Summary

- In conventional surgical aortic valve replacement (SAVR), which requires open heart surgery, the aortic valve is replaced with a prosthetic valve that is sutured into place. Up to one-third of patients are ineligible for SAVR.

- Transcatheter aortic valve replacement (TAVR) is a less invasive option, in which the prosthetic valve is passed into the heart through a catheter inserted into the left ventricle or a leg artery. However, TAVR is associated with a higher rate of paravalvular leakage.

- Sutureless aortic valve replacement (SU-AVR) employs a prosthetic valve that is held in place by the outward radial force of its circular frame and requires minimal suturing. It allows for quick valve placement and reduces the time required on a heart-lung machine.

- Initial evidence suggests that SU-AVR has comparable outcomes to SAVR, but results in higher rates of paravalvular leakage and pacemaker implantation. However, SU-AVR has lower rates of paravalvular leakage and pacemaker implantation than TAVR.

- Evidence to date also suggests potential savings due to lower procedural costs for SU-AVR relative to SAVR.

- Demand for minimally invasive valve replacement is likely to grow, and as the indications for SU-AVR expand, the number of patients who may be treated with this procedure could increase.

- It is currently unclear which patients are the best candidates for SU-AVR, or whether one valve type is superior to another in certain patients.

Background

The heart’s aortic valve opens and closes during heart contractions to allow the one-way flow of oxygenated blood from the heart into the aorta. If the aortic valve becomes narrowed (stenosed), the heart must work harder to push the blood into the aorta.1 The heart muscle thickens over time to compensate for the extra workload, but after 10 to 20 years, symptoms of heart weakness develop in some individuals. These symptoms — which include chest pain, heart palpitations, breathlessness, and dizziness or faintness — often occur during exertion. Without treatment, most patients with symptomatic aortic stenosis will develop heart failure and die within five years. Patients have a mean survival time of 4.5 years after the onset of chest pain, 2.6 years after the onset of fainting, and less than a year after the onset of left heart failure.2-4

The Technology

Surgical replacement of the aortic valve, which requires open heart surgery, is the standard treatment for severe aortic stenosis. In conventional surgical aortic valve replacement (SAVR), the breastbone is fully or partially split (sternotomy or mini-sternotomy).
and the aorta is closed off with a clamp (aortic cross-clamping). The heart is then stopped and the patient’s blood is routed through a heart-lung machine (cardiopulmonary bypass). The aortic valve is removed and the aortic annulus (the ring of heart tissue where the valve sits) is cleared of calcified deposits. A mechanical or bioprosthetic (made of animal heart tissue) valve is then sewn into place.\(^5\)\(^7\)

In sutureless aortic valve replacement (SU-AVR), the bioprosthetic valve is composed of animal heart tissue mounted on a self-expanding nitinol or stainless steel frame or stent. The valve is inserted using a special delivery device and one to four sutures are used to guide placement. Once the valve is correctly positioned, the sutures are removed, and the valve is held in place by the outward radial force of the circular frame.\(^4\)\(^6\) The sutureless valves come in various sizes to allow for correct matching with the patient’s anatomy, which is critical given the lack of sutures to anchor the valve in place.\(^8\)

Quick placement of the valve during SU-AVR reduces the aortic cross-clamp and cardiopulmonary bypass (CPB) time, potentially reducing post-operative complications.\(^9\)\(^10\) Damage to the aortic annulus and surrounding tissue is minimized during SU-AVR and the removal of aortic calcifications reduces the risk of an embolism (blockage of blood vessels by undissolved material in the bloodstream).\(^6\)\(^11\) Other purported advantages of SU-AVR include the ability to conduct other cardiac procedures, such as heart bypass surgery, at the time of valve replacement, as well as a shorter ventilation time and length of hospital and intensive care unit (ICU) stay.\(^7\)\(^10\)

<table>
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<th>Table 1: Types of Sutureless Aortic Valves</th>
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<tr>
<td><strong>Valve Name</strong></td>
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<tr>
<td>3f Enable Aortic Bioprosthesis</td>
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<tr>
<td>EDWARDS INTUITY Elite Valve System</td>
</tr>
<tr>
<td>Perceval S Aortic Heart Valve</td>
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</tbody>
</table>

FDA = US Food and Drug Administration; IDE = investigational device exemption.

