to TAVR, but without an improvement in survival. The authors also noted the contradictory nature of an association between increased BP and improved outcomes, especially in elderly patients with the most arterial stiffness. In 2017, Lindman *et al* showed that higher systolic BP is associated with improved overall, but this study was limited to 1 year post-TAVR.¹⁸ In this study, we extended the period of HTN and outcome monitoring to better associate new onset or worsening HTN with improved outcomes.

METHODS

A hospital-based, single institution case–control study was conducted using data from one large single-centre, tertiary care referral centre. We performed a retrospective chart review of 343 consecutive patients who underwent TAVR at Sanford Health in Fargo, ND from August 2012 to November 2016. The last date of data acquisition was 1 April 2017. The entire cohort was divided in two groups: the patients who developed new onset HTN or increased systolic or diastolic BP meeting study criteria within a 1-year postoperative follow-up period or by the last date of data acquisition, and those who did not meet this criteria. Patients with HTN needed to meet at least one of the following three criteria: (1) a sustained (48 hours) systolic pressure 140 mm Hg or diastolic pressure 90 mm Hg that was not present at baseline, (2) a need to increase the dosage of an antihypertensive



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Table 1 Baseline characteristics

	Increased BP (193)	Stable BP (150)	P value
Age	81 (74–85)	81 (74–86)	0.802
Male sex	96 (50)	96 (64)	0.009
BMI	29.55 (26.43–34.29)	29.66 (26.05–32.99)	0.668
Caucasian race	191 (99)	149 (99)	1.000
EuroSCORE (%)	7.09 (4.50–11.28)	6.96 (4.77–10.08)	0.523
STS risk score (%)	5.4 (3.6–8.8)	6.1 (4.0–9.1)	0.178
Preprocedural HTN	172 (89)	130 (87)	0.506
Preprocedural CAD	145 (75)	107 (71)	0.461
Baseline ejection fraction <40%	23 (12)	26 (17)	0.165
Preprocedural NYHA class III or IV symptoms	85 (44)	67 (45)	0.913
Preprocedural DM	70 (36)	52 (35)	0.820
Prior stroke/TIA	27 (14)	12 (8)	0.089
Preprocedural atrial fibrillation	54 (28)	50 (33)	0.290
Preprocedural eGFR <60 mL/min	95 (49)	69 (46)	0.587
Preprocedural AAA	18 (9)	20 (13)	0.298
Preprocedural carotid artery stenosis >50% or prior CEA	54 (28)	39 (26)	0.715
Preprocedural dyslipidaemia	171 (89)	134 (89)	0.864
Prior CABG	57 (30)	40 (27)	0.629
Prior PCI	65 (34)	61 (41)	0.214
Prior permanent pacemaker	24 (12)	17 (11)	0.867
Prior aortic valvuloplasty	31 (16)	28 (19)	0.565

Values are median (IQR) or n (%).

AAA, abdominal aortic aneurysm; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CEA, carotid endarterectomy; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate HTN, hypertension; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS, TIA, transient ischaemic attack.

drug by twofold or more from the preprocedural dose to achieve control of systemic BP or (3) a need to add an additional anti-hypertensive medicine to the preprocedural regimen in order to achieve control of systemic BP. Primary outcomes were overall survival at 1 month, 6 months, 1 year and 2 years post-TAVR. Secondary outcomes were procedural complications, post-TAVR permanent pacemaker implantation, major adverse cardiovascular and cerebrovascular events (MACCE) defined as death from any cause, myocardial infarction, rehospitalisation for stroke, cardiovascular mortality, myocardial infarction, stroke/TIA, heart failure (HF) exacerbation or rehospitalisation for any reason in defined time periods. Preprocedural and postprocedural echocardiographic data along with baseline, immediate postprocedural and 1-year HTN data were also compared. The clinical outcomes were assessed in accordance with the standardised endpoint definitions for TAVR of the Valve Academic Research Consortium-2.¹⁹ HF exacerbation was defined as a gradual or rapid change in HF signs and symptoms resulting in a need for a change in therapy or hospitalisation.

A waiver for informed consent was granted due to the retrospective nature of the study. The Fisher's exact test was performed to determine statistical significance of categorical data and t-test or Wilcoxon two-sample test was used to determine the statistical significance continuous variables. All p values were two-sided, and p values <0.05 were considered significant.

