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Transcatheter aortic valve replacement—state of the art and a glimpse to the future: 'the Tailored Approach'

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Transcatheter aortic valve replacement determined a paradigm shift in the treatment of high-risk patients with severe symptomatic aortic valve stenosis. Notwithstanding the impressive results of the first-generation prostheses, a fast-paced technological evolution is taking place to overcome their limitations, in particular the vascular access damage and the paravalvular leak. Nowadays, with the availability of several different devices, the expert operator can select the right prosthesis for the specific anatomical and clinical situation. As 'One does not fit all', the 'Tailored TAVR Approach' we describe will conceivably become the future of this therapy.

The 'state of the art'

The first transcatheter aortic valve replacement (TAVR) was performed by Cribier *et al.*[1] in 2002 in a compassionate case of inoperable patient admitted for cardiogenic shock as a consequence of severe symptomatic aortic valve stenosis. After a long period of technical development, a large amount of literature reported promising results confirming the feasibility of TAVR.[2–9] Since then, about 100, 000 transcatheter valves have been implanted worldwide and this number is sharply increasing. The results of several large multicentre registries,[10–18] and some randomized controlled trials,[19–22] consistently showed that TAVR should appropriately be considered the standard of care for high or prohibitive surgical risk patients with severe symptomatic aortic stenosis. The recently published randomized CoreValve US High Risk Pivotal Trial[22] was the first to demonstrate a significantly higher rate of survival at 1 year with TAVR compared with surgical aortic valve replacement (SAVR) in high- risk patients. More recent publications[23–25] have shown by propensity score matching no difference in terms of mortality even in lower-risk patients. These groundbreaking results achieved in the last decade are consequences of the progressive technological improvement of the devices and of operator's experience. The size of the valves and delivery systems has decreased from 24–25 Fr to the current 14–18 Fr, thus increasing the deliverability through the femoral route and reducing the access complication rate. On the other hand, the accurate sizing and procedure planning obtained with the routine use of CT scan allowed the physicians to choose the optimal approach and to minimize the paravalvular leak rate that, however, remains the major Achille's heel of this procedure.

Limitations and complications of first-generation devices

The first phase of TAVR was characterized by a high rate of peri-procedural complications that deeply affect the survival.[13–19] The main issues were vascular complications, conduction disturbances, paravalvular leaks, stroke, coronary occlusion, and annular rupture.

Vascular complications

Vascular complications have been minimized by the technique of main access protection via the contralateral access as well as by the significant downsize of the delivery systems and devices.[10–25]

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Conduction disturbances

Although generally considered benign, conduction disturbances may portend significant clinical and economic effects, in particular when leading to the implantation of a permanent pacemaker (PM) or to the development of permanent atrial fibrillation.

Left bundle branch block

The main cause of left bundle branch block (LBBB) after TAVR is presumed to be the mechanical compression exerted on the atrioventricular conduction tissue. A persistent LBBB has been associated with a worse outcome in one study,[26] whereas in two large multicentre registries with Edwards SAPIEN[27] or CoreValve[28] this association has been denied. However, the persistence of an LBBB has been consistently associated with a higher incidence of advanced atrioventricular (AV) block requiring a PM implantation.[27–29]

Atrioventricular block and permanent pacemaker implantation

A high-degree atrioventricular block is reported after CoreValve implantation in 14–44% of the cases, while in up to 12% after Edwards SAPIEN implantation.[30] These figures are consistent with the subsequent rate of PM implantation of 18–49% for CoreValve and 0–12% after Edwards SAPIEN implantation.[31,32] Although generally considered a minor issue, PM implantation not only implies an additional intervention that is not free from complications *per se*, but may also have effects on long-term cardiac function as a consequence of left-to-right ventricle dyssynchrony. The latter will become an issue when TAVR technology will be adopted for younger and lower risk patients. On the other hand, it is well known that the rate of long-term PM dependency is overtly lower than the number of the PMs implanted for an acute high-degree AV block.[33–35] Clear-cut guidelines specifically addressing the topic of PM implantation in the setting of TAVR do not exist; however, the common practice is to leave a temporary pace maker for the first 24–48 h post-TAVR and then evaluate on a case-by-case level the risk–benefit ratio of implanting a permanent PM. Being such a lowest risk procedure, it is conceivable that, especially in the early phase of the TAVR experiences, PM has been cautiously implanted in a large number of cases.

Paravalvular leaks: causes and evolution

Multiple studies have reported the frequency and severity of paravalvular leak (PVL) after TAVR.[36] There is, however, significant heterogeneity that is caused by differences in: (i) imaging modalities (transthoracic echocardiography, transoesophageal echocardiography, and angiography); (ii) timing of assessment (immediately after implantation, before discharge, and at 30 days); (iii) transcatheter heart valve (THV) system; (iv) grading scale, and (v) adjudication of events. Paravalvular leak tends to be stable over time and in some cases, it can even improve.[36]

Although it was generally believed that only moderate or severe regurgitation would impact long-term outcomes, the 2-year results from the PARTNER trial showed that even mild PVL was associated with significant mortality.[37]

In general, first-generation prostheses were associated with a higher rate of PVL, especially the CoreValve; second-generation valves have been designed yet to overcome this issue. Of note, large data directly comparing first vs. second generation are still lacking.

Stroke and cerebrovascular accident

The risk of cerebrovascular accident (CVA) is inherently related to both patient-based and procedure-related risks. The variability of CVA rates among studies might be due to study design, sample size, methodology, and patient- and site-specific factors, as well as different event ascertainment and definitions.[38]

In a recent meta-analysis, the early stroke rate (<30 days) was as low as 2.9% and CVA rates did not differ significantly according to the valve type (SAPIEN 2.9% vs. CoreValve 3.6%, $P =$ not significant).[39] The time distribution of strokes is inherently correlated with the underlying pathophysiology. Strokes occurring in the acute (<24 h) and subacute early (<30 days) post-TAVR period are strongly related to procedural factors, whereas late events (1–12 months) are mostly connected to patient and disease factors.[38] Cerebral protection devices have been developed and designed to fit the aortic arch or the anonymous and common carotid arteries: these devices have been developed to avert cerebral embolism either by filtration (Claret Montage Device, Claret Medical, Inc., Santa Rosa, CA, USA; and EMBOL-X, Edwards Lifesciences) or by diversion (Embrella Embolic Deflector, Edwards Lifesciences; and TriGuard Cerebral Protection Device, Keystone Heart, Caeserea, Israel) of debris away from the cerebral circulation while maintaining normal cerebral perfusion. Safety, feasibility, and efficacy are currently being tested in ongoing trials.

