Circulation Reports
Circ Rep 2022; **4:** 92–98
doi:10.1253/circrep.CR-22-0004

ORIGINAL ARTICLE
Valvular Heart Disease

Cardio-Ankle Vascular Index and Heart Failure Hospitalization in Patients With Aortic Stenosis Following Transcatheter Aortic Valve Implantation

Mitsuo Sobajima, MD, PhD; Teruhiko Imamura, MD, PhD; Yohei Ueno, MD;
Hiroshi Onoda, MD, PhD; Shuhei Tanaka, MD, PhD; Ryuichi Ushijima, MD, PhD;
Nobuyuki Fukuda, MD, PhD; Hiroshi Ueno, MD, PhD; Koichiro Kinugawa, MD, PhD

Background: The cardio-ankle vascular index (CAVI) is associated with the severity of vascular stiffness and heart failure (HF). However, little is known about CAVI in aortic stenosis (AS) patients, probably because of the difficulty of accurately measuring CAVI in these patients owing to their slow-rising pulse. In this study, we investigated the prevalence and prognostic impact of abnormally elevated CAVI measured after transcatheter aortic valve implantation (TAVI).

Methods and Results: Among patients with AS who underwent TAVI, those with bilateral peripheral artery disease, atrial fibrillation, and systolic HF were excluded. The effect of post-TAVI elevated CAVI (defined as ≥9.0) on HF readmission after the index discharge was investigated. In all, 149 patients (mean [±SD] age 84.8±5.6 years, 24.2% men, mean [±SD] post-TAVI CAVI 9.6±1.4) were included in the study. There was no significant difference in baseline characteristics between groups with and without elevated CAVI, except for lower high-density lipoprotein cholesterol (HDL-C) and a higher prevalence of HF history in the group with elevated CAVI (P<0.05 for both). Post-TAVI elevated CAVI (n=102) was associated with lower freedom from HF recurrence during the observational period (89.1% vs. 100%; median 726 days [interquartile range 329–1,104 days]; P<0.05). Moreover, CAVI was an independent predictor of HF occurrence (hazard ratio 1.62; 95% confidence interval 1.07–2.46; P=0.022).

Conclusions: Elevated CAVI was associated with HF occurrence before and after TAVI.

Key Words: Aortic stenosis; Cardio-ankle vascular index; Heart failure with preserved ejection fraction

One of the dominant drivers of aortic stenosis (AS) is age-related degeneration. Aging is strongly associated with atherosclerosis. As a result, many patients with AS are elderly and have atherosclerosis.[1–3] In contrast, according to recent studies, aortic valve degeneration and atherosclerosis may not stem from a similar mechanism.[4,5] Some patients with AS have few risk factors for atherosclerosis. The progression of atherosclerosis in patients with AS has not been well investigated thus far.

Clinically, the cardio-ankle vascular index (CAVI) is widely used to assess vascular stiffness, which is independent of arterial blood pressure. CAVI is associated with risk factors for atherosclerosis, including hypertension and ischemic heart disease.[6] CAVI is a major risk factor for the development of heart failure with preserved ejection function (HFpEF), as well as impaired flow-mediated dilatation, which is an index of endothelial function.[7–9]

The survival of patients with AS has improved considerably owing to the development of transcatheter aortic valve implantation (TAVI). Of note, recent studies indicate that TAVI can be used even in intermediate- and low-risk elderly cohorts with favorable results.[10,11] However, the occurrence of heart failure after TAVI remains an unsolved issue.[12] Several risk factors for the occurrence of heart failure after TAVI have been reported, including atrial fibrillation, low left ventricular ejection fraction (LVEF), ischemic heart disease, and pulmonary hypertension,[12,13] but the effect of vascular stiffness remains unknown.

