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Letters

RESEARCH LETTER

Fibrotic vs Calcific Aortic Stenosis

Characteristics and Outcomes in Patients Undergoing Transcatheter Aortic Valve Replacement

One in 9 patients with high-gradient severe aortic stenosis (AS) have fibrosis as the dominant pathomechanism.[1] One-half of patients with low-calcification severe AS have low-gradient AS compared with only 14% of patients with severely calcified AS.[1] The mechanisms contributing to fibrotic AS have not been precisely determined, and long-term outcomes after transcatheter aortic valve replacement (TAVR) for fibrotic compared with calcific AS remain unclear.[1-3] The aims of this study were to investigate characteristics associated with fibrotic AS and to compare outcomes after TAVR for fibrotic vs calcific high-gradient AS.

From 2007 to 2023, consecutive patients undergoing TAVR were enrolled in the Bern TAVI Registry, which forms part of the SwissTAVI Registry (NCT01368250). Detailed methods have been described previously.[4] We included patients who had native severe AS with mean aortic valve gradients ≥40 mm Hg and who had aortic valve calcium volume measured pre-TAVR. Because of the latency between radiotherapy and valve disease, we defined a history of mediastinal radiotherapy as radiotherapy >15 years before the TAVR procedure. Aortic valve calcium volume was quantified on contrast-enhanced computed tomographic images, using a predefined threshold of 850 HU, and patients were categorized according to quartiles of calcium volume in the aortic valve complex (AVC). The lowest quartile was defined as fibrotic AS, the highest quartile was defined as highly calcific AS, and the intermediate quartiles were also classified as calcific AS (**Figure 1**). Multivariable logistic regression was performed to identify characteristics associated with fibrotic AS. Cox regression (adjusted for bicuspid anatomy, valve design [balloon-expandable vs mechanical-expandable vs self-expandable] and Society of Thoracic Surgeons Predicted Risk of Mortality score) was used to assess associations with clinical outcomes.

Among 1,358 patients undergoing TAVR to native valves for high-gradient severe AS, the median AVC calcium volume was 326 mm^3 (Q1-Q3: 164-569 mm^3), and 349 (11%) had fibrotic AS (defined as calcium volume ≤ 163 mm^3 in the AVC) (**Figure 1**). The mean ages of patients with fibrotic AS (81.9 ± 5.9 years) and calcific AS (82.1 ± 6.2 years) were comparable ($P = 0.590$). Overall, 51.7 % were women, and 9.3% had bicuspid aortic valves.

Female sex (OR: 4.39; $P < 0.001$), autoimmune disease (OR: 1.83; $P = 0.038$), hypertension (OR: 1.83; $P = 0.038$), body mass index ≥ 25 kg/m^2 (OR: 2.54; $P < 0.001$), and tricuspid anatomy (OR: 2.01; $P < 0.001$) were independently associated with fibrotic compared with highly calcific AS (**Figure 1**). Mediastinal radiotherapy pre-TAVR was associated with fibrotic AS on univariable (OR: 2.24; $P = 0.045$) but not multivariable analysis ($P = 0.360$). The presence or absence of rheumatic heart disease was not associated with fibrotic AS ($P = 0.633$).

Fibrotic compared with calcific AS had similar technical procedural success (89.1% vs 88.8%; OR: 1.03; 95% CI: 0.69-1.52; $P = 0.890$) and similar rates of moderate or greater hemodynamic valve deterioration throughout 5-year follow-up (5.0% vs 5.1%; OR: 1.07; 95% CI: 0.55-2.05; $P = 0.848$). All-cause mortality (26.5% vs 27.0%; HR: 0.92; 95% CI: 0.73-1.17; $P = 0.507$) and cardiovascular mortality (18.0% vs 18.2%; HR: 0.93; 95% CI: 0.69-1.24; $P = 0.599$) throughout 5-year follow-up were similar for fibrotic vs calcific AS.

In summary, fibrotic high-gradient severe AS is associated with a higher prevalence of autoimmune disease, higher body mass index, female sex, hypertension, and tricuspid anatomy and has similar clinical outcomes compared with calcific AS. However, as this is an observational study, causality cannot be inferred, and the outcomes could be biased by the long time frame of inclusion with different prosthetic valve iterations.

