

## Interventional Cardiology Current Status and Future Directions in Coronary Disease and Valvular Heart Disease

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Percutaneous cardiac interventions were introduced in the 1960s, and, with the introduction of percutaneous coronary interventions by Gruentzig in 1978, the field has had an astounding growth. Percutaneous coronary intervention (PCI) is the most commonly preformed revascularization technique in the United States today with an estimated 492 000 procedures done in 2010<sup>1</sup> (Figure 1). This exceeds the number of coronary bypass operations estimated to be 397 000. Likewise, the growth of structural heart disease, in particular, valvular heart disease, has been remarkable with >10 000 procedures in 2013 in the United States 2 years after approval and 38 000 over the first 5 years of approval in Europe.<sup>2</sup> It is estimated that > 200 000 transcatheter aortic valve replacement (TAVR) procedures have been done worldwide to date. Growth in TAVR has increased the volume of surgical aortic valve replacement as well<sup>3</sup> (Figure 2). Invasive pediatric interventions have accelerated over the past decade with better devices and improved success. Peripheral vascular interventions have also grown, expanding into venous in addition to arterial interventions. The field of interventional cardiology is now much broader and more complex than ever before and specialization within interventional cardiology is increasing.<sup>4</sup> This review will discuss 2 areas where change has been most dramatic: coronary and valvular interventions.

### Coronary Artery Interventions

#### The Current Status of Coronary Interventions

Studies over the past decade have shown that the procedure is effective in relieving symptoms in patients with stable ischemic heart disease. In patients with moderate- to high-risk acute coronary syndrome and ST-segment-elevation myocardial infarction, PCI reduces not only symptoms, but also death and myocardial infarction and is the treatment of choice for most patients.<sup>5,6</sup> It is not surprising that PCI has grown steadily and dramatically between 1980 and 2006. Recent studies show that this growth has plateaued for patients with acute coronary syndrome and fallen for patients with stable ischemic heart disease.<sup>7,8</sup>

The growth of the procedure has been driven by remarkable technological advances over the past 25 years with the development of progressively smaller profile balloon catheters,

improved guidewires, and the introduction of bare metal stents in 1985 and subsequently drug-eluting stents (DES) in 2001. Adjunctive devices such as laser, atherectomy, thrombectomy, and filter devices have been used for specific anatomic situations with success. These advances have resulted in improved acute success (>95%) and reduced mortality (0.7% in patients without myocardial infarction) and the need for emergency coronary artery bypass grafting (<0.3%) while reducing restenosis to <10%.<sup>9</sup>

Despite the improved outcomes, PCI continues to be limited by significantly lower success or higher complication rates in patients with unfavorable coronary anatomy, such as diffuse disease, dense calcification, chronic total occlusion, and complex bifurcation lesions. In addition, the problem of early (<1 month), late (1–12 months), and very late (>12 months) stent thrombosis continues to plague DES.<sup>10</sup>

Other advances over the past decade have contributed to the better outcomes such as improved adjunctive pharmacology with the introduction of bivalirudin and new antiplatelet agents. Trials have consistently shown lower bleeding rates with use of bivalirudin, although this has been associated with a small increase in early stent thrombosis.<sup>11</sup> Dual-antiplatelet therapy with aspirin and clopidogrel has been the standard of care to prevent stent thrombosis. Trials have shown that the more potent and more rapid onset agents, prasugrel and ticagrelor, are superior to clopidogrel in reducing ischemic events but are associated with a small increased risk of bleeding. Ticagrelor is now the preferred agent in combination with aspirin in patients undergoing primary PCI for ST-segment-elevation myocardial infarction.<sup>12</sup>

Vascular access from the femoral artery is associated with bleeding, particularly when potent antithrombotic and antiplatelet regimens are used in PCI. Major bleeding has been shown to be a significant risk factor for death and myocardial infarction following PCI. The introduction of radial access has resulted in a significant reduction in bleeding in comparison with the femoral approach. It also has been shown to reduce mortality in patients with ST-segment-elevation myocardial infarction undergoing primary angioplasty. The growth of the radial approach over the past 10 years has been significant with most centers preferring this approach, and it is likely to continue to grow in popularity in the future.<sup>13</sup>

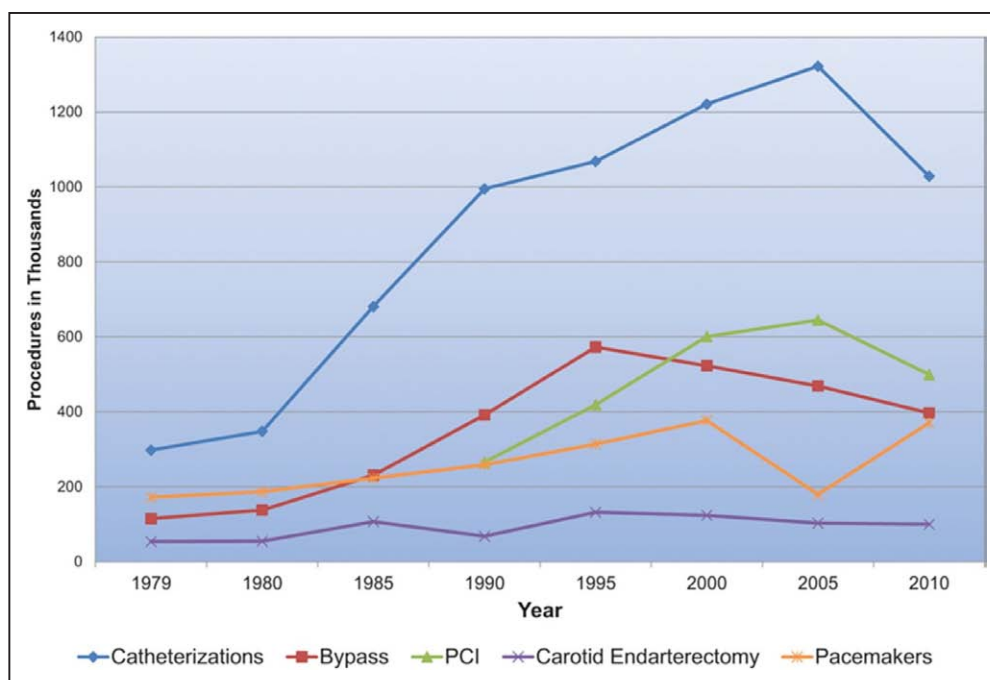
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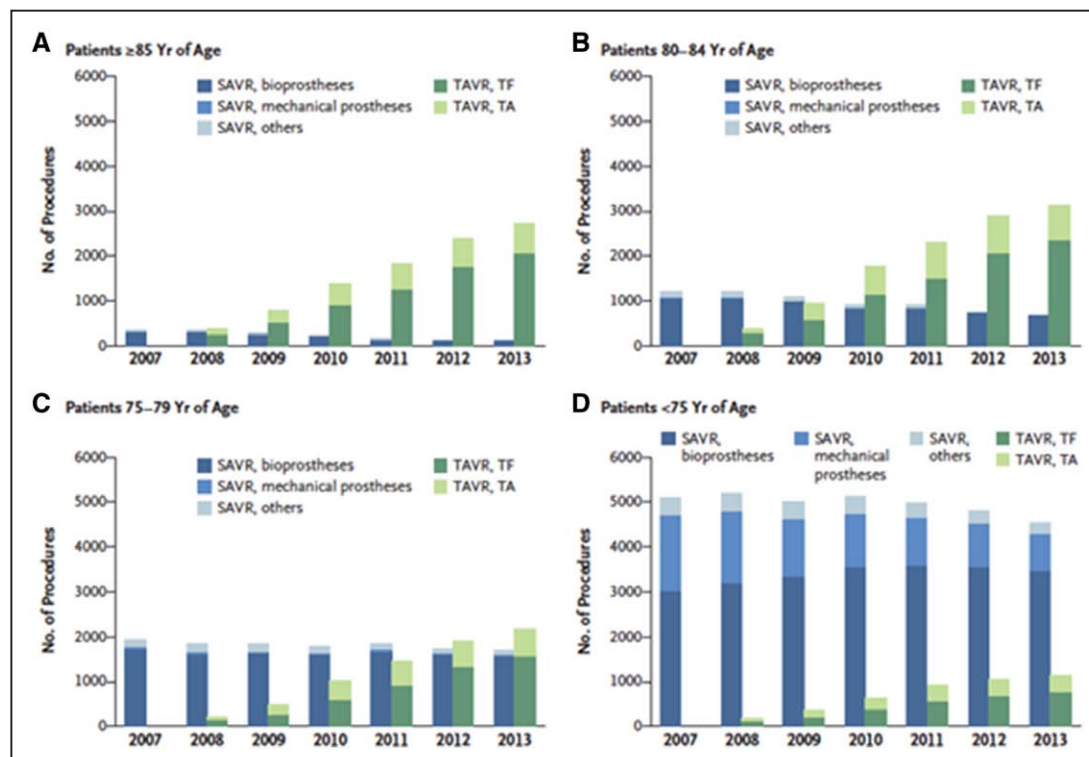
**Figure 1.** Trends in cardiovascular procedures, United States: 1979 to 2010; inpatient procedures only.<sup>1</sup> PCI indicates percutaneous coronary intervention. Original Source: National Hospital Discharge Survey, National Center for Health Statistics, and National Heart, Lung, and Blood Institute.

