Bioprosthetic valves are increasingly used in patients with aortic stenosis. Compared with mechanical valves, bioprosthetic valves are associated with a lower risk of thromboembolic events and do not require long-term anticoagulation. However, bioprosthetic valves have limited durability; the best current valves can be expected to degenerate within 10 to 20 years, resulting in stenosis or regurgitation. Surgical valve replacement is the current standard of care for these patients. However, reoperative morbidity and mortality risk is significant, not only because of the complexity of reoperation but also because many of these patients have comorbidities, particularly advanced age.

Transcatheter heart valve (THV) implantation for native aortic valve stenosis has evolved as a viable, less invasive alternative to open heart surgery in selected patients. Recently, THV implantation within failed surgically implanted bioprostheses has proven feasible. Here, we review what is known of the potential and challenges of valve-in-valve (VinV) implantation in patients with failing surgical aortic bioprostheses.

Bioprosthetic Surgical Aortic Valves

Bioprosthetic valves incorporate leaflets made from animal tissue. Xenografts are fashioned from porcine aortic valves, from more durable bovine pericardium, or rarely from porcine pericardium. Homografts are fashioned from human aortic valves. Tissue is generally preserved in glutaraldehyde, which cross-links collagen fibers, reducing antigenicity and in vivo enzymatic degradation. Various proprietary anticalcification treatments are commonly used. Surgical bioprostheses are commonly stratified into stented and stentless valves (Figure 1).

Stented Bioprostheses

Stented valves are usually constructed with bovine pericardium or whole porcine aortic valves attached to a support structure such as a stent or frame. Current bioprosthetic frames are composed of alloy or polymer materials that absorb some of the forces acting on the leaflets. The frame of the bioprosthesis is responsible for its unique fluoroscopic appearance (Figure 2). The frame is attached to a basal ring, which may be circular or scallop shaped. Typically, the basal ring is covered with a fabric sewing cuff that facilitates suturing to native tissue.

Stentless Bioprostheses

Stentless surgical valves are most often constructed from porcine or human aortic root tissue. Although stentless valves tend to have more laminar flow and lower transvalvular gradients than stented valves, increased durability has not been demonstrated. Sizing of stentless grafts is even less standardized, with the labeled size offering only a general guide for the surgeon at the time of implantation. The most common stentless valves encountered in the Global Valve-in-Valve Registry (47, 23.3%) were homografts (30%), Biocor (21%), Freedom (9%), Epic (8%), and Hancock (8%) were most common.

Bioprosthetic Failure

Freedom from structural deterioration is reportedly 70% to 90% at 10 years and 40% to 70% at 15 years. However, the significant potential for earlier failure of surgical valves is evidenced by a median time to valve degeneration in the Global Valve-in-Valve Registry of only 9 years (interquartile range, 7–13 years). Bioprosthetic valve failure may present as stenosis that occurs as a consequence of calcification or less commonly as a result of pannus, thrombosis, or infection or as regurgitation as a consequence of wear and tear, calcification,
or infection. In the Global Valve-in-Valve Registry, 42% of patients had predominant stenosis, 34% had predominant regurgitation, and 24% had both important stenosis and regurgitation.

The VinV Procedure

Clinical Experience

Experience with the aortic VinV procedure has primarily been with 2 transcatheter valves: the Edwards SAPIEN/SAPIEN XT and CoreValve (Figure 4). Initial reports of feasibility appeared in 2007, A Canadian registry (n=24) was soon followed by an Italian registry (n=25), 2 German registries (n=20, n=47), and numerous other small case series and isolated case reports documenting favorable outcomes. The Global Valve-in-Valve Registry, an industry-independent collaboration, was introduced in 2010 to collate this increasing but widely distributed experience. Currently, this self-reported registry includes >500 cases collected from >60 centers worldwide. In addition, a prospective aortic VinV nested registry incorporated into the Placement of Aortic Transcatheter Valves (PARTNER) trial has recently completed enrollment in the United States and Canada.

