Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: Perceval S Sutureless Valve for Aortic Valve Replacement: A Review of the Clinical Effectiveness, Safety, and Cost-Effectiveness

DATE: 29 January 2015

CONTEXT AND POLICY ISSUES

Degenerative aortic stenosis, with stiffening and calcification of the aortic valve leaflets and narrowing of the aperture, affects an estimated 3% of people aged 75 years and over.[1] Prior to the development of methods for replacing a stenotic aortic valve with a prosthesis, the mean survival once symptoms of angina or insufficient cardiac output developed was two years.[2] Valve replacement substantially improves survival; however approximately one third of patients are considered not to be suitable candidates for standard surgical approaches because of anatomic abnormalities, past thoracic surgery or radiation, comorbidities, or overall frailty.[1] For one recent trial of aortic valve replacement via catheter, inoperable patients were those with greater than 50% risk of death or disability from surgery; in this severe group, one-year mortality with standard management was 50%.[3] Authors of a previous CADTH review estimated the number of people with aortic stenosis in the Canadian population to be 62,060,[1] with 20,000 considered not suitable candidates for surgery.

Transcatheter aortic valve implantation (TAVI) was initially developed as a palliative measure for patients considered inoperable.[3,4] It involves implanting a replacement bioprosthetic valve within the native valve via a catheter threaded through the arterial vasculature.[3] The native valve is dilated and left in position. TAVI has been extremely successful and widely adopted, and is now being offered to patients who might otherwise be considered for surgical valve replacement.[3,4] However, not all patients are candidates for TAVI due to abnormalities of the aortic valve or root, and TAVI carries with it an increased risk of stroke.[5] A substantial proportion of patients who are potential candidates for valve replacement also require additional procedures (eg, for other valve disease, myocardial revascularization, or repair of the aortic root). TAVI may be paired with myocardial revascularization by percutaneous coronary intervention, but other procedures, such as coronary artery bypass grafting or valve repair, require surgical intervention.

Sutureless aortic valve replacement, where the diseased valve is surgically excised but the implanted valve is mounted on a TAVI-valve-like stent and therefore does not need to be

sutured in place, is being explored as an approach to reducing the impact of surgery.[6] By removing the need for suturing, the surgery can be completed through a smaller incision, avoiding sternotomy and potentially shortening the overall duration of surgery and the length of time that the patient needs to be on artificial ventilation and on cardiopulmonary bypass. Surgical valve implantation also allows other surgical interventions to be performed as part of the same procedure, avoiding the need for successive operations.

The Perceval S sutureless valve consists of a bioprosthetic valve mounted on a self-expanding nitinol stent. It received European regulatory approval in January 2013,[7] and is currently undergoing US registration trials.[8] In Canada it is available on a named-patient basis through the Health Canada special access program. This report reviews the evidence for the effectiveness, safety and cost effectiveness for the Perceval S sutureless valve for patients with aortic stenosis.

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of the Perceval S sutureless valve for patients requiring aortic valve replacement?
2. What is the cost-effectiveness of the Perceval S sutureless valve for patients requiring aortic valve replacement?

KEY FINDINGS

Based on preliminary results from single-arm studies and small non-randomized comparisons with alternative methods for valve replacement, sutureless valve implantation has a high initial success rate, with low rates of in-hospital death, strokes, endocarditis, and renal failure. Rates of paravalvular regurgitation and heart arrhythmias leading to pacemaker implantation are raised compared to standard surgical valve implantation. However, long-term evidence on valve stability, durability, and safety are lacking, and criteria for selecting the best procedure for patients who are also potential candidates for conventional surgery or TAVI.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 12), University of York Centre for Reviews and Dissemination (CRD) databases, and Canadian and major international health technology assessment agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and January 16, 2015.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Patients currently receiving trans-catheter aortic valve implantation (TAVI) Patients at high risk for aortic valve replacement
Intervention	Perceval S Sutureless Valve
Comparator	Any comparator or none
Outcomes	Clinical benefit (reduced risk of stroke, ease of implantation, reduced pump time and cross-clamp time, reduced number of patients waiting for TAVI, improved hemodynamic performance) Clinical harm (complication rates, post-operative migration) Cost effectiveness
Study Designs	HTAs, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were in languages other than English, they were duplicate publications, or were published prior to 2009. Studies that had been previously described in systematic reviews were not included separately.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using AMSTAR.[9] Case series were appraised using the checklist by Moga, 2012,[10] and non-randomized studies using propensity-matching were appraised using the criteria described by Austin, 2008.[11]

Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Appendix 1 includes the PRISMA flowchart of the study selection. Study characteristics, critical appraisal, and study findings are summarized in Appendices 2, 3, and 4, respectively. Additional studies of interest are included in Appendix 5.

Quantity of Research Available

A total of 414 citations were identified in the literature search. Following screening of titles and abstracts, 377 citations were excluded and 37 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 27 publications were excluded for various reasons, while 14 publications met the inclusion criteria and were included in this report (Appendix 1).

A non-systematic search identified abstracts presented at the European Association for Cardio-Thoracic Surgery conference, October 2014, which extended the available information on the European pivotal trials. These are summarized in Appendix 5.