CAVI is calculated by measuring brachial-ankle pulse wave velocity. Patients with AS have a slow-rising pulse, making CAVI measurement challenging.[6] Following TAVI, this issue is resolved and CAVI can be measured correctly. CAVI measured immediately after TAVI would be similar to that measured just before TAVI. In the pres-

Received January 13, 2022; accepted January 13, 2022; J-STAGE Advance Publication released online January 29, 2022 Time for primary review: 1 day
Second Department of Internal Medicine, Graduate School of Medicine, University of Toyama, Toyama, Japan
K.K. is a member of *Circulation Reports*' Editorial Team.
Mailing address: Teruhiko Imamura, MD, PhD, FAHA, FACC, FESC, FHFSA, FJCC, FAPSC, FACP, FASA, FICA, Second Department of Internal Medicine, Graduate School of Medicine, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan. E-mail: teimamu@med.u-toyama.ac.jp

ISSN-2434-0790

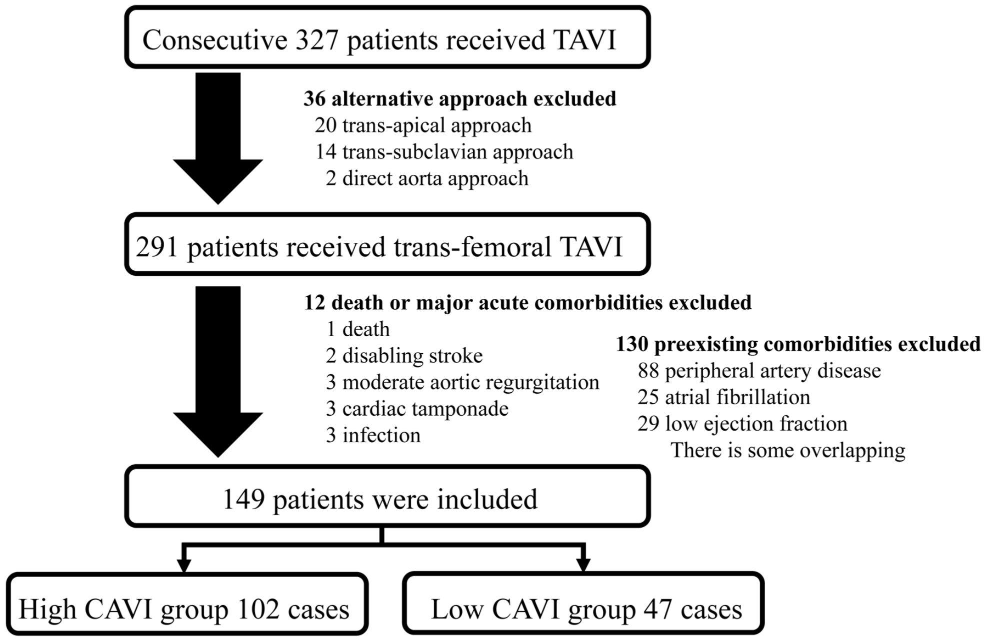

Figure 1. Study flowchart. CAVI, cardio-ankle vascular index; TAVI, transcatheter aortic valve implantation.

ent study, we investigated the effect of post-TAVI CAVI on heart failure occurrence after the index discharge.

Methods

Subjects and Study Design

Consecutive patients with symptomatic severe AS, which was defined as an aortic valve area <1.0 cm^2 and peak velocity thorough the aortic valve >4.0 m/s,[14,15] who finally received TAVI were prospectively enrolled in this study. Patients with reduced LVEF (<50%), bilateral peripheral artery disease, or atrial fibrillation were excluded from the study, given the effects of these conditions on CAVI.

In addition, post-TAVI data from patients who underwent an alternative approach or had major comorbidities, including death, cardiac tamponade, disabling stroke, severe infection, and moderate or greater aortic regurgitation, were excluded given their effects on heart failure events.

CAVI examinations were performed 1–2 weeks after TAVI. Patient cohorts were stratified into 2 groups (i.e., high and low CAVI groups) using a cut-off CAVI value of 9.0 according to the manufacturer's instructions.[16] The effect of CAVI on the incidence of heart failure readmission after TAVI was investigated.