Preliminary data from the initial 202 high-risk patients in the Global Valve-in-Valve Registry have been published. The majority of procedures in this registry were performed with the CoreValve device (61.4%); the remainder were with the Edwards SAPIEN/SAPIEN XT device (38.6%). The mean
Society of Thoracic Surgeons–predicted risk of procedural mortality with reoperation was 11.8%, with an actual mortality with the VinV procedure of 9.4%. At 30 days, survival was 90.6%; mean transaortic gradient was 15.9±8.6 mm Hg; 95% of patients had residual aortic regurgitation grade 1 or less; and 84.1% were in New York Heart Association functional class II or less. However, there were concerns with respect to elevated (>20 mm Hg) residual transaortic gradients in some patients (28.4%), a high rate of device malposition (15%), and a high rate of coronary obstruction (3.5%).

The solid sewing ring of stented surgical bioprostheses may actually protect against aortic root rupture and against compression of the conduction system in the basal septum, resulting in atrioventricular conduction defects. To date, annular rupture has not been reported as a consequence of a VinV procedure, and the frequency of pacemaker implantation after both CoreValve and SAPIEN VinV procedures is lower than that generally reported with native valve THV implantation.

Transvalvular Gradients

Because bioprosthetic rings are relatively nondistensible, THV underexpansion can be anticipated with most VinV implants. Although transaortic mean gradients average 5 to 15 mm Hg after THV implantation in the setting of native aortic valve disease, postprocedural VinV implantation mean gradients are often higher (10–25 mm Hg). In 1 in vitro study, the mean gradient across an Edwards SAPIEN THV was 9.1±4.1 mm Hg in a 23-mm Perimount surgical valve, 19.5±5 mm Hg in a 21-mm bioprosthesis, and 46.5±9.3 mm Hg in a 19-mm bioprosthesis. Data from the global registry document that mean gradients ≥20 mm Hg were common (28.4%) after VinV procedures. Elevated gradients after SAPIEN VinV procedures were highly related to the size of the surgical valve, although this relationship was not seen with CoreValve VinV procedures. When Edwards SAPIEN and CoreValve devices were implanted in small surgical valves (internal diameter <20 mm), elevated postprocedural gradients (>20 mm Hg) were found in 59% versus 20%, respectively.

It has been suggested that this difference between Edwards SAPIEN and CoreValve hemodynamics when implanted in very small bioprosthetic surgical valves may be a consequence of the structural dissimilarity between the devices. The leaflets of the CoreValve device are located higher in the frame than are those of the Edwards SAPIEN valve. Supra-annular leaflets may allow for a larger orifice than can be achieved with annular leaflets constrained within the bioprosthetic valve ring. Importantly, low CoreValve implantation (>8 mm below the native annulus) may place these leaflets inside the bioprosthetic ring, resulting in elevated gradients. More recently, the availability of a smaller 20-mm-diameter SAPIEN XT THV has allowed implantation in smaller surgical bioprostheses with significantly improved hemodynamics than achieved with the previous smallest available SAPIEN 23-mm THV (Figure 5).

Figure 3. Dimensions of stented bioprosthetic valves. The labeled valve size generally corresponds to the outer diameter. For valve-in-valve procedures, the internal diameter is more relevant.

Figure 4. Valve-in-valve procedures. A, A 26-mm CoreValve device (Medtronic) implanted inside a 25-mm Mitroflow valve (Sorin). B, A 23-mm Edwards SAPIEN (Edwards Lifesciences) implanted inside a 23-mm Carpentier-Edwards porcine valve (Edwards Lifesciences).
Although VinV gradients are typically higher than seen with the original normally functioning bioprosthesis, residual moderate stenosis may be a very reasonable alternative in patients with severe stenosis or severe regurgitation. However, severe prosthetic-patient mismatch may not be acceptable in patients in whom reoperation is a reasonable option.