Summary of Study Characteristics

Study Design

One systematic review with meta-analysis,[12] two English language HTAs,[13,14] and a single rapid review[15] were identified on the topic of sutureless aortic valve replacement, each of which reviewed *all* commercially available types of sutureless valves, up to three (Appendix 2 Table 2A). Perceval S was the most widely used.

No RCTs compared implantation of Perceval S sutureless bioprosthesis with alternative management. Complete results for three prospective, single arm, multicentre European registration trials (Perceval Pilot, Perceval Pivotal, and Perceval Cavalier) have been reported only in abstract (Appendix 5), and as a subgroup analysis of 243 patients who underwent concomitant procedures.[16]

Twenty additional full-text articles describe results of individual sites and groups of sites from these trials. These articles had discernable but often poorly-documented overlap with each other and with the registration studies. The more recently published, larger series also include additional patients who received implants after European regulatory approval as part of routine practice. They are therefore treated here as case series, with the most recent and largest summarized. Articles that were included in a systematic review, or that represented a previous publication or a subset of a series included in a systematic review, were excluded. Following these exclusions, and with the addition of reports of post-marketing and North American studies, four reports of case series remained concerning Perceval S in aortic stenosis: Mazine, 2015,[17] König, 2014,[18] Michelena, 2014,[19] and Rubino, 2014.[20]

The case series also contributed patients to five non-randomized studies that reported comparisons of sutureless aortic valve replacement (SU-AVR) with the Perceval S valve with sutured surgical valve replacement (AVR, 4 studies)[21-24] and/or TAVI (3 studies).[21,24,25] In all but one,[21] the cohort was created by propensity-score matching (Appendix 2 Table 2C).

Relationship between case series and comparative studies

The case series by Rubino, 2014,[20] reported in-hospital and short term follow-up on 314 patients at five European centres, two of which participated in Perceval registration studies (Klinikum Nürnberg, Nürnberg, Germany; University Hospital Leuven, Leuven, Belgium) and three did not. The same authors, with the addition of a sixth centre, compared the in-hospital results for SU-AVR versus TAVI in a propensity matched analysis for 374 patients(Biancari, 2015).[25] In collaboration with a second Perceval Cavalier site in Münster, Germany, Klinikum Nurnberg authors conducted two propensity-matched comparisons of Perceval S versus surgical valve implantation(Pollari, 2014),[23] and Perceval S versus TAVI (Santarpino, 2014)[26]; the latter study was included in the Phan, 2014 systematic review and meta-analysis, and therefore excluded.[12]

Micelli, 2014,[27] published longer term follow-up for 281 patients treated in Massa, Italy and Klinikum Nürnberg, Germany. The latter also contributed to the series described by Rubino,

2014, as described above; the extent of duplication is unknown. The patients from Massa, Italy, were also included in a two-center propensity matched comparison of sutureless versus sutured valve implantation (Gilmanov, 2014),[22] at this and another site in Italy, and an eight-centre retrospective comparison with propensity matching of Perceval S sutureless valve versus surgical valve replacement versus TA-TAVI (D'Onofrio, 2013).[24]

Country of Origin

The published evidence comes almost exclusively from centres within Europe (Germany, Italy, Sweden, Belgium, Finland), as the device has yet not been licensed in other jurisdictions, with the exception of one Canadian multicentre study of 214 patients[17] who received Perceval S under a special access program and a preliminary report of 8 patients from a US registration trial.[19]

Patient Population

The first two Perceval S registration studies selectively recruited patients aged 75 years and over; and the third recruited patients aged 65 years and over.[6] This selection was reflected in the mean age of the patients in the pooled studies (Appendix 5), 78 years, in the meta-analysis, 77.3 years,[12] and the later case series, the lowest of which was 77.9 years.[20] The majority of patients were female, with a weighted mean of 61% in the meta-analysis,[12] and proportions ranging from 54%[17] to 86%[18] in the case series. According to the EuroSCORE, surgical risk (perioperative death or major disability) in the meta-analysis was 11.7%, and in the case series ranged from 7.2%,[17] to 12.1%.[16] Proportions of comorbidities, diabetes, renal and respiratory diseases, and previous cardiovascular procedures were high, as expected for an elderly population.

Interventions and Comparators

With the exception of one study, all patients received a Perceval S sutureless bioprosthesis; the exception was a propensity-matched analysis which a minority of patients (6%) received another sutureless valve.[22] Surgical approaches varied: in the meta-analysis, 20.1% patients underwent a ministernotomy, 16.8% a minithoracotomy, and 64% conventional full sternotomy, while in the case series the corresponding ranges were 6%[16] to 41.7%,[20] 0[16] to 11%,[17] and 55%[20] to 94%.[16] A substantial proportion underwent concomitant procedures; in the meta-analysis, 26.8% had coronary artery bypass grafting (CABG);[12] while in the case series the proportion undergoing CABG ranged from 25%[19] to 75%.[16] The latter study was a subgroup in which all patients underwent a concomitant procedure.