Informed consent was obtained from all participants before they were enrolled in the study. This study was approved by the Ethics Committee of the University of Toyama (Reference no. 28-404).

TAVI

Patient selection for TAVI was determined by a heart team, which comprised cardiologists, cardiovascular surgeons, and anesthesiologists, according to the indications of the PARTNER trial.[17] All patients received balloon-expandable valves (Sapien XT or Sapien 3; Edwards Lifesciences, Irvine, CA, USA) or self-expandable valves (Corevalve or Evolut R; Medtronic, Minneapolis, MN, USA) via a transfemoral approach under general anesthesia.

Transthoracic Echocardiography

Transthoracic echocardiography was performed 2 days before TAVI and 1–2 weeks after TAVI. Standard M-mode, 2-dimensional, Doppler, and tissue Doppler studies were performed using standard techniques. The aortic valve area was calculated using a continuity equation.[18]

CAVI Measurement

CAVI was measured using a commercial device (Vasera; Fukuda Denshi, Tokyo, Japan) according to previously described methods.[19] Briefly, the brachial and ankle pulse waves were determined using inflatable cuffs, with the pressure maintained between 30 and 50 mmHg to ensure that the cuff pressure had minimal effect on systemic hemodynamics. Blood and pulse pressures were determined simultaneously, with the patient lying supine for 10 min in a quiet room.

Bilateral CAVI values were averaged in general. Patients with bilateral peripheral artery disease with an ankle-brachial index <0.9 were excluded. For those with unilateral disease, CAVI values obtained from the healthy leg were used.

Statistical Analysis

Continuous variables are expressed as the mean ± SD or median and interquartile range (IQR) depending on their distribution and were compared between groups using unpaired t-tests or the Mann-Whitney U test, as appropriate. Categorical variables are expressed as numbers and percentages and were compared between the 2 groups

Table 1. Patient Characteristics Before TAVI

	High CAVI (n=102)	Low CAVI (n=47)
Age (years)	85.3±5.9	83.7±4.8
Male sex (%)	25.5	21.3
Height (cm)	148.9±9.0	146.2±8.7
Body weight (kg)	49.3±8.9	50.8±10.7
Body surface area (m^2)	1.40±0.17	1.41±0.16
Body mass index (kg/m^2)	22.2±3.2	23.7±4.1*
CSHA frailty scale	4 [3–4]	4 [3–4]
Hypertension (%)	71.3	80.8
Dyslipidemia (%)	47.5	44.7
Diabetic (%)	12.9	14.9
History of smoking (%)	21.8	14.9
Ischemic heart disease (%)	25.7	27.7
History of HF hospitalization (%)	34.7	12.7*
β-blocker (%)	27.5	27.7
ACEI/ARB (%)	59.7	70.1
Loop diuretics (%)	53.9	46.8
Mineralocorticoid receptor antagonist (%)	20.6	21.3
Statin (%)	55.9	46.8
Serum albumin (g/dL)	3.7±0.4	3.8±0.4
Hemoglobin (g/dL)	11.1±1.5	11.3±1.6
Serum creatinine (mg/dL)	0.97±0.39	1.04±0.54
eGFR ($mL/min/1.73 m^2$)	52±19	50±19
HDL-C (mg/dL)	52±14	57±16*
LDL-C (mg/dL)	97±30	96±30
HbA1c (%)	6.0±0.5	6.0±0.8
Plasma BNP (pg/mL)	172 [93–421]	150 [77–300]
Aortic valve area (cm^2)	0.57±0.16	0.58±0.14
Maximum velocity across the aortic valve (m/s)	4.6±0.7	4.6±0.7
Left ventricular ejection fraction (%)	66.1±8.0	66.0±8.8

Unless indicated otherwise, data are presented as the mean ± SD or median [interquartile range]. *P<0.05 compared with the high cardio-ankle vascular index (CAVI) group. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; CHSA, Canadian Study of Health and Aging; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; TAVI, trans-catheter aortic valve implantation.

using Chi-squared test. Multivariable Cox proportional hazard ratio models were used to assess the impact of CAVI values on heart failure hospitalizations. Variables with P<0.05 in univariable analyses were included in the multivariable analysis. Survival curves were derived using the Kaplan-Meier method and compared by the log-rank test. Two-sided P<0.05 was considered statistically significant. Statistical analyses were performed using JMP pro ver15 (SAS Institute Japan, Tokyo, Japan).