## Recent Advances in Interventional Cardiology and Future Directions

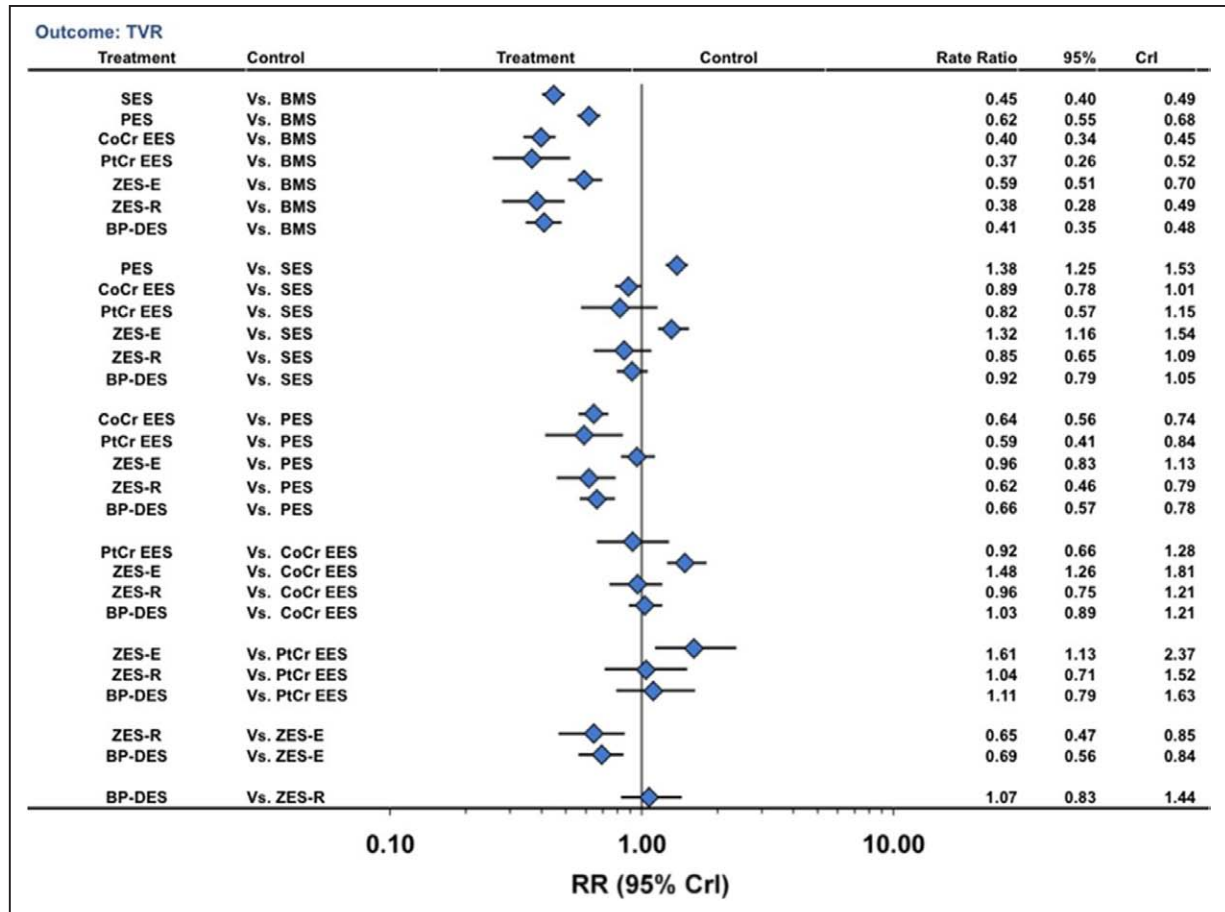
### Biodegradable Polymer Stents

Second-generation DES have been shown to provide easier delivery and are associated with lower stent thrombosis rates

and improved long-term outcomes in comparison with the first-generation DES (Table). The thinner struts and more flexible structure coupled with the use of more effective antiproliferative agents such as everolimus, biolimus, and tacrolimus in comparison with sirolimus and paclitaxel have been



**Figure 2.** Growth of TAVR in Germany 2007 to 2013.<sup>3</sup> Number of transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) procedures performed, according to type of procedure and age group, 2007 to 2013. TA indicates transapical; and TF, transfemoral.



**Figure 3.** Network comparison of various stents.<sup>16</sup> Stent type and risk of target vessel revascularization from network of all trials. BP-DES indicates biodegradable polymer stent; CoCr, cobalt chromium; CrI, credibility interval; EES, everolimus-eluting stent; PES, paclitaxel-eluting stent; PtCr, platinum chromium; RR, risk ratio; SES, sirolimus-eluting stent; ZES-E, zotarolimus-eluting stent Endeavor; and ZES-R, zotarolimus-eluting stent Resolute.

responsible. The everolimus chromium cobalt stent, in particular, has been shown to result in a lower late stent thrombosis rate in comparison with bare metal stents and is one of the most commonly used stents today.<sup>14</sup>

Early stent thrombosis is often attributable to inadequate stent apposition or incomplete expansion, whereas the mechanism of late stent thrombosis has been thought to be attributable to delayed vascular healing over the stent struts. Observational studies of the first-generation DES have suggested that this may in part be attributable to an inflammatory response that impedes healing. Pathological analysis of patients who died of late stent thrombosis and studies of thrombus material aspirated at the time of late stent thrombosis both show evidence of eosinophil infiltration, consistent with a hypersensitivity reaction.<sup>15</sup> Because late stent thrombosis occurs after the antiproliferative agent has eluded from the stent, it has been suspected that the durable polymer on the stent that is used to attach the antiproliferative drug to the struts may be responsible. This had led to the development of stents without any polymer or with a biodegradable polymer. Studies have shown that biodegradable polymers are more efficacious than bare metal stents and the first-generation DES, but not better than the durable polymer second-generation stents<sup>16</sup> (Figure 3). Of all the currently available stents, the everolimus chromium

cobalt stents has been shown to have the best combination of efficacy and lowest stent thrombosis rates in comparison with the other available stents. The SYNERGY bioabsorbable polymer stent (Boston Sci) is a unique stent that uses ultrathin stent struts with abluminal surface of the stent that directs the antiproliferative drug into the vessel wall and not into the lumen. The drug and polymer coating is absorbed by 3 months.<sup>17</sup> Recently, the polymer-free biolimus A9 stent was tested against bare metal stents in patients with a high risk of bleeding, and it was found to be superior with lower rates of target vessel revascularization and similar safety despite only 1 month of dual-antiplatelet therapy.<sup>18</sup> Further refinements in coating and stent design are likely to continue to reduce late complications.