Two retrospective non-randomized studies compared surgical aortic valve replacement with the Perceval S valve with conventional sutured aortic valve replacement and with TAVI,[21,24] one with TAVI by all access routes,[21] and one with TAVI only by the transapical access route.[24] Two studies compared SU-AVR with surgery alone,[22,23] and one study compared SU-AVR with TAVI alone.[25]

Outcomes

Single arm studies reported mortality associated with the procedure in the form of peri-operative, in-hospital, and 30-day mortality, and procedure-relevant adverse events of reintervention for valve displacement, paravalvular regurgitation or leak (PVR), or bleeding,

need for renal replacement therapy, new arrhythmias, particularly those requiring pacemaker implantation, stroke/TIA, myocardial infarction, and endocarditis. Operative parameters included operating time, aortic cross-clamping (ACC) time and time on cardiopulmonary bypass (CPB). In follow-up, studies reported overall survival, and rates of cardiac death or valve related mortality, reoperation, stroke, or endocarditis, or alternatively, freedom from these endpoints.

Studies that involved a comparison reported proportions for in-hospital/30 day mortality, reoperation for bleeding, stroke, MI, atrioventricular (AV) block and/or pacemaker implantation, and acute renal failure or renal replacement therapy. Three studies[21-23] compared mortality in longer term follow-up.

Cost effectiveness

No cost-effectiveness studies were identified. One study[23] compared calculated costs for SU-AVR with TAVI for their propensity-matched cohort.

Summary of Critical Appraisal

The evidence summaries consisted of a well-conducted systematic review, two rapid reviews in which various methodological compromises were made, and an HTA whose objective and methods were not described (Appendix 3, Table 3A). Two of the studies involved a comprehensive search, only one clearly stated that there was duplicate data selection. Three of the four provided a table of characteristics. Only one formally assessed and tabulated the scientific quality of the individual studies but all mentioned limitations of the evidence in formulating conclusions. The best-quality systematic review was also the most recent,[12] and has been given the most weight in this review.

In general, the case series were well-conducted and described (Appendix 3 Table 3B). Most were retrospective analyses of prospectively recruited patients, and all were conducted at multiple centres, with appropriate inclusion/exclusion criteria, description of interventions and surgical cointerventions (but not antithrombotic therapy). Length of follow-up was given, although loss to follow-up was not clearly described in some of the series. The outcome measures were standard for valve interventions.

In the propensity-matched comparisons, the methods for matching were described in only two of the four studies (Appendix 3 Table 3C), and only one indicated whether matching was with or without replacement. All reports included a table of baseline characteristics between the two matched groups. Standard statistical tests were used to detect for difference between individual characteristics, which is not recommended.[11] Only one study used paired statistical tests to assess difference between all outcomes, while one used them for continuous but not categorical outcomes. The incomplete description of the method of matching and the lack of appropriate testing for overall balance means that we cannot be certain whether observed differences are due to baseline differences rather than treatment effects.

Summary of Findings

1. What is the clinical effectiveness and safety of the Perceval S sutureless valve for patients requiring aortic valve replacement?

Single arm studies

Intraoperative ACC and CPB. For all patients in the meta-analysis of sutureless valve studies, the weighted mean ACC was 45 min,[12] with a range from 22 to 70 minutes in individual studies. For isolated SU-AVR, mean ACC in the meta-analysis was 33 min, and in the later case series, 37.3[18] to 40.5[17] min. For combined procedures in the case series, the mean ACC duration was 50.7[16] to 69.6[17] minutes.

For all patients in the meta-analysis of sutureless valve studies, the weighted mean CPB was 73 min,[12] with a range from 46 to 111 min for individual studies. For isolated SU-AVR, mean CPB in the meta-analysis was 57 min, and in the later case series 56.6[17] to 66 min.[20] For combined procedures in the case series, the mean CPB duration was 74.8[18] to 88.7 min.[17]

Perioperative safety. Perioperative (to 30 days) or in-hospital mortality in the meta-analysis of sutureless valve studies was 2.1%[12] and in the case series ranged from none[18,19] to 4%.[17] Where isolated AVR was reported separately from AVR with concomitant procedures, mortality was higher in the latter.[20]

Reoperation for bleeding was needed in 1.2%[12] of patients in the meta-analysis and in 2.5%[20] to 7.1%[18] of patients in the case series. One series reported that valve explantation or revision was not required,[17] while in two others it was required in 0.5%[28] to 2.1%[16] of patients. Severe PVR was the most common reason for explantation. PVR of mild or greater degree was reported in 3.0%[12] of patients in the meta-analysis, and none[19] to 12.7%[20] patients in the case series, although studies were not consistent as to when and how PVR was measured.

Perioperative stroke was reported in 1.5%[12] of patients in the meta-analysis and in none[19] to 7.1%[18] (representing one patient in a small study) of patients in the case series. Myocardial infarction occurred in 0[20] to 0.8%[16] patients. Endocarditis was reported for 2.2% of patients in the meta-analysis,[12] was not reported in two case series,[17,20] and in the other one occurred in 0.4%[16] of patients. In the meta-analysis, the rate of new pacemaker implantation was 5.6%,[12] while in the case series, implantation ranged from 5.9%[16] to 37.5%.[19] The range across the studies may reflect regional variation in pacemaker criteria.