Results

Baseline Characteristics

In all, 327 consecutive patients who underwent TAVI between May 2015 and May 2021 were considered for inclusion in this study. Of these patients, 36 who underwent an alternative approach (transapical, n=20; trans-subclavian, n=14; direct aorta, n=2), 12 with major comorbidities (death, n=1; moderate aortic regurgitation, n=3; disabling stroke, n=2; cardiac tamponade, n=3; infection, n=3), 88 with peripheral artery diseases, 25 with atrial fibrillation, and 29 with a LVEF <50% were excluded. Finally, 149 patients were included in the study (**Figure 1**).

Patients' baseline characteristics are summarized in **Table 1**. The mean age was 84.7 years and 24% of patients were male. Mean CAVI was 9.64±1.36 and 102 (68.5%) patients were assigned to the high CAVI group, defined as CAVI ≥9.0.

There were no statistically significant differences in baseline characteristics between the high and low CAVI groups, except for the higher prevalence of former heart failure admission and lower HDL-C levels in the high CAVI group (P<0.05 for both).

Post-TAVI Clinical Data

Clinical data following TAVI are summarized in **Table 2**. There were no statistically significant differences in post-TAVI data, except for a lower LVEF in the high CAVI group (P<0.01).

There were also no significant differences between the low and high CAVI groups in the rates of periprocedural complications, such as vascular complications (4.2% vs. 3.9%, respectively), bleeding requiring transfusion (23.4% vs. 26.5%, respectively), acute kidney injury (6.4% vs.

Table 2. Patient Characteristics After TAVI

	High CAVI (n=102)	Low CAVI (n=47)
CAVI	10.3±1.1	8.2±0.6**
Hemoglobin (g/dL)	10.2±1.6	10.2±1.1
Serum albumin (g/dL)	3.4±0.5	3.4±0.4
Serum creatinine (mg/dL)	0.94±0.41	0.98±0.48
eGFR (mL/min/1.73 m²)	53±19	52±20
Plasma BNP (pg/mL)	81 [52–155]	75 [38–114]
Aortic valve area (cm²)	1.4±0.3	1.5±0.3
Maximum velocity across the aortic valve (m/s)	2.1±0.5	2.1±0.5
Left ventricular ejection fraction (%)	65.4±11.5	69.0±7.4**
Left ventricular mass (g)	179.7±55.6	178.2±55.3
Left ventricular mass index (g/m²)	127.4±36.4	127.1±38.4
Septal wall thickness (mm)	10.8±2.1	10.6±1.8
Posterior wall thickness (mm)	10.8±1.7	10.8±1.3
E (cm/s)	80.0±28.0	82.6±25.1
A (cm/s)	109.6±28.1	11.5±28.7
E/A ratio	0.8±0.4	0.8±0.5
Lateral E' (cm/s)	5.3±1.7	5.7±1.9
Septal E' (cm/s)	4.2±1.1	4.3±1.2
E/E' ratio	17.8±6.3	18.2±7.2
Left atrium diameter (mm)	41.7±8.7	42.5±7.9
TVR flow pressure gradient (mmHg)	23.7±7.5	23.0±7.1

Data are presented as the mean±SD or median [interquartile range]. *P<0.05, **P<0.01 compared with the high CAVI group. A, peak late diastolic filling velocity; E, peak early diastolic filling velocity; E', peak early diastolic mitral annular velocity; TVR, tricuspid valve regurgitation. Other abbreviations as in Table 1.