RESULTS

A total of 193 of the 343 patient met study criteria for post-TAVR HTN. Baseline characteristics for both groups are given in table 1. The two study cohorts were well matched, except for an increased proportion of female subjects in the cohort meeting the post-TAVR HTN criteria. Significant comorbidities existed in

both groups. The overall prevalence of preprocedural HTN was 88% in the entire cohort. The mean age of the entire cohort was 79.2 years. Procedural characteristics for both groups are given in table 2. There were no statistical differences in the approach used for TAVR, however there was small, but statistical significantly increase in the utilisation of the first-generation Edwards Sapien valve in the cohort that met study post-TAVR HTN criteria. Preprocedural and postprocedural echocardiographic data are given in table 3. No sustained differences in ejection fraction or stroke volume were found. Primary and secondary outcomes are detailed in table 4. Overall survival for the entire study cohort was 79.7% at 1 year and 60.5% at 2 years. Patients

Table 2 Procedural characteristics

	Increased BP	Stable BP	P value
Approach			
Transfemoral	154 (80)	125 (83)	0.485
Transapical	31 (16)	19 (13)	0.442
Transaortic	5 (3)	2 (1)	0.474
Trans-subclavian	2 (1)	4 (3)	0.410
Transcaval	1 (1)	0 (0)	1.000
Mean LOS after TAVR (days)	5.2 (8.6)	4.2 (4.7)	0.214
Valve type			
First generation Sapien	60 (31)	32 (21)	0.049
Sapien XT	29 (15)	23 (15)	1.000
Sapien S3	62 (32)	52 (35)	0.645
First-generation CoreValve	37 (19)	37 (25)	0.236
CoreValve evolute	5 (3)	6 (4)	0.544
Mean valve size (mm)	25.8 (2.7)	26.3 (2.7)	0.079

Values are mean (SD) or n (%).

BP, blood pressure; LOS, length of stay; TAVR, transcatheter aortic valve replacement.

Table 3 Echocardiographic data

	Increased BP	Stable BP	P value
Baseline			
Aortic valve area (VTI) (cm ²)	0.87 (0.31)	0.89 (0.43)	0.984
Peak aortic velocity (cm/s)	417 (62.3)	412 (70.8)	0.777
Peak aortic gradient (mm Hg)	71.3 (19.9)	70.4 (21.7)	0.684
Mean aortic gradient (mm Hg)	45.0 (12.7)	44.4 (13.3)	0.909
Ejection fraction (%)	58.8 (11.7)	55.8 (13.8)	0.056
Stroke volume (mL)	86.4 (21.8)	85.8 (20.1)	0.864
Moderate aortic regurgitation (%)	44 (23)	22 (15)	0.055
Severe aortic regurgitation (%)	7 (4)	4 (3)	0.760
Moderate mitral regurgitation (%)	46 (24)	31 (21)	0.515
Severe mitral regurgitation (%)	7 (4)	5 (3)	1.000
24 hours post-TAVR			
Aortic valve area (VTI) (cm ²)	2.13 (0.60)	2.27 (0.70)	0.052
Peak aortic velocity (cm/s)	223 (54.5)	220 (57.1)	0.666
Peak aortic gradient (mm Hg)	21.0 (10.9)	20.7 (11.7)	0.852
Mean aortic gradient (mm Hg)	12.5 (6.7)	12.1 (7.2)	0.677
Ejection fraction (%)	62.7 (11.6)	59.4 (13.8)	0.017
Stroke volume (mL)	92.3 (25.9)	97.2 (29.9)	0.133
Moderate aortic regurgitation (%)	5	5	1.000
Moderate mitral regurgitation (%)	12	7	0.102
Severe mitral regurgitation (%)	3	1	0.145
1 year post-TAVR			
Aortic valve area (VTI) (cm ²)	1.92 (0.59)	2.13 (0.60)	0.045
Peak aortic velocity (cm/s)	224 (53.0)	215 (43.1)	0.363
Peak aortic gradient (mm Hg)	21.5 (11.0)	19.2 (8.2)	0.192
Mean aortic gradient (mm Hg)	12.4 (6.5)	10.6 (4.4)	0.0696
Ejection fraction (%)	57.6 (13.9)	59.0 (11.2)	0.509
Stroke volume (mL)	93.8 (28.8)	92.9 (27.9)	0.862
Moderate aortic regurgitation (%)	12	15	0.612
Moderate mitral regurgitation (%)	14	9	0.602
Severe mitral regurgitation (%)	9	0	0.051

Values are mean (SD) or %.

BP, blood pressure; TAVR, transcatheter aortic valve replacement; VTI, velocity time integral.

with new onset or worsening HTN had significantly better survival than non-hypertensive patients up to 2 years after TAVR (table 4). Baseline, immediate postprocedural, and 1-year HTN and antihypertensive medication data are given in table 5. Overall antihypertensive medications, particularly beta-adrenergic blockers, were utilised at a high rate in both study groups, with a statistically significant difference in the mean number of antihypertensive medication at 1 year.