In the meta-analysis, the rate of renal failure was 1.2%,[12] while in the case series that reported it rates of renal failure or need for renal replacement therapy were 1.6%[20] and 2%.[17]

Longer-term survival. In the meta-analysis of all sutureless valves, pooled one-year mortality over 11 studies was 4.9%.[12] Later studies of Perceval S valve reported post-discharge follow-up of a median 0.9 years[20] and a mean 444 days (1.2 years),[16] the latter in a subset of patients from the pooled registration trials who had undergone concomitant procedures. Kaplan-Meier estimates for survival were, at 1 year 90.5%,[20] and at 2 years 86.4%[16] and 87%.[20] One-year valve-related survival was estimated at 99.0%.[20]

Other longer-term outcomes. Freedom from reoperation at one year was 98.3%.[20] One year freedom from stroke was 98.1%,[20] and one year freedom from endocarditis, 99.2%.[20]

Hemodynamic outcomes. In the meta-analysis of all sutureless valves, the mean aortic valve gradient (AVG) at discharge was 11.13 mmHg,[12] while case series reported mean AVGs of 13.3[17] and 13 mmHg[18] measured prior to discharge. Mean peak AVG at discharge was 19.6 mmHg for the meta-analysis,[12] and at pre-discharge was 24.5[17] and 24.8 mmHg in the case

series. Mean AVA at discharge was 1.77 cm^2 in the meta-analysis,[12] and 1.56 cm^2 in one case series.[16]

At one year follow-up, mean AVG in the meta-analysis was 9.6 mmHg,[12] and in one case series mean AVG was 8.9 mmHg.[16] Mean peak AVG in the meta-analysis was 17.3 mmHg, [12] and in the case series, 17.5 mmHg.[16] Mean AVA was 1.73 cm^2 in the meta-analysis,[12] and in the case series 1.6 cm^2.[16]

Comparative studies: Sutureless aortic valve implantation versus surgical aortic valve implantation

For two of the studies that compared overall survival for SU-AVR versus surgical AVR in follow-up, the survival estimates were similar, 96% versus 95% at 10 months[22] and 97.6% versus 96.2% at 13 months.[23] For the third study the two-year survival was 89.5% versus 83.8%, which was not statistically significant.[21]

Comparisons of periprocedural adverse events are summarized in Table 1. In-hospital mortality tended to be slightly higher for surgical AVR. There was no consistent trend in reoperation for bleeding, stroke, or MI, but rates of PVR were substantially higher with Perceval S SU-AVR than with sutured AVR.

TABLE 1 Proportion of patients with adverse events in comparative non-randomized studies, Perceval S versus sutured aortic valve

Endpoint	Muneretto, 2015[21]		Gilmanov, 2014[22]		Pollari, 2014[23]		D'Onofrio, 2013[24]	
	SU-AVR N=53	AVR N=55	SU-AVR N=133	AVR N=133	SU-AVR N=88	AVR N=88	SU-AVR N=31	AVR N=112
In-hospital/30 day mortality, %	0	0	0.8	1.5	2.4	3.7	0	1.8
Reexploration for bleeding, %	7.5	10.5	6.8	3.8	2.4	6.1	NR	NR
PVR, %	1.9	0	NR	NR	NR	NR	19.4	1.0
Stroke, %	0	1.8	NR	NR	3.7	7.3	0	0
MI, %	0	0	1.5	0	NR	NR	0	0.9
AV block/ pacemaker, %	2	1.8	NR	NR	6.1	8.5	3.2	0.9
ARF/renal replacement, %	7.5	12.7	NR	NR	NR	NR	3.2	0

ARF = acute renal failure; AV = atrioventricular; AVR = aortic valve replacement; MI = myocardial infarction; NR = not reported; PVR = paravalvular regurgitation; SU-AVR = sutureless aortic valve replacement.

Comparative studies: Sutureless aortic valve implantation versus TAVI

In-hospital mortality tended to be numerically higher in TAVI than for SU-AVR, which may represent a difference in baseline risk, since patients at high operative risk tend to be referred for TAVI.[25] Mortality ranged from 0[21,24,26] to 1.4%[25] in SU-AVR patients, and from 1.8%[21] to 6.9%[25] for TAVI. TAVI was associated with lower rates of periprocedural bleeding.

Comparisons of periprocedural adverse events are summarized in Table 2. There was no consistent trend across studies in rates of stroke, MI, or acute renal failure/renal replacement therapy. Rates of PVR were substantially higher in all studies for SU-AVR than for AVR, and rates of pacemaker implantation tended to be higher.