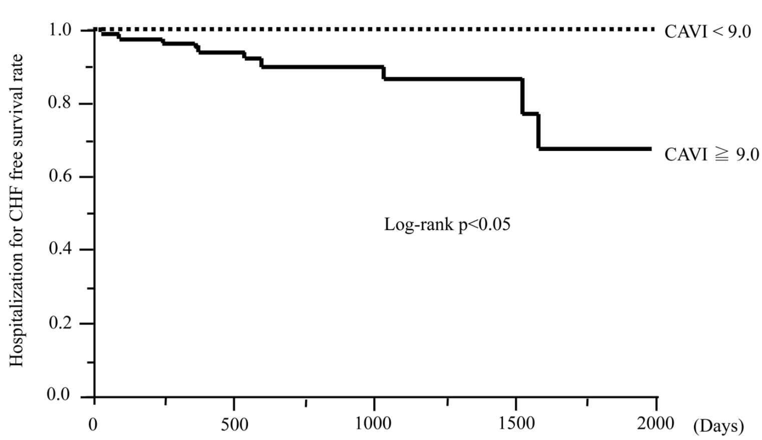

Figure 2. Freedom from heart failure readmissions following transcatheter aortic valve implantation stratified by cardio-ankle vascular index (CAVI) levels. CHF, chronic heart failure.

5.9%, respectively), and pacemaker implantation (14.9% vs. 9.9%, respectively).

Effect of CAVI on the Primary Endpoint

During the observation period (median 726 days; IQR 326–1,104 days) after the index discharge, 11 patients (7.4%) were readmitted for heart failure. Of note, no patients in the low CAVI group experienced heart failure readmission. Freedom from heart failure readmissions was significantly lower in the high CAVI group (89.1% vs. 100%; P<0.05; **Figure 2**). Overall, 11 (7.4%) patients died, and there was no significant difference between the low and high CAVI groups in freedom from all-cause death (2.1% vs. 9.8%, respectively; P=0.10).

After adjusting for the estimated glomerular filtration rate, which was another significant variable in the univariate analyses, the hazard ratio for CAVI to predict heart failure readmissions was 1.62 (95% confidence interval 1.07–2.46; P=0.022; **Table 3**).

Renal function impairment was significantly greater and CAVI values were significantly higher in patients with heart failure readmissions after TAVI (**Table 4**).

Discussion

In this study we investigated the association between CAVI

Table 3. Univariate and Multivariate Analysis for the Prediction of HF Hospitalization After TAVI						
	Univariable			Multivariable		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Age	1.06	0.94–1.24	0.357	–	–	–
Male sex	1.69	0.44–5.62	0.401	–	–	–
Body mass index	0.97	0.92–1.02	0.189	–	–	–
Serum albumin	0.38	0.09–1.80	0.206	–	–	–
Hemoglobin	0.96	0.82–2.54	0.617	–	–	–
eGFR	0.96	0.93–0.99	0.027	0.96	0.92–0.99	0.017
Plasma BNP/SD	1.12	0.60–1.70	0.669	–	–	–
Left atrial diameter	0.99	0.92–1.07	0.896	–	–	–
E/E' ratio	1.00	0.91–1.09	0.932	–	–	–
CAVI	1.55	1.03–2.30	0.036	1.62	1.07–2.46	0.022
HF hospitalization before TAVI	2.86	0.86–9.92	0.084	–	–	–

Univariable and multivariable analyses were performed using Cox proportional hazard models for continuous variables. CI, confidence interval; E/E', ratio of peak early diastolic filling velocity to peak early diastolic mitral annular velocity. Other abbreviations as in Table 1.