Antithrombotic treatment is believed to be a cornerstone for the prevention of ischaemic CVAs during and after TAVR. Although TAVR procedures have been performed for more than a decade, little is known about optimal antiplatelet and anticoagulation therapy and recommendations are based over consensus. Thus, there is an unmet need for better antithrombotic therapies, given the fact that major stroke rate has not declined significantly over time.[40–42]

Coronary occlusion

Coronary occlusion is a very rare although ominous complication of TAVR with a mortality rate as high as 50%.[19,20,22] It is a consequence of the obstruction of coronary ostia by the frame of the prosthesis and immediate countermeasures (snaring of the valve or percutaneous coronary intervention of the coronary ostium) must be performed to restore adequate coronary flow. This complication is far more common during the 'valve-in-valve' procedure, as described in the appropriate section.

Annular rupture/left ventricular outflow tract rupture/periaortic haematoma

According to recent data, this complication happens cumulatively in 1.1.% of the cases.[39]

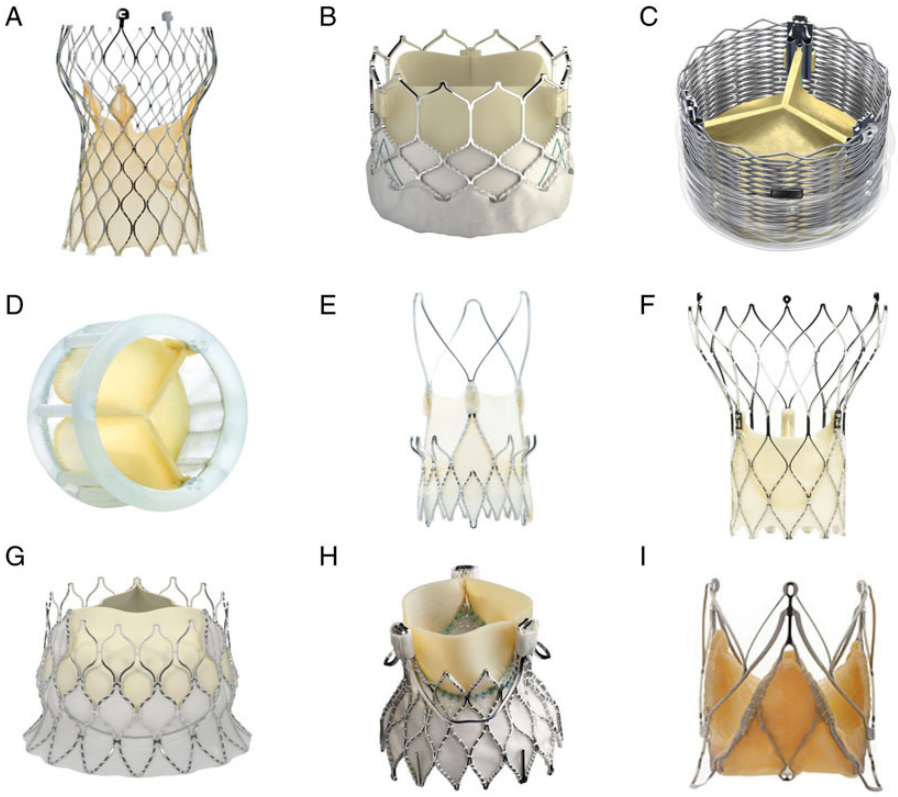

Figure 1 Currently available and under development transcatheter valves. (*A*) Medtronic Evolut (Medtronic, Inc., Minneapolis, MN, USA). (*B*) SAPIEN 3 (Edwards Lifesciences, Irvine, CA, USA). (*C*) Lotus Medical (Boston Scientific Corporation, Natick, MA, USA) valve. (*D*) Direct Flow Medical valve (Direct Flow Medical, Santa Rosa, CA, USA). (*E*) Symetis Accurate (Symetis SA, Lausanne, Switzerland) valve. (*F*) Portico (St Jude Medical, St Paul, MN, USA) valve. (*G*) Centera (Edwards Lifesciences). (*H*) Engager (Medtronic, Inc.) transapical valve. (*I*) Transapical JenaValve (JenaValve Technology, Munich, Germany).

Possible predictors are the presence of moderate/severe left ventricular outflow tract (LVOT) calcification and the significant oversize of the prosthesis.[43] This mechanical complication is obviously able to acutely worsen the haemodynamic conditions with a very high mortality rate, in particular when the rupture is uncontained.[43] Conversion to surgery is almost always required as the only life-saving option.[43]

Next (and current) generation of transcatheter valves

From the first quarter of 2014, a new generation of transcatheter valves (*Figure 1*) has CE mark approval for clinical use in Europe and under scrutiny for FDA approval in the USA. These new valves aim to overcome or to reduce the major limitations of first-generation valves (Edwards XT and Corevalve) as PVL, vascular complications, cardiac rhythm disturbances, and stroke.

Medtronic Evolut R

The CoreValve Evolut R (*Figure 1*) is designed to be recaptured up to the 80% of the deployment and repositioned during implant, for a maximum of two times. Evolut R has been available since the fourth quarter of 2014 and very few clinical data are available. In a CE study of 60 patients, Evolut R showed excellent procedural and 30-day outcomes and strong safety profile (0% mortality rate).[44]

Edwards SAPIEN 3

The Edwards SAPIEN 3 (*Figure 1*) is the last evolution of balloon expandable valves and it has been available since the first quarter of 2014. An important new feature of this valve is the presence of a skirt surrounding the distal part of the stent frame to reduce the PVLs with a better contact with calcifications. Recently, at ACC meeting held in San Diego on March 2015, Kodali presented 30-day results of S3 implant in high- and intermediate-risk patients. The rates of mortality and stroke were very low in both populations.[45] PARTNER 2 randomized trial is enrolled and it will compare S3 results vs. surgical results in intermediate-risk profile.

Boston (BSI) Lotus

The Lotus™ device (*Figure 1*) is a transcatheter valve system designed to be released retrogradely. The major advantages of this system are the possibility of a complete resheathing until the valve is released and the presence of the outer adaptive membrane facilitating the contact with the native valve, compensating the anatomical variations

and minimizing the PVL. The bulky delivery system is the major disadvantage of Lotus, but in the fourth quarter 2015 the new trackable and lower profile delivery system will be available. In the REPRISE II CE Mark Study, 6-month mortality rate was 8.4%, and Pace Maker rate 29.4%. In this study, only 1% of patients had more than mild PV regurgitation and no severe aortic regurgitation was reported. At EuroPCR 2015, Van Mieghem presented the first 250 Interim analysis of RESPOND Post Market Safety and Performance Study. All-cause mortality rate was 2.0%, stroke 3.3%, and no moderate or severe aortic regurgitation was reported.[46,47]

Saint Jude Portico

The Portico valve (*Figure 1*) can be fully recaptured, retrieved, and repositioned until 80–90% of deployment. The acute and 1-year results after implantation of the Portico valve were presented by G. Manoharan at PCR and TCT 2014: 103 high-risk patients were treated. The 1-year mortality rate was 8.7%, stroke rate 3.9%, PM implantation rate 10.7%, and moderate/severe aortic regurgitation 11.7%.[48] An European post-market registry (PORTICO I) and a prospective randomized study for FDA approval in the USA are ongoing.