DISCUSSION

This study suggests an association between the development or exacerbation of HTN and improved survival up to 2 years after TAVR. The improvement in survival may reflect the presence of myocardial contractile reserve, improvement in ventricular compliance and diastolic function in the setting of decreased arterial compliance associated with advanced age and long-standing HTN. A lack of a hypertensive response to TAVR may correlate with poor myocardial contractile reserve, myocardial fibrosis and fixed restrictive diastolic dysfunction. These hypotheses warrant further study since the presence or absence of these conditions may assist in determining those who may benefit most from TAVR.

The data from this study also demonstrate an observed mortality benefit in patients with new or exacerbated HTN in

regard to inhospital mortality. The causative factors for this are uncertain, that is there were no differences in hospital HF exacerbations, pacemaker dependence or arrhythmias between the two groups. Furthermore, there were no significant differences in echocardiographic parameters directly after the procedure which would explain this difference. We believe that this is evidence of dormant myocardial reserve and suggests that there may be a 'window period' in which TAVR is most protective of the cardiac myocardium. This demonstrated benefit may indicate that the lack of an increase in afterload after TAVR suggest that there exists little preservable myocardium in some patients after TAVR. It may also suggest that the patients with increased BP differ only from the control group in this study in that the increased BP cohort was intervened on before myocardial remodelling became significant. We speculate that further improvements in TAVR outcomes could be made through earlier intervention in more closely monitored patients before TAVR and may indicate a role for cardiac MRI (cMRI) in pre-TAVR patient selection. The superior spatial resolution of cMRI over other imaging modalities may help identify patients with little subendocardial fibrosis, who potentially would have the best response to TAVR.²⁰

Correspondingly, patients who lack a hypertensive response may benefit from a more intensive cardiac rehabilitation

Table 4 Primary and secondary outcomes

	Increased BP	Stable BP	P value
% Survival >1 month	99 (192/193)	88 (132/150)	<0.001
% Survival >6 month	96 (152/159)	79 (92/116)	<0.001
% Survival >1 year	89 (116/130)	67 (65/97)	<0.001
% Survival >2 year	72 (59/82)	46 (30/65)	0.002
Periprocedural major vascular	14 (7)	15 (10)	0.435
Periprocedural minor vascular	15 (8)	15 (10)	0.564
Post-TAVR PPM implantation	18 (9)	10 (7)	0.430
Inhospital			
CV mortality	1 (1)	18 (12)	<0.001
MI	1 (1)	1 (1)	1.000
Stroke/TIA	3 (2)	6 (4)	0.187
HF exacerbation	36 (19)	37 (25)	0.186
Discharge to 30 days			
MACCE	36 (19)	21 (16)	0.554
CV mortality	0 (0)	1 (1)	0.410
Myocardial Infraction	2 (1)	2 (2)	1.000
Stroke/TIA	2 (1)	1 (1)	1.000
HF exacerbation	32 (17)	19 (14)	0.642
Rehospitalisation For any reason	35 (18)	21 (16)	0.654
30 days–6 months			
MACCE	45 (29)	24 (25)	0.472
CV mortality	4 (3)	1 (1)	0.652
MI	1 (1)	3 (3)	0.160
Stroke/TIA	4(3)	2 (2)	1.000
HF exacerbation	30 (19)	8 (8)	0.018
Rehospitalisation for any reason	44 (28)	19 (20)	0.137
6 months–1 year			
MACCE	39 (34)	17 (25)	0.189
CV mortality	3 (3)	1 (1)	1.000
MI	3 (3)	1 (1)	1.000
Stroke/TIA	2 (2)	1 (1)	1.000
HF exacerbation	33 (29)	2 (3)	<0.001
Rehospitalisation for any reason	37 (32)	14 (20)	0.090

Values are % (n).

BP, blood pressure; CV, cardiovascular; HF, heart failure; MACCE, major adverse cardiovascular and cerebrovascular events, defined as death from any cause, MI, rehospitalisation and stroke; MI, myocardial infarction; PPM, permanent pacemaker; TAVR, transcatheter aortic valve replacement; TIA, transient ischaemic attack.

programme following TAVR. Regular BP monitoring may be appropriate to risk stratify patients post-TAVR, identifying those at risk for adverse outcomes. Intensification of HF treatment and cardiac rehabilitation in higher risk patients may lead to an improvement in functional status, quality of life, reduce hospitalisation and mortality after TAVR.²¹

Optimal management of HTN after TAVR is unclear. Aggressive BP management has the potential to increase adverse events in this high-risk population. Adding to this complexity, the recent SPRINT trial and JNC8 guidelines provide conflicting evidence on the benefits and risks of intensive BP lowering in elderly and frail patients.^{22,23} Based on our study, we believe that allowing for moderately increased BP targets may be the most prudent approach after TAVR to avoid the risks of hypotension.