TABLE 2 Proportion of patients with adverse events in comparative non-randomized studies, Perceval S versus TAVI

Endpoint	Biancari, 2015[25]		Muneretto, 2015[21]		D'Onofrio, 2013[24]	
	SU-AVR N=144	TAVI N=144	SU-AVR N=53	TAVI N=55	SU-AVR N=31	TAVI N=143
In-hospital/30 day mortality, %	1.4	6.9	0	1.8	0	7
Reoperation for bleeding, %	4.2	0	7.5	0	NR	NR
PVR, %	2.8	53.5	1.9	9	19.4	28.7
Stroke, %	0	2.1	0	0	0	2.8
MI, %	0	0	0	1.8	0	3.5
AV block/ pacemaker, %	11.2	15.4	2	25.5	3.2	4.9
ARF/renal replacement, %	2.1	0	7.5	9.0	3.2	4.9

ARF = acute renal failure; AV = atrioventricular; AVR = aortic valve replacement; MI = myocardial infarction; NR= not reported; PVR = paravalvular regurgitation; SU-AVR = sutureless aortic valve replacement.

2. What is the cost-effectiveness of the Perceval S sutureless valve for patients requiring aortic valve replacement?

No cost-effectiveness studies were retrieved.

One propensity-matched study from Germany included a cost comparison between SU-AVR and sutured AVR.[23] Resource-use data was retrospectively collected from patient records and associated costs from the hospitals' finance department. Costs were aggregated into three categories: operating room, including anaesthesia; hospital stay, including ICU; and diagnostic imaging.

For the 82 matched pairs in the propensity analysis, the total procedural costs were €13,498 versus €17,905, for SU-AVR versus sutured AVR, respectively. All categories of cost were lower for SU-AVR: operating room, €5527 versus €5879, hospital stay, €6584 versus €9873, and diagnostic imaging, €1387 versus €2153. These costs are driven by the difference in procedural time, length of stay in ICU and hospital, and certain adverse events.

Limitations

Intervention in the form of replacement of the diseased valve is established therapy in symptomatic aortic stenosis. For surgical aortic valve replacement with the Perceval S sutureless aortic valve prosthesis the primary limitations of the evidence to date are the incomplete publication of the European multicentre registration trials, the lack of long-term follow-up, and the lack of randomized controlled evidence for comparison of sutureless aortic valve replacement with alternative methods, principally surgical replacement with a sutured valve, and TAVI.

The available published evidence consists of a collection of frequently overlapping reports from single centres and groups of centres, primarily in Europe. The outcomes reported by these studies are consistent with those reported in abstracts for the pooled European prospective registration studies, and the full publications for these studies should appear within the year. Ongoing follow-up is planned – both the Perceval Pivotal and the Perceval Cavalier study will follow patients to 5 years – and will establish the durability of the stentless bioprostheses.

In clinical practice, patients' options for aortic valve replacement are assessed individually, optimally by multidisciplinary teams. The available comparative data comes in the form of non-randomized comparisons between SU-AVR and AVR or TAVI with propensity matching, which frequently involves patients operated on at different times and in different centres. These studies use a subset of the available data on SU-AVR, and their results are dependent on the quality of the match, which the results of quality appraisal suggest is unclear. Furthermore, the relatively short experience with sutureless AVR means that criteria for optimal patient selection and sizing and selection of implants according to aortic root anatomy are better established for AVR and TAVI than for SU-AVR, thereby potentially leading to poorer results. Conversely, sites involved in the initial SU-AVR studies are self-selected early adopters of the technology whose results may be better.

Although part of the rationale for surgery over TAVI is allowing concomitant procedures, most of the data published to date concerns isolated AVR; comparative studies have yet to be released. Another part of the rationale is the potential for minimal access surgery. Systematic comparisons of surgical approaches have yet to be made.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Preliminary, single arm study evidence suggests that sutureless AVR in aortic stenosis with the Perceval S prosthesis is technically feasible, may enable less invasive surgical approaches, and has short-term safety and effectiveness in restoring aortic valve function. Longer term (i.e. more than one year) safety and effectiveness is essential, and should be forthcoming as ongoing studies are reported. Determination of optimal surgical approaches is ongoing.

There is no randomized evidence suggesting which strategy is optimal: standard AVR, SU-AVR, or TAVI, for those patients that might be candidates for more than one strategy. Data comparing sutureless aortic valve replacement with alternative procedures is limited: the non-randomized comparisons are small, and their methodological quality is unclear. Currently patients are selected for procedures by individual case review and expert opinion, and there are at present no comparative trials in progress.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

