

## Structural Valve Deterioration 4 Years After Transcatheter Aortic Valve Replacement Imaging and Pathohistological Findings

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**T**ranscatheter aortic valve replacement (TAVR) has been developed as an alternative treatment modality for those patients with severe symptomatic aortic valve stenosis in whom the risk for conventional surgical aortic valve replacement (AVR) is considered too high or prohibitive.<sup>1</sup> However, knowledge regarding longer-term valve durability, especially in younger patients, is very limited. Herein, we report on a 48-year-old female patient presenting with structural valve deterioration 4 years after rescue percutaneous TAVR with a CoreValve bioprosthesis (Medtronic Inc, Minneapolis, Minn). We show the imaging features as well as the macro- and microscopic findings of a deteriorated transcatheter heart valve.

### Case Presentation

In 2010, our then 44-year-old female patient was admitted to the hospital because of rapidly progressive decompensated heart failure. She presented in a markedly reduced general health condition with severe dyspnoea (New York Heart Association class IV), pronounced pulmonary congestion, and bilateral leg edema. Medical history revealed pulmonary embolism in October 2009. At the age of 10 she had undergone previous cardiac surgery for correcting postductal aortic isthmus stenosis. Clinical chemistry showed elevated liver enzymes and signs of beginning renal failure. NT-proBNP was 16,000 ng/L (reference level, <170 ng/L). Echocardiography (iE33, Philips Healthcare, Hamburg, Germany) revealed a stenotic bicuspid valve with bulky calcifications (effective orifice area 0.5 cm<sup>2</sup>, maximum systolic pressure gradient 81 mmHg, mean pressure gradient 42 mmHg), concomitant mild regurgitation, and severe left ventricular dysfunction (left ventricular ejection fraction 30%). Additionally, moderate tricuspid regurgitation and reduced right ventricular function was detected. Doppler analysis of tricuspid regurgitant velocity spectrum revealed an estimated systolic pulmonary artery pressure of 70 mmHg. Because operative risk was considered too high (logEuroScore 45%), primarily because of severe reactive pulmonary hypertension and biventricular hemodynamic compromise, TAVR was planned. Because femoral arteries were only 4 mm in diameter and the left subclavian

artery was unsuitable after surgical correction of aortic isthmus stenosis, the right subclavian artery was chosen as access site. Although 2 episodes of cardiopulmonary resuscitation with a total duration of 8 minutes were necessary after balloon valvuloplasty, the patient underwent successful TAVR with a CoreValve bioprosthesis (26 mm, Medtronic Inc). After an uneventful postoperative course, the patient was discharged on day 9 postimplant. Echocardiogram obtained at 6 months and 1 year postimplant demonstrated full recovery of left ventricular function (left ventricular ejection fraction 65%) and only a slight increase in mean pressure gradients (18 and 23 mmHg, respectively) without significant concomitant aortic regurgitation. Echocardiogram at 3 years showed an increased mean pressure gradient of 32 mmHg and a decline of the effective orifice area to 1.1 cm<sup>2</sup>. The course of echocardiographic functional parameters is depicted in Figure 1. After progressive symptom deterioration (dyspnoea New York Heart Association class III), echocardiographic follow-up examination at 4 years, however, revealed a marked increase of transprosthetic aortic peak velocity (4.2 m/s), a rise of maximum and mean pressure gradients to 70 mmHg and 45 mmHg, respectively, concomitant moderate valvular insufficiency (see Figure 2), and worsened left ventricular function (left ventricular ejection fraction 40%). There was no history of fever. On echocardiography, no vegetation was identified, and there were no signs of thrombus formation. Preoperative multidetector computed tomography (Somatom Flash CT scanner; Siemens Medical Solutions, Forchheim, Germany) revealed regular positioning of the CoreValve prosthesis but was also suggestive of calcified leaflets (see Figure 3). In the absence of high surgical risk, she now underwent mechanical AVR. The in situ inspection confirmed correct positioning of the CoreValve prosthesis. The upper portion of the nitinol frame was covered with a translucent neointimal layer. No signs suggestive of endocarditis were present. Surgical extraction of the CoreValve bioprosthesis was successfully performed without damaging the aortic root. The native aortic valve was severely deformed by the TAVR device but still recognizable as a bicuspid, heavily calcified valve. The free edges of the CoreValve leaflets were thickened and