Regurgitation

Although some surgical bioprostheses have asymmetrical scalloped sewing rings, the circularity of these rings appears to facilitate THV sealing. Significant intervalvular leaks between the surgical and transcatheter valves are rare and are primarily the result of malposition (THV too high or too low) or implantation of a THV that is too small. Significant regurgitation was reported in ≈5% of patients in the global registry.\(^{14}\)

Device Malposition

Implantation of the THV that was too aortic or too ventricular was common in the very early VinV experience, ≈15% of cases in the Global Valve-in-Valve Registry experience.\(^{7,14}\) This resulted in a relatively high rate of additional maneuvers: a second THV in 8.4%, attempted THV retrieval in 8.9%, and postimplantation balloon valvuloplasty in 12.4%.\(^{14}\)

Inexperience and an incomplete understanding of the procedure were no doubt major factors. The absence of fluoroscopic factors can be troublesome with stentless valves (Figure 6A and 6B), certain stented but radiolucent valves (eg, Aspire, Vascutek; Epic, St. Jude Medical), and valves with radiolucent basal rings (eg, Mosaic, Medtronic; Figure 6C). Lack of leaflet calcification may at times contribute to difficulty with THV positioning. Bioprosthetic leaflets are rarely as densely calcified as seen with native aortic valve stenosis. With some stentless bioprostheses, calcification may be most prominent within the root itself. It is incumbent on the operator to fully understand the radiographic correlates for a particular valve before the procedure.

Coronary Obstruction

It was initially thought that coronary obstruction would be rare because the THV device would remain entirely within the bioprosthetic frame. Unfortunately, the risk of coronary ostial obstruction has proved to be more common than anticipated.\(^{35-38}\) Left coronary ostial occlusion is most common, although right coronary occlusion may rarely occur (Figure 7). The majority of recognized events have been associated with immediate hemodynamic collapse and fatality. The reported frequency of 3.5% in the global registry experience is much higher than associated with native valve procedures (0.7%).\(^{14,39}\) It is possible that this may be an underestimate when coronary obstruction is partial, bypass grafts are present, or manifestations occur late.

Rarely, coronary obstruction may result from the THV sealing cuff overlying a coronary ostia or sinotubular ridge. This might occur with high implantation of a CoreValve device.
where the sealing cuff might well extend above the bioprosthesis, but it is unlikely with the shorter SAPIEN device. 40 A more common scenario is for the displaced leaflets of the failing bioprosthetic valve to come in direct contact with the coronary ostia or with the sinotubular junction overlying the coronary ostia, a concern common to all THV designs. The risk of coronary obstruction is determined primarily by the characteristics of the specific surgical bioprosthesis, its position in relation to the coronary ostia, and the anatomy of the aortic root (Table 1). Although it is common to examine the distance from the annulus to the coronary ostia in the setting of native valve transcatheter aortic valve replacement, this dimension is less relevant in the VinV setting. The major factor in the VinV setting is the proximity of the coronary artery ostia to the bioprosthetic posts and to the anticipated final position of the bioprosthetic leaflets. Some physicians gain reassurance from measuring the distance from the bioprosthetic stent posts to the coronary ostia. However, surgeons typically implant their surgical bioprostheses in such a manner that the stent posts are not in front of the coronary ostia. Although the bioprosthetic posts may be implanted at some distance from the ostia at the time of surgery, the leaflets may extend up in a tubular fashion after VinV implantation. Perhaps more relevant is whether the stent posts or leaflets extend above the coronary ostia.

Factors that may predispose to coronary obstruction include a supra-annular bioprosthetic valve, low-lying coronaries, a narrow and low-lying sinotubular junction, bulky bioprosthetic leaflets, a narrow aortic root (shallow sinuses, prior root reconstruction), and reimplanted coronaries. Coronary obstruction may be more common with stenotic than with regurgitant bioprostheses.14

Bioprosthetic valves that are stentless (eg. Freedom, Sorin) or are internally stented (eg. Mitroflow, Sorin) require particular care because the leaflets may extend outward in a tubular fashion after VinV implantation.35 However, coronary obstruction may also occur more rarely in the setting of a supra-annular externally stented bioprosthesis.