Direct Flow

The Direct Flow Medical Transcatheter Aortic Valve System (*Figure 1*) is designed to be fully repositionable and retrievable prior to final deployment, but it cannot be resheathed. Schofer *et al.*[49] published in 2014 the non-randomized multicentre DISCOVER CE trial. There was 99% freedom from all-cause mortality at 30 days (primary endpoint). VARC criteria defined that 30-day combined freedom from patient safety event rate was 91% and overall device success rate was 93%. The same author presented at EuroPCR 2014 the 1-year results of this trial that confirmed the safety and efficacy of this valve. The survival rate at 1 year was 90% with no more than mild aortic regurgitation and 17% PM rate. The IDE trial SALUS in the USA is ongoing for FDA approval.

Symetis Acurate Neo

The system consists of two components: the bioprosthetic aortic valve Acurate Neo (*Figure 1*) and a disposable delivery system, the Acurate TFTM System. The transapical CE mark trial that was conducted between 2009 and 2011 in 90 patients achieved 80% 1-year survival rate,[50] and recently, the transfemoral valve received the CE mark after the accurate TF CE mark trial that achieved 3.4% 30-day morality rate, 2.2% stroke, 9.0% PM rate, and only 4.9% ≥grade 2 paravalvular leak.[51]

The 'Tailored Approach'

These second-generation valves associated with the increasing experience of operators are leading to a dramatic improvement in the results and to a simplification of the procedure that is now safer and more predictable. An overview of studies reporting 30-day results of first-generation

Table 1 An overview of published clinical results at 30 days

	CoreValve[22] (US Pivotal Extreme Risk)	SAPIEN (PARTNER)[20]	SAPIENT 21 (PARTNER 1)	SAPIEN 3 58	Direct Flow 66	Lotus Valve 52	Portico 63
Death (%)	7.9	5.0	3.5	2.1	1.3	4.2	2.9
Stroke (disturbing) (%)	2.4	5.0	5.2	0.0	4.0	1.7	2.9
New pacemaker (%)	22.2	3.4	5.4	12.5	17.0	28.6	9.8
MI (%)	1.5	0.0	1.6	2.1	1.3	3.3	2.0
Major vascular complications (%)	6.3	16.2	9.6	5.2	2.7	2.5	3.9
Disabling bleeding (%)	11.7	16.8	7.8	2.1	2.7	5.0	3.9
Mean gradient (mmHg)	8.5	11	10	10.7	12.5	11.5	8.7
PVL (moderate/severe) (%)	11.5	11.8	24.2	2.5	2.0	1.0	3.0

A comparison between first- and second-generation transcatheter valves.
PVL, paravalvular leak; MI, myocardial infarction.

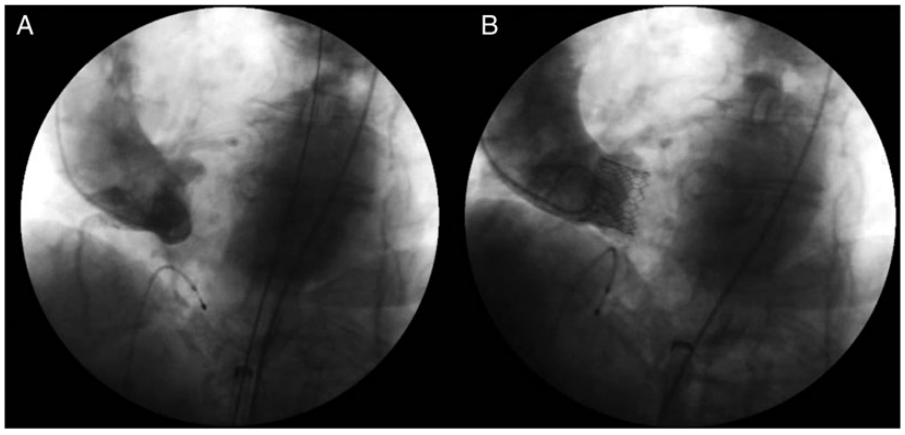

Figure 2 (*A*) Horizontal aorta frequently leads to challenging implantation, mostly due to inadequate coaxiality between the device shaft and the aorta/ventricle axis. (*B*) Optimal result after SAPIEN 3 implantation.

