



## Aortic Regurgitation After Transcatheter Aortic Valve Replacement

### – Nothing to Worry About Anymore? –

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Paravalvular aortic regurgitation (AR) negatively affects prognosis following transcatheter aortic valve replacement (TAVR). As transcatheter heart valves (THV) are anchored using a certain degree of oversizing at the level of the aortic annulus, incomplete stent frame expansion because of heavily annular calcifications, suboptimal placement of the prosthesis, and/or annulus-prosthesis size-mismatch can contribute to paravalvular AR with subsequent increased mortality risk. Echocardiography is essential to differentiate between transvalvular and paravalvular AR and to further elucidate the etiology of AR during the procedure. However, because echocardiographic quantification of AR in TAVR patients remains challenging, especially in the implantation situation, a multimodal approach to the evaluation of AR with use of hemodynamic measurements and imaging modalities is useful to precisely quantify the severity of AR immediately after valve deployment. “Next-generation” THVs are already on the market and first results show that paravalvular AR related to design modifications (eg, paravalvular space-fillers, full repositionability) are rarely seen in these valve types. (*Circ J* 2014; **78**: 811–818)

**Key Words:** Aortic regurgitation; Paravalvular aortic regurgitation; Paravalvular leakage; Periprosthetic regurgitation; Transcatheter aortic valve replacement

**T**ranscatheter aortic valve replacement (TAVR) has been shown to be non-inferior to surgical aortic valve replacement (SAVR) for surgical high-risk patients with severe aortic stenosis and to be superior to conservative management in inoperable patients.<sup>1–3</sup> Transcatheter heart valves (THVs) are implanted in a sutureless fashion using oversizing to anchor the prosthesis at the level of the native aortic annulus. Therefore, incomplete circumferential apposition of the prosthesis with the annulus, which can be caused by incomplete stent frame expansion because of heavy annular calcification, too deep or to shallow placement of the prosthesis, and/or annulus-prosthesis size-mismatch because of malsizing, might lead to paravalvular aortic regurgitation (AR). Several studies have demonstrated that up to 70% of all TAVR patients suffer from paravalvular AR after the procedure; in approximately 15–20% of patients it is graded as more than mild. Because significant paravalvular AR has a negative effect on prognosis following TAVR, this procedure-related shortcoming has to be addressed to provide satisfying long-term clinical outcomes.<sup>4–17</sup>

This review focuses on the quantification of paravalvular AR in TAVR patients, provides therapeutic options to manage AR following TAVR, and summarizes the current status of next-generation THVs, which address this device-related issue by design modifications.

### Quantification of Paravalvular AR

#### Angiographic Assessment

The angiographic grading of AR is only qualitative, because the regurgitant flow within each angiographic grade varies widely, and there is considerable overlap between grades.<sup>18,19</sup> AR can be classified according to a visually estimated density of opacification of the left ventricle (LV) into 3 degrees adapted to the VARC-2 criteria:<sup>20</sup> (1) mild (reflow of contrast in the outflow tract and middle portion of the LV but clearing with each beat), (2) moderate (reflow of contrast in the whole left ventricular cavity with incomplete washout in a single beat and faint opacification of the entire LV over several cardiac cycles), and (3) severe (opacification of the entire LV with the same intensity as in the aorta and persistence of the contrast after a single beat). The degree of AR depends on the flow and amount of contrast dye, the position of the pigtail catheter, and heart rate. Additionally, in patients with chronic renal failure and/or at high risk for the development of acute kidney injury, the use of additional contrast dye may be deleterious.

#### Echocardiographic Assessment

The echocardiographic quantification of paravalvular AR is a true challenge despite the updated VARC-2 criteria.<sup>20</sup> Most parameters refer to recommendations for “traditional” surgical