#### Drug-Coated Balloons

Drug-coated balloons (DCBs) were introduced in 2003 to treat in-stent restenosis, and be an alternative to balloon angioplasty, as well, when stent placement was not possible or desirable. They have also been studied in lower extremity peripheral vascular disease where flexing of the vessel precludes stent placement.<sup>19</sup> Adherence of the antiproliferative drug is usually accomplished by use of an excipient that facilitates drug uptake by the vessel. The initial devices used paclitaxel as the antiproliferative agent, but recently

**Table. Types of Stents From Initial Introduction of the First-Generation Stents to Third-Generation Stents**

|                                       |   |
|---------------------------------------|---|
| First-generation drug-eluting stents  | Sirolimus-eluting stent (Cypher)<br>Paclitaxel-eluting stent (TAXUS)  |
| Second-generation drug-eluting stents | Thin strut, permanent polymer<br>Everolimus chromium cobalt stent (Xience)<br>Everolimus platinum chromium stent<br>Zotarolimus stent (Endeavor, Resolute)<br>Bioabsorbable polymer<br>BP-Biolimus stent (Biosensor, Biomatrix, Nobori)<br>BP-Everolimus stent (Synergy)<br>No polymer<br>Biolimus A9 polymer free stent (BioFreedom) |
| Third-generation drug-eluting stents  | Bioresorbable/absorbable stents<br>Absorb stent<br>Magnesium stent (Dreams)   |

sirolimus DCBs have been developed. There are currently 8 coronary devices, with all but 1 having CE mark approval in Europe, and 8 devices for peripheral use, with all but 2 approved. None are approved in the United States. The initial clinical trials showed that a paclitaxel-coated balloon was more effective than a plain balloon catheter in the treatment of bare metal stent in restenosis.<sup>20</sup> Subsequent studies comparing the paclitaxel DCB with paclitaxel-eluting stent showed that DCB was equivalent to paclitaxel-eluting stent in the treatment of DES in-stent restenosis, and both were better than balloon angioplasty.<sup>21</sup> More recent studies and a meta-analysis comparing DCB with the everolimus-eluting stent showed less favorable outcome than with everolimus-eluting stent.<sup>22</sup> Mixed results have been seen when DCBs have been compared to DES in de novo lesions with most studies showing a less favorable outcome. The findings in trials of DCBs in peripheral vascular disease have shown that DCBs are superior to balloon angioplasty alone. The role of these devices in the future will likely be for the treatment of in-stent restenosis and in unfavorable anatomy where stenting is not recommended.

### **Bioabsorbable Stents**

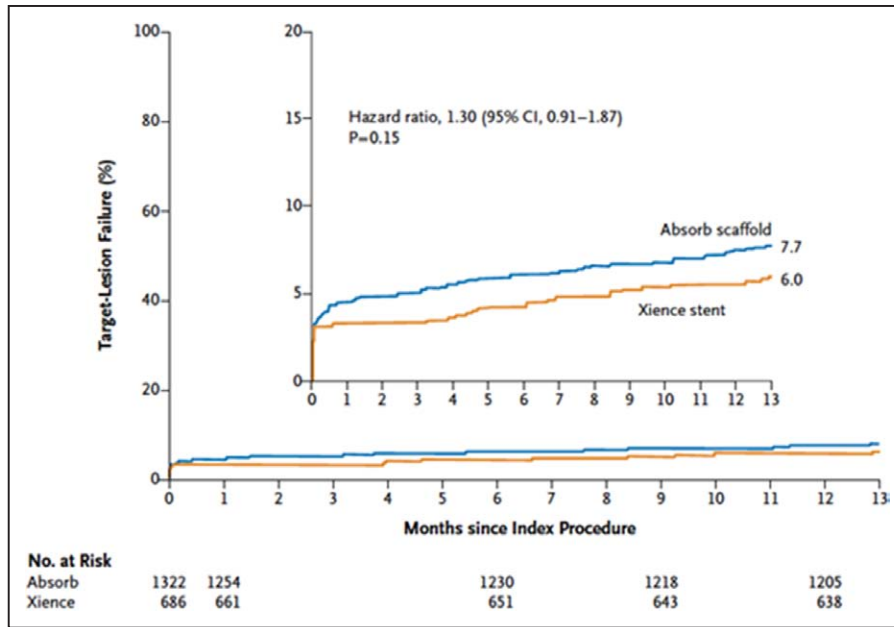
All metal stents effectively provide a scaffold that prevents elastic recoil and mechanically hold the balloon-induced arterial dissections against the vessel wall. However, once healing is complete, the presence of the stent is no longer needed and may be a disadvantage by preventing restoration of normal vessel vasomotion and positive vascular remodeling. Stents also can block access to side branches and limit the options for treatment of in-stent restenosis. In addition, all types of metal stents continue to have a low but steady rate of very late stent thrombosis (0.2%–0.4%/y) for years after implantation despite prolonged dual-antiplatelet therapy.<sup>23</sup>

Bioabsorbable stents have been introduced to overcome these limitations of metallic stents. First studied in the early 1990s, it was not until the past few years that randomized clinical trials of the everolimus bioabsorbable vascular scaffold (ABSORB, Medtronic) have been published.<sup>24</sup> The stent is composed of high-molecular-weight poly-L-lactic acid that degrades through breakdown and absorption of the struts over a 12-month period. It was introduced clinically in 2008 and has been shown to provide excellent efficacy and safety in nonrandomized trials. This stent was approved for use in Europe in 2011. The ABSORB II Randomized Controlled Trial (ABSORB II) trial randomly assigned patients to the ABSORB stent or the everolimus eluting metallic stent (XIENCE). Interim results at 1 year showed similar composite device outcomes and similar major adverse cardiac events.<sup>24</sup> Vascular reactivity studies have demonstrated that the vessel segments respond normally to vasodilators and constrictors after 12 to 24 months.<sup>25</sup> The lack of metal struts permits visualization of the artery segments with computerized tomography that allows noninvasive follow-up of patients over time.<sup>26</sup> The ABSORB III Randomized Controlled Trial (RCT; ABSORB III) trial is the largest trial to date. It randomly assigned 2008 patients to the ABSORB stent or an everolimus cobalt-chromium stent (Xience)<sup>27</sup> (Figure 4). The primary end point of target lesion failure (cardiac death, infarction, or revascularization) was not different (7.8% for ABSORB versus 6.1% for everolimus-eluting stent). Stent thrombosis was not different but numerically higher with the ABSORB stent. This study has significantly accelerated the interest in the further development of bioabsorbable stents.

The major limitation of the bioabsorbable ABSORB stent is that the struts are larger in diameter and less flexible than metal stents, which makes them less deliverable in tortuous or calcified vessels. This can lead to stent malapposition and an increase in stent thrombosis because of the inability to adequately postdilate the stent to achieve a larger size. The use in bifurcation lesions has been reported, but the outcomes have been less favorable for similar reasons. The scaffold has been primarily studied in patients with stable angina, but recently studies in acute coronary syndrome and ST-segment-elevation myocardial infarction have shown it to be effective in these clinical presentations as well.