Durability
Little is known of the long-term durability of aortic VinV implants. Preliminary data from the global registry show that gradients, competency, and functional class are maintained at a 1-year follow-up with both CoreValve and Edwards SAPIEN VinV procedures.14 Durability of both SAPIEN and CoreValve VinV implants has been reported beyond 3 years and more recently to 5 years.41–44 Although these results are encouraging, incomplete THV expansion can be expected to result in perturbation of leaflet mechanics, coaptation, flow dynamics, and leaflet/frame contact. It seems reasonable to anticipate a reduction in THV durability in the setting of VinV implants, particularly when THV underexpansion is extreme.

Stroke
Degenerated tissue leaflets are typically thickened, calcified, friable, and susceptible to tearing. Consequently, early concerns about VinV procedures included a possible high risk of stroke. Fortunately, stroke risk has been lower than anticipated, with a 2% rate of major stroke reported in the Global Valve-in-Valve Registry, comparable to current experience with native valve procedures. Stroke risk seems similar with the CoreValve and Edwards SAPIEN devices.14

Evaluation of the Potential VinV Candidate
Evaluation is largely similar to the standard evaluation of potential candidates for transcatheter valve implantation in native aortic valve stenosis. However, there are issues specific to VinV procedures (Table 2). The specific bioprosthesis

Table 1. Risk Factors for Coronary Obstruction With Valve-in-Valve Implantation

<table>
<thead>
<tr>
<th>Anatomic factors</th>
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<tbody>
<tr>
<td>Low-lying coronary ostia</td>
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<tr>
<td>Narrow sinotubular junction/low sinus height</td>
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<tr>
<td>Narrow sinuses of Valsalva</td>
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<tr>
<td>Prior root repair (eg, root graft, coronary reimplantation)</td>
</tr>
<tr>
<td>Bioprosthetic valve factors</td>
</tr>
<tr>
<td>Supra-annular position</td>
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<tr>
<td>High leaflet profile</td>
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<tr>
<td>Internal stent frame (eg, MitroFlow, Trifecta)</td>
</tr>
<tr>
<td>No stent frame (homograft, stentless valves)</td>
</tr>
<tr>
<td>Bulky leaflets</td>
</tr>
<tr>
<td>Thrombus/endocarditis</td>
</tr>
<tr>
<td>Transcatheter valve factors</td>
</tr>
<tr>
<td>Extended sealing cuff</td>
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<tr>
<td>High implantation</td>
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and its labeled size must be identified. Characteristics of the prior surgery such as supra-annular or intra-annular positioning, root reconstruction, or bypass grafts should be known; a surgical report is often helpful. The manufacturer’s reported internal diameter can generally be obtained from their Web site, although gated multislice computed tomography and transesophageal echocardiography may often suggest a smaller internal diameter. Several publications can assist in understanding the fluoroscopic appearance of various bioprosthetic valves and the implications for THV positioning.7–10,13 The risk of coronary obstruction requires specific evaluation and is detailed below.

Mode of Degeneration

Echocardiography is key to determining the mode and severity of valve failure, and transesophageal echocardiography should be relatively routine. Valve stenosis may be the consequence of leaflet degeneration but may also be the result of thrombus or endocarditis. Paravalvular regurgitation is often mistaken for valvular regurgitation. Smaller (19 and 21 mm) bioprosthetic valves commonly have much smaller orifice areas and higher gradients than generally appreciated. Elevated gradients in small valves are often mistakenly assumed to be due to valve failure. Stable but high gradients and mobile leaflets on transesophageal echocardiography not infrequently document relatively normal function of an inappropriately small valve with prosthesis-patient mismatch. It is helpful to refer to published tables of expected transvalvular gradients to support this diagnosis.45