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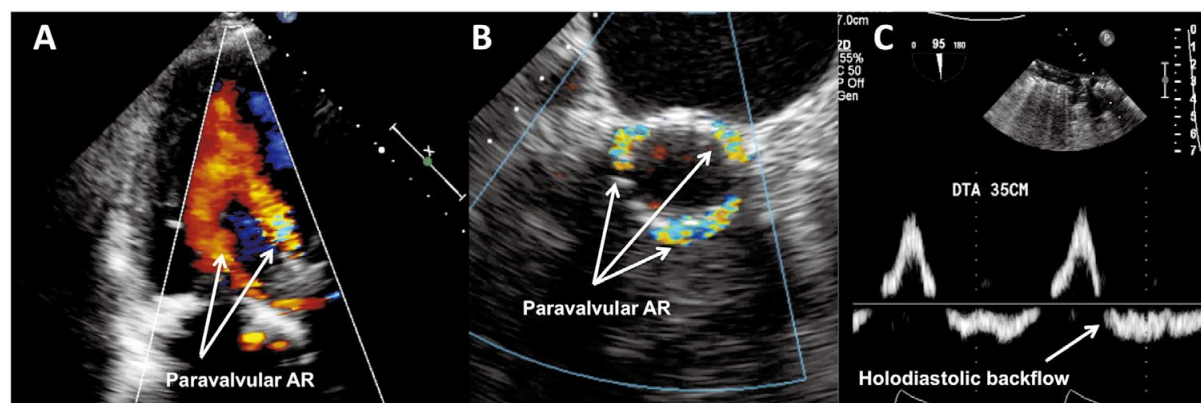
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**Figure 1.** Echocardiographic assessment of paravalvular aortic regurgitation (AR). Color transthoracic echocardiography (TTE) 3-chamber view of a Medtronic CoreValve 31-mm prosthesis with too-ventricular placement leading to severe paravalvular (AR) (A). Color 3D-TEE (transesophageal echocardiography) of malposition-related paravalvular AR following low implantation of the prosthesis. The jet passes from within the aortic portion of the stent frame above the tissue skirt ("supraskirt" AR) into the paravalvular space and the left ventricular outflow tract (B). Prominent holodiastolic backflow in the descending aorta indicates clinically significant paravalvular AR (C).

prosthetic heart valves that have not yet been validated as THVs.<sup>21</sup> For the following reasons, the grading of paravalvular AR remains imprecise: (1) acute hemodynamic changes, including heart rate, during the procedure confound Doppler and color flow assessment; (2) semiquantitative parameters of AR severity such as jet width, vena contracta, or pressure half time (PHT) are not ideal for the quantification of the eccentric, circumferential paravalvular AR jets, which are observed in TAVR patients; and (3) acoustic shadowing by the prosthesis and calcification of the native aortic valve may also obscure paravalvular AR jets. Given these limitations, transesophageal echocardiography (TEE) AR quantification criteria include a jet depth extending beyond the LV outflow tract (LVOT), the circumferential extent of the AR jet in the short-axis view (<10%, mild; 10–29%, moderate; ≥30%, severe paravalvular AR), and holodiastolic flow reversal in the descending aorta.<sup>12,20,21</sup> Nonetheless, TEE is essential to differentiate transvalvular and paravalvular AR and is helpful to clarify the underlying etiology of paravalvular AR. Furthermore, "supraskirt" and "infraskirt" AR jets that are caused by imprecise prosthesis placement are easily recognized by echo (Figure 1).<sup>12</sup>

### Hemodynamic Assessment

Hemodynamic parameters were helpful in determining the severity of paravalvular AR and to estimate the prognosis following TAVR in 2 recent studies using the AR index.<sup>4,8</sup> The index is the ratio of the end-diastolic transvalvular gradient between the diastolic blood pressure ( $DBP=RR_{dia}$ ) in the aorta and the LV end-diastolic pressure (LVEDP) to systolic blood pressure ( $SBP=RR_{sys}$ ) in the aorta:  $[(RR_{dia}-LVEDP)/RR_{sys}] \times 100$ . In both studies, the AR index showed an inverse association with the degree of AR and helped to differentiate patients suffering from mild, moderate, or severe paravalvular AR. In addition to aortography or echocardiography, the AR index enables identification of patients who will benefit from corrective measures to improve paravalvular AR.

Similar to the previously mentioned methods, the AR index depends on the heart rate and thus should be determined as mean value over several cardiac cycles (especially in patients with

atrial fibrillation) with a heart rate of 60–80 beats/min and without extrasystolic beats. With increasing heart rate and shortened duration of the diastole, the diastolic pressure in the aorta also increases and thereby might incorrectly lead to a "higher" (false negative) AR index.<sup>12</sup>