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immobile. Several calcified areas on the aortic and ventricular aspect of the prosthesis were noticed (see Figure 4A and 4B). On postoperative day 2, the patient had to undergo transvenous dual-chamber pacemaker implantation because of permanent pacemaker dependency attributable to third-degree atrioventricular block. After an otherwise uneventful postoperative course, the patient could be discharged on postoperative day 11. Histopathology showed fibrosis and focal calcifications of valve leaflets corroborating structural degeneration of the CoreValve bioprosthesis (Figure 4C and 4D). A low grade chronic and ongoing inflammation was detectable in the valve stroma. Infectious endocarditis could be ruled out after special stains for bacteria (gram) or fungi (Periodic acid-Schiff) proved negative (not shown).

**Discussion**

After the first implantation in 2002, TAVR has gained rapid clinical acceptance and has even quickly become the standard of care in the treatment of appropriately selected individuals with inoperable aortic valve stenosis during recent years. The Medtronic CoreValve (Medtronic) prosthesis obtained Conformité Européenne mark approval in March 2007.<sup>1</sup> However, clinical experience regarding long-term valve durability, especially in younger patients, is very limited. Patients currently referred for and treated by TAVR are elderly and are suffering from a concomitant variable spectrum of multiple comorbidities, which is why life expectancy is often too limited before structural valve deterioration (SVD) becomes a clinically relevant problem. SVD of bioprosthetic valves, especially in younger patients, remains a major issue still unsolved. Typical reasons for SVD in bioprosthetic valves in the aortic position are primarily calcific degeneration, postendocarditis lesions, thrombus formation, and leaflet failure.<sup>2</sup> Similar mechanisms can be assumed for the development of SVD in transcatheter heart valves. However, although there are few anecdotal reports in the literature,<sup>3</sup> evidence is lacking. Infectious endocarditis and thrombus or acute leaflet rupture

as underlying mechanism could be excluded in the described patient because follow-up echocardiograms, in situ inspection, and immunohistopathology did not reveal any suspicious findings in this respect (see Figure 4C and 4D). Moreover, past medical history was negative for fever, systemic autoimmune disease, or hyperparathyroidism.

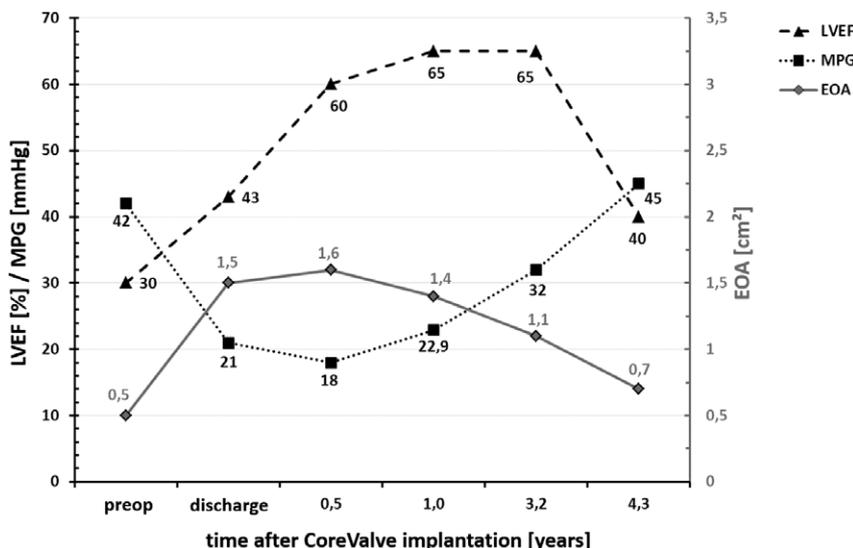
As demonstrated in this case, TAVR can be used as a rescuing treatment option in young high-surgical risk patients. However, as seen also with conventional bioprosthetic heart valves, an increased risk of accelerated SVD should be anticipated in younger patients. Because there is some evidence suggesting that patient selection criteria are evolving away from the premarket inclusion and exclusion criteria, expanding the indications for TAVR to the population of lower-risk and younger patients, close attention is required to determine the long-term durability of transcatheter heart valves.<sup>4</sup>