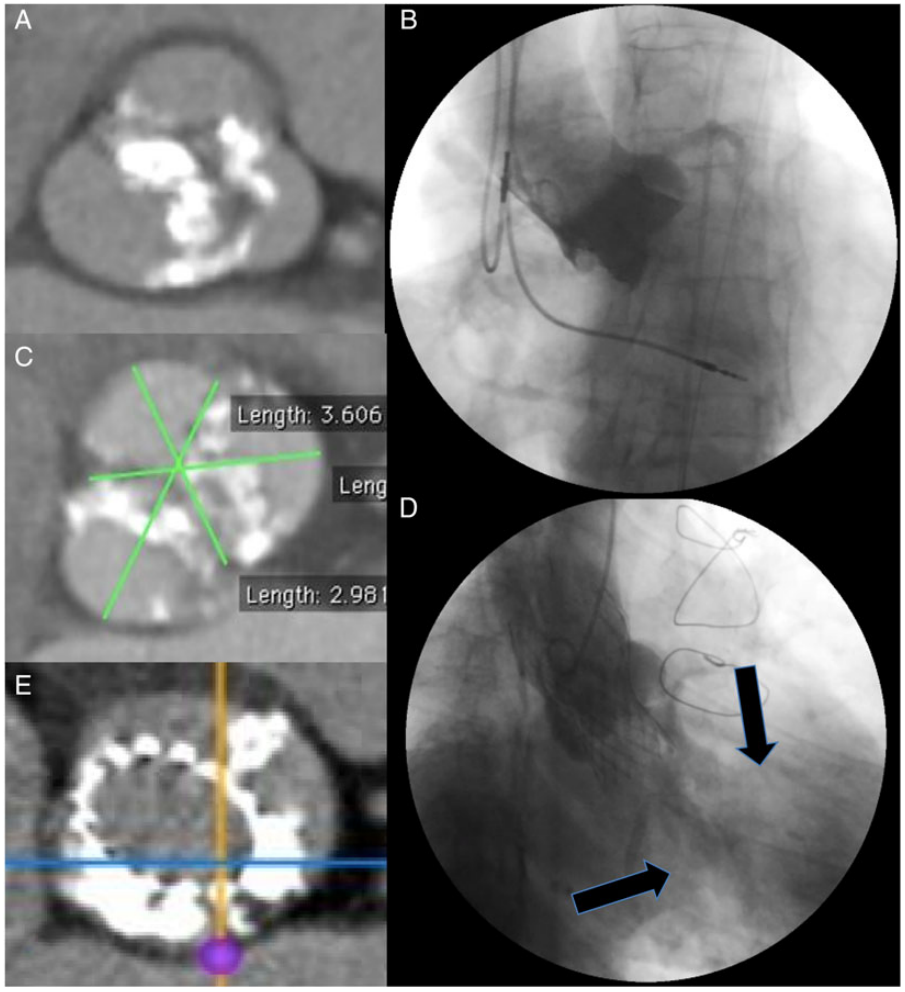

Figure 3 (*A*) Aortic annulus in the heavy calcified bicuspid valve. (*B*) Final result after Lotus valve implantation; its adaptive seal ensures good sealing even in such challenging anatomy. (*C*) Extremely eccentric annulus with diffuse calcifications in the bicuspid aortic valve. (*D*) Moderate paravalvular leak (arrows) after CoreValve implantation. (*E*) Incomplete valve expansion due to severe calcifications.

vs. second-generation valves is reported in *Table 1*. There is evidence of reduction in terms of death rate, PVL, and bleeding complications. The major advantage in terms of efficacy was reached by the new devices in reducing the degree of aortic regurgitation due to the PVL. Any further improvement in the results largely relies on the possibility to individualize the treatment. Every patient shows peculiar clinical and anatomical features that can significantly affect the overall result of the TAVR procedure. Thus, the selection of the proper device requires the knowledge of

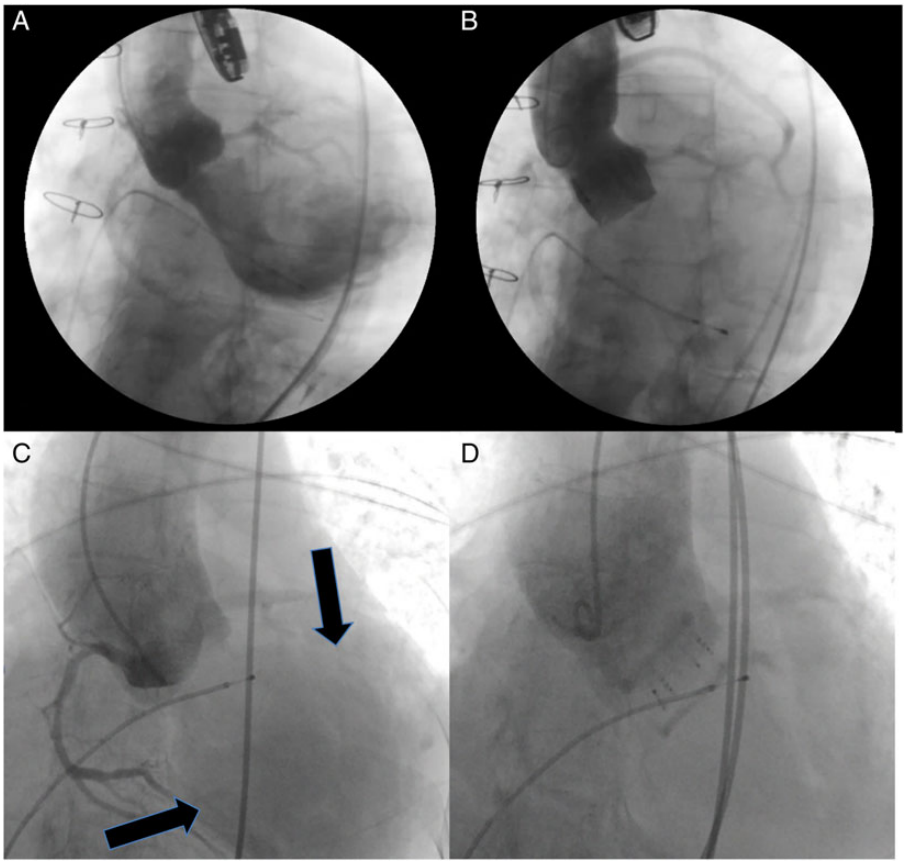

Figure 4 (*A*) Severe aortic regurgitation. (*B*) Final result with Lotus valve, showing no paravalvular leak. (*C*) Arrows showing severe aortic regurgitation. (*D*) No paravalvular leak after the Direct Flow valve.

the different available prostheses as well as a clear understanding of the behaviour of that specific device in that specific situation.

In other words, 'One does not fit all'. We thus hereby describe how to select the appropriate device for different clinical and/or anatomical situations that are common in the real world.

Small, tortuous, diseased peripheral arteries

Femoral access portends the best long-term results, thus the possibility to use that approach with a low-profile device with adequate trackability is of extreme value. In case of tortuous or diseased ilio-femoral axes, Evolut R and Sapien 3 valves seem to ensure the best chance of optimal safety.

Tortuous, Porcelain aorta

In this setting, self-expandable devices with low-profile and good trackability should be preferred: Evolut R, Portico, and Symetis. On the other hand, the use of stiffer devices such as the currently available Lotus is contraindicated.

Horizontal aorta

This setting is associated with a high risk of malapposition, inadequate coaxiality, and subsequent PVL. Thus, devices with very good handling of the tip, perhaps a steerable tip such as in the case of Sapien 3 (*Figure 2*), may be the optimal solution. Valid alternatives are the Direct Flow or the Symetis valves. The Lotus valve has also a good performance in this setting.

Bicuspid/extremely eccentric aortic valve annulus

Bicuspid aortic valve has always been a challenging situation, and often misdiagnosed and thus managed in improper way. An extremely eccentric annulus, diffuse calcifications, and the frequent coexistence of aortic regurgitation make the bicuspid aortic valve a very peculiar setting in which the Lotus device, when slightly undersized, with its adaptive seal seems to be the best option (*Figure 3*). When the Lotus is not available, the suprannular function of the Evolut R is the only acceptable alternative although results are suboptimal (*Figure 3*).