Table 4. Patient Characteristics According to HF Rehospitalization Status		
	HF readmission (n=11)	No HF readmission (n=138)
Age (years)	86.3±3.9	84.7±5.7
Male sex (%)	36.4	23.2
Height (cm)	154.3±12.0	147.5±8.5
Body weight (kg)	55.7±11.3	49.3±9.2
Body surface area (m^2)	1.46±0.34	1.40±0.15
Body mass index (kg/m^2)	23.2±1.7	22.6±3.7
Serum albumin (g/dL)	6.5±0.8	6.4±0.5
Hemoglobin (g/dL)	10.2±1.4	10.3±1.2
Serum creatinine (mg/dL)	1.20±0.36	0.93±0.41*
eGFR (mL/min/1.73 m^2)	41±11	54±19**
HDL-C (mg/dL)	39±10	44±11
Plasma BNP (pg/mL)	103 [84–233]	77 [43–137]
Aortic valve area (cm^2)	1.51±0.25	1.44±0.29
Maximum velocity across the aortic valve (m/s)	2.2±0.6	2.1±0.4
E (cm/s)	86±43	80±26
A (cm/s)	114±19	110±27
E/A ratio	0.76±0.36	0.78±0.41
Left ventricular ejection fraction (%)	64.4±8.4	66.7±7.8
Left atrium diameter (mm)	42.3±7.7	42.0±8.2
CAVI	10.3±0.8	9.6±1.4*

Unless indicated otherwise, data are presented as the mean ± SD or median [interquartile range]. *P<0.05, **P<0.01 compared with patients readmitted for HF. Abbreviations as in Tables 1–3.

values and heart failure hospitalization following TAVI in patients with severe AS. The major findings of this study are as follows: (1) in patients with severe AS undergoing TAVI, mean CAVI was 9.64±1.36 and approximately 70% of patients had high CAVI (≥9.0); (2) there were no significant differences in baseline characteristics, regardless of CAVI values, except for a higher prevalence of former heart failure hospitalization in the high CAVI group; and (3) high CAVI was an independent predictor of heart failure readmissions following TAVI.

Vascular Stiffness and AS

The degree of vascular stiffness in patients with AS remains controversial. Mean CAVI in healthy Japanese volunteers aged >80 years was 9.8±1.3,[20] which is comparable to that in the present cohort. Patients with AS may not necessarily have considerably higher CAVI than those without AS. The prevalence of atherosclerosis risk factors was comparable between the low and high CAVI groups. The pathophysiology of AS progression involves endothelial dysfunction, immune cell infiltration, myofibroblast and osteoblast differentiation, and, subsequently, calcification of the aortic valve, all of which seem to be different from the pathophysiology of atherosclerosis.[4,5] The severity of AS and the progression of vascular stiffness may not necessarily be dependent on each other.

One possible explanation for the high CAVI in some patients is the high-density lipoprotein cholesterol (HDL-

C) level. HDL-C is associated with anti-inflammation and stabilization of endothelial function, as well as improvements in diastolic function in patients with diastolic dysfunction.[21,22] In the present cohort, the low HDL-C may have contributed to the progression of vascular stiffness and incremental CAVI levels.

Vascular Stiffness and Diastolic Dysfunction

In patients without AS, vascular stiffness is associated with diastolic dysfunction.[23] In the present cohort, almost all patients had diastolic dysfunction, defined as an E/e' ratio >14, an E' value at the lateral wall <10 cm/s, and an E' value at the septal wall <7 cm/s.[24] These values did not differ significantly regardless of CAVI values: the progression of diastolic dysfunction in AS patients would predominantly come from the stenotic aortic valve, rather than incremental vascular stiffness.

Prognostic Impact of Vascular Stiffness Following TAVI

High CAVI was an independent predictor of heart failure readmissions following TAVI. In addition, the prevalence of previous heart failure hospitalizations was higher among patients with high CAVI. In patients with HFpEF, a cohort that may have similar physiology to the present cohort following TAVI, high CAVI was an independent predictor of heart failure recurrence.[25]

Following TAVI, patients with low CAVI had a greater LVEF. Although further studies are warranted, low CAVI, indicating low vascular stiffness, may allow further cardiac reverse remodeling via lesser afterload on the left ventricle.