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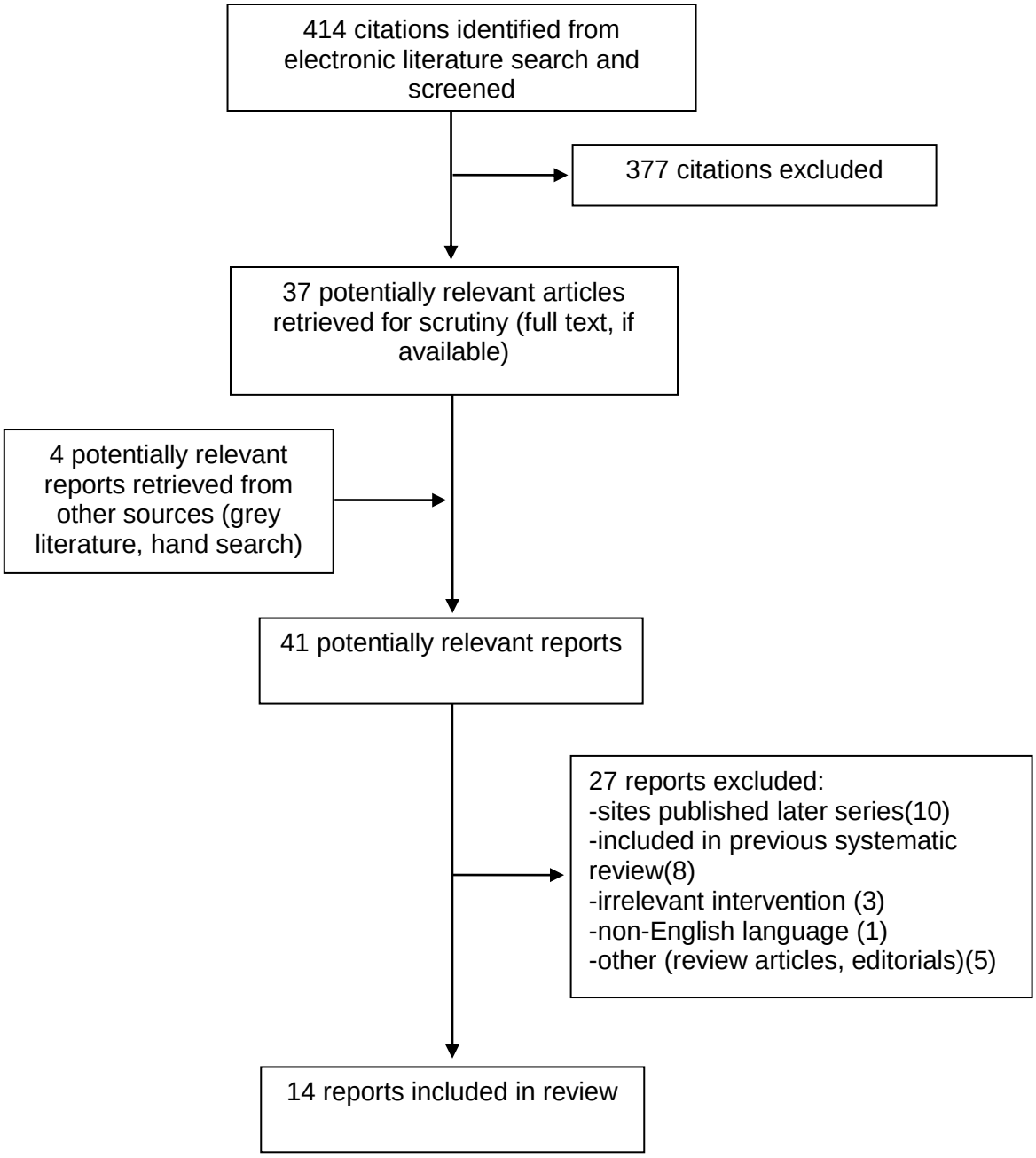
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table 2A: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Character-istics	Inter-vention	Compar-ator(s)	Clinical Outcomes, Length of Follow-Up
Phan, 2014[12]	12 non-randomized (6 Perceval S)	Patients underwent AVR using a sutureless aortic valve. Studies were excluded if they did not report mortality or complications	Any sutureless aortic valve.	Not specified.	Mean ACC and CPB duration. Mean, peak AVG, AVA, LVEF. Mortality: 30 days, 1 year. Reoperation for bleeding, endocarditis, PVR, pacemaker implantation, structural valve deterioration, neurological events, renal failure.
National Institute for Health and Clinical Excellence, 2013[13]	1 propensity-matched, 6 case series, 1 case report. (6 Perceval S)	Patients with aortic stenosis receiving a sutureless aortic valve.	Any sutureless aortic valve.	Not pre-specified	Safety and efficacy prespecified. Efficacy reported: Mean ACC and CPB times, mean and peak AVG, AVA, LVEF. NYHA. Safety reported: In-hospital, 30-day and follow-up mortality. Bleeding, valve-related reintervention/ explants, endocarditis, PVR, pacemaker, heart failure, thromboembolism, renal replacement therapy.
Australian Safety and Efficacy Register for New Interventional Procedures –	3 case series (1 Perceval S)	Patients with severe aortic stenosis	Any sutureless aortic valve.	Not specified.	Not pre-specified. Reported efficacy: Implant success. Mean ACC and CPB times, mean and peak AVG, AVA,

Table 2A: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Character-istics	Inter-vention	Compar-ator(s)	Clinical Outcomes, Length of Follow-Up
Surgical, 2012[14]					LVEF. NYHA. Reported safety: Mortality: perioperative, 30 day, and follow-up. Post-operative and follow-up: Bleeding, reoperation for bleeding, valve explantation, endocarditis, MI, stroke, PVR, pacemaker. Echocardiographic results at various time-points.
Sepehrinpour, 2012[15]	6 case series (2 Perceval S)	High risk patients undergoing surgery for aortic valve disease with any sutureless valve	Any sutureless aortic valve.	Surgical or percutan-eous aortic valve replace-ment.	Not pre-specified. Reported outcomes: Mortality: perioperative, 30 day, and follow-up. ACC and CPB times. NYHA. Post-operative complications, bleeding, reoperation for bleeding, valve explantation, endocarditis, MI, stroke, PVR, pacemaker. Echocardiographic results at various time-points.