Heavy calcifications: diffuse, aortic valve, left ventricle outflow tract

This condition is a frequent challenge where the self-expandable prostheses may have suboptimal results for the insufficient adherence of the frame to the calcific nodules which can also determine a deformation of the frame stent itself. Nevertheless, a balloon expandable prosthesis poses a higher risk of annulus rupture. As in the bicuspid aortic valve, the conformability of the Lotus

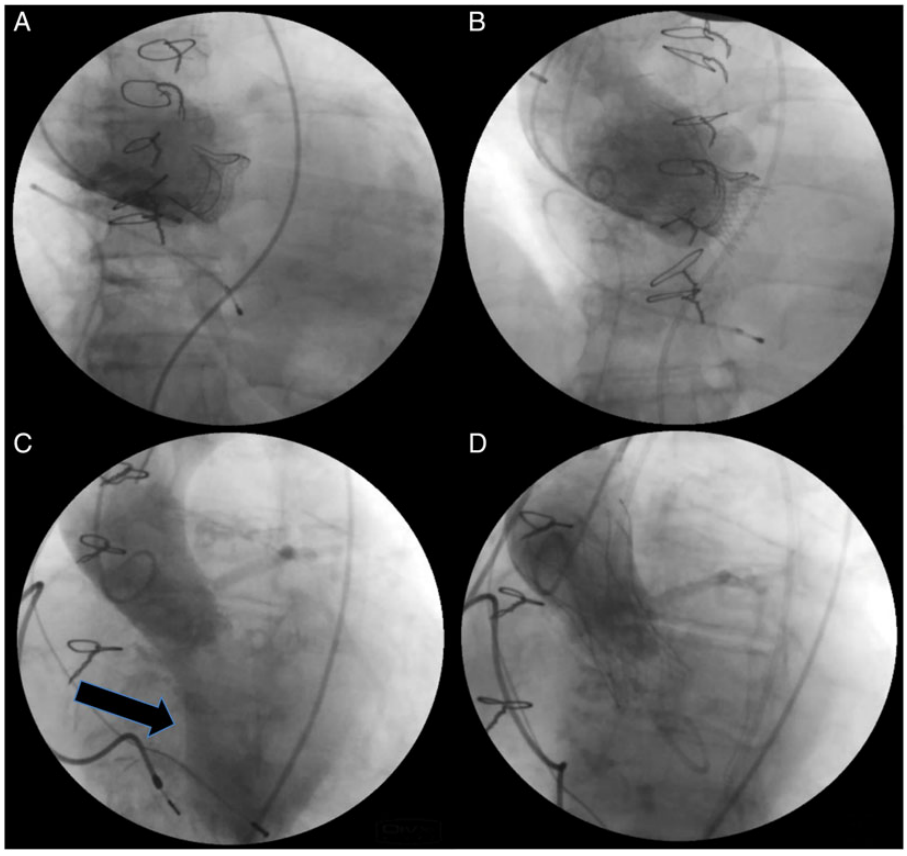

Figure 5 (*A*) Stented bioprostheses and severe stenosis. (*B*) Evolut R final result; its suprannular position is indicated in stented valves. (*C*) Stentless bioprostheses with severe aortic regurgitation (arrow). (*D*) Final result with Portico; due to high risk of coronary occlusion, left main protection technique is advisable.

valve, as it can be adapted to the irregular shape of the valve, LVOT and aortic root, may ensure the best results

Pure aortic regurgitation

Previous experience[52,53] are limited and aortic regurgitation is still off label. There are technical issues related to the poor anchoring of the prosthesis in the absence of calcification and to the common presence of very large annuli. The treatment of a pure aortic regurgitation is characterized by a higher incidence of PVL when compared with the stenosis, and a high incidence of 'valve in valve'.[52,53] In this setting, the use of balloon expandable seems inadequate as a consequence of the poor fixation of the device.

On the other hand, we observed good results with oversized Direct Flow and Lotus (*Figure 4*) with respect to the manufacturers' indications. Transapical Jena Valve and Engager have interesting features for these indications, but are currently not available.

Valve in valve for degenerated surgical bioprostheses

The widespread use of surgical bioprostheses has determined an increasing rate of failed bioprostheses over time. As a consequence of the high risk of comorbidity/mortality of a surgical redo, the indication to TAVR is expanding sharply[54,55] This is a completely different setting when compared with the diseased native aortic valve and every surgical prosthesis has its own features and poses specific procedural issues. In this setting, the risk of acute coronary occlusion is much higher than that in the native aortic valve treatment and it appears to be related with specific bioprosthesis. The residual valve orifice and gradient are the predictors of mortality at follow-up. Both corevalve revalvyng system and ESV showed to be safe and effective, thus it is conceivable that their evolution such as the Evolut R and the Sapien 3 could be the devices of choice. Perhaps, in small annuli, the Evolut R should be preferred because of its suprannular position (*Figure 5*). Very good alternatives are the Portico valve as being retrievable, and having large frame cells that allow a good coronary access: despite being intrannular, the residual gradient is usually acceptable. In the case of a high risk of coronary occlusion, the use of a coronary protection technique is advisable.

Low ejection fraction/severe hypertrophy

In these settings, the risk of PVL must be minimized as patients do not tolerate suboptimal results. Thus, the devices that showed the lowest percentage of PVL, namely, Lotus, Sapien 3, and DFM could be the devices of choice. However, Lotus has some limitations regarding the LV size/hypertrophy, Sapien 3 requires rapid pacing that can harm patients with low-flow, low-gradient condition, and

the DFM has limitations regarding small annuli as they are prone to determine significant gradients.

Conclusions

Over the years, operators gradually developed the necessary experience to safely perform the procedure and rapidly manage possible complications. Meticulous risk-stratification and accurate procedural planning with the necessary imaging modalities should always be performed as they were pivotal for the observed groundbreaking results of TAVR. In the upcoming 5 years, the results from randomized trials and large registries with the new devices, the awaited long-term durability data, and the expected further downsizing of the vascular access sheaths will definitely lead to an even safer and more predictable procedure: in the long term, this will be an essential requirement to challenge the TAVR procedure against surgical aortic valve replacement in lower-risk patients.

On the other hand, as the 'perfect transcatheter aortic valve prosthesis' does not exist, the very next future of the TAVR will be the 'Tailored TAVR Approach', i.e. an individualized treatment that will take into account all the clinical and anatomical features that an operator can face during its daily practice. It requires a deep knowledge of the different available devices and enough experience to master the TAVR procedure with all of them: 'One does not fit all'.

Conflict of interest: F.B. is medical proctor for Medtronic, St Jude and Boston Scientific. N.B. is medical proctor for Boston Scientific.