Taking all these findings in consideration, following TAVI, persistently elevated vascular stiffness may increase afterload on the left ventricle and disturb cardiac unloading/reverse remodeling, resulting in heart failure recurrence. Among the patients with heart failure recurrence, one patient experienced de novo atrial fibrillation. Atrial fibrillation is strongly associated with the development of heart failure. The persistently elevated vascular stiffness may have also triggered anatomical and electrical remodeling in the atrium, resulting in the progression of left heart impairment.[26]

Given our findings, CAVI may be a useful marker to risk stratify patients who undergo TAVI. Those with higher CAVI should be carefully monitored to prevent worsening heart failure.

Interventions for Vascular Stiffness Following TAVI

Thus far, there are no established therapeutic or prophylactic strategies to improve clinical outcomes following TAVI by interventions targeting vascular stiffness. A sodium-glucose cotransporter 2 inhibitor, which was recently demonstrated to improve clinical outcomes in patients with HFpEF,[27] may be a potential therapeutic tool because of its diuretic and renoprotective effects.[28] The medication may further improve vascular stiffness and endothelial function.[29] Such novel medications may ameliorate vascular stiffness and further improve clinical outcomes in patients undergoing TAVI.

Study Limitations

This study has several limitations that should be considered. First, the sample size was moderate. Second, we restricted variables included in the multivariable analysis given such a small number of events. Third, there may be any other uninvestigated confounders. Given that CAVI is independent of hemodynamics, we assumed post-TAVI CAVI was a unique fixed variable in each patient. Fourth, trends in CAVI during the observation period remain uninvestigated. Fifth, we excluded patients with bilateral peripheral artery diseases, atrial fibrillation, and heart failure with reduced ejection fraction given the effects of these conditions on CAVI. The applicability of our findings to these excluded cohorts remains unknown. Sixth, some patients were lost follow-up. Finally, the association between CAVI and flow-mediated dilation was not investigated.

Conclusions

Among patients with severe AS, an elevated CAVI was associated with worsening heart failure before and after TAVI.

Acknowledgments

None.

Sources of Funding

This study did not receive any specific funding.

Disclosures

K.K. is a member of *Circulation Reports*' Editorial Team.

IRB Information

This study was approved by the Ethics Committee, University of Toyama (Reference no. 28-404).

References

1. Eveborn GW, Schirmer H, Heggelund G, Lunde P, Rasmussen K. The evolving epidemiology of valvular aortic stenosis: The Tromso study. *Heart* 2013; **99:** 396–400.
2. Thaden JJ, Nkomo VT, Enriquez-Sarano M. The global burden of aortic stenosis. *Prog Cardiovasc Dis* 2014; **56:** 565–571.
3. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, et al. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. *J Am Coll Cardiol* 1997; **29:** 630–634.
4. Goody PR, Hosen MR, Christmann D, Niepmann ST, Zietzer A, Adam M, et al. Aortic valve stenosis: From basic mechanisms to novel therapeutic targets. *Arterioscler Thromb Vasc Biol* 2020; **40:** 885–900.
5. Cowell SJ, Newby DE, Boon NA, Elder AT. Calcific aortic stenosis: Same old story? *Age Ageing* 2004; **33:** 538–544.
6. Shirai K, Hiruta N, Song M, Kurosu T, Suzuki J, Tomaru T, et al. Cardio-ankle vascular index (CAVI) as a novel indicator of arterial stiffness: Theory, evidence and perspectives. *J Atheroscler Thromb* 2011; **18:** 924–938.
7. Farrero M, Blanco I, Batlle M, Santiago E, Cardona M, Vidal B, et al. Pulmonary hypertension is related to peripheral endothelial dysfunction in heart failure with preserved ejection fraction. *Circ Heart Fail* 2014; **7:** 791–798.
8. Chow B, Rabkin SW. The relationship between arterial stiffness and heart failure with preserved ejection fraction: A systemic meta-analysis. *Heart Fail Rev* 2015; **20:** 291–303.
9. Kishimoto S, Kajikawa M, Maruhashi T, Iwamoto Y, Matsumoto T, Iwamoto A, et al. Endothelial dysfunction and abnormal vascular structure are simultaneously present in patients with heart failure with preserved ejection fraction. *Int J Cardiol* 2017; **231:** 181–187.
10. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 2019; **380:** 1695–1705.
11. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med* 2019; **380:** 1706–1715.
12. Panagides V, Alperi A, Mesnier J, Philippon F, Bernier M,