Currently, there are 16 bioabsorbable and biodegradable stents in early clinical trials, and these are likely to continue to grow in number in the future.<sup>28</sup> Although many use poly-L-lactic acid in different formulations for the struts, the REVA stent uses desaminotyrosine polycarbonate and has a lock-and-slide mechanism, whereas the DESolve stent uses novolimus as the antiproliferative agent. A preliminary first-in-man study shows feasibility. A biodegradable magnesium stent has been studied in the Clinical Performance and Angiographic Results of Coronary Stenting (PROGRESS AMS) study. It showed an acceptable rate of major adverse cardiac events but a high target lesion revascularization of 39%. To prevent the high restenosis rate, the DREAMS stent combines the magnesium stent with paclitaxel, and initial studies show potential.<sup>29</sup> In addition, there are a number of other bioabsorbable and biodegradable stents being developed.





**Figure 4.** Target-lesion failure at 1 year. ABSORB III trial: The 1-year target vessel failure rate of the Absorb bioresorbable stent and the everolimus chromium cobalt (Xience) stent.<sup>27</sup>

It seems likely that a stent that dissolves or resorbs after it is needed would translate into a better long-term outcome, but this has not yet been shown to date. The bar is high, given the safety and effectiveness of current metallic DES. To achieve this, the bioresorbable stents need to be more flexible, with thinner struts that allow significant postdilation and degrade at an optimal time for maximal efficacy. If these changes occur and studies show an improved long-term outcome, then the bioabsorbable stents will become the primary devices for coronary use in the future.

#### *Approaches for Unfavorable Coronary Anatomy*

The most common coronary anatomic situations that pose the greatest challenges for the interventional cardiologist are stenosis involving coronary bifurcations and chronic total occlusions.

Randomized trials have clearly shown that a single-stent technique (with provisional stenting of the side branch if it occludes or restricts flow) is better than a two stent technique.<sup>30</sup> A number of dedicated bifurcation stents have been developed. The TRYTON stent is a dedicated non-drug-eluting side branch stent. Minimal struts in the proximal portion of the stent allow for a second stent to be placed into the proximal main and both branch vessels. It is disappointing that randomized trials have shown no significant difference in major adverse cardiac events and restenosis in comparison with a single-stent technique.<sup>31</sup> Other dedicated bifurcation stents are under development, but none have been shown to be better than a single- or current double-stent technique. The future of dedicated bifurcation stents remains unclear.

The most common unfavorable anatomic lesion is a chronic total occlusion. Given the low success rate, it is the most common reason for not considering PCI and referring the patient for coronary bypass surgery. The development of specialized guidewires, improved antegrade and retrograde techniques and improved patient selection, success

has increased to the 80% range in selected patients and a successful procedure is associated with a better long-term outcome.<sup>32,33</sup> However, most patients (30%–50%) are not candidates for PCI given unfavorable anatomy or they would receive incomplete revascularization because of unfavorable anatomy. Improved success in the treatment of chronic total occlusion will require further advances in technology, including real-time imaging of the occluded vessel. If this can be accomplished, then patients who are not now candidates for PCI because of unfavorable anatomy will be able to be considered for the procedure.

#### *Emergence of Intravascular Imaging and Physiology Assessment of Stenosis*

Coronary imaging and hemodynamic assessment have been shown to be critical in patient selection, assisting in the performance of the procedure and in determining the success of PCI. Numerous studies have shown that estimation of the degree of stenosis by visual estimation is often inaccurate.<sup>34</sup> The Fractional Flow Reserve Versus Angiography for Multivessel Evaluation Trial (FAME) trial showed that 65% of intermediate lesions (50%–70% stenosis) were not hemodynamically significant when assessed by fractional flow reserve.<sup>35</sup> Fractional flow reserve measures the pressure gradient across the stenosis during maximal vasodilation. FAME showed that deferring PCI in an intermediate stenosis was associated with a favorable outcome. The clinical use of fractional flow reserve is growing as a result. Intravascular imaging (intravascular ultrasound and optical coherence tomography) have both found an important place in the assessment of coronary disease and in guiding PCI as well.<sup>36</sup> Intravascular ultrasound is best at determining the morphological characteristics of the vessel wall, lumen dimensions, and plaque volume, whereas optical coherence tomography can more precisely assess the luminal surface and identify thrombus, ruptured plaques, and stent malapposition. Newer imaging techniques, like Near

Infra Red imaging, also show promise in better defining the plaque.<sup>37</sup>

The future may involve integrating imaging techniques to combine the advantages of each technique. Studies have shown that combining angiography and intravascular ultrasound or optical coherence tomography can lead to far more information than 1 modality alone.<sup>38,39</sup> These fusion images are difficult to obtain and to process, but it is likely that in the future they can be real-time tools to guide diagnosis, understand pathophysiology, and guide PCI in complex anatomy. Combining imaging and hemodynamic data will also allow much more understanding of the pathophysiology of coronary disease. Three-dimensional (3D) imaging can be used to model flow and better understand the factors responsible for plaque progression. A number of clinical and experimental studies using 3D imaging have shown that low shear stress is an important factor in the development of vulnerable plaques.<sup>40,41</sup> In the future, 3D models using 3D printing can provide more accurate models for the study of pathophysiology and assist in evaluating optimal interventional techniques for a patient.<sup>42</sup>

## Summary

For the past 30 years, the focus in coronary interventions has been to decrease the acute complications, early and late stent thrombosis, and restenosis. The future directions will be to develop bioabsorbable stents that preform to the same level as metal stents but allow normal restoration of vascular function after they are absorbed. Advances in technology will continue to increase the success of PCI in chronic total occlusions and other unfavorable anatomic lesions. The interventional approaches to the treatment of diffuse disease are another attractive horizon for future development. The integration of imaging techniques that can provide much more detail about the vessel disease is likely. This could lead to real-time 3D images that could be coupled with hemodynamic assessment and 3D printing to develop new stenting strategies. This would significantly improve patient selection and interventional treatment. The continued growth of coronary interventions seems likely given the potential advances in the future.

## Valvular Heart Disease Interventions

### Transcatheter Aortic Valve Replacement

The history of catheter-based treatment for valvular aortic stenosis began in 1983 with the performance of the first balloon valvuloplasty.<sup>43</sup> This procedure involved introducing a balloon-tipped catheter into the femoral artery and advancing it over a guidewire under fluoroscopic guidance until it straddled the aortic valve. Balloon inflation then fractured the valve and, in part, relieved obstruction. Despite initial favorable results, the procedure was abandoned as isolated therapy because valve restenosis was frequent and significant. Balloon valvuloplasty, however, remains as a potential diagnostic tool for evaluating patients with low-gradient aortic stenosis in the setting of left ventricular dysfunction and as a procedure to afford temporary relief of aortic stenosis wherein clinical circumstances require that valve replacement be delayed.

In 2002, Cribier and colleagues performed the first percutaneous aortic valve replacement.<sup>44</sup> A 57-year-old man with severe aortic stenosis, depressed left ventricular function, and extensive peripheral arterial disease had undergone balloon valvuloplasty. Because of a persisting shock state, a catheter-based approach to aortic valve replacement was attempted. With the use of a transeptal approach, a crude bioprosthesis was crimped onto a special balloon catheter that was then advanced over a guidewire through a large (24F) sheath to the aortic valve position. Following balloon inflation and deflation, confirmation of stent-valve function was confirmed by transesophageal echocardiography. The patient died 17 weeks thereafter primarily because of sepsis.

Subsequently, the equipment to perform TAVR has been refined extensively and commercialized. Currently, the Edwards SAPIEN valves and the Medtronic CoreValve are approved for clinical use in the United States. The SAPIEN valves are balloon expandable, whereas the CoreValve is self-expanding.