**Disclosures**

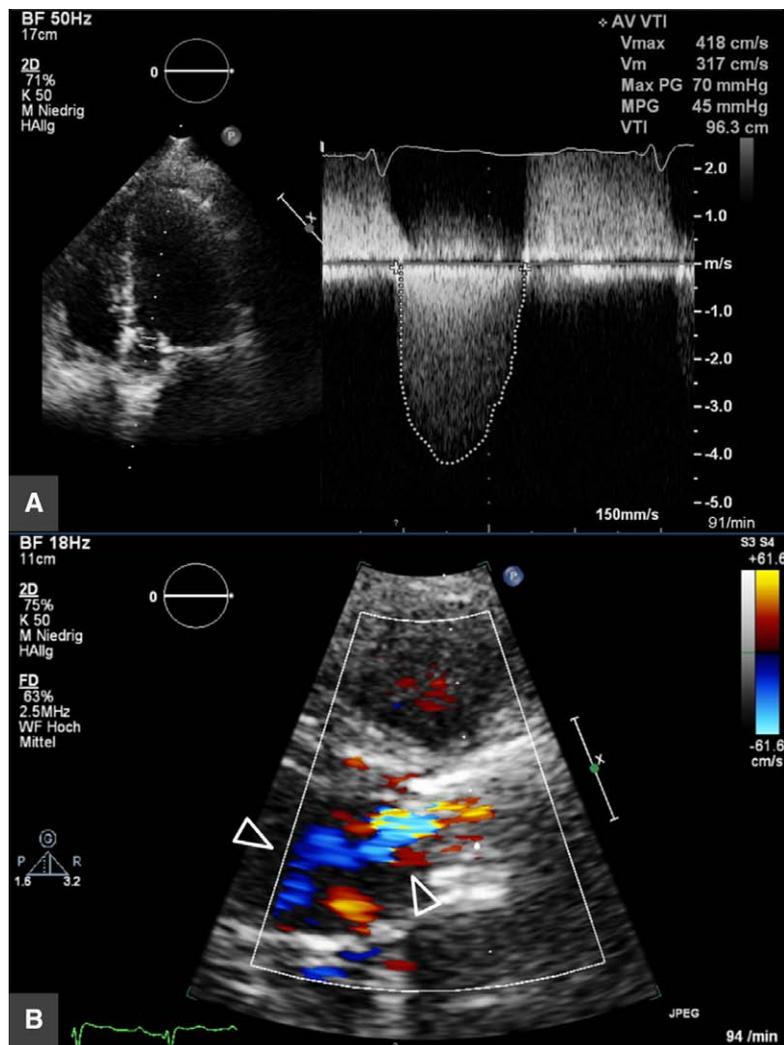
Dr Bleiziffer is proctor for Medtronic Inc, Boston Scientific Inc, and JenaValve Technology Inc. Dr Piazza is proctor and consultant for Medtronic Inc, and JenaValve advisory board member. Dr Lange is member of the Medtronic advisory board. The other authors report no conflicts.