Table 2. Practical Recommendations for Valve-in-Valve Procedures

<table>
<thead>
<tr>
<th>Before the procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Understand the failed bioprosthetic valve (model, size, structure, position, mode of failure)</td>
</tr>
<tr>
<td>Exclude thrombosis, endocarditis</td>
</tr>
<tr>
<td>Exclude paravalvular regurgitation</td>
</tr>
<tr>
<td>Assess risk factors for coronary obstruction</td>
</tr>
<tr>
<td>Review images of a procedure that is as similar as possible</td>
</tr>
<tr>
<td>Identify the fluoroscopic targets for implantation</td>
</tr>
<tr>
<td>During the procedure</td>
</tr>
<tr>
<td>Select a transcatheter heart valve that is slightly larger than the internal diameter of the bioprosthesis</td>
</tr>
<tr>
<td>Consider a transcatheter heart valve with supra-annular leaflets (eg. CoreValve) when the bioprosthesis is small</td>
</tr>
<tr>
<td>Use no, or cautious, balloon predilation when there is predominant stenosis</td>
</tr>
<tr>
<td>Avoid predilation when there is predominant regurgitation</td>
</tr>
<tr>
<td>Use transesophageal echocardiography, especially with radiolucent valves</td>
</tr>
<tr>
<td>Identify a fluoroscopic view that is perpendicular to the valve ring and allows assessment of coaxial deployment</td>
</tr>
<tr>
<td>Implant the transcatheter heart valve as high as possible to maximize orifice area</td>
</tr>
<tr>
<td>Implant the transcatheter heart valve low enough to allow fixation on the surgical ring</td>
</tr>
<tr>
<td>Consider pacing during implantation of a self expanding THV (eg. CoreValve) to optimize positioning</td>
</tr>
</tbody>
</table>

### Surgical Bioprosthetic Sizing

As discussed earlier, the description of surgical valve size is not standardized. Generally, the manufacturer’s labeled size corresponds roughly to the outer diameter of the stent frame and is intended to match the surgeon’s estimate of the aortic annulus at the time of operation. However, the internal dimension of the surgical valve is the relevant measure for VinV sizing. The difference between the label size and the manufacturer’s reported internal diameter varies dramatically, from <1 to 4 mm. The reported internal diameter may not include an allowance for leaflet attachments or cuff material and does not allow for par- nus. Manufacturer’s estimates of bioprosthetic internal diameter can be thought of as offering a theoretical maximum internal diameter. These can be obtained from manufacturer’s Web sites and various publications.8–10,12,13 These can be integrated with estimates of internal diameter from transesophageal echocardiography and gated multislice computerized tomography. Rarely, cautious balloon dilation may be considered to allow an assessment of the functional bioprosthetic internal diameter.

### Assessing the Risk of Coronary Obstruction

Coronary obstruction occurs more commonly than in the setting of native aortic valve stenosis as a result of an interplay between the aortic root, the bioprosthesis, and the transcatheter valve; all must be considered (Table 2). The type of bioprosthesis (leaflet profile and relationship to a valve stent), valve configuration (stented/stentless), position (intra-annular supra-annular), mode of failure, and leaflet bulkiness are important in the evaluation of risk. Echocardiography, fluoroscopy, aortography, and computed tomography may all help identify a bulky leaflet and proximity to the coronary ostia. An aortogram performed in a plane perpendicular to both the valve plane and the coronary ostia can be extremely helpful. For evaluation of the left main artery, an aortic root injection in a left anterior oblique/cranial view will often show the proximity of the mobile bioprosthetic leaflets to the left coronary ostium. Computed tomography imaging can show whether the bioprosthetic posts extend above or close to the coronary ostia, although evaluation of the leaflets is limited. Ultimately, aortography during balloon valvuloplasty may be extremely helpful to evaluate the risk of coronary obstruction. Ideally, the valvuloplasty balloon would approximate the diameter of the THV, and the fluoroscopic projection would allow visualization of the coronary ostium in profile.

### Procedural Considerations

#### Access

Aortic VinV procedures have been successfully performed using femoral arterial, axillary arterial, apical, and direct aortic access. Apical access has been previously advocated during Edwards SAPIEN XT VinV procedures because of the proximity of the aortic valve; however, there is no evidence to support improved outcomes with this approach.30 Generally, the least invasive approach allowing good coaxial catheter engagement and control should be favored.