### Edwards SAPIEN Valve

The initial, largest, and most comprehensive investigational efforts to evaluate TAVR were performed by the Placement of Aortic Transcatheter Valve (PARTNER) investigators. PARTNER is an industry-sponsored study that included 2 pivotal randomized clinical trials, PARTNER A and PARTNER B.

PARTNER B was completed first and included patients who had severe valvular aortic stenosis and who were not suitable candidates for surgical valve replacement.<sup>45</sup> Patients were randomly assigned to continued medical therapy or TAVR with the SAPIEN valve. The primary end point was all-cause mortality. This study enrolled 358 patients at 21 medical centers, 17 in the United States. At enrollment, average aortic valve area was 0.6±0.2 cm<sup>2</sup> for both groups. Many patients had chronic obstructive pulmonary disease, atrial fibrillation, peripheral, cerebral, or coronary artery disease, or pulmonary hypertension. At baseline, these features were balanced between the 2 treatment groups. Mean age was 83 years. All but 6 of the 179 patients assigned to TAVR received the device. There was also crossover from medical therapy alone to surgery in 12 of 179 patients. A substantial number of the medical therapy-only patients received balloon valvuloplasty.

At 1 year, death from any cause was observed in 30.7% of TAVR patients and in 49.7% of patients receiving standard therapy,  $P<0.01$ . Significant differences were also noted for repeat hospitalizations and for the combined end point favoring TAVR. Subgroup analysis was also performed, and, for each variable, death was less frequent among TAVR patients. Stroke was observed more frequently among TAVR patients at 1 year, 7.8% versus 3.9%,  $P=0.18$ . In addition, the rate of 1-year death and stroke combined was significantly lower among TAVR than among patients receiving standard care, 33.0% versus 51.3%,  $P<0.001$ . Adverse events that were more common among TAVR patients included vascular complications and major bleeding. Echocardiography was performed serially in TAVR patients and demonstrated marked improvement in aortic valve gradients acutely and at 1 year.

The 2- and 5-year follow-up of PARTNER B patients has also been reported. At 2 years, all-cause mortality was 68.0% in patients receiving standard care and 43.3% among TAVR patients,  $P<0.001$ .<sup>46</sup> At 5 years, the rates of death continued to rise with TAVR 71.8% and standard therapy 93.6%,  $P<0.001$ .<sup>47</sup>

Following the completion of PARTNER B, TAVR was approved for clinical use and provided a validated, effective therapy for patients with aortic stenosis for whom there was no surgical option. Overall, TAVR demonstrated significant benefits in regard to quality and extent of life for patients who did not have the option of surgical valve replacement. However, given the high observed 5-year mortality rates, even for patients treated with TAVR, one can question offering TAVR to such high-risk patients who may die in a short time of causes other than valvular aortic stenosis.<sup>48</sup>

The PARTNER A trial was completed after PARTNER B.<sup>49</sup> PARTNER A randomly assigned 699 patients who had critical aortic stenosis and were high risk for surgery to TAVR using the SAPIEN heart valve system or surgical valve replacement. High risk was defined as having conditions associated with a risk of death following surgical valve replacement of at least 15% by 30 days. TAVR was performed by either the transfemoral or transapical approach. Again the primary end point was death at 1 year. The study hypothesis was that TAVR was not inferior to surgical valve replacement. Of the 348 patients assigned to TAVR, 244 had transfemoral placement, whereas 104 had transapical placement. A total of 351 patients were assigned to surgery separately randomly assigned to the transfemoral ( $n=248$ ) or transapical ( $n=103$ ) cohorts. At 1 year, there was no significant difference in mortality between the TAVR and surgical cohorts, 24.2% and 26.8%, respectively.

Although the rates of repeat hospitalization were also similar, the rate of combined stroke or transient ischemic attack was more common among TAVR than among surgical patients, 8.3% versus 4.3%,  $P=0.04$ . Although vascular complications were also more common with TAVR, major bleeding was observed more often among surgery patients, 25.7% versus 14.7%,  $P<0.001$ . Moderate or severe aortic regurgitation at 1 year, determined by echocardiography, was more common among TAVR than among surgery patients, 6.8% versus 1.9%,  $P<0.001$ .

There was no disadvantage of TAVR for patients with significant left ventricular dysfunction defined as a left ventricular ejection fraction  $<50\%$ .<sup>50</sup> In this subset study of PARTNER A, 1-year mortality rates and functional recovery of left ventricular function were comparable between the 2 treatment groups.

Five-year data from PARTNER A have also been reported.<sup>51</sup> Mortality rates were higher but remained similar. Unlike the 1-year findings, rates of stroke between the TAVR and surgical groups became similar. Echocardiographic moderate/severe aortic regurgitation remained more common among TAVR patients than among surgical patients, 14% versus 1%, and was also associated with an increased risk of death. The results of this trial provided support for offering TAVR as an option for selected patients who would otherwise be treated with surgery.

### Medtronic Core Valve

In 2014, Adams and colleagues<sup>52</sup> reported the results of a self-expanding aortic valve prosthesis, the Medtronic CoreValve. This study was performed in patients with severe aortic stenosis who were at increased risk of death from surgical valve replacement. In an as-treated analysis, the rate of death at 1 year among 795 randomly assigned patients was 14.2% in the TAVR group and 19.1% in the surgical group,  $P=0.04$  for superiority. Similar differences were noted by the intention-to-treat analysis. These findings were observed across a variety of clinical subsets. Major vascular complications and pacemaker implantation were significantly more common among TAVR patients whereas bleeding, acute kidney injury, and atrial fibrillation were more common among surgical patients.

Two-year follow-up data are available from the comparison of the CoreValve and surgery.<sup>53</sup> All-cause mortality was lower among TAVR patients than among surgical patients (22.2% versus 28.6%,  $P<0.05$ ). Unlike the PARTNER trial, stroke was observed less often among the TAVR than the surgical group (10.9% versus 16.6%,  $P<0.05$ ). However, moderate or severe paravalvular aortic regurgitation was more common among TAVR-treated patients (6.1% versus 0.6%,  $P<0.001$ ) as was the need for permanent pacemaker implantation (25.8% versus 12.8%,  $P<0.001$ ).

The CoreValve was also evaluated in patients for whom aortic valve replacement was not an option. In this safety and efficacy study of very high-risk patients, the results of CoreValve implantation were compared with a calculated optimal performance goal for all-cause mortality and stroke.<sup>54</sup> The primary objective was to demonstrate a combined end point of  $<43\%$  at 12 months. Iliofemoral implantation was attempted in 489 patients and accomplished in 99.4%. The rate of death or stroke at 12 months was 26.0%, significantly lower than the optimal performance goal. Interestingly, most deaths were observed beyond 30 days and rates of both death and stroke were lower than those observed in PARTNER. Moderate or severe aortic regurgitation at 30 days was uncommon, and permanent pacemakers were required in 21.6%. These data led to the approval for selective use of the CoreValve device in the United States.

### Registry Findings

Several observational analyses have reported progressive improvement in the results of TAVR over time. In a study of both transfemoral and apical approaches, 30-day mortality among 168 TAVR-treated patients declined from 14.3% to 8.3% as clinical experience increased.<sup>55</sup> As might be anticipated, late readmissions and death were not procedure related but predominantly attributable to coexisting morbidities. Early mortality was more common among patients treated by the transapical approach. A subsequent report of a combined Canadian experience confirmed the finding that late mortality was often noncardiac in origin and that normal prosthetic valve function was maintained.<sup>56</sup>

In 2012, investigators from the French Transcatheter Aortic Valve Intervention (FRANCE 2) registry reported the outcomes of 3195 patients treated with TAVR.<sup>57</sup> Mean age was 82.7 years and approximately half of the patients were women. All patients were high risk for surgical valve replacement and



both SAPIEN and CoreValve were used. Procedural success was high (96.9%), whereas survival was 9.7% at 30 days and 24.0% at 1 year. Again significant aortic insufficiency and the transapical approach were associated with higher 1-year mortality.