### Regulatory Status

Three manufacturers currently produce sutureless aortic valves; each valve has a distinct design and deployment system, but none are commercially available in North America (Table 1). The Perceval S valve has been used in Canada through the Health Canada Special Access Programme.\(^12\) A recent conference abstract reported that 63 patients received the 3f Enable aortic valve at the McGill University Health Centre between September 2012 and October 2014 (also through the Special Access Programme).\(^13\)\(^14\) A patient registry has been established to collect evidence on the McGill centre’s experience with this technology. There is no indication that the EDWARDS INTUITY Elite valves have been used in Canada to date.

### Patient Group

Aortic stenosis, the most common heart valve disease in North America, may be caused by congenital (present at birth) aortic valve defects or, more frequently, acquired. Acquired stenosis is typically caused by age-related progressive buildup of calcium and scarring of the aortic valve.\(^11\) It affects 2% of people older than 65 years, 3% of people older than 75 years, and up to 8% of people aged 80 years or older.\(^3\) The risk factors for degenerative

**The Perceval S Aortic Heart Valve**

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Current Practice

Currently, there are no effective medical therapies for preventing the progression of aortic stenosis. Replacement of the stenosed valve with a mechanical or bioprosthetic valve is the only treatment. Although mechanical valves are strong and durable, they tend to cause blood clots. Consequently, patients with these valves need to take blood-thinning medication for the rest of their lives. Bioprosthetic valves, which are made of tissue derived from an animal or a donated human heart, do not require blood thinners. However, these valves are less durable than mechanical valves and can break down over time.

An aortic valve can be replaced by SAVR or transcatheter aortic valve replacement (TAVR). SAVR is a similar procedure to SU-AVR, except that it takes longer to complete because the prosthetic valve requires multiple sutures to hold it in place. The long-term survival following SAVR for aortic stenosis is close to that observed in the general population of similar age.

Up to one-third of patients with severe aortic stenosis are ineligible for SAVR due to age, comorbidities, or technical constraints (e.g., scarring from previous cardiac surgery or calcification of the aorta). TAVR is a less invasive procedure, in which the valve is passed into the heart through a catheter inserted into the femoral artery in the leg or between the ribs into the left ventricle. The new valve is positioned within the existing dysfunctional valve. However, this can interfere with the attachment of the new valve, and up to 18% of patients have moderate to severe paravalvular regurgitation (leakage of blood around the valve) after TAVR. In addition, the closed nature of the procedure precludes removal of any calcified deposits on the original valve. TAVR is not suitable for patients with small peripheral vessels or a heavily diseased aorta, and other cardiac procedures cannot be done at the same time.

Methods

Literature Search

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, and the Cochrane Library (2015, Issue 2). Grey literature was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/resources/grey-matters). No methodological filters were applied. The search was limited to English language documents published between January 1, 2005 and February 19, 2015. Regular alerts were established to update the search until April 30, 2015. Conference abstracts were excluded from the search results.

Study Selection Criteria

Published studies were included if they reported on clinical outcomes. Systematic reviews and comparative studies were included, as well as case series that reported on at least 100 patients or followed up patients for longer than any previously published study. When studies reported overlapping patient groups, only the paper containing the most comprehensive data set was used. Studies reported in selected reviews were excluded.

The Evidence

Numerous studies of overlapping patient groups have been published on the three sutureless valves currently available, but the degree of duplication was often not clearly reported. The Perceval S, the only truly sutureless valve that does not require guiding sutures during deployment, is the most widely studied (Table 2).

A recent CADTH Rapid Response Summary of the Perceval S valve also included secondary analyses of the 3F Enable and EDWARDS INTUITY Elite valves. The evidence suggested that SU-AVR had a high initial success rate but resulted in higher rates of paravalvular leakage than SAVR. SU-AVR had lower rates of mortality, paravalvular leakage, and pacemaker implantation than TAVR. This Bulletin summarizes the comparative and case series studies published since the CADTH Rapid Response Summary, including the largest patient cohort with the longest follow-up data available to date.

Perceval S

A retrospective, non-randomized comparative study compared SU-AVR via mini-sternotomy with SAVR. To reduce bias, the patients were paired according to several baseline characteristics (propensity matching)
associated with increased post-operative risk (including age, gender, height, body mass index, diabetes, insulin dependence, renal insufficiency, coronary artery disease, recent myocardial infarction, chronic pulmonary disease, left ventricular ejection fraction, extracardiac arteriopathy, non-elective procedures, and predictive operative mortality). Data from 171 patient pairs showed that the aortic cross-clamp and CPB times were 25 and 18 minutes shorter, respectively, in the SU-AVR group, and fewer blood transfusions were needed relative to the SAVR group. However, more patients required a permanent pacemaker after SU-AVR, compared with those in the SAVR group.29