ACC = aortic cross clamp (duration); AVA = aortic valvular area; AVG = aortic valvular gradient; AVR = aortic valve replacement; CPB = cardiopulmonary bypass (duration); LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PVR = paravalvular regurgitation; SU-AVR = sutureless aortic valve replacement.

Table 2C: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s) versus Comparator(s)	Clinical Outcomes
Single arm studies				
Mazine, 2015[17]. Six centres, Canada. June 2011 to May 2013.	Propective, multicentre.	N=214 Underwent SU-AVR with Perceval S.	SU-AVR with Perceval S. No comparator.	Perioperative mortality and adverse events (bleeding requiring reoperation, MI, acute kidney injury, renal replacement therapy, pacemaker). ICU length of stay. Hospital length of stay. Hemodynamic parameters.
König, 2014[18]. Cologne, Germany. September 2013 to February 2013.	Retrospective, single-centre.	N=14. Adults who received a Perceval S sutureless bioprosthesis.	SU-AVR with Perceval S. Paper reported comparison with patients receiving sutured valve.	In-hospital survival, complication rates. ICU length of stay. Hospital length of stay. Hemodynamic parameters.
Michelena, 2014[8,19]. Rochester and New York, US. (US FDA IDE trial)	One centre from preliminary prospective multicentre single-arm study.	N=8 Adults with severe aortic stenosis and suitable aortic root geometry.	SU-AVR with Perceval S. No comparator (historical controls).	Survival, valve success, complication rates. (In-hospital reported; long-term planned) Hemodynamic performance, NYHA at follow-up.
Rubino, 2014.[20] Leuven, Belgium†; Oulu,	Retrospective, multicentre.	N=314 Operated on for aortic stenosis with	SU-AVR with Perceval S. No comparator.	All-cause mortality, in-hospital mortality, valve

Table 2C: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s) versus Comparator(s)	Clinical Outcomes
Finland; Nürnberg, Germany†, Catania, Italy; Stockholm, Sweden. September 2007-September 2013		perceived high operative risk. Aortic annulus of size compatible with available prosthesis.		related mortality. Successful implantation, stroke, reoperation, endocarditis.
Comparative non-randomized studies				
Biancari, 2015.[25] Oulu, Finland, Catania, Italy, Nurnberg, Germany, Leuven, Belgium, Stockholm, Sweden, Triest, Italy. June 2007 to April 2014.	Retrospective cohort, propensity-matched comparison (1:1) SU-AVR patients from 5 centres. TAVI patients from sixth.	N=379. Any patient undergoing SU-AVR±CABG. N=394. Any patient undergoing TAVI±myocardial revascularization. Matched N=144.	SU-AVR with Perceval S. TAVI with any valve. SU-AVR with CABG 26.4%. TAVI with PCI 0.7%.	Main endpoint: In-hospital mortality. Secondary endpoints: device success, bleeding, reoperation for valve related complications, stroke, PVR, permanent pacemaker implantation, de novo dialysis.
Muneretto, 2015.[21] Brescia, Mantova and Seriate, Italy. October 2010 to February 2013	Prospective cohort, unmatched comparison. Patients assigned to interventions by multidisciplinary evaluation. October 2010 to February 2013.	Severe aortic valve stenosis, STS score>4%. SU-AVR N=53; other two groups N=55.	SU-AVR with Perceval S or Freedom Solo versus SAVR versus TAVI. Midline incision or ministernotomy at surgeon's discretion.	In-hospital mortality, peri-operative and post-operative adverse events (bleeding, MI, arrhythmia or heart block, pacemaker or circulatory support, acute renal failure). Early postoperative hemodynamic performance.

Table 2C: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s) versus Comparator(s)	Clinical Outcomes
				Follow-up: Freedom from death or major adverse cardiac events (cardiac death, MI, hemorrhage, stroke).
Gilmanov, 2014[22]. Massa and Rozzano, Italy. August 2004 (surgical), 2011 (SU-AVR) to January 2014.	Retrospective non-randomized cohort with propensity score matching (1:1). Patients assigned by surgeons to interventions.	Sutureless (94% Perceval S): N=246. Indication for isolated AVR, candidate for surgery via right anterior minithoracotomy. Surgical: N=269. Indication for isolated AVR, candidate for surgery via right anterior minithoracotomy. Propensity matched: N=133.	SU-AVR with Perceval S (mainly) versus SAVR. No concomitant procedures.	In-hospital mortality, perioperative adverse events, reintervention for bleeding, stroke, heart block, measures of hospitalization. Follow-up: survival, freedom from reoperation, AVA.
Pollari, 2014[23], Nürnberg and Münster, Germany. March 2010 to April 2013.	Retrospective non-randomized cohort with propensity score matching. Patients assigned to interventions by multidisciplinary conference.	Perceval S: N=166. Aged ≥65 years, indication for AVR, candidate for surgery, compatible echocardiogram findings. Surgical valve: N=400. Aged ≥65 years, candidate for surgery, incompatible echocardiographic findings or trained surgeon not available.	SU-AVR with Perceval S valve versus SAVR with sutured prosthesis.	Operative time, CPB and ACC time. In-hospital survival. Length of ICU and hospital stay. Follow-up: Survival, reoperation, stroke, endocarditis. Costs.

