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Research Article

Structural Bioprosthetic Aortic Valve Degeneration In Peripheral Artery Disease

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Abstract

Objective: The purpose of this study was to determine the impact of peripheral artery disease (PAD) on the development of bioprosthetic structural valve degeneration (SVD) in patients with severe aortic stenosis. **Background:** Bioprosthetic valves, both open surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR), are subject to structural valve degeneration which impacts valve durability. The impact of peripheral artery disease on the viability of bioprosthetic structural valves is unclear. **Methods:** We screened patients over the age of 65 years who had undergone bioprosthetic aortic valve replacements (SAVRs or TAVRs) for degenerative severe aortic stenosis between 2007 and 2013 in our institution. We retrospectively analyzed clinical and echocardiographic data collected within three months post intervention and at least 3.5 years post intervention to determine the rates of predefined structural valve degeneration. **Results:** Eighty-two patients were included in the PAD cohort and 72 patients were included in the non-PAD cohort. The PAD cohort had higher rates of hypertension and coronary artery disease. The two groups had similar mean pressure gradient, dimensionless valve index, and effective orifice area at baseline post-intervention and at follow-up. At follow-up, there was a statistically significant difference in the rates of clinically relevant SVD in the PAD patients versus non-PAD patients [6 (7.3%) vs. 0 (0.0%), p = 0.03].**Conclusion:** Our study suggests a greater prevalence of SVD in patients with PAD. Future confirmatory studies are needed to explore the impact of PAD and related co-morbidities on valve durability.

Keywords: Bioprosthetic Aortic Valve, Peripheral Arterial Disease, Structural Valve Degeneration

Introduction

Degenerative aortic stenosis is one of the most common valvular diseases associated with aging. In elderly patients (over 75 years old) the estimated prevalence of aortic stenosis is 12.5% and the estimated prevalence of severe aortic stenosis is 3.4 % [1]. Symptomatic severe aortic stenosis carries an average life expectancy of 2 years and aortic valve replacement (AVR), including surgical bioprosthetic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR) are the standards of care [2]. Over 30,000 isolated surgical aortic valve replacements and close to 10,000 TAVRs were performed in the US in 2013, and the TAVR volume has markedly risen to almost 40,000 TAVRs performed in 2016 [3] with an indication for use in both high and intermediate surgical risk patients with severe symptomatic aortic stenosis [4]. The expanding role for surgical bioprosthetic valves and TAVRs raises the important question of valve durability, particularly as it relates to structural valve degeneration, an acquired multifactorial process of leaflet thickening, calcification, and degradation, culminating in valve obstruction and stenosis or leaflet tears and regurgitation. Defining the prevalence of structural valve degeneration (SVD), and by extension bioprosthetic valve durability, proves to be challenging despite efforts to standardize the definition and severity for SVD due to variability in the hemodynamic performance of different types of bioprostheses [5]. Known risk factors for SVD include traditional cardiovascular risk factors (including hypertension, diabetes, end stage renal disease) in addition to younger age of valve implantation, elevated body surface area, tobacco use, and patient prosthesis mismatch [6].

Peripheral artery disease, defined as atherosclerosis of the abdominal aorta, renal and mesenteric arteries, and lower extremity arteries [7], to our knowledge has not been identified as a risk factor for SVD. Lower extremity PAD itself is estimated to impact over 8-12 million Americans with a prevalence of 14.5% in patients aged greater 69 years [8]. Age, tobacco use, and diabetes are among the most strongly associated risk factors [8, 9]. The presence of PAD increases the risk of overall mortality, as well as cardiovascular morbidity and mortality more specifically [10]. Furthermore, progression of PAD is associated with worse cardiovascular outcomes relative to stable disease [11]. Patients with PAD may be asymptomatic or may present with intermittent claudication or critical limb ischemia. The ankle-brachial index is the primary tool utilized for establishing the diagnosis of PAD, with computed tomography angiography, magnetic resonance angiography and contrast arteriography reserved for those patients in whom revascularization is considered [8]. Importantly, despite similarities in age-related prevalence of PAD with degenerative aortic stenosis, there is a lack of robust data examining the potential impact of PAD on SVD in patients with bioprosthetic valves for the treatment of aortic stenosis.