This study also uncovered an association between post-TAVR HTN and HF exacerbations which is the first documented postprocedural risk factor for HF exacerbation in this patient population. The specific aetiological factors for this increase is unknown, but is likely secondary to uncontrolled HTN and challenges in medication titration in the post-TAVR time period. Previous studies have indicated that uncontrolled HTN may be the causative factor in up to 13% of HF exacerbations in patients

with reduced ejection fraction and 16% in cases of preserved ejections factors.²⁴ This uncontrolled HTN may also lead to subclinical myocardial ischaemia and an increased propensity for atrial fibrillation, which may further predispose patients who underwent TAVR to HF exacerbations.²⁵

Still, the relationship between TAVR, cardiac haemodynamics and heart exacerbations remains uncertain. In a study by Chrissoheris *et al* it was demonstrated that TAVR is associated with improvements in stroke volume, cardiac output and central venous pressure in the first 24 hours after TAVR.²⁶ Our study did not show these same significant improvement which draws into question the sustainability the acute changes in cardiac haemodynamic noted in this study. It would appear that controlling BP and blunting the acute and long-term changes in cardiac haemodynamics may be critical in reducing heart exacerbations and hospitalisations.

This study is limited by its retrospective design, single-centre experience and inequalities in the length of post-TAVR follow-up. The potential for confounding factors which were not identified and addressed in the study's baseline patient characteristics does exist. Patients in both groups were well matched overall, except that the increased BP group had statistically more female patients

Table 5 HTN and antihypertensive data

	Increased BP	Stable BP	P value
Mean preprocedural systolic BP (mm Hg)	125.1 (17.8)	120.2 (16.1)	0.180
Mean preprocedural diastolic BP (mm Hg)	67.0 (10.2)	67.0 (10.3)	0.910
Mean preprocedural pulse pressure (mm Hg)	58.2 (16.1)	53.9 (13.3)	0.006
Mean # of preprocedural BP meds	2.23 (1.08)	2.41 (1.17)	0.150
ACE inhibitor (%)	31	35	0.415
Angiotensin II receptor blocker (%)	18	18	1.000
Beta blocker (%)	70	79	0.083
Calcium channel blocker (%)	27	31	0.470
Thiazide diuretic (%)	21	21	1.000
Loop diuretic (%)	48	50	0.827
Spironolactone (%)	4	3	1.000
Mean post-TAVR systolic BP (mm Hg)	125.2 (18.7)	123.2 (20.1)	0.350
Mean post-TAVR diastolic BP (mm Hg)	59.6 (15.0)	59.0 (14.3)	0.713
Mean post-TAVR pulse pressure (mm Hg)	65.6 (18.2)	64.2 (18.3)	0.500
Mean # of BP meds at 1 year post-TAVR	2.77 (0.92)	2.19 (1.06)	<.001
ACE inhibitor (%)	39	27	0.176
Angiotensin II receptor blocker (%)	22	20	1.000
Beta blocker (%)	88	81	0.250
Calcium channel blocker (%)	24	20	0.702
Thiazide diuretic (%)	20	17	0.687
Loop diuretic (%)	65	47	0.034
Spironolactone (%)	11	2	0.036

Values are mean (SD) or %.

BP, blood pressure; HTN, hypertension; TAVR, transcatheter aortic valve replacement.

and a greater utilisation of the first-generation Edwards Sapien valve. There is conflicting evidence on the impact of female sex on the outcomes of TAVR, and this could have influenced the findings of our study.^{4 27}

Key messages

What is already known about this subject?

- ▶ Previous studies have found that a transcatheter aortic valve replacement (TAVR) is associated with an increase in blood pressure (BP) in about half of patients after the procedure. This has been associated with a paradoxical improvement in long and intermediate outcomes including overall survival and procedural outcomes.

What does this study add?

- ▶ This study is important because it adds to what is previously known about the relationship between BP and TAVR and extends out the period of monitoring beyond 1 year post-TAVR.
- ▶ This study also provides important data on the potential long-term impact of TAVR on echocardiographic parameters.
- ▶ Furthermore, this study is the first to associated increased BP after TAVR and an increased risk in heart failure (HF) exacerbations in the first year following TAVR.

How might this impact on clinical practice?

- ▶ This study helps to establish a pragmatic way of risk stratifying patients for outpatient follow-up after TAVR.
- ▶ It is also the first study to associated hypertension (HTN) after TAVR and an increase risk in HF exacerbations, which could also serve as a guide for outpatient monitoring and pharmacological management of post-TAVR HTN. These findings could be an important first step in redesigning outpatient follow-up for patients after TAVR.

CONCLUSION

In this study, an association between the development or worsening of HTN after TAVR and improved clinical outcomes, most notably increased overall survival, was found. Additionally, the development or worsening of HTN after TAVR was also associated with a statistically significant increase in postprocedural HF exacerbations. The association between BP and post-TAVR mortality could lead to further study of methods to risk stratify patients who underwent TAVR in the preoperative and postoperative period.

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