The five-year follow-up results of 731 consecutive patients were pooled from three prospective case series studies (Pilot, Pivotal, and CAVALIER) involving 25 centres in eight European countries.9 The patients’ mean age was 78.5 years (range 62 to 92); 43% were at least 80 years old. Prior to surgery, 89% of patients were classified as New York Heart Association (NYHA) Functional Class II/III (slight to marked activity limitation). Of the 731 patients who underwent SU-AVR, 542 (74%) had median sternotomy and 189 had a less invasive surgical approach. Nearly one-third had other procedures at the time of valve replacement. Late complications (> 30 days after surgery) included reoperation for valve removal (1.5%) and major paravalvular leakage (1%). There were no cases of valve deterioration or migration during the five-year follow-up. Two years after surgery, 91% of patients had no or slight activity limitation (NYHA Class I/II).

3f Enable
A retrospective study compared outcome data from 41 patients undergoing SU-AVR with data from 42 patients who received SAVR, both via partial sternotomy.30 The two groups (mean age 76 years) were similar with respect to patient characteristics (including age, gender, body mass index, hypertension, left ventricular ejection fraction, NYHA class, predictive operative mortality, and presence of chronic illnesses such as diabetes and coronary artery disease). The average cross-clamp and CPB times were 44% and 36% shorter, respectively, in the SU-AVR group, but the length of ICU stay and rate of paravalvular leakage were comparable between the groups. Three patients (7%) who received SU-AVR required a pacemaker, whereas none were required in the SAVR patients. There were no cases of valve deterioration or prosthesis migration after SU-AVR (mean follow-up 19 months), but one patient in the SAVR group had valve deterioration (mean follow-up 32 months). The degree of improvement in NYHA class was similar for both procedures.

Long-term results were reported for 141 patients (mean age 76; standard deviation 5.7 years) from a clinical trial involving 10 European sites.31,32 The heart was accessed by sternotomy in 81% of patients and by partial sternotomy in 19%; other procedures were performed in 30% of patients at the time of SU-AVR. Before surgery, 63% of patients had marked or severe activity limitation (NYHA Class III/IV). Three to six months after SU-AVR, 90% had no or slight activity limitation (Class I/II). No valve deterioration was detected during a mean follow-up of 2.8 years (range two days to 5.1 years), although 3% of patients experienced paravalvular leakage and 5% had valve dysfunction; reoperation was required in 4% of patients.3

A single-centre case series reported outcomes up to 18 months in 120 patients (mean age 76.7 years) undergoing SU-AVR.3 Prior to surgery, 91% were NYHA Class III/IV. By approximately three months post-surgery, five patients (4%) needed valve replacement. Permanent pacemakers were required in 7% of patients due to newly developed arrhythmia.

**Adverse Effects**

The CADTH Rapid Response Summary reported that sutureless SU-AVR had similar rates of adverse events to SAVR (including reoperation for bleeding, stroke, and myocardial infarction) and TAVR (including stroke, myocardial infarction, and acute renal failure), but had a lower rate of mortality than TAVR. It was unclear whether the latter effect was due to the treatment or to baseline differences between the patient groups because of reporting and methodological deficiencies in the included studies.12 Further information on adverse events from the comparative and case series studies published since the Rapid Response Summary is summarized below.

**Perceval S**
The rates of 30-day mortality and two-year survival for SAVR and SU-AVR were similar in one non-randomized comparative study.29 However, more patients in the SU-AVR group required a pacemaker after surgery (10% versus 3%). In a series of 731 consecutive patients, the overall survival rate for SU-AVR was 92% at one year and 75% at five years.9 Early complications (≤ 30 days after surgery) included blood clots (4%), valve dysfunction (2%), heart inflammation (0.3%), and reoperation for valve removal (1%). Late complications (> 30 days after surgery) included cardiac-related death (1.4%), cardiac rhythm
disorders (6%), and blood clots (2.3%), six of which led to stroke. There were no cases of valve thrombosis (blood clots) during the five-year follow-up.

### 3f Enable

A non-randomized comparative study reported no valve-related deaths after SU-AVR (mean follow-up 19 months), in contrast to one case reported in the SAVR group (mean follow-up 32 months).30

In a single-arm study of 141 SU-AVR patients with a mean follow-up of 2.8 years, 2% developed heart inflammation, 1% experienced blood clots, and 4% had major bleeding.35 Freedom from valve-related death was 97% after one year (n = 113 patients), 95% at three years (n = 79 patients), and 94% at five years (n = 24 patients).