In this study, we investigated the impact of PAD on SVD in patients who have undergone bioprosthetic valve replacement (SAVR or TAVR) for degenerative severe aortic stenosis. We hypothesize that there is an increased rate of SVD in patients with bioprosthetic valves and PAD versus those without PAD.

Material and Methods

Patient Population

We screened our institutional Surgical Thoracic Society (STS) Adult Cardiac Surgery Database for patients over 65 years of age who had undergone previous surgical aortic valve replacement using a bioprosthetic valve (including SAVR or TAVR) from June 2007 to June 2013 according to predefined inclusion and exclusion criteria. Participants were included if they had echocardiographic data within 3 months of aortic valve intervention, as well as at least 3.5-year clinical and echocardiographic follow-up. Patients who received AVR or TAVR for endocarditis or bicuspid aortic valve or valve-in-valve TAVR were excluded. The study was approved by the Institutional Review Board of the University of Pennsylvania with waiver of consent.

Clinical Data Collection

Clinical data of included patients were retrospectively gathered from the STS database which included age, body mass index, ethnicity, gender, co-morbidities (including hypertension, hyperlipidemia, diabetes mellitus, tobacco use, end stage renal disease, coronary artery disease (CAD)/myocardial infarction), and medications (including aspirin, adenosine diphosphate receptor inhibitors, anticoagulants, and statin).

Echocardiographic Assessment

The echocardiographic assessments at baseline and at follow-up were carried out within 3 months and more than 3.5 years after the initial intervention, respectively. Echocardiographic parameters of bioprosthetic aortic valvular function included mean pressure gradient (MPG), effective orifice area (EOA) and Doppler velocity index (DVI). The MPG was calculated by using the modified Bernoulli formula. The change in MPG was calculated as the gradient at follow-up minus the gradient at baseline. The EOA of the prosthesis was calculated by using the continuity equation. The change in EOA was calculated as the area at follow-up minus the area at baseline. The DVI was also calculated as the ratio between the proximal velocity-time integral in the left ventricular outflow tract (LVOT) and the velocity-time integral through the prosthesis valve. The change in DVI was calculated as the DVI at follow-up minus the DVI at baseline. The origin of prosthetic valve regurgitation was observed by using multiple color Doppler

views and a multiparameter integrative approach was used to assess its severity.

SVD Definitions

We used the echocardiographic criteria of stage 2 SVD according to the Valve Academic Research Consortium 3 (VARC-3) consensus statement defined as an increase in mean transvalvular gradient ≥10 mmHg resulting in a MPG of ≥20 mm Hg with a concomitant decrease in the EOA ≥0.3cm2 or ≥25% (and/or decrease in Doppler velocity index ≥0.1 or ≥20%), leading to severe aortic stenosis according with clinical symptoms, and/or new occurrence or increase of at least 1 grade of intra-prosthetic regurgitation leading to moderate or greater aortic regurgitation[5]. We also included patients who underwent re-do aortic valve replacement due to SVD.

PAD Assessment and Grouping

Patients were included in the PAD groups as determined by STS database. As a confirmatory measure, patients were randomly selected to undergo chart review to identify the presence of PAD. Presence of PAD was identified by a history of prior peripheral revascularization, claudication with positive ankle -brachial index (ABI < 0.9), or imaging (computed tomographic angiography, magnetic resonance angiography or angiography) suggestive of PAD. Involved subjects were divided into PAD group and non-PAD group.

Statistical Analysis

Statistical analysis involved use of IBM SPSS Statistics version 21.0 software (IBM Inc., New York, USA), Continuous variables are described as mean ± standard deviation (SD) if they were normally distributed, or median (interquartile range) if not. Categorical variables are described as number (percent). Group comparisons were analyzed with the Student's t-test or Wilcoxon rank sum test for continuous variables and the chi-square test or Fisher exact test for categorical variables. Two tailed $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics

154 patients were identified to meet the inclusion criteria and did not meet the exclusion criteria (Figure 1). The mean age was 79.7 ± 7.3 years (range 65 - 92); 93 were males. 82 patients had PAD and 72 patients did not. There were no significant differences in the following baseline characteristics between the PAD and non-PAD patients: age, sex, race, body mass index, tobacco use, hyperlipidemia, diabetes, renal failure, dialysis, prior myocardial infarction, and medication use (including aspirin, adenosine diphosphate inhibitor, statin, and warfarin) (Table 1). Rates of hypertension and CAD burden were statistically different between the two groups. Eighty patients (97.6%) had hypertension in PAD group and 63 (87.5%) in non-PAD group ($p<0.05$). In the PAD group, there were 19 patients with triple-vessel CAD (23.2%), 20 patients with two-vessel disease (24.4%), 11 patients with single-vessel disease (13.4%) and 32 patients with non-significant CAD (39.0%), while in the non-PAD group, 7 patients had triple-vessel disease (9.7%), 12 patients had two-vessel disease (16.7%), 5 patients had single-vessel disease (6.9%) and 48 patients had non-significant CAD (66.7%).

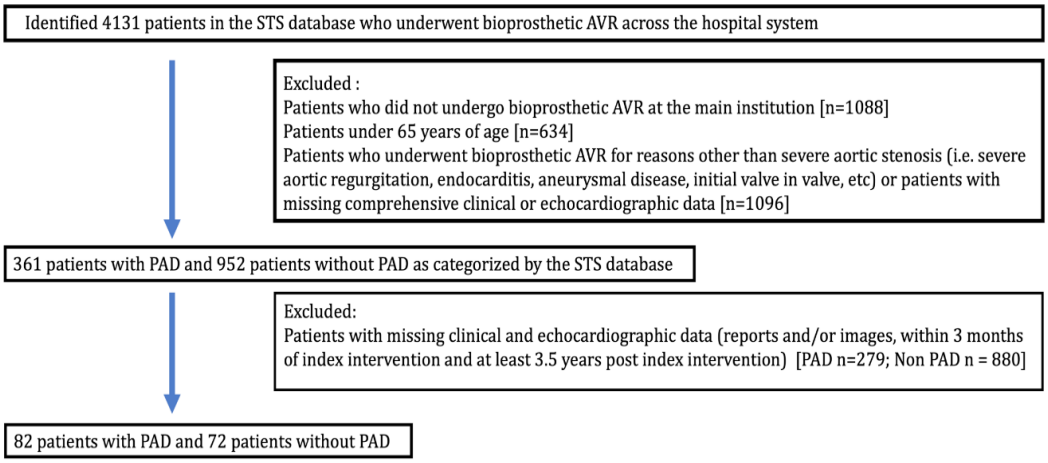

Figure 1. Flowchart describing process of patient selection.

	PAD group (n=82)	Non-PAD group (n=72)	p
Age, years	81.0 (73.7-86.0)	78.0 (73.0-85.7)	0.18
Sex (male), n, %	46(56.1)	47(65.3)	0.25
Race, n, %	Caucasian 73(89.0)	54 (86.1)	0.36
	Asian 6 (7.3)	3(4.2)	
	African American 0 (0)	1(1.4)	
	Other 3 (3.7%)	3(4.2)	
Body Mass Index (kg/m2)	28.1 (24.9 – 31.1)	28.4 (24.7 - 32.5)	0.59
Tobacco use, n, %	27 (32.9)	21(30.4)	0.74
Hypertension, n, %	80(97.6)	63(87.5)	0.02
Hyperlipidemia, n, %	76(92.7)	60(83.3)	0.07
Diabetes, n, %	32(39)	23(31.9)	0.36
Renal failure, n, %	5(6.1)	4(5.6)	1.0
Dialysis, n, %	0(0)	0(0)	-
Prior myocardial infarction, n, %	21 (25.6)	16 (22.2)	0.62
Coronary artery disease, n, %	Nonsignificant, 32(39.0)	48 (66.7)	0.006
	Single vessel, 11 (13.4)	5(6.9)	
	Two vessels, 20 (24.4)	12(16.7)	
	Three vessels, 19 (23.2)	7(9.7)	
Aspirin use, n, %	75(91.5)	68(94.4)	0.47
Adenosine diphosphate receptor inhibitor, n,%	37 (45.1)	26(36.1)	0.26
Statin use, n, %	66 (80.5)	58 (80.6)	0.99
Warfarin, n, %	29(35.4)	20(27.8)	0.31
PAD = Peripheral arterial disease. Value ranges represent mean ± standard deviation			

Table 1. General clinical characteristics in two groups.