**References**

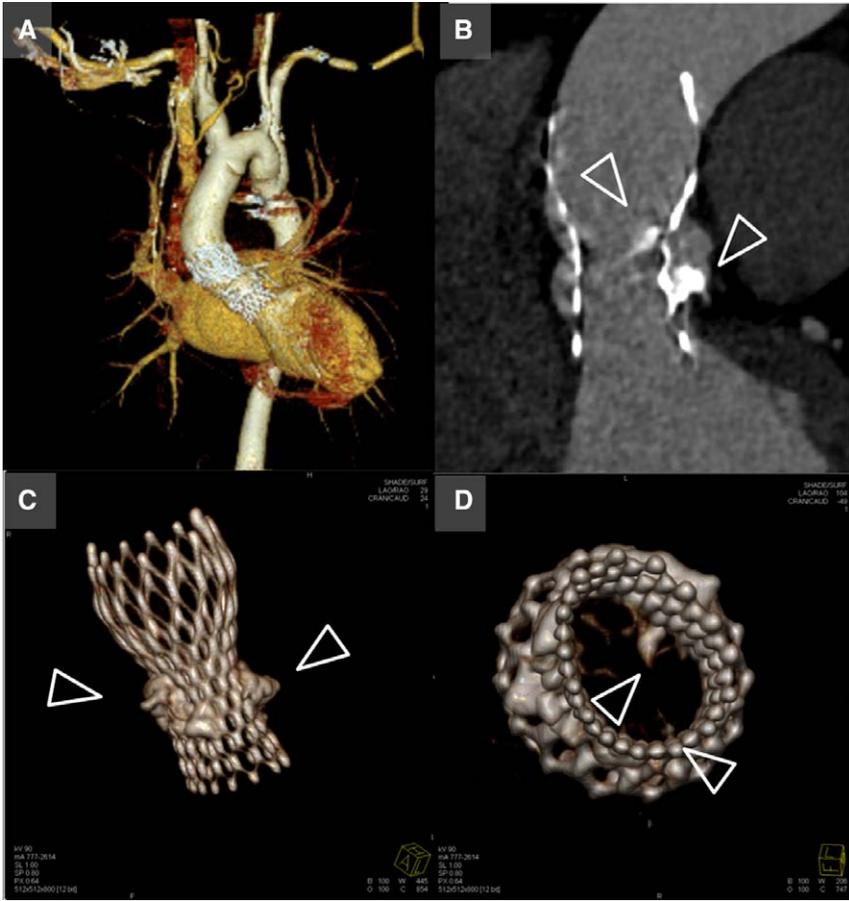
1. Rodés-Cabau J. Transcatheter aortic valve implantation: current and future approaches. *Nat Rev Cardiol.* 2012;9:15–29. doi: 10.1038/nrcardio.2011.164.
2. Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. *Circulation.* 2009;119:1034–1048. doi: 10.1161/CIRCULATIONAHA.108.778886.
3. Mylotte D, Andalib A, Thériault-Lauzier P, Dorfmeister M, Girgis M, Alharbi W, Chetrit M, Galatas C, Mamane S, Sebag I, Buihthieu J, Bilodeau L, de Varennes B, Lachapelle K, Lange R, Martucci G, Virmani R, Piazza N. Transcatheter heart valve failure: a systematic review. *Eur Heart J.* 2014 Sep 28. pii: ehu388. [Epub ahead of print].
4. Lange R, Bleiziffer S, Mazzitelli D, Elhmidy Y, Opitz A, Krane M, Deutsch MA, Ruge H, Brockmann G, Voss B, Schreiber C, Tassani P, Piazza N. Improvements in transcatheter aortic valve implantation outcomes in lower surgical risk patients: a glimpse into the future. *J Am Coll Cardiol.* 2012;59:280–287. doi: 10.1016/j.jacc.2011.10.868.