Another series of 120 SU-AVR patients reported no valve-related blood clots or bleeding up to 18 months after surgery.32 The 30-day mortality rate was 1.4% for the 71 patients who had stand-alone SU-AVR and 14% for the 49 patients who had another operation at the time of SU-AVR.

An alert was issued by Medtronic PLC for the Model 6000 3f Enable after 17 incidents of valve migration were reported, some of which required reoperation. The instructions for use were subsequently amended to ensure that the two guiding sutures remain in the patient after the valve is deployed.33

### Administration and Costs

The CADTH Rapid Response Summary identified one retrospective, propensity analysis of 82 matched pairs who underwent either SU-AVR or SAVR.12 The mean total procedural costs were 25% lower for SU-AVR (€13,498 versus €17,905 for SAVR), mainly due to differences in procedure time, hospital stay, and certain adverse events.34

The McGill University Health Centre Technology Assessment Unit reported that the SU-AVR and SAVR devices cost $7,750 and $4,000, respectively.14 Thus, the budget impact of replacing SAVR with SU-AVR is an extra $3,750 per patient. Using data from 853 surgical valve procedures conducted between 2008 and 2012 at the McGill University Health Centre, as well as information from published literature and the McGill experience with SU-AVR in 19 patients, the calculated procedure cost was $15,666 for SU-AVR and $17,395 for SAVR (excluding drugs, tests, and physician costs).

### Concurrent Developments

All prosthetic valves deteriorate over time.11 Attempts have been made to use tissue engineering techniques to create a replacement aortic valve that is durable, flexible, and can resist injury. A cardiac valve could be grown from stem cells seeded onto a synthetic scaffold, or the scaffold could be implanted in the patient and then seeded with stem cells or primitive circulating cells from the patient’s blood.36,37

Newer generations of TAVR devices are being developed to lower the rate of paravalvular leakage, and less invasive methods of valve delivery (e.g., through the neck) are also being investigated, which may enhance its safety profile and applicability relative to SAVR and SU-AVR.36,37

Virtual algorithms are being explored as a way to generate a three-dimensional blueprint of the patient’s valve anatomy prior to surgery, to optimize prosthesis sizing and placement.38

### Rate of Technology Diffusion

Most patients with aortic stenosis are elderly and have an elevated operative risk. In some countries, more than 20% of SAVR is performed in patients older than 80 years.19 With estimates that seniors will constitute 21% of the Canadian population by 2026,39 the demand for minimally invasive valve replacement is likely to increase.

It has been estimated that approximately 62,000 Canadians have aortic stenosis and that just less than a third of these people are not suitable for SAVR.40 As the indications for SU-AVR continue to expand, patients who were previously ineligible for surgery may be treated — particularly those who are frail and elderly; may require complex cardiac procedures; or may have special anatomic conditions, such as small aortic annuli or calcified aortic roots.32,41 SU-AVR has also been successfully used in patients requiring prosthetic valve replacement.42,43 Minimally invasive approaches, such as right anterior thoracotomy,44 continue to be explored.

Currently there are limited comparative data on SU-AVR. The diffusion rate of this surgical option will be influenced by technological developments, regulatory considerations, and the availability of further long-term comparative data on clinically relevant outcomes. If the long-term efficacy and durability of SU-AVR are not comparable to SAVR, cost-effectiveness considerations may also be a factor in the diffusion of this technology.
Implementation Issues

The use of minimal access approaches in SU-AVR increases technical difficulty, leading to longer CPB and cross-clamp times and potentially offsetting one of the main advantages over SAVR. In addition, choosing the correct valve size for each patient is an ongoing challenge that can affect the rates of cardiac conduction disorders and paravalvular leakage, migration, and distortion experienced after SU-AVR. It is currently unclear which patients are the best candidates for SU-AVR, or whether one valve type is superior to another in certain patients. Owing to the general similarity between SAVR and SU-AVR in method and patient outcomes, debate continues on whether the shorter procedure time of SU-AVR confers a benefit. No randomized controlled trial of SU-AVR has been conducted, but there are several large ongoing case series studies that will be completed within five years. The largest of these, the TRANSFORM trial, is taking place in the United States and will report five-year follow-up data on 950 patients undergoing SU-AVR. The results of these trials will affect the regulatory status of sutureless valves in North America and will help better define the durability and appropriate application of SU-AVR.