Differences in echocardiographic parameters between PAD group and Non-PAD group

Transthoracic echocardiographic examinations were performed within 3 months of the index aortic valve replacement (SAVR or TAVR) and at least 3.5 years post procedure. The median follow-up was similar [51 (49-66) months vs. 51 (49-62) months, $p > 0.05$) (Table 2). The two groups had no obvious differences in MPG, DVI, and EOA at baseline post-operation, or at follow-up (all $p > 0.05$) (Table 2). The changes in MPG, DVI, and EOA were also the same between both groups (all $p > 0.05$) (Table 2). The left ventricular ejection fraction (EF) at baseline post-operation was different between the two groups: it was lower in the PAD group than that in the non-PAD group [60.0% (55.0%-67.5%) vs. 65.0% (56.2%-70.0%), p=0.04] (Table 2). The EF at follow-up and the changes of EF were not significantly different between groups ($p > 0.05$) (Table 2).

	PAD group (n=82)	Non-PAD group (n=72)	p
TAVR, n,%	46(62)	42 (60%)	0.79
MPG_{po}, mmHg	11.0 (7.0-15.0)	11.0 (7.0-15.0)	0.87
MPG_{fu}, mmHg	11.0 (7.5-15.0)	10.0 (7.0-13.0)	0.26
ΔMPG, mmHg	0.0 (-4.0-3.25)	-1.0 (-4.0-1.0)	0.13
EOA_{po}, cm^2	1.49±0.57	1.66±0.63	0.34
EOA_{fu}, cm^2	1.40 (1.10-1.70)	1.30 (1.10-1.85)	0.87
ΔEOA, cm^2	0.08±1.09	-0.05±0.76	0.66
DVI_{po}	0.52±0.15	0.56±0.16	0.18
DVI_{fu}	0.47 (0.38-0.53)	0.48 (0.41-0.60)	0.08
ΔDVI	-0.02±0.26	-0.01±0.19	0.88
EF_{po}, %	60.0 (55.0-67.5)	65.0 (56.2-70.0)	0.04
EF_{fu}, %	60.0 (45.0-66.2)	60.0 (55.0-68.7)	0.29
ΔEF, %	0.0 (-10.0-5.0)	-5.0(-10.0-5.0)	0.94
Follow-up, months	59 (49-66)	59 (49-62)	0.92

Table 2 Valve gradients and LV function at baseline post-op and at follow up Values are mean ± SD or median (interquartile range). MPGpo: mean pressure gradient at post-operation; MPGfu: mean pressure gradient at follow-up; ΔMPG: the change of mean pressure gradient; EOApo: effective orifice area at post-operation; EOAfu: effective orifice area at follow-up; ΔEOA: the change of effective orifice area; DVIpo: Doppler velocity index at post-operation; DVIfu: Doppler velocity index at follow-up; ΔDVI: the change of Doppler velocity index; EFpo: ejection fraction at post-operation; EFfu: ejection fraction at follow-up; ΔEF: the change of ejection fraction.

Structural valve degeneration

At follow-up, there was a statistically significant difference in the rates of clinically relevant SVD in the PAD patients versus non-PAD patients [6 (7.3%) vs. 0 (0.0%), p = 0.03]. The echocardiographic parameters of bioprosthetic aortic valvular function of 6 patients with clinically relevant SVD are detailed in (Table 3). One example of initial prosthetic valve gradients and follow-up high gradients on echocardiography is shown in (Figure 2). Of note, not all the echocardiographic parameters were available for each patient and structural valve degeneration was identified based on all available data in addition to subsequent redo valve replacement for SVD.