Rodes-Cabau J. Heart failure following transcatheter aortic valve replacement. *Expert Rev Cardiovasc Ther* 2021; **19:** 695–709.
13. Auffret V, Bakhti A, Leurent G, Bedossa M, Tomasi J, Belhaj Soulami R, et al. Determinants and impact of heart failure readmission following transcatheter aortic valve replacement. *Circ Cardiovasc Interv* 2020; **13:** e008959.
14. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2017; **38:** 2739–2791.
15. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; **63:** 2438–2488.
16. Kabutoya T, Kario K. Comparative assessment of cutoffs for the cardio-ankle vascular index and brachial-ankle pulse wave velocity in a nationwide registry: A cardiovascular prognostic coupling study. *Pulse (Basel)* 2019; **6:** 131–136.
17. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011; **364:** 2187–2198.
18. Zoghbi WA, Farmer KL, Soto JG, Nelson JG, Quinones MA. Accurate noninvasive quantification of stenotic aortic valve area by Doppler echocardiography. *Circulation* 1986; **73:** 452–459.
19. Shirai K, Utino J, Otsuka K, Takata M. A novel blood pressure-independent arterial wall stiffness parameter; cardio-ankle vascular index (CAVI). *J Atheroscler Thromb* 2006; **13:** 101–107.
20. Kabutoya T, Hoshide S, Fujiwara T, Negishi K, Nishizawa M, Yamamoto M, et al. Age-related difference of the association of cardiovascular risk factors with the cardio-ankle vascular index in the Cardiovascular Prognostic Coupling Study in Japan (the Coupling Registry). *J Clin Hypertens (Greenwich)* 2020; **22:** 1208–1215.
21. Kontush A. HDL-mediated mechanisms of protection in cardiovascular disease. *Cardiovasc Res* 2014; **103:** 341–349.
22. Yano M, Nishino M, Ukita K, Kawamura A, Nakamura H, Matsuhiro Y, et al. High-density lipoprotein cholesterol/C reactive protein ratio in heart failure with preserved ejection fraction. *ESC Heart Fail* 2021; **8:** 2791–2801.
23. Ambrosino P, Papa A, Buonauro A, Mosella M, Calcaterra I, Spedicato GA, et al. Clinical assessment of endothelial function in heart failure with preserved ejection fraction: A meta-analysis with meta-regressions. *Eur J Clin Invest* 2021; **51:** e13552.
24. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016; **29:** 277–314.
25. Takagi K, Ishihara S, Kenji N, Iha H, Kobayashi N, Ito Y, et al. Clinical significance of arterial stiffness as a factor for hospitalization of heart failure with preserved left ventricular ejection fraction: A retrospective matched case-control study. *J Cardiol* 2020; **76:** 171–176.
26. Nakamura K, Takagi T, Kogame N, Hashimoto H, Asami M, Toyoda Y, et al. The association of cardio-ankle vascular index (CAVI) with biatrial remodeling in atrial fibrillation. *J Atheroscler Thromb* 2021; **28:** 590–603.
27. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Bohm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021; **385:** 1451–1461.
28. Heerspink HJ, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020; **383:** 1436–1446.
29. Sakai T, Miura S. Effects of sodium-glucose cotransporter 2 inhibitor on vascular endothelial and diastolic function in heart failure with preserved ejection fraction: Novel prospective cohort study. *Circ Rep* 2019; **1:** 286–295.