References

1. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, Derumeaux G, Anselme F, Laborde F, Leon MB. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation* 2002;**106**:3006–3008.
2. Cribier A, Eltchaninoff H, Tron C, Bauer F, Agatiello C, Sebagh L, Bash A, Nusimovici D, Litzler PY, Bessou JP, Leon MB. Early experience with percutaneous transcatheter implantation of heart valve prosthesis for the treatment of end-stage inoperable patients with calcific aortic stenosis. *J Am Coll Cardiol* 2004;**43**:698–703.
3. Webb JG, Pasupati S, Humphries K, Thompson C, Altwegg L, Moss R, Sinhal A, Carere RG, Munt B, Ricci D, Ye J, Cheung A, Lichtenstein SV. Percutaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis. *Circulation* 2007;**116**:755–763.
4. Lichtenstein SV, Cheung A, Ye J, Thompson CR, Carere RG, Pasupati S, Webb JG. Transapical transcatheter aortic valve implantation in humans: initial clinical experience. *Circulation* 2006;**114**:591–596.
5. Walther T, Simon P, Dewey T, Wimmer-Greinecker G, Falk V, Kasimir MT, Doss M, Borger MA, Schuler G, Glogar D, Fehske W, Wolner E, Mohr FW, Mack M. Transapical minimally invasive aortic valve implantation: multicenter experience. *Circulation* 2007;**116**(11 Suppl):I240–I245.
6. Walther T, Kasimir MT, Doss M, Schuler G, Simon P, Schächinger V, Mohr FW, Wimmer-Greinecker G. One-year interim follow-up results of the TRAVERCE trial: the initial feasibility study for trans-apical aortic-valve implantation. *Eur J Cardiothorac Surg* 2011;**39**:532–537.
7. Rodés-Cabau J, Dumont E, De LaRochellière R, Doyle D, Lemieux J, Bergeron S, Clavel MA, Villeneuve J, Raby K, Bertrand OF, Pibarot P. Feasibility and initial results of percutaneous aortic valve implantation including selection of the transfemoral or transapical approach in patients with severe aortic stenosis. *Am J Cardiol* 2008;**102**:1240–1246.
8. Kodali SK, O'Neill WW, Moses JW, Williams M, Smith CR, Tuzcu M, Svensson LG, Kapadia S, Hanzel G, Kirtane AJ, Leon MB. Early and late (one year) outcomes following transcatheter aortic valve implantation in patients with severe aortic stenosis (from the United States REVIVAL trial). *Am J Cardiol* 2011;**107**:1058–1064.
9. Grube E, Schuler G, Buellesfeld L, Gerckens U, Linke A, Wenaweser P, Sauren B, Mohr FW, Walther T, Zickmann B, Iversen S, Felderhoff T, Cartier R, Bonan R. Percutaneous aortic valve replacement for severe aortic stenosis in high-risk patients using the second- and current third-generation self-expanding core valve prosthesis: device success and 30-day clinical outcome. *J Am Coll Cardiol* 2007;**50**:69–76.
10. Rodés-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Feindel CM, Osten M, Natarajan MK, Velianou JL, Martucci G, DeVarennes B, Chisholm R, Peterson MD, Lichtenstein SV, Nietlispach F, Doyle D, DeLarochellière R, Teoh K, Chu V, Dancea A, Lachapelle K, Cheema A, Latter D, Horlick E. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. *J Am Coll Cardiol* 2010;**55**:1080–1090.
11. Thomas M, Schymik G, Walther T, Himbert D, Lefèvre T, Treede H, Eggebrecht H, Rubino P, Colombo A, Lange R, Schwarz RR, Wendler O. One-year outcomes of cohort 1 in the Edwards SAPIEN aortic bioprosthesis European outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation* 2011;**124**:425–433.
12. Piazza N, Grube E, Gerckens U, den Heijer P, Linke A, Luha O, Ramondo A, Ussia G, Wenaweser P, Windecker S, Laborde JC, de Jaegere P, Serruys PW. Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 Fr) CoreValve Revalving system: results from the multicentre, expanded evaluation registry 1-year following CE mark approval. *EuroIntervention* 2008;**4**:242–249.
13. Tamburino C, Capodanno D, Ramondo A, Petronio AS, Ettori F, Santoro G, Klugmann S, Bedogni F, Maisano F, Marzocchi A, Poli A, Antoniucci D, Napodano M, De Carlo M, Fiorina C, Ussia GP. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. *Circulation* 2011;**123**:299–308.
14. Eltchaninoff H, Prat A, Gilard M, Leguerrier A, Blanchard D, Fournial G, Iung B, Donzeau-Gouge P, Tribouilloy C, Debrux JL, Pavie A, Gueret P. FRANCE Registry Investigators. Transcatheter aortic valve implantation: early results of the FRANCE (FRench Aortic National CoreValve and Edwards) registry. *Eur Heart J* 2011;**32**:191–197.
15. Zahn R, Gerckens U, Grube E, Linke A, Sievert H, Eggebrecht H, Hambrecht R, Sack S, Hauptmann KE, Richardt G, Figulla HR, Senges J. German Transcatheter Aortic Valve Interventions-Registry Investigators. Transcatheter aortic valve implantation: first results from a multi-centre real-world registry. *Eur Heart J* 2011;**32**:198–204.
16. Bosmans JM, Kefer J, De Bruyne B, Herijgers P, Dubois C, Legrand V, Verheye S, Rodrigus I; Belgian TAVI Registry Participants. Belgian TAVI Registry Participants. Procedural, 30-day and one year outcome following CoreValve or Edwards transcatheter aortic valve implantation: result of the Belgian national Registry. *Interact CardioVasc Thorac Surgery* 2011;**12**:762–767.
17. Moat NE, Ludman P, de Belder MA, Bridgewater B, Cunningham AD, Young CP, Thomas M, Kovac J, Spyt T, MacCarthy PA, Wendler O, Hildick-Smith D, Davies SW, Trivedi U, Blackman DJ, Levy RD, Brecker SJ, Baumbach A, Daniel T, Gray H, Mullen MJ. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom transcatheter aortic valve implantation) registry. *J Am Coll Cardiol* 2011;**58**:2130.
18. Linke A, Wenaweser P, Gerckens U, Tamburino C, Bosmans J, Bleiziffer S, Blackman D, Schäfer U, Müller R, Sievert H, Søndergaard L, Klugmann S, Hoffmann R, Tchétché D, Colombo A, Legrand VM, Bedogni F, lePrince P, Schuler G, Mazzitelli D, Eftychiou C, Frerker C, Boekstegers P, Windecker S, Mohr FW, Woitek F, Lange R, Bauernschmitt R, Brecker S; ADVANCE study Investigators. Treatment of aortic stenosis with a self-expanding transcatheter valve: the International Multi-centre ADVANCE Study. *Eur Heart J* 2014;**35**:2672–2684.

19. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S. PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;**363**:1597–1607.
20. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;**364**:2187–2198.
21. Popma JJ, Adams DH, Reardon MJ, Yakubov SJ, Kleiman NS, Heimansohn D, Hermiller J Jr, Hughes GC, Harrison JK, Coselli J, Diez J, Kafi A, Schreiber T, Gleason TG, Conte J, Buchbinder M, Deeb GM, Carabello B, Serruys PW, Chenoweth S, Oh JK. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis in extreme risk for surgery. *J Am Coll Cardiol* 2014;**63**:1972–1981.
22. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J Jr, Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK. The U.S. CoreValve clinical Investigators. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014; **370**:1790–1798.
23. Latib A, Maisano F, Bertoldi L, Giacomini A, Shannon J, Cioni M, Ielasi A, Figini F, Tagaki K, Franco A, Covello RD, Grimaldi A, Spagnolo P, Buchannan GL, Carlino M, Chieffo A, Montorfano M, Alfieri O, Colombo A. Transcatether vs surgical aortic valve replacement in intermediate surgical risk patients with aortic valve stenosis: a propensity score matched case-control study. *Am Heart J* 2012;**164**:910–917.
24. Piazza N, Kalesan B, van Mieghen N. A 3-center comparison of 1 year mortality outcomes between transcatheter aortic valve implantation and surgical aortic valve replacement on the basis of propensity score matching among intermediate risk patients. *JACC Cardiovasc Interv* 2013;**6**:443–451.
25. D'Errigo P, Barbanti M, Santini F, Grossi C, Ranucci M, Onorati F, Covello RD, Rosato S, Tamburino C, Santoro G, Fusco D, Seccareccia F. Risultati dello studio OBSERVANT. Caratteristiche cliniche e risultati a breve termine nella popolazione arruolata sottoposta a sostituzione valvolare aortica (Transcatetere vs Chirurgica). *G Ital Cardiol* 2014; **15**:177–184.
26. Houthuizen P, Van Garsse LA, Poels TT, de Jaegere P, van der Boon RM, Swinkels BM, Ten Berg JM, van der Kley F, Schalij MJ, Baan J Jr, Cocchieri R, Brueren GR, van Straten AH, den Heijer P, Bentala M, van Ommen V, Kluin J, Stella PR, Prins MH, Maessen JG, Prinzen FW. Left bundle-branch block induced by trans-catheter aortic valve implantation increases risk of death. *Circulation* 2012;**126**:720–728.
27. Urena M, Mok M, Serra V, Dumont E, Nombela-Franco L, DeLarochellière R, Doyle D, Igual A, Larose E, Amat-Santos I, Côté M, Cuéllar H, Pibarot P, de Jaegere P, Philippon F, Garcia del Blanco B, Rodés-Cabau J. Predictive factors and long-term clinical consequences of persistent left bundle branch block following trans-catheter aortic valve implantation with a balloon-expandable valve. *J Am Coll Cardiol* 2012;**60**:1743–1752.
28. Testa L, Latib A, De Marco F, De Carlo M, Agnifili M, Latini RA, Petronio AS, Ettori F, Poli A, De Servi S, Ramondo A, Napodano M, Klugmann S, Ussia GP, Tamburino C, Brambilla N, Colombo A, Bedogni F. Clinical impact of persistent left bundle-branch block after transcatheter aortic valve implantation with CoreValve Revalving System. *Circulation* 2013;**127**:1300–1307.
29. van der Boon RM, Nuis RJ, Van Mieghem NM, Jordaens L, Rodés-Cabau J, van Domburg RT, Serruys PW, Anderson RH, de Jaegere PP. New conduction abnormalities after TAVI–frequency and causes. *Nat Rev Cardiol* 2012;**9**:454–463.
30. Sinhal A, Altwegg L, Pasupati S, Humphries KH, Allard M, Martin P, Cheung A, Ye J, Kerr C, Lichtenstein SV, Webb JG. Atrioventricular block after transcatheter balloon expandable aortic valve implantation. *JACC Cardiovasc Interv* 2008;**1**:305–309.
31. Jilaihawi H, Chin D, Vasa-Nicotera M, Jeilan M, Spyt T, Ng GA, Bence J, Logtens E, Kovac J. Predictors for permanent pacemaker requirement after trans-catheter aortic valve implantation with the CoreValve bioprosthesis. *Am Heart J* 2009;**157**:860–866.
32. van der Boon RM, Van Mieghem NM, Theuns DA, Nuis RJ, Nauta ST, Serruys PW, Jordaens L, van Domburg RT, de Jaegere PP. Pacemaker dependency after transcatheter aortic valve implantation with the self-expanding Medtronic CoreValve System. *Int J Cardiol* 2013;**168**:1269.
33. Simms AD, Hogarth AJ, Hudson EA, Worsnop VL, Blackman DJ, O'Regan DJ, Tayebjee MH. Ongoing requirement for pacing post-transcatheter aortic valve implantation and surgical aortic valve replacement. *Interact CardioVasc Thorac Surg* 2013;**17**:328–333.
34. Pereira E, Ferreira N, Caeiro D, Primo J, Adão L, Oliveira M, Gonçalves H, Ribeiro J, Santos E, Leite D, Bettencourt N, Braga P, Simões L, Vouga L, Gama V. Transcatheter aortic valve implantation and requirements of pacing over time. *Pacing Clin Electrophysiol* 2013;**36**:559–569.
35. van der Boon RM, Houthuizen P, Nuis RJ, van Mieghem NM, Prinzen F, de Jaegere PP. Clinical implications of conduction abnormalities and arrhythmias after transcatheter aortic valve implantation. *Curr Cardiol Rep* 2014;**16**:429.
36. Généreux P, Head SJ, Van Mieghem NM, Kodali S, Kirtane AJ, Xu K, Smith C, Serruys PW, Kappetein AP, Leon MB. Clinical outcomes after transcatheter aortic valve replacement using Valve Academic Research Consortium definitions: a weighted meta-analysis of 3,519 patients from 16 studies. *J Am Coll Cardiol* 2012;**59**:2317–2326.
37. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, Fontana GP, Dewey TM, Thourani VH, Pichard AD, Fischbein M, Szeto WY, Lim S, Greason KL, Teirstein PS, Malaisrie SC, Douglas PS, Hahn RT, Whisenant B, Zajarias A, Wang D, Akin JJ, Anderson WN, Leon MB. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2012;**366**:1686–1695.
38. Mastoris I, Schoos MM, Dangas GD, Mehran R. Stroke after transcatheter aortic valve replacement: incidence, risk factors, prognosis, and preventive strategies. *Clin Cardiol* 2014;**12**:756–764.
39. Khatri PJ, Webb JG, Rodés-Cabau J, Fremes SE, Ruel M, Lau K, Guo H, Wijeysundera HC, Ko DT. Adverse effects associated with transcatheter aortic valve implantation: a meta-analysis of contemporary studies. *Ann Intern Med* 2013;**158**:35–46.
40. Holmes DR Jr, Mack MJ, Kaul S, Agnihotri A, Alexander KP, Bailey SR, Calhoon JH, Carabello BA, Desai MY, Edwards FH, Francis GS, Gardner TJ, Kappetein AP, Linderbaum JA, Mukherjee C, Mukherjee D, Otto CM, Ruiz CE, Sacco RL, Smith D, Thomas JD, Harrington RA, Bhatt DL, Ferrari VA, Fisher JD, Garcia MJ, Gardner TJ, Gentile F, Gilson MF, Hernandez AF, Jacobs AK, Kaul S, Linderbaum JA, Moliterno DJ, Weitz HH. 2012 ACCF/AATS/ SCAI/STS expert consensus document on transcatheter aortic valve replacement. *J Am Coll Cardiol* 2012;**59**:1200–1254.
41. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg* 2012;**42**:S1–S44.
42. Webb J, Rodés-Cabau J, Fremes S, Pibarot P, Ruel M, Ibrahim R, Welsh R, Feindel C, Lichtenstein S. Transcatheter aortic valve implantation: a Canadian Cardiovascular Society position statement. *Can J Cardiol* 2012;**28**:520–528.
43. Barbanti M, Yang TH, Rodès Cabau J, Tamburino C, Wood DA, Jilaihawi H, Blanke P, Makkar RR, Latib A, Colombo A, Tarantini G, Raju R, Binder RK, Nguyen G, Freeman M, Ribeiro HB, Kapadia S, Min J, Feuchtner G, Gurtvich R, Alqoofi F, Pelletier M, Ussia GP, Napodano M, de Brito FS Jr, Kodali S, Norgaard BL, Hansson NC, Pache G, Canovas SJ, Zhang H, Leon MB, Webb JG, Leipsic J. Anatomical and procedural features associated with aortic root rupture during Balloon expandable transcatheter aortic valve replacement. *Circulation* 2013;**128**:244–253.
44. Meredith IT. Early results from the CoreValve Evolut R CE Study [2101–295]. In: *Presented at the Annual Meeting of the American College of Cardiology*, 14 March 2015.
45. Kodali S. on behalf of PARTNER investigators. American College of Cardiology (ACC) 2015 March 15, San Diego, CA, 2015.
46. Meredith Am IT, Walters DL, Dumonteil N, Worthley SG, Tchétché D, Manoharan G, Blackman DJ, Rioufol G, Hildick-Smith D, Whitbourn RJ, Lefèvre T, Lange R, Müller R, Redwood S, Allocco DJ, Dawkins KD. Transcatheter aortic valve replacement for severe symptomatic aortic stenosis using a repositionable valve system: 30-day