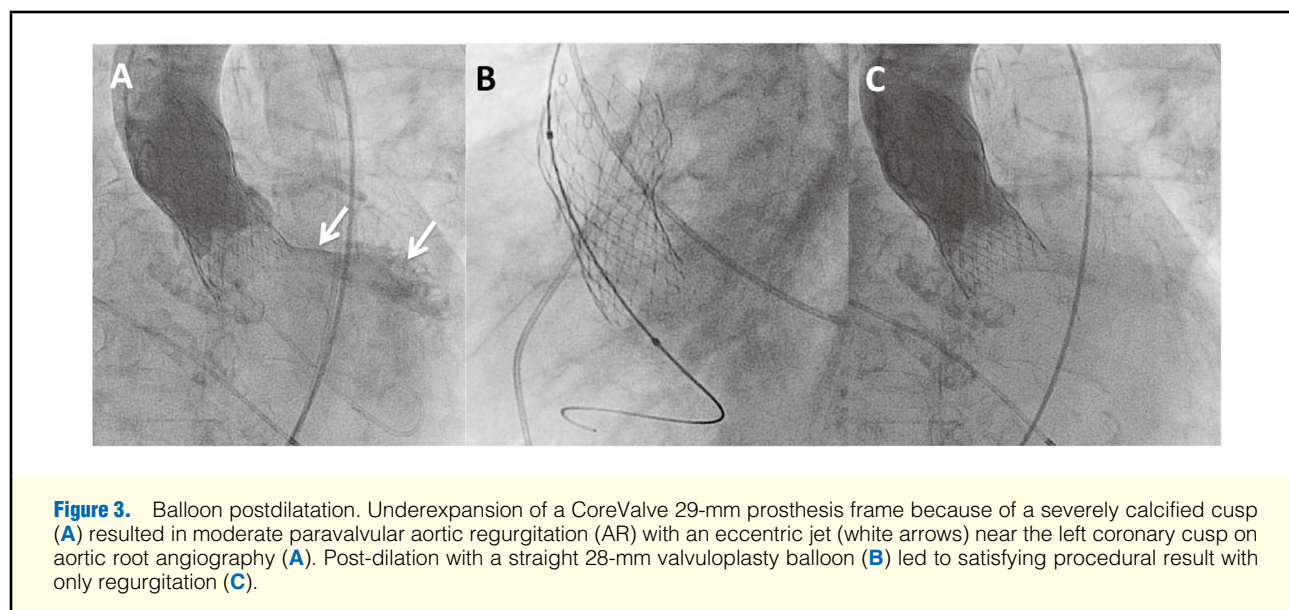
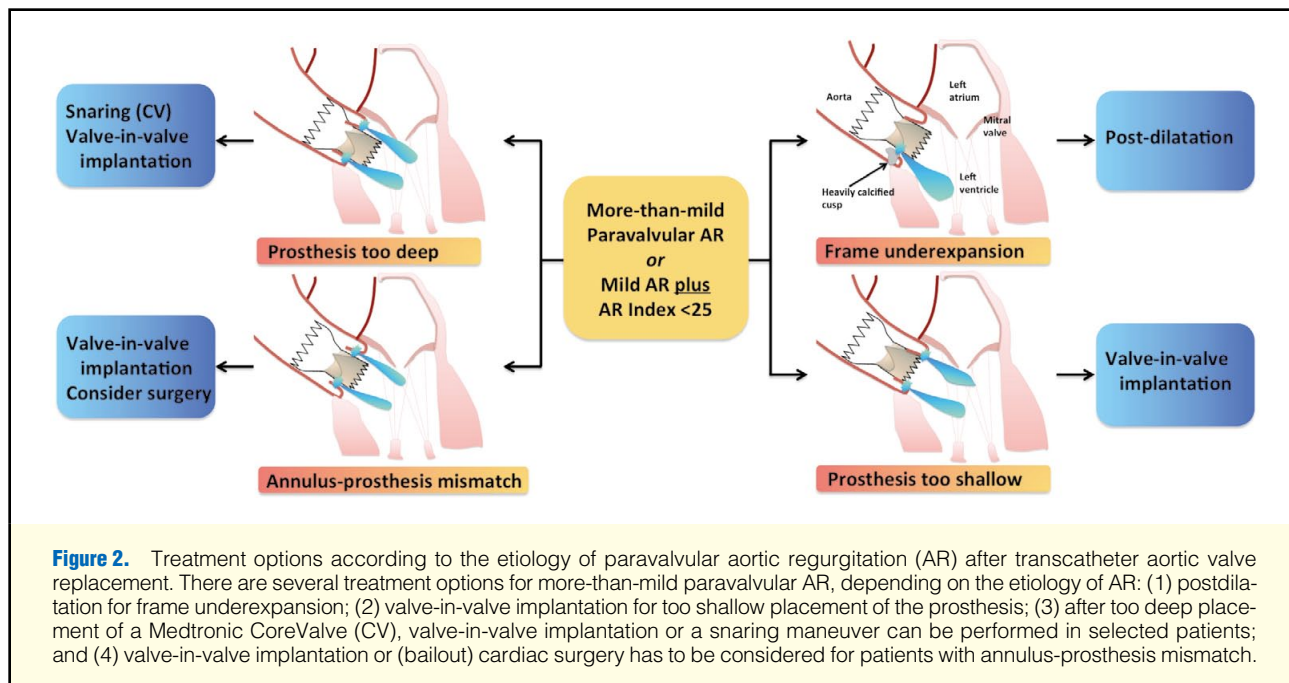
A modification of the AR index include the relative amplitude index (RAI). For its development, AR was prospectively evaluated by echocardiography before discharge in 110 patients. The RAI was calculated according to the formula:  $[(\text{Post-TAVI BP amplitude})/(\text{Post-TAVI SBP}) - (\text{Pre-TAVI BP amplitude})/(\text{Pre-TAVI SBP})] \times 100\%$ . It was shown that the RAI significantly increased from 2, when paravalvular AR was <2+, to 7 when paravalvular AR was ≥2+. A cut-off value ≥14 was associated with increased perioperative and 1-year mortality.<sup>22</sup>