	MPG_{po}, mmHg	**MPG_{fu}, mmHg**	**EOA_{po}, cm^2**	**EOA_{fu}, cm^2**	**DVI_{po}**	**DVI_{fu}**	**AR_{po}**	**AR_{fu}**	**Pertinent Follow up**
1	9	11	1.97	1.13			None	Moderate - severe	
2	7	38	NA	0.6	NA	0.17			Underwent viv TAVR
3	9	33	1.90	0.87	0.63	0.31			
4	31	50	1.00	0.60	0.39	0.25			Underwent re-do SAVR
5	25	48	NA	0.66	NA	0.33			Underwent re-do SAVR
6	6	42	2.8	0.7	0.9	0.2			Underwent viv TAVR

Table 3 Echocardiographic parameters of bioprosthetic aortic valvular function of 6 patients with clinically relevant SVD. MPGpo: mean pressure gradient at post-operation; MPGfu: mean pressure gradient at follow-up; EOApo: effective orifice area at post-operation; EOAfu: effective orifice area at follow-up; DVIpo: Doppler velocity index at post-operation; DVIfu: Doppler velocity index at follow-up; ARpo: Aortic valvular regurgitation at post-operation (only included if moderate to severe or greater). ARfu: Aortic valvular regurgitation at follow-up; viv: valve-in-valve.

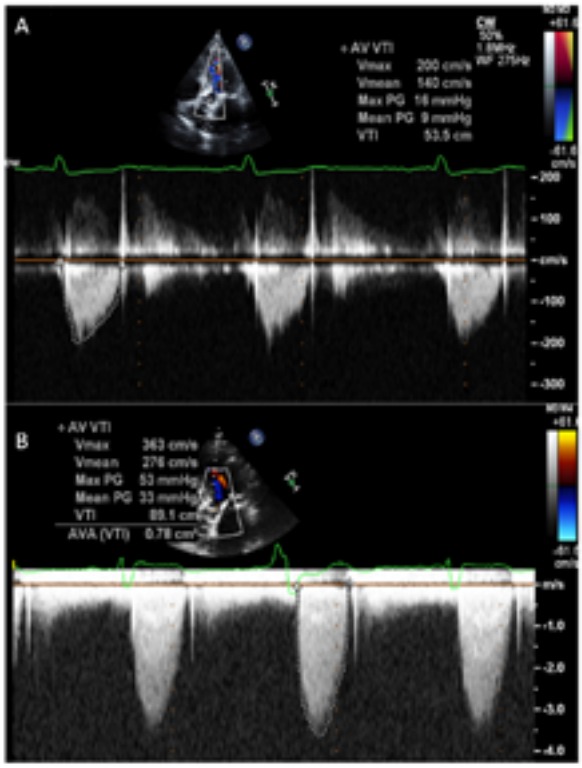

Figure 2. Apical five chamber view on echocardiogram with continuous wave Doppler demonstrating normal mean gradient across bioprosthetic aortic valve (top) and subsequent elevated mean gradient across the bioprosthetic aortic valve, suggestive of structural valve degeneration (bottom).

Discussion

Our study suggests an association between PAD and SVD when we retrospectively compared patients with and without PAD after bioprosthetic aortic valve replacement and followed for at least 3.5 years. There were more patients with hypertension and higher burden of coronary artery disease in PAD patients compared to non-PAD patients and these factors could contribute to higher SVD in patients with PAD.

The expanding role for surgical bioprosthetic valves and TAVR [12-17] raises the important question of valve durability. The biological valve tissue is subject to structural valve degeneration, an acquired multifactorial process of leaflet thickening, calcification, and degradation, culminating in valve obstruction and stenosis or leaflet tears and regurgitation [18]. The discussion on this complex issue is beyond the scope of this study and has been reviewed elsewhere [5, 19].

Recent studies evaluating the long-term outcomes of a cohort of consecutive SAVR in the pre-TAVR era reported a 6.6% prevalence of clinically relevant SVD defined similarly at 10 years [20]. A meta-analysis including 13 studies and over 8,000 patients undergoing TAVR found the pooled incidence rate for SVD to be 28 per 10,000 patient years [21]. A recent TAVR long term durability study utilizing United Kingdom registry had 241 patients with baseline and 5-year echocardiography follow up and determined that 91% patients were free of SVD between 5-10 years post implantation with no particular risk factor identified[22]. Of note, risk factors such as hypertension, CAD, or PAD were not compared between the SVD and no SVD groups [22].