primary endpoint results from the REPRISE II study. *J Am Coll Cardiol* 2014;**64**:1339–1348.
47. Van Mieghem NM, on behalf of the RESPOND Investigators. First report from the RESPOND study: post-market evaluation of a fully repositionable and retrievable aortic valve in 250 patients treated in routine clinical practice. *EuroPCR* 2015.
48. Manoharan G. On behalf of the Portico™ Valve CE Mark Investigators. Multicentre clinical study evaluating a novel resheatable self-expanding transcatheter aortic valve system preliminary results: acute and 1-year outcomes. *EuroPCR* 2014. Oral Presentation.
49. Schofer J, Colombo A, Klugmann S, Fajadet J, DeMarco F, Tchétché D, Maisano F, Bruschi G, Latib A, Bijuklic K, Weissman N, Low R, Thomas M, Young C, Redwood S, Mullen M, Yap J, Grube E, Nickenig G, Sinning JM, Hauptmann KE, Friedrich I, Lauterbach M, Schmoeckel M, Davidson C, Lefevre T. Prospective multicenter evaluation of the direct flow medical transcatheter aortic valve. *J Am Coll Cardiol* 2014;**63**:763–768.
50. Kempfert J, Holzhey D, Hofmann S, Girdauskas E, Treede H, Schröfel H, Thielmann M, Walther T. First registry results from the newly approved ACURATE TA™ TAVI system. *Eur J Cardiothorac Surg* 2015;**48**:137–141.
51. Möllmann H, Diemert P, Grube E, Baldus S, Kempfert J, Abizaid A. Symetis ACURATE TF™ aortic bioprosthesis. *EuroIntervention* 2013;**9**: S107–S110.
52. Testa L, Latib A, Rossi ML, De Marco F, De Carlo M, Fiorina C, Oreglia J, Petronio AS, Ettori F, De Servi S, Klugmann S, Ussia GP, Tamburino C, Panisi P, Brambilla N, Colombo A, Presbitero P, Bedogni F. CoreValve implantation for severe aortic regurgitation: a multicentre registry. *EuroIntervention* 2014;**10**:739–745.
53. Roy DA, Schaefer U, Guetta V, Hildick-Smith D, Möllmann H, Dumonteil N, Modine T, Bosmans J, Petronio AS, Moat N, Linke A, Moris C, Champagnac D, Parma R, Ochala A, Medvedofsky D, Patterson T, Woitek F, Jahangiri M, Laborde JC, Brecker SJ. Transcatheter aortic valve implantation for pure severe native aortic valve regurgitation. *J Am Coll Cardiol* 2013;**61**:1577–1584.
54. Dvir D, Webb JG, Bleiziffer S, Pasic M, Waksman R, Kodali S, Barbanti M, Latib A, Schaefer U, Rodés-Cabau J, Treede H, Piazza N, Hildick-Smith D, Himbert D, Walther T, Hengstenberg C, Nissen H, Bekeredjian R, Presbitero P, Ferrari E, Segev A, de Weger A, Windecker S, Moat NE, Napodano M, Wilbring M, Cerillo AG, Brecker S, Tchetche D, Lefèvre T, De Marco F, Fiorina C, Petronio AS, Teles RC, Testa L, Laborde JC, Leon MB, Kornowski R; Valve-in-Valve International Data Registry Investigators. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. *JAMA* 2014;**312**: 162–170.
55. Bedogni F, Laudisa ML, Pizzocri S, Tamburino C, Ussia GP, Petronio AS, Napodano M, Ramondo A, Presbitero P, Ettori F, Santoro G, Klugman S, De Marco F, Brambilla N, Testa L. Transcatheter valve-in-valve implantation using CoreValve Revalving System for failed surgical aortic bioprostheses. *JACC Cardiovasc Interv* 2011;**4**: 1228–1234.