Recently, other observational reports have confirmed findings from initial randomized trials. The Italian OBSERVANT study noted similar 1-year mortality and stroke rates between surgical and TAVR-treated patients with aortic stenosis in a low- to intermediate-risk population.<sup>58</sup> The United Kingdom Transcatheter Aortic Valve Implantation Registry identified depressed left ventricular function, chronic obstructive pulmonary disease, and moderate/severe aortic regurgitation as factors associated with late mortality.<sup>59</sup>

Following the completion of the PARTNER randomized trial, a Nonrandomized Continued Access registry was established.<sup>60</sup> This registry included patients treated with the newer SAPIEN delivery system that had a smaller external diameter. This registry included 1023 patients treated by the transfemoral approach. Procedure variables reflected improved procedural technique, as the proportion of patients having surgical cut down and the need for postdilation were less frequent in the registry. Also, total procedure time was less. The rate of major stroke at 1 year was 3.6%. Cumulative rates of death and bleeding complications at 1 year were substantially lower in the registry than in PARTNER, demonstrating improved outcomes with operator experience and device refinements.

More data regarding the nature of death following TAVR are now available. In a multicenter study, 666 of 3726 (17.8%) patients died following TAVR at a mean follow-up of 22 months.<sup>61</sup> The mechanism of death was cardiac in 50.7%, most commonly attributed to advanced heart failure. Overall, procedure-related complications, cardiac and noncardiac, were responsible for 35.9% of deaths. Factors associated with death from advanced heart failure included chronic obstructive lung disease, atrial fibrillation, ejection fraction <40%, low mean gradient, pulmonary artery pressure >60 mm Hg, transapical approach, and post-TAVR moderate/severe aortic insufficiency. Predictors of sudden death were also evaluated and included ejection fraction <40% and new-onset left bundle-branch block. Interestingly, there was no difference in survival among patients with new left bundle-branch block according to whether a permanent pacemaker had been implanted.

There is a recognized need for new, permanent pacemaker implantation following TAVR. In PARTNERS, the incidence was 8.8%.<sup>62</sup> Preexisting right bundle-branch block, larger prosthesis to left ventricular outflow tract ratio, and smaller left ventricular end-diastolic dimension were factors associated with the need for pacemaker implantation. Permanent pacemaker implantation was associated with more frequent repeat hospitalization and renal insufficiency, perhaps reflecting the overall health of patients who required pacemaker implantation. Notable overall mortality, but not cardiac mortality, was higher among patients who had pacemakers, yet not statistically significantly so, supporting this potential explanation.

Recently, a small randomized clinical trial compared the SAPIEN and Core Valves for TAVR.<sup>63</sup> In this multicenter study, 214 patients scheduled for TAVR by the femoral approach were evaluated for device success. Device success

was defined as achieving successful vascular access, correct positioning, absence of moderate or severe aortic insufficiency, and only 1 valve implanted in the proper location. Device success was achieved more often in SAPIEN-treated patients than in CoreValve-treated patients, 95.9% versus 77.5%,  $P<0.001$ . The primary difference was that the CoreValve resulted in more significant aortic insufficiency, 18.3% versus 4.1%,  $P<0.001$ , and greater frequency of requiring >1 valve, 5.8% versus 0.8%,  $P=0.03$ . Cardiovascular mortality and bleeding and vascular complications were similar between the 2 groups. As might have been expected, permanent pacemaker implantation was more common among CoreValve patients, 37.6 versus 17.3%,  $P=0.001$ .

In comparison of the 2 Food and Drug Administration–approved TAVR devices, differences in technical features exist. The development of postimplantation moderate to severe aortic insufficiency and left bundle-branch block and the need to implant a permanent pacemaker are clearly more common following the CoreValve than the SAPIEN valve. Although some of these features are associated with mortality, differences in survival for comparable patients have not yet been detected in comparing 1 valve with the other.

Modifications to the procedural approach to TAVR have expanded since the original transfemoral procedures. Transapical is the next most common approach. Technically positioning of the valve is less challenging, although, aside from the need for an operative suite and general anesthesia, the apical approach is associated with unique complications including significant left ventricular dysfunction and apical aneurysm formation. Importantly, no differences in late mortality have been detected between the 2 approaches.<sup>64,65</sup> Additional peripheral arterial access sites have included the subclavian and carotid arteries. Finally, an inferior vena cava to abdominal aortic approach has also been described.<sup>66</sup>

### Subgroup Analyses

Several reports have attempted to determine whether there are certain subgroups of patients who may benefit more or less from TAVR than from cardiac surgery. PARTNER investigators examined a subset of high-risk patients according to preprocedural impairment of left ventricular function, a factor well known to be related to mortality.<sup>50</sup> In patients with preexisting depressed left ventricular ejection fraction, there was no difference in all-cause 1-year mortality between the 2 approaches. Other clinical features associated with reduced survival include the presence of tricuspid insufficiency, right heart failure, body mass index <20 kg/m<sup>2</sup>, and pulmonary hypertension.<sup>67–69</sup> These reports suggest that, from a technical standpoint, TAVR can be performed with reasonable short-term safety, in comparison with surgery, even in high-risk patients with advanced aortic stenosis.

The relationship between sex and outcome following TAVR has been investigated. Although no differences were detected in survival to 30 days, female sex was independently associated with improved survival at a mean of 387 days.<sup>70</sup>

Aortic annulus size and its relationship to outcome have also been assessed in patients having TAVR. In PARTNER A, patients with a small annulus who were assigned to surgery had a greater incidence of valve mismatch, effective aortic



orifice valve area  $<0.65 \text{ cm}^2/\text{m}^2$ , than patients assigned to TAVR, 37.5% versus 19.7%,  $P=0.03$ .<sup>71</sup> This difference did not persist in the subsequent continued access registry, although an increased mortality rate was noted among patients with a large annulus in comparison with others.

### Complications Following TAVR

A continued concern for TAVR has been the incidence of cerebral complications associated with the procedure. In early trials, the incidence of stroke at 1 year approached 9%. Now, reported rates of acute stroke, within 30 days, are typically between 2% and 4%.<sup>72,73</sup> Although initially stroke appeared to be more common with TAVR than surgery, recently described rates are now comparable. Several clinical factors have been associated with an increased incidence of stroke including balloon postdilation, previous or new-onset atrial fibrillation, acute kidney injury, major vascular complications, and female sex. Of these factors, new atrial fibrillation appears to be detected most often. New cerebrovascular events in this setting, whether stroke or transient ischemic attacks, are associated with an increased rate of death. Route of access, that is femoral or transapical, and types of device, CoreValve or SAPIEN, are not uniquely associated with risk for stroke. Importantly, the risk of stroke following TAVR is declining over time.