The finding that a subset of patients with severe AS have valve fibrosis and have different associated comorbidities compared with those with calcific AS may suggest a separate pathologic AS phenotype. The

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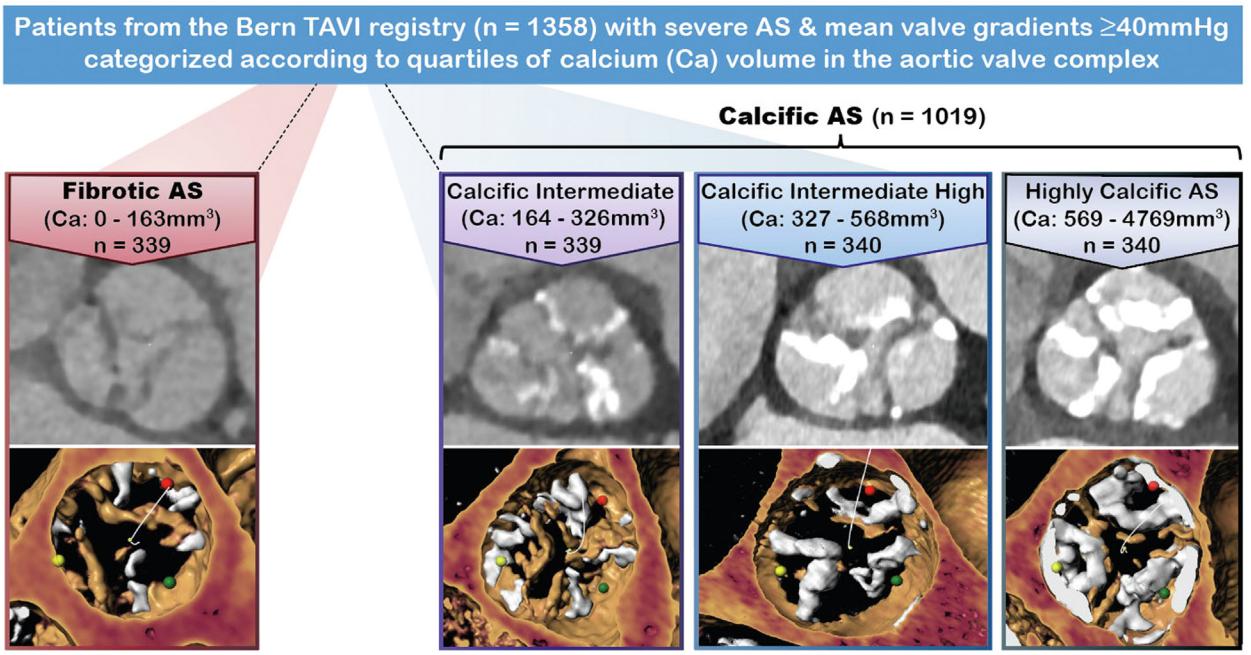
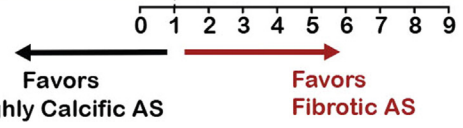
FIGURE 1 Quartiles of Calcium Volume in the Aortic Valve Complex and Characteristics Associated With Fibrotic AS



Multivariable associations of population characteristics with fibrotic AS vs. highly calcific AS

	Fibrotic AS	Highly Calcific AS	OR [95% CI] P-value
Female sex	70%	37%	4.39 [3.07, 6.27] P < 0.001
Mediastinal Radiotherapy	3%	1%	2.03 [0.49, 8.36] P = 0.329
Autoimmune Disease	15%	8%	1.83 [1.04, 3.34] P = 0.038
BMI ≥25kg/m²	73%	55%	2.54 [1.75, 3.70] P < 0.001
Hypertension	88%	77%	1.83 [1.15, 2.93] P = 0.010
Diabetes Mellitus	28%	21%	1.30 [0.86, 1.96] P = 0.210
Tricuspid Anatomy	97%	80%	2.01 [1.52, 2.68] P < 0.001



AS = aortic stenosis; BMI = body mass index; Ca = calcium; TAVI = transcatheter aortic valve implantation.

notion that fibrotic AS is a distinct clinical entity is supported by a histopathologic study of extracted aortic valves from patients with AS undergoing surgical aortic valve replacement, which demonstrated phenotypically different mechanisms of valve thickening.[5] This suggests that the pathogenesis of fibrotic AS may differ from that of calcific AS. There are no pharmacologic treatments to alter the progression of AS, but it is conceivable that potential targets for drug development may differ in patients with fibrotic compared with calcific AS. Importantly, there is no consistent calcification threshold or methodology for defining fibrotic AS.[1-3]

In conclusion, fibrotic AS is associated with distinct patient characteristics and has similar clinical outcomes after TAVR compared with calcific AS. A consistent definition is needed to diagnose fibrotic severe AS. Further research is warranted to elucidate

the pathogenesis of fibrotic AS and to investigate novel therapeutic targets to prevent the progression of AS.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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