Furthermore, the ratio of the diastolic over the systolic pressure time integral (DPTI:SPTI) has been proposed as an estimate of myocardial oxygen supply vs. demand and the propensity for myocardial ischemia. Patsalis et al<sup>23,24</sup> elegantly estimated the myocardial supply-demand ratio from the planimetric integration of the diastolic and systolic pressure-time area (DPTI and SPTI), respectively. Interestingly, DPTI:SPTI decreased with increasing Sellers grade of paravalvular AR. Cardiovascular mortality at 30 days and 1 year was increased in patients with DPTI:SPTI ≤0.7 compared with DPTI:SPTI >0.7.

All those studies demonstrate that hemodynamic parameters evaluated invasively or by echocardiographic measures help to stratify the degree of paravalvular AR and should be used as helpful parameters to evaluate paravalvular AR but also monitor the improvement after applying countermeasures to improve paravalvular AR.

### Trouble Shooting for Paravalvular AR

The effect of corrective measures to reduce paravalvular AR (ie, post-dilation, valve-in-valve implantation) predominantly originate from smaller series as yet.<sup>25–27</sup> Recently, we and others recommended a multimodal algorithm for the assessment and management of paravalvular AR after TAVR.<sup>12,17,28–31</sup> After valve deployment, the degree of paravalvular AR should be as-



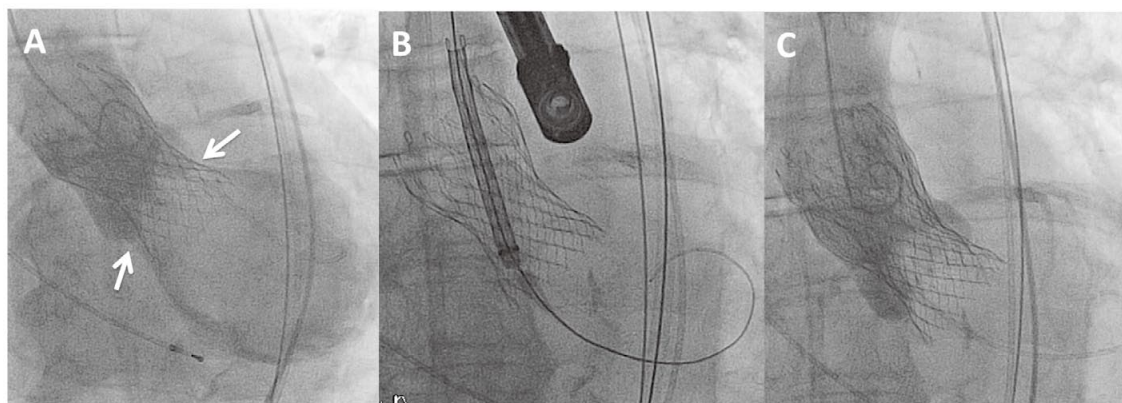
sessed by aortography and/or echocardiography. If more than trace paravalvular AR occurs after TAVR, the determination of hemodynamics is helpful to more precisely quantify the extent of paravalvular AR and to provide a quantitative point of reference before corrective measures are undertaken. In our practice, in patients with more-than-mild paravalvular AR and/or an AR index  $<25$ , the evaluation of paravalvular AR by TEE is recommended to elucidate the underlying mechanism and whether AR is para- or transvalvular (Figure 2). After post-dilatation or valve-in-valve implantation in patients with clinically significant paravalvular AR, the severity of paravalvular AR should be re-assessed by the same imaging modalities, together with hemodynamics, in order to provide evidence for the reduction of paravalvular AR.