Cardiac conduction disturbances have been noted frequently after TAVR and more commonly than following surgical valve replacement.<sup>52</sup> The most common abnormality is new left bundle-branch block (LBBB) that may be observed in about one-third of patients following TAVR and is substantially more common among patients treated with CoreValve than with the SAPIEN valve.<sup>74,75</sup> LBBB may resolve before hospital discharge in about half of patients who experience it. Prosthesis low implantation depth and baseline QRS duration may be associated with an increased incidence of persistent LBBB.<sup>75,76</sup> In 1 study, the development of new LBBB was associated with mortality during follow-up,<sup>74</sup> although others have not substantiated this finding.<sup>75,76</sup>

New permanent pacemaker implantation has been required in 9% to 30% who undergo TAVR and more often among those who experience new LBBB.<sup>62,75</sup> Clinical factors associated with new pacemaker implantation include preexisting right bundle-branch block, use of CoreValve prosthesis, interventricular septum diameter, prolonged QRS duration, balloon predilation left ventricular outflow tract ratio, and left ventricular end-diastolic diameter.<sup>62</sup> Although an association between a permanent pacemaker following TAVR and the incidence of repeat hospitalizations has been reported, there are no data to suggest such a relationship between the need for permanent pacing and death.<sup>77</sup>

It is noteworthy that coronary obstruction is a rare but very serious complication of TAVR. Typically the left main coronary artery is involved and factors such as low left coronary height and sinus of Valsalva diameters are related to the likelihood of obstruction.<sup>78</sup>

### TAVR for Aortic Regurgitation

Although TAVR has been successfully applied to patients with predominant aortic stenosis, with or without mild aortic

insufficiency, the procedure has little role in patients with pure aortic regurgitation. The primary reason is because such patients often have an annulus too large or too elliptical for a TAVR prosthesis. An additional technical issue related to the lack of calcium in an insufficient valve that makes valve positioning more difficult. Furthermore, patients with aortic regurgitation requiring surgery are more often younger than patients with aortic stenosis, and the durability of TAVR in a younger population is yet to be determined. A few observational reports, however, indicate that TAVR may be feasible for selected patients with aortic insufficiency, but that the need for a second valve, valve-in-valve technique, may be higher than seen in patients with aortic stenosis because of failing to treat aortic insufficiency adequately.<sup>79,80</sup>

TAVR has been evaluated in a small sample of patients with bicuspid aortic valves.<sup>81</sup> Although the procedure was feasible, clinically significant aortic insufficiency was present in 28% of patients.

### TAVR and Coronary Artery Disease

The approach to treatment of TAVR-eligible patients with concomitant coronary artery disease is unclear. Early on, patients would have coronary disease treated by percutaneous coronary intervention before proceeding with TAVR. More recently, TAVR has been performed in the setting of significant coronary artery disease with coronary artery disease treated only if required from a clinical standpoint apart from the TAVR procedure. Questions have also been raised about the safety of PCI in the setting of severe aortic stenosis. A strategy of initial balloon valvuloplasty, followed by PCI and then TAVI, has been suggested. In any event, such cases are examples of the value of a heart team approach in evaluating treatment options.

Although clinical myocardial infarction is uncommon following TAVR, elevation of cardiac markers is not.<sup>82</sup> In a study of cardiac MRI, 18% of TAVR patients had evidence of an ischemia by late enhancement. The presence of late enhancement was not related to preexisting coronary artery disease. That finding and the pattern of distribution were suggestive of embolic debris as the explanation for the infarctions.

### Valve-in-Valve Therapy

Transcatheter valves used for native aortic valve stenosis have been used for failed bioprosthetic valves in various valve locations. In fact, the distribution of locations for TAVR for failed bioprosthetic valves differs from native valve disease, because many have been used in the mitral location and pulmonary and tricuspid sites, as well. Although both the SAPIEN and CoreValve have been used for failed aortic bioprostheses, only the SAPIEN is used widely in the mitral position. Several unique features of valve-in-valve TAVR are worth noting. The prosthesis sewing ring anchors the TAVR valve.<sup>83</sup> Bioprosthetic valves typically have radio-opaque sewing rings that serve as markers for TAVR positioning. Positioning the TAVR valve above the bioprosthesis may be required in cases of a small annulus to avoid patient-prosthesis mismatch.

An initial report from the Global Valve-in-Valve Registry described findings in 202 patients with degenerated bioprosthetic valves.<sup>84</sup> Both CoreValve and SAPIEN valves were used

and success rates were high (93.1%). The types and frequencies of TAVR complications differed from de novo aortic valve TAVT. Initial device malposition, ostial coronary obstruction, and higher gradients than normal were most common. The rate of death at 30 days was 8.4%.

### Future of Transcatheter Aortic Valve Implantation

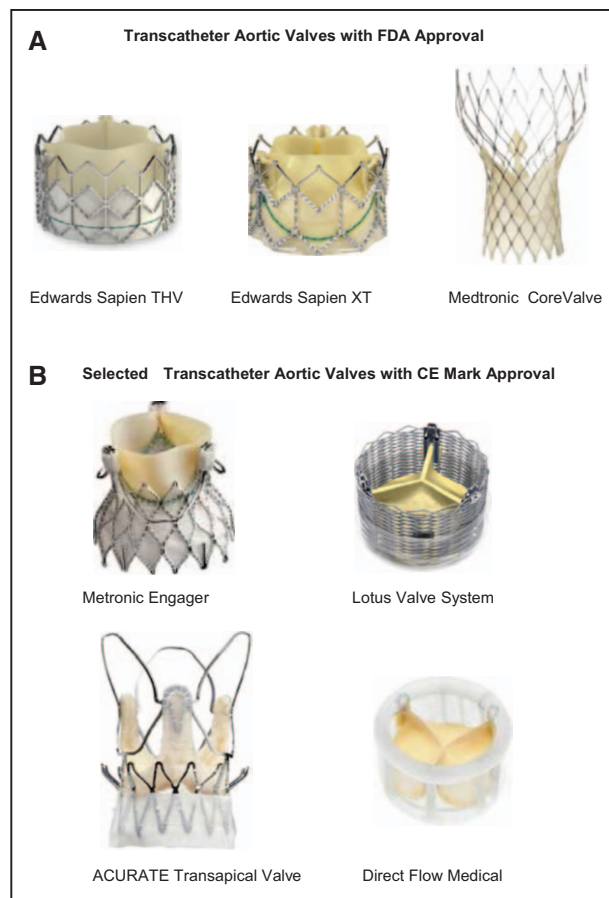
TAVR has become a care standard. Initially, the approach was limited to patients without a surgical option and the benefit of TAVR was clearly demonstrated in this very challenging subset. Subsequent trials have compared TAVR with surgery and, to this point in time, results are comparable. As experience with TAVR increases, we can expect this nonsurgical alternative to be offered to patients at lower risk for surgical valve replacement. One such example is the NOTION trial that has compared TAVR with the CoreValve to surgery for patients with severe aortic stenosis whose only other criterion for inclusion was age >70 years.<sup>85</sup> One-year findings, reported in a small group of patients, demonstrated no difference in rates of death, stroke, or myocardial infarction. Significant differences were noted in other end points, however, that could influence the selection of 1 therapy or the other. It is likely that other studies will evaluate TAVR in lower-risk groups. Given the excellent long-term results of surgical valve replacement, questions related to valve durability, excellent with mechanical valves, can only be answered by extended follow-up of TAVR-treated patients.

The application of a percutaneous approach to treatment of failed bioprosthetic valves, either insufficient or stenotic, by TAVR has major implications. To this point in time, this role for TAVR appears very safe and effective. Furthermore, it is likely that new TAVR valves and tools will be designed specifically for valve-in-valve therapy and will become the standard of care for the management of failed bioprosthetic valves.

One potential shortcoming for TAVR is that tissue valves, inherent to all TAVR devices, are known to fail over time and, accordingly, their surgical use has been limited to older patients. However, as TAVR has already been used for failed surgically implanted tissue valves, the TAVR procedure can be performed for a previously implanted TAVR valve. Given this ability, it is likely that the TAVR approach will be extended to an even younger population of patients in the future.

Although 2 types of devices have been extensively evaluated for TAVR, others are in development<sup>86</sup> (Figure 5). Some of these valves have been used for aortic insufficiency, and for aortic stenosis, as well, including the JennaValve, the ACURATE TA, the Lotus Valve System, the J-Valve, and the Edwards SAPIEN XT when coupled with the Helio docking device. Other investigational valves offer unique features such as the Colibri valve that is precrimped and the HLT valve that can be repositioned and retrieved. Other aortic valves being evaluated for the transapical approach include the Braile Biomedical Innovare and the Medtronic Engager.