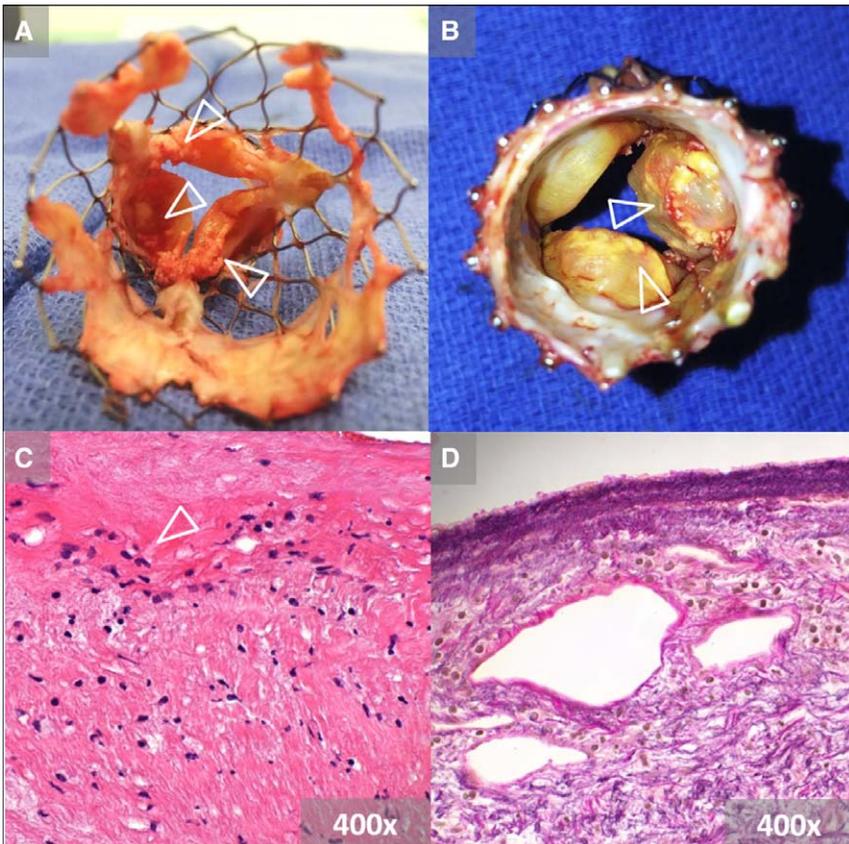
**Figure 1.** Echocardiographic functional parameters (left ventricular ejection fraction [LVEF], mean pressure gradient [MPG], and effective orifice area [EOA]) before CoreValve implantation and during follow-up. LVEF fully recovered 6 months after successful CoreValve implantation. Note a linear increase of transvalvular MPG 1 year postimplant and a corresponding decline in the EOA. Finally, 4 years after transcatheter aortic valve replacement (TAVR), along with an increase in MPG, LVEF again worsened, indicating the need for reoperation.



**Figure 2. A and B,** Echocardiography 4 years postimplant revealed an increase of transprosthetic aortic peak velocity (4.2 m/s) and a rise of maximum and mean pressure gradients (**A**). Concomitant moderate valvular regurgitation was detected (**B**).



**Figure 3.** A–D, Multidetector computed tomography visualized a regular position of the CoreValve prosthesis (A and B). Note a bulky calcified native aortic valve outside the nitinol frame (B and C) and calcified leaflets of the CoreValve bioprosthesis (B and D).



**Figure 4.** A–D, Axial macroscopic view of the explanted CoreValve bioprosthesis (A and B) and histopathologic studies of explanted leaflet tissue (C and D). The aortic (A) as well as the ventricular aspect (B) show clearly visible calcific leaflet lesions (arrowheads). Active infective endocarditis as an underlying cause could be excluded by periodic acid-Schiff (PAS) and Gram staining (not shown). However, some infiltrating granulocytes suggestive of ongoing low-grade inflammation could be detected (C; HE staining). D (Elastica-van-Giesson staining) clearly shows evidence of fibrosis.