#### Balloon Predilation

Predilation is usually not necessary in the setting of VinV implantation, particularly in the presence of regurgitation.
The argument against predilation is that degenerated bioprosthetic valves are often friable, with a potential risk of embolization and stroke or disintegration and acute regurgitation. The argument for predilation is that crossing a severely stenotic surgical valve can sometimes be difficult and suboptimal expansion of a self-expanding THV may sometimes require postdilation. Cautious predilation with an undersized balloon may be considered in the presence of a severely calcified and bulky stenotic valve. Rarely, predilation may be considered to assist in estimating the internal diameter of a poorly documented bioprostheses or when pannus may be present. Of note, balloon predilation was performed in 28% of cases in the Global Valve-in-Valve Registry, with no complications reported.14

THV Positioning
Optimal positioning requires a thorough understanding of the structural and fluoroscopic characteristics of the specific bioprosthetic device.13 It may be useful to study images from a prior successful VinV implant in an identical bioprosthetic valve. Transesophageal echocardiography can be extremely helpful, particularly with stentless valves, in stented valves in which the bioprosthetic basal ring is radiolucent, or when the leaflets are noncalcified or regurgitant.

As with conventional transcatheter aortic valve replacement procedures, it is helpful to determine the appropriate fluoroscopic view perpendicular to the bioprosthetic annular plane. Typically, this can be accomplished by lining up the bioprosthetic fluoroscopic markers (Figure 8), although aortography may be helpful.46 Coaxial positioning during transfemoral procedures is often best appreciated when imaging in a left anterior oblique view, which best visualizes angulation of the delivery catheter as it rounds the aortic arch.

Gradual inflation in the early phase of balloon-expandable THV (eg. SAPIEN XT) deployment may reduce jumping and allow minor adjustments as needed. Generally, the valve can be expected to pivot around the point of first contact with the bioprosthetic basal ring. Repositioning with self-expanding valves (eg, CoreValve) and adjusting the depth of implantation may not be possible after initial contact with the bioprosthetic frame. Device depth should be controlled from the onset, and rapid pacing should be considered, particularly with regurgitant valves.9,10

Coronary Obstruction
Several strategies can be considered when an increased risk of coronary obstruction is suspected. Selection of a relatively smaller THV implant will result in less displacement of the bioprosthetic leaflets, as will low implantation. A retrievable THV may allow prompt removal, at least while the delivery system is still attached. Transesophageal echocardiography may be helpful in evaluating the presence of coronary obstruction or other causes of procedural hypotension. One strategy has been to place a bailout angioplasty wire, balloon, or stent within the artery at risk, offering the potential to displace an occlusive bioprosthetic leaflet or THV away from the coronary ostia.47–49 The reliability of this approach is unclear, and the potential need for cardiopulmonary support and a surgical solution should be evaluated. Perhaps the safest strategy in patients at high risk would be to avoid a VinV procedure altogether.

Future Directions
The morbidity and mortality associated with valve reoperation seem likely to ensure that the VinV option will be increasingly appealing to both patients and physicians. The relatively
high incidence of malposition in the early VinV experience most likely reflects inexperience, and improvements should be achievable. The incidence of coronary obstruction is concerning. However, improved understanding of the factors that contribute to this complication should improve patient selection. Stroke risk appears to be relatively low but requires further study.

A major limitation of a VinV approach is that THV under-expansion in smaller surgical bioprostheses may result in high residual gradients. Currently, this may argue against VinV implants in many patients with smaller surgical valves. Development of purpose-specific VinV devices may improve positioning, sealing, gradients, and durability. It seems reasonable to anticipate that success with a VinV strategy may lead surgeons to favor larger bioprostheses more suited to VinV strategies. Even more speculative is a concept of a THV-first strategy, with the knowledge that this can be repeated once or twice until such time as surgical valve replacement is necessary. It will be some time before we can fully appreciate the durability and clinical consequences of this promising new option for patients with failing bioprosthetic valves.

Disclosures
Dr Webb is a consultant to Edwards Lifesciences Inc. Dr Dvir reports no conflicts.

References
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Transcatheter Aortic Valve Replacement for Bioprosthetic Aortic Valve Failure: The Valve-in-Valve Procedure

John G. Webb and Danny Dvir

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