Table 2: Summary of Included Studies and Main Results

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<tr>
<th>Authors</th>
<th>Study Design; Follow-up</th>
<th>Intervention; Number of Patients</th>
<th>Main Results</th>
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<tr>
<td>CADTH 2015</td>
<td>Rapid Response Summary</td>
<td>Focuses on Perceval S, but includes reviews on all sutureless valves (3f Enable, Edwards Intuity Elite, Trilogy Aortic Valve System)</td>
<td>Pooled data for all valve types: Mean aortic cross-clamp time: 33 minutes for stand-alone SU-AVR</td>
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<td>Mean aortic CPB time: 57 minutes for stand-alone SU-AVR</td>
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<td>30-day mortality rate: 2% (range 0% to 4% in case series)</td>
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<td>1-year mortality rate: 4.9%</td>
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<td>Rate of reoperation for bleeding: 1% (range 3% to 7% in case series)</td>
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<td>Rate of paravalvular leakage: 3% (0% to 13% in case series)</td>
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<td></td>
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<td>SU-AVR versus SAVR: 693 patients</td>
<td>SU-AVR with Perceval S versus SAVR: Higher rate of perioperative bleeding for SU-AVR</td>
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<td>SU-AVR versus TAVR: 570 patients</td>
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<td>Case series studies: 550 patients</td>
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<tr>
<td>Perceval S</td>
<td>Retrospective non-randomized comparative study with mixed historical and concurrent controls (matched pairs)</td>
<td>SU-AVR with Perceval S (171 patients) SAVR with a stented valve (171 patients)</td>
<td>Shorter aortic cross-clamp and CPB time ($P &lt; 0.001$) in the SU-AVR group</td>
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<td>Mean 2.7 ± 2.1 years</td>
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<td>Higher rate of pacemaker implantation ($P &lt; 0.02$) in the SU-AVR group</td>
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<td>Fewer units of packed red blood cells required ($P &lt; 0.001$) in the SU-AVR group</td>
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<td>No difference in 30-day mortality or 2-year survival between the 2 groups</td>
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<tr>
<td>Shrestha et al. 2015⁹</td>
<td>Prospective case series 5 years</td>
<td>SU-AVR with Perceval S (731 patients)</td>
<td>Survival rates: 92% at 1 year and 75% at 5 years&lt;br&gt;30-day complication rates: thromboembolic events (4%; 29 patients); major paravalvular leakage (1.4%; 10 patients); valve removal (1.4%; 10 patients)&lt;br&gt;Late complications (&gt; 30 days): thromboembolic events (2%; 17 patients); major paravalvular leakage (1%; 7 patients); valve removal (1.5%; 11 patients); cardiac rhythm disorder (6%; 44 patients)</td>
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<td>3f Enable</td>
<td>Retrospective non-randomized comparative study with historical controls Mean 31.7 months for SAVR; mean 19.1 months for SU-AVR</td>
<td>SU-AVR with 3f Enable (41 patients)&lt;br&gt;SAVR with conventional valve (42 patients)</td>
<td>Shorter aortic cross-clamp and CPB time ($P &lt; 0.0001$) in SU-AVR group&lt;br&gt;No differences in mean ICU stay or rates of pacemaker implantation, reoperation due to bleeding, valve deterioration, and paravalvular leakage</td>
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<tr>
<td>Englberger et al. 2014³²</td>
<td>Prospective case series Mean 2.7 years (range 2 days to 5.1 years)</td>
<td>SU-AVR with 3f Enable (141 patients)</td>
<td>Freedom from valve-related mortality: 97% (n = 113) at 1 year and 94% (n = 24) at 5 years&lt;br&gt;Reoperation rate: 4.2% (6 patients)&lt;br&gt;No valve deterioration occurred</td>
</tr>
<tr>
<td>Eichstaedt et al. 2014⁸</td>
<td>Retrospective case series Mean 313 days</td>
<td>SU-AVR with 3f Enable (120 patients)</td>
<td>30-day mortality rate: 7% (8 patients) overall and 1% (1 patient) for stand-alone SU-AVR&lt;br&gt;Reoperation rate: 4.2% (5 patients)&lt;br&gt;Permanent pacemaker required: 7% (8 patients)&lt;br&gt;No thromboembolic events or hemorrhages occurred</td>
</tr>
</tbody>
</table>

CPB = cardiopulmonary bypass; ICU = intensive care unit; SAVR = conventional surgical aortic valve replacement; SU-AVR = sutureless aortic valve replacement; TAVR = transcatheter aortic valve replacement

⁎ Development of the Trilogy valve appears to have been discontinued.

References