Devices to reduce the incidence of cerebral emboli have been developed for catheter-based treatments for carotid disease. Given the high rates of cerebral emboli associated with surgical aortic valve replacement and percutaneous valve therapies, similar technology has been created for



**Figure 5.** A, Transcatheter aortic valves with Food and Drug Administration approval. B, Selected transcatheter aortic valves with CE mark approval.

these procedures.<sup>87</sup> One of these devices that has been evaluated in PROTAVI-C, a small randomized clinical trial, is the Embrella. This device is positioned just before the passage of the TAVR device into the ascending aorta. It is made of a nitinol frame covered with a porous polyurethane membrane and introduced from the right arm to cover the carotid and brachiocephalic arteries. In comparison with no device, however, there was no reduction in the incidence of microemboli by transcranial Doppler or silent cerebral lesions by diffusion-weighted MRI.

More encouraging results were observed in Claret Embolic Protection and TAVI Trial (CLEAN-TAVI), a randomized trial that compared patients treated with the Claret Sentinel filter with an unprotected control. In this trial, the number and volume of cerebral lesions assessed by diffusion-weighted MRI during TAVR was reduced in the Claret group.<sup>88</sup> However, in a similar but smaller subsequent trial (MATRIX-C), nonsignificant trends for improvement for fewer and smaller lesions were detected.<sup>89</sup>

A third device, the TriGuard, is introduced from the femoral site. In a randomized trial of 85 patients, this device demonstrated fewer ischemic brain lesions and neurological deficits and better cognitive function following TAVR than controls at 30 days.<sup>90</sup> To this point in time, the investigation of these devices designed to reduce the incidence or consequences of cerebral emboli associated with TAVR have been inconsistent.

Furthermore, the number of patients enrolled has been small. Although some reports are encouraging, larger studies across multiple clinical sites will be required to clarify the benefits and potential risks of these adjunctive devices.

### Percutaneous Mitral Valve Repair

In several ways, a percutaneous approach to mitral valve replacement for native mitral regurgitation represents a greater challenge than that for aortic valve stenosis. A competent mitral valve depends on many aspects of valve and left ventricular anatomy and function. As with aortic insufficiency, local anatomy changes as a consequence of the reflux of blood into the left atrium. Percutaneous approaches to this point in time for mitral regurgitation have focused on coaptation of mitral leaflets or reducing annular diameter.

Several bioprosthetic valves for the mitral position have been designed for percutaneous delivery. For the most part, evaluation has been limited to animal models or human cadaver study.<sup>91</sup>

The percutaneous procedure that has been evaluated the most for the treatment of mitral regurgitation has been the MitraClip procedure. This approach, conceptually derived from the surgical Alfieri or double-orifice technique, uses  $\geq 1$  small metallic clips to approximate the edges of mitral leaflets.<sup>92</sup> Access is achieved from a femoral vein followed by a transeptal puncture to access the left atrium. Unlike many cardiac interventional procedures, MitraClip implantation is guided more by transesophageal ultrasound than by fluoroscopy. The feasibility of approximating the mitral leaflets by a catheter-delivered clip was originally demonstrated in a porcine model using a thoracotomy approach.<sup>93</sup> EVEREST I was a safety and feasibility study of MitraClip in patients with moderate to severe mitral regurgitation.<sup>94</sup> Implantation was attempted in 27 patients and successful in 24. At 6 months, 14 of 27 patients experienced reduction of mitral regurgitation to grade 2 or less. At 30 days, there were no deaths, but 1 patient experienced a stroke and 3 patients experienced clip detachment from 1 leaflet. Cardiac surgery was performed in 7 patients.

In EVEREST II patients with significant mitral regurgitation were randomly assigned to MitraClip or cardiac surgery.<sup>95</sup> The primary efficacy end point was the combination of freedom from death, surgery for mitral valve dysfunction, and presence of grade 3 or 4 mitral regurgitation. The primary safety end point was freedom from major adverse events at 30 days. Although there was no difference in the rates of death or presence of severe mitral regurgitation at follow-up, subsequent surgery was required in 20% of MitraClip patients in comparison with 2 surgical patients. The end point of any adverse event was more common among surgical patients but was primary because of the need for postoperative mechanical ventilation and transfusion of blood. Both procedures demonstrated a reduction in left ventricular end-diastolic volume by 12 months, although the change was greater with surgery.

Data from a larger number of patients treated with MitraClip are available from ACCESS-EU, a prospective post-approval study in Europe.<sup>96</sup> Substantial improvements were observed in the rate of successful clip implantation, 99.6%. Single-leaflet attachment was uncommon (4.8%). Relief of

severe mitral regurgitation was observed in 78.9% of patients at 12 months. Functional, as opposed to degenerative, mitral regurgitation was the most common cause of valvular insufficiency. All-cause mortality at 30 days was 3.4%. This study demonstrated progressive improvement in ability to deliver the MitraClip more effectively and with greater safety.

### Future of Mitral Valve Replacement

To this point in time, most use of TAVR-type valves in the mitral or tricuspid position has been limited to patients with failed bioprosthetic devices. TAVR valves have also been placed in patients with severe mitral regurgitation in the setting of a previous annular ring surgery. These procedures are more complicated than TAVR for failed mitral tissue valves, and presently their outcomes are unclear.<sup>86</sup>

TAVR valves for failed mitral valves can be implanted by the transapical approach without the need for cardiopulmonary bypass. The apical approach, however, is more problematic than the percutaneous approach. It is likely that eventually a valve delivered by a percutaneous method will be available for the mitral position rendering edge-to-edge coaptation obsolete.

The currently enrolling COAPT trial is a randomized clinical investigation comparing the MitraClip patients with to patients who have symptomatic heart failure with moderate or severe functional mitral regurgitation who are not candidates for valve surgery. This study randomly assigns patients to either MitraClip or best medical therapy. The trial will provide important additional information about the role for MitraClip and will likely demonstrate better results of the device than previous trials as experience and procedural technique continue to be more refined. The primary effectiveness end point is hospitalization for heart failure over 24 months.

Several new approaches for the treatment of tricuspid valve insufficiency have been developed, and some have demonstrated substantial effectiveness for reducing tricuspid regurgitation in patients.<sup>86</sup> Precise safety and effectiveness profiles for these devices will be forthcoming.

Several prosthetic valves are also being developed for the treatment of mitral regurgitation by the percutaneous approach. Transcatheter mitral valve replacement is in a phase of product development with only limited clinical experience. Valves include the CardiAQ, Tiara, Medtronic TMV, Highlife TMV, Fortis, Cardiovalve, EndoValve, Gorman TMV, and MitrAssist.<sup>91</sup> To this point in time, clinical usage has been limited to isolated cases, although it is likely that results of formal clinical trials will be forthcoming soon.

### Summary

The practice of interventional cardiology has seen remarkable changes over the past decade with new, more effective stents, the introduction of bioresorbable stents, and the incredible growth of TAVR with smaller, more effective, and safer valves. The future will likely continue to bring new stents to more effectively treat coronary disease, smaller more effective transcatheter valves, and transcatheter valves to effectively treat other valves. The development of real-time 3D imaging will be necessary and likely to facilitate the use of new technology. The future breakthroughs are not clear, but, based



on the changes already seen, it is clear that they will be significant. The invasive treatment of heart disease is already the dominant method to treat patients with heart disease and will likely continue to grow further. The collaboration with cardiac surgery and a team approach to decision making for each patient will be essential for success. Change is inevitable, and it will undoubtedly lead to better and more effective invasive treatment of patients with heart disease.

## Disclosures

None.

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