### Balloon Post-Dilation

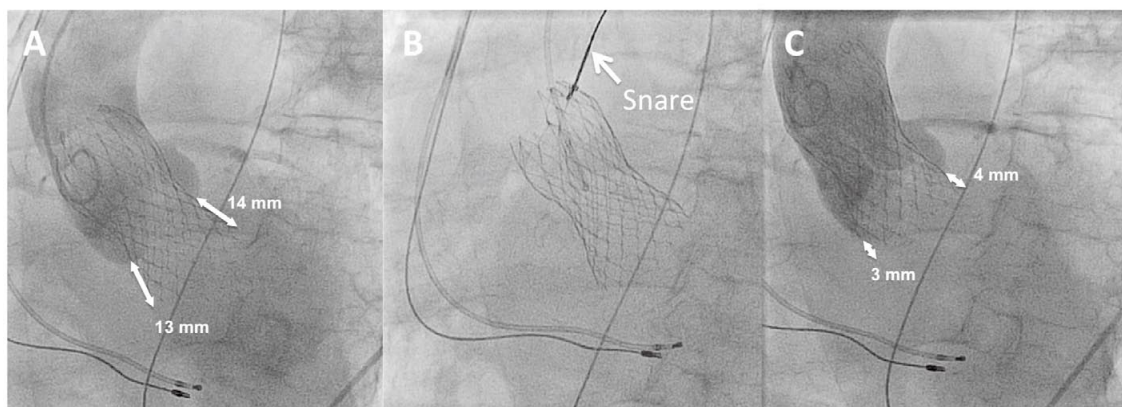
Heavy calcification of the native aortic valve or the LVOT might be the reason for suboptimal frame expansion, with incomplete apposition leading to an eccentric AR jet (Figure 3). Several studies have identified the severity of native aortic valve calcification as the most important reason for the occurrence of more-than-mild paravalvular AR.<sup>32,33</sup> Balloon post-dilatation in most cases reduces the degree of paravalvular AR by obtaining better expansion of the prosthetic stent frame and a better sealing of the paravalvular space.<sup>28,30,31,34</sup>

The size of the balloon for post-dilatation should correspond to the dimensions of the aortic annulus. For the Medtronic CoreValve prosthesis (Medtronic, Minneapolis, MN, USA), a straight valvuloplasty balloon with a maximum diameter of 22,





**Figure 4.** Valve-in-valve implantation. Too-ventricular deployment of a CoreValve 31-mm prosthesis led to severe paravalvular aortic regurgitation (AR) (white arrows) on aortic root angiography (A). After implantation of a second CoreValve 31-mm prosthesis using the valve-in-valve-technique, which delivered the second prosthesis 5 mm higher than the first under transesophageal echocardiographic guidance (B), only trivial paravalvular AR remained on angiography (C).



**Figure 5.** Snare technique. Deep implantation of a CoreValve prosthesis (left coronary cusp (LCC): 14 mm; non-coronary cusp (NCC): 13 mm) resulted in severe, “supraskirt” paravalvular aortic regurgitation (AR) (A). Via left-sided transbrachial access, the CoreValve prosthesis was pulled into a more favorable position (LCC: 4 mm; NCC: 3 mm) with the use of an Amplatz gooseneck snare catheter (B) without evidence of residual paravalvular AR (C).

25, 28, and 30 mm is recommended for the 23-, 26-, 29-, and 31-mm CoreValve, respectively.<sup>12</sup> For the Edwards-SAPIEN prosthesis (Edwards Lifesciences, Irvine, CA, USA), balloon post-dilation should be performed with the same balloon used for delivery of the valve prosthesis but with stepwise addition of 1 ml saline to the total volume to increase its diameter.<sup>31</sup>

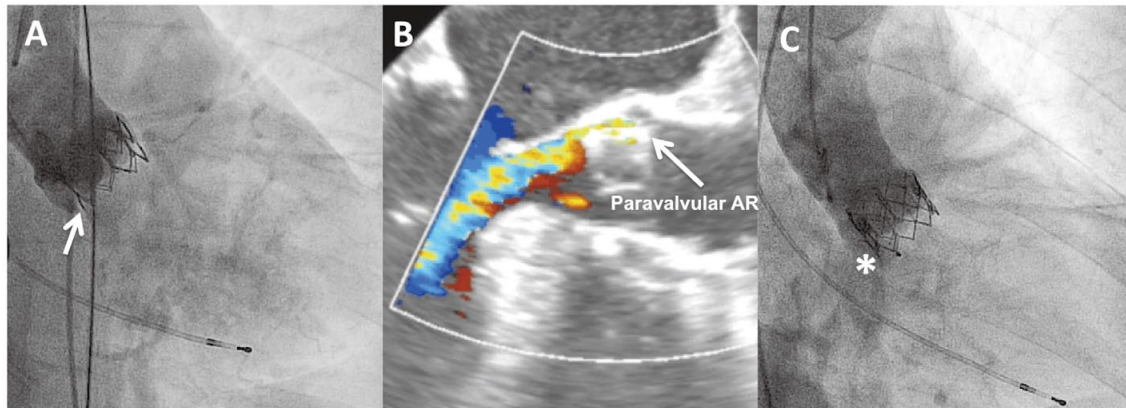
### Valve-in-Valve Implantation

A malpositioned THV with too shallow or too deep implantation of the prosthesis leads to incomplete sealing of the native aortic annulus by the pericardial skirt of the stent frame, allowing diastolic backflow into the LV. In most cases, valve-in-valve implantation is a treatment option to reduce paravalvular AR (Figure 4). The second valve is deployed several millimeters deeper or higher, allowing the pericardial skirts of both valves to overlap and ensure sealing of the native aortic annulus.<sup>29,35,36</sup> Thus, initial procedural failure can be converted into proce-