Recognized patient-related risk factors for SVD include younger age at implantation, elevated body surface area, tobacco use, and patient prosthesis mismatch [6]. Studies have also implicated common cardiovascular risk factors such as hypertension, hyperlipidemia, diabetes, metabolic syndrome in addition to renal insufficiency and associated secondary hyperparathyroidism [23]. There is a lack of robust data studying the potential impact of PAD on SVD, as its incidence, similarly to degenerative aortic stenosis, increases with age [9]. A recent prospective registry is established to study the pre-existing comorbidities on outcomes of patients undergoing surgical aortic valve replacement with primary outcome of all-cause mortality but also include the secondary outcomes of structural valve degeneration [24].

In our study, we focused on the comparison of patients with and without PAD and found higher rates of clinically significant SVD in patients with PAD. One potential explanation for this finding may be related to a shared pathophysiologic mechanism driven by calcification, central to the development of SVD and seemingly to the development of PAD. Given that PAD and CAD share multiple cardiovascular risk factors, it is often assumed that both develop from the same atherosclerotic process. However, in contrast to numerous histologic studies highlighting the role of atherosclerosis in CAD, data exploring the histologic basis of peripheral artery disease has historically been limited and more recently is being investigated. O'Neill et al examined arterial histologic specimens from lower extremity amputations in patients with end stage renal disease and found that primary arterial lesions were non-atheromatous intimal thickening and medial arterial calcification, distinct from atherosclerosis described in CAD [25]. Yin et al utilized intravascular ultrasound to evaluate the morphological differences between lesions in the coronary arteries and peripheral arteries and found that compared to CAD lesions, PAD lesions had smaller vessel volumes, longer lesion length, and contained more concentric, diffuse, and calcified plaque [26]. Such data raises the question of whether potentially distinct pathophysiologic mechanisms for PAD, driven by calcification and

thrombotic lesions, may contribute to potential accelerated SVD. Importantly, medial arterial calcification is well known to be more prevalent in patients with diabetes and chronic kidney disease, co-morbidities which were similar between our two cohorts. As noted in our patient cohorts, the PAD patients had a greater burden of CAD and hypertension versus the non-PAD patients. The contribution of those differences on the prevalence of SVD is unclear but warrant future study.

Limitations

Our study is subject to many of the limitations inherent to its retrospective design. The relatively small sample size, single-center study, limited duration of follow up, and inclusion of heterogeneous collection of bioprostheses with varying hemodynamic profiles. Identification of PAD was based on pre-specified categorization in the STS database and randomly sampled patients underwent chart review to ensure presence of PAD. However, variability in degree of PAD likely exists. As with other studies examining durability of TAVRs, we included TAVRs implanted up until 2013, which was only 2 years after TAVR was approved by the FDA for commercial use. Improvements in valve design and operator experience/ implantation technique may impact the future development of SVD not represented in the current study. Due to these limitations, this work should be considered hypothesis generating.

Conclusion

Bioprosthetic valve remain vulnerable to structural valve degeneration which affect valve durability. Our study suggests a greater prevalence of SVD in patients with PAD. Further studies are needed to explore the impact of PAD and related co-morbidities such as hypertension and coronary artery disease on valve durability.

Author Contributions

Conceptualization, NQ and YH; Data curation, NQ, ZL and YK; Formal analysis, NQ and ZL; Methodology, NQ and YH; Supervision, YH; Writing – original draft, NQ and ZL; Writing – review & editing, all authors. All authors have read and agreed to the final submitted version of the manuscript.

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Consent to Participate and Consent to Publish

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of University of Pennsylvania (protocol number 824358 and approved on 9/26/2018). Informed consent was waived by the Institutional Review Board of University of Pennsylvania under the protocol.

Data Availability Statement

The data that support the findings of this study include the University of Pennsylvania STS database and University of Pennsylvania echocardiographic laboratory. These data are not openly available due to privacy concerns for human data and are available from the corresponding author upon reasonable request. Institutional Review Board of University of Pennsylvania granted access to this data under the protocol 824358.

Conflicts of Interest

Dr. Herrmann received research funding from Edward LifeSciences, Abbott, Boston Scientific, and Medtronic. Dr. Herrmann also reports receiving consultant fees and speaking honorarium from Edward LifeSciences and Medtronic. All other authors report no relative disclosures.

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