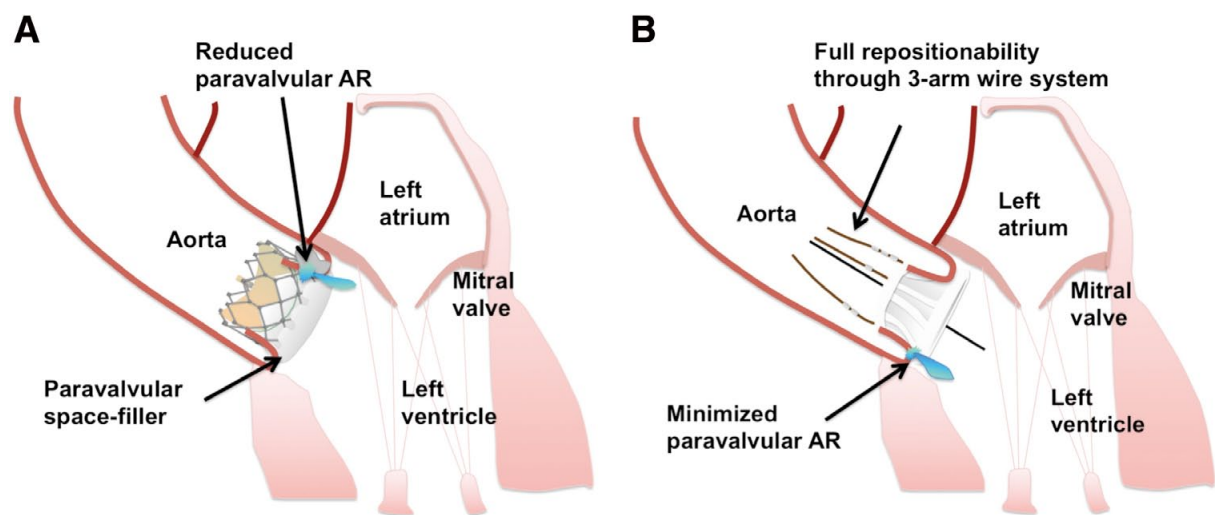
dural success in up to 90% of cases.<sup>29,35,36</sup> The valve-in-valve technique is also a viable treatment strategy for significant transvalvular AR caused by severe prosthetic leaflet dysfunction and for late failure of the THV.<sup>37,38</sup>

### Snare Technique

In selected cases, snaring of the implanted valve may be considered for a Medtronic CoreValve with too-ventricular placement of the prosthesis (Figure 5). Correction of the device's position may be achieved by engaging one of the anchoring hooks and pulling with a snare catheter.<sup>28</sup> To increase the leverage effect, the snaring maneuver can be performed via transbrachial access. However, the snare technique lacks predictability and has the potential risk of THV embolization into the ascending aorta, causing vascular complications (eg, aortic dissection).<sup>4,12,30</sup> If the snare technique fails, valve-in-valve implantation can be considered to prevent conversion to emergency



**Figure 6.** Interventional closure of paravalvular leakage. Despite balloon post-dilation and oversizing with a straight 22-mm valvuloplasty balloon, moderate aortic regurgitation (AR) because of incomplete circumferential apposition of an Edwards-SAPIEN 23-mm prosthesis with the annulus as a result of a severely calcified cusp (arrow, **A**) remained 2 months after implantation of this accurately sized prosthesis (**C**). Transesophageal echocardiography (TEE) was used to identify the paravalvular AR pathomechanism and identified the localized paravalvular leak (arrow, **B**). After deployment of an Amplatzer Vascular Plug III under guidance with real-time 3D-TEE and successful leak closure, only trace PAR remained on angiography (\*, **C**).



**Figure 7.** Repositionability and adaptive seals as features to minimize paravalvular aortic regurgitation (AR). Repositionability of the Direct Flow Medical Valve (Direct Flow Medical, Santa Rosa, CA, USA) (**A**) is ensured by 3 positioning wires, which are used to align the inflatable ring frame within the native annulus. During positioning, the polyester rings of the prosthesis are filled with contrast dye. Before final deployment of the valve, contrast dye is replaced by a 2-component hardening medium. The Edwards-SAPIEN 3 Aortic Valve (Edwards Lifesciences, Irvine, CA, USA) (**B**) is designed to ensure paravalvular sealing and further minimize paravalvular AR through an internal PET skirt as a paravalvular space filler.

open-heart surgery.

### Interventional Closure

Interventional closure of paravalvular leaks after TAVR has been described for the Edwards-SAPIEN prosthesis (**Figure 6**).<sup>39,40</sup> If significant paravalvular AR remains because of heavy calcification of the native aortic valve despite balloon valvuloplasty and a localized AR jet can be identified, transcatheter device closure with an Amplatzer Vascular Plug (AGA Medical Corp, Plymouth, MN, USA) can be attempted, analogous to paraval-

vular leak closure in surgical heart valves.<sup>41</sup> However, potential risks associated with transcatheter device closure of paravalvular leaks following TAVR include stroke, THV dislodgement, and embolization of the closure device itself.<sup>40,42</sup>

### Next-Generation THVs: Can We Forget About Paravalvular AR?

“Next-generation” THVs are designed to further improve procedural results and to overcome remaining procedure-related

issues (eg, vascular complications, paravalvular AR) by design modifications (eg, small sheath sizes, paravalvular space-fillers, full repositionability).<sup>43,44</sup> The recently published data from the DISCOVER trial (Direct Flow Medical Valve) and the REPRISE II Trial (Boston Lotus Valve) showed very promising first results in terms of reduction of paravalvular leakage.<sup>45,46</sup> In the following overview, we introduce the new valves and discuss the currently available study data.

### Direct Flow Medical Aortic Valve

The Direct Flow Medical Aortic Valve (Direct Flow Medical, Santa Rosa, CA, USA) consists of a tricuspid bovine pericardial tissue valve mounted between 2 inflatable polyester rings. The prosthesis is 18F-catheter compatible and repositioning of the valve is ensured by 3 position wires, which are used to align the inflatable ring frame in the native annulus. During positioning, the polyester rings of the prosthesis are filled with contrast dye. Before final deployment of the valve, contrast dye is replaced by a 2-component hardening medium (Figure 7). The multicenter non-randomized DISCOVER trial in 100 patients with logistic EuroSCORE  $\geq 20$  or other high surgical risk features not reflected by the log EuroSCORE showed a 30-day survival rate of 99% and mild or no AR in 99% (73/74 patients).<sup>45</sup> Initially observed higher residual gradients after valve implantation were not significant in the DISCOVER trial because of a clear strategy that included repositioning of the valve in cases of significant residual stenosis. The mean echocardiographic gradient decreased from an average of  $45.9 \pm 9.6$  mmHg ( $n=72$ ) to an average of  $12.6 \pm 7.1$  mmHg ( $n=72$ ) post-procedure over 30 days. The effective orifice area at baseline was  $0.65 \pm 0.18$  cm<sup>2</sup> ( $n=60$ ) and increased to  $1.50 \pm 0.56$  cm<sup>2</sup> ( $n=64$ ) at 30 days. The valve has had the CE-Mark in Europe since 2013 and is available in 3 sizes.

### Boston Lotus Aortic Valve

The Boston Lotus Valve (Boston Scientific, Natick, MA, USA) consists of a tri-leaflet bovine pericardial tissue valve mounted on a braided nitinol stent structure that expands in the native annulus as it shortens ("Chinese finger trap" principle). The Boston Lotus system is delivered percutaneously over an 18F introducer sheath and its design enables repositionability and recapturability of the device at any time point prior to release. The preloaded prosthesis is positioned over a 3-armed, self-centering system. An adaptive seal at the lower part of the prosthesis skirt is designed to prevent paravalvular AR. The results of the REPRISE II Trial (TCT 2012) were promising, with a 30-day mortality rate of 4.2% (5/120 patients) and mild or no AR in 98.1% (104/106 patients).<sup>46</sup> Stroke rate (5.9%) and pacemaker implantation rate (28.6%) were higher than expected. Because of its design with a significant part of the valve within the LVOT, pacemaker rates will probably remain higher than with the Edwards-SAPIEN valve for example. In addition, careful evaluation of the LV dimensions is highly advised because major parts of the valve are developed within the LV and/or OT. The company has developed a special pre-curved stiff wire in order to ensure safe manipulation and implantation of the valve. The wire comes in 2 sizes, which allow optimal treatment of small and larger ventricles. The valve has had the CE-Mark in Europe since 2013 and is currently available in 2 sizes.

### Symetis ACURATE TF Aortic Valve

The Symetis ACURATE Aortic Valve (Symetis, Lausanne, Switzerland) consists of an aortic stentless porcine valve that is mounted in a self-expanding nitinol alloy stent. Deployment of the device begins with the release of stabilization arches and

the upper crown of the valve in the ascending aorta. This is different to the Medtronic CoreValve, for example, which starts to open in the LVOT, and the aim is stabilizing of the valve during employment. After the upper crown has engaged the cusps of the native leaflets, the lower crown is fully expanded and anchors the valve within the native annulus. During release, the stabilization arches self-position the device with axial alignment of the THV. A polyethylene terephthalate skirt at the lower crown provides a seal at the level of the native aortic annulus, with the aim of reducing paravalvular leakage.

Symetis received CE-Mark approval for the transapical ACURATE TA valve at the end of September 2011. The trans-femoral ACURATE TF valve has enrolled 80 patients and showed a 30-day mortality rate of 3.8% and no or only mild paravalvular AR in 94.6% (74/80 patients).<sup>47</sup> The valve comes in 3 sizes, but is currently only CE-approved for the transapical valve.

### Medtronic Evolut R Aortic Valve

The Medtronic Evolut R represents a further development of the Medtronic CoreValve. Compared with the current CoreValve, the Evolut frame is tailored to reduce the overall height by approximately 10%, while the height of the pericardial skirt remains at 12 mm. However, as a design change, the skirt reaches down to the inflow tract to provide better sealing of the valve. The Evolut R design maintains the cell geometry of the CoreValve prosthesis to optimize frame adaptation to the native aortic annulus, especially in patients with complicated anatomies (eg, non-circular or asymmetrically calcified annuli).<sup>48</sup> The valve is now recapturable and repositionable.

For delivery of the Evolut R, a novel system has been developed (EnVeo R delivery system), which includes the new, catheter-mounted InLine sheath, equivalent to a 14F inner diameter system and an improvement in terms of a lower profile. The first-in-human study for the Evolut R started in fall of 2013 and the CE-Mark is expected in 2014.

### Edwards-SAPIEN 3 Aortic Valve

The Edwards-SAPIEN 3 (S3) includes a lower profile, balloon-expandable valve. The inflow of the S3 is covered by an internal PET skirt. In addition, an outer PET sealing cuff intends to reduce paravalvular AR (Figure 7). For the first-in-human study, the S3 THV was available in a 26-mm version (height of 20 mm when fully expanded). For the CE-Mark, which is expected in February 2014, additional sizes (23 mm and 29 mm) will be available. The increased valve length may facilitate optimal positioning of the S3 within the native aortic valve. However, it is expected that the increased length will increase the risk of atrioventricular block and conduction disturbances. For percutaneous use, the S3 will be delivered with the new Commander delivery system through an expandable 14F sheath. The profile for the transapical approach will also be reduced considerably.<sup>49</sup>

## Future Perspective

Paravalvular AR has been the "Achilles' heel" of transcatheter-based treatment of aortic valve stenosis. Every operator has experienced procedures in which paravalvular leakage because of severe calcification, valve misplacement or incorrect sizing has occurred. In the early years of TAVR, paravalvular AR was regarded as a negligible flaw, but we have since learned from numerous studies that AR significantly influences outcome. With the current and upcoming devices, it is expected that paravalvular AR because of heavy calcifications or misplacement of the valve will become less of a problem, mainly attributable to



adaptive seals and the ability to reposition the valve (Figure 7), especially in difficult anatomies such as horizontal aorta or severe hypertrophy of the LVOT. However, new issues will arise: improper sizing will continue to be a major issue, and with increasing valve types and sizes, choosing the correct valve size have even higher importance. In this respect, virtual implantation, with which the proper placement of a transcatheter heart valve can be simulated in the corresponding anatomy, may help the operator to choose the optimal valve and evaluate the perfect position. Other problems include the learning curve when available valve types increase. From the past, we know that the learning curve for each valve type determines not only procedural success but also the outcome for the patient. An unsolved problem is still the access size. Although all companies are working on smaller devices, an inner diameter of 14F (with an outer diameter of approximately 18F) is still the lowest profile available on the market. Intelligent sheath devices such as inflatable and recollapsible sheaths may broaden the spectrum of patients treated transfemorally and even more importantly, may further reduce vascular injury. Finally, with an increasing number of valves on the market, selection algorithms appear necessary to treat the individual patient with the perfectly fitting valve, as the first step on the way to the “tailored THV”. With accurate annulus sizing, the currently available and upcoming new valves will definitely reduce the number of patients with perivalvular AR, which will influence the outcome of patients significantly and make the procedure even more safe.

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