Table 2C: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s) versus Comparator(s)	Clinical Outcomes
		Propensity matched: N=82		
D'Onofrio, 2013[24]. Italy. Reanalysis of data from D'Onofrio, 2012. April 2008 to December 2011.	Retrospective non-randomized cohort with propensity score matching of surgical AVR (either valve) versus TA-TAVI. March to September 2011. SU-AVR patients collected at three different institutions, Italy. SVR patients from 1 centre, Italy. January 2009 to December 2011. TA-TAVI patients from the Italian Registry of Trans-Apical Aortic Valve Implantation. April 2008 to May 2011	Perceval S: N=38. Severe symptomatic AS, age >75 years, high surgical risk profile. TA-TAVI: N=566. Severe symptomatic AS, high surgical risk (EuroSCORE>20%; STS score>10%) or porcelain aorta, or other serious comorbidities. Surgical: N=349. Matching the above definitions. Matched N=137 (both surgical versus TA-TAVI). N=31 SU-AVR.	Surgical AVR with Perceval S valve; surgical AVR with sutured valve; TA-TAVI.	All-cause 30-day mortality, disabling stroke, permanent pacemaker, renal replacement therapy, acute MI within 72 hours, AR at discharge, transaortic gradient at discharge.

† Site collected data for PERCEVAL registration trials during study period.

Abbreviations: ACC = aortic cross clamp (duration); AVA = aortic valvular area; AVG = aortic valvular gradient; AVR = aortic valve replacement; CPB = cardiopulmonary bypass (duration); EuroSCORE = European System for Cardiac Operative Risk Evaluation; ICU = intensive care unit; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PVR = paravalvular regurgitation; SU-AVR = sutureless aortic valve replacement; TA-TAVI = transapical TAVI; TAVI = transcatheter aortic valve implantation.

APPENDIX 3: Critical Appraisal of Included Publications

Table 3A: Critical Appraisal of Systematic Reviews

	Phan, 2014[12]	NICE, 2013[13]	ASERNIP/S, 2012[14]	Sepehrinpour, 2012[15]
An 'a priori' design was provided.	Yes	Yes	No	Yes
There was duplicate study selection and data extraction.	Yes	Not clear (rapid review)	Can't answer	Not clear (rapid review)
A comprehensive literature search was performed.	Yes	Yes	Can't answer	No
The status of publication was used as an inclusion criterion.	Yes	No	Can't answer	Not clear
A list of studies (included and excluded) was provided.	Included only	Included only	Yes	Included only
Characteristics of the included studies were provided.	Yes	Yes	No	Yes
The scientific quality of the included studies was assessed and documented.	Yes	No	Can't answer	No
The scientific quality of the included studies was used appropriately in formulating conditions.	Yes	Yes	Yes	Yes
The methods used to combine the finding of studies were appropriate.	Yes	Not applicable	Not applicable	Not applicable
The likelihood of publication bias was assessed.	Yes	Yes	Can't answer	No
Any conflict of interest was stated.	Yes	Yes	No	No

Table 3B: Critical Appraisal of Case Series

	Mazine, 2015[17]	König, 2015[18]	Michelena, 2014[19]	Rubino, 2014[20]	Shrestha, 2014[16]
The objective of the study is stated clearly.	Yes	Yes	Yes	Yes	Yes
The characteristics of the included participants are well described.	Yes	Yes	Yes	Yes	Yes
The cases were collected in more than one centre.	Yes	No	No	Yes	Yes
The inclusion/exclusion criteria were explicit and appropriate.	Yes	Yes	Yes	Yes	Yes
Participants were recruited prospectively.	Yes	Yes	Yes	Yes	Yes
Participants entered the study at a similar point in the disease.	Yes	Yes	Yes	Yes	Yes
The intervention was clearly described.	Yes	Yes	Yes	Yes	Yes
Co-interventions were clearly described.	Yes	Yes	Yes	Yes	Yes
The outcome measures were clearly defined.	Yes	Yes	Yes	Yes	Yes
Outcomes were appropriately measured.	Yes	Yes	Yes	Yes	Yes
Outcomes were measured before and after the intervention.	Yes	Yes	Yes	Yes	Yes
Appropriate statistical tests were used to assess the outcomes.	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Length of follow-up was reported.	Yes	Yes	Yes	Yes	Yes
Loss to follow-up was reported.	No	No	No	No	Yes
Estimates of the random variability for outcomes were provided.	Yes	Yes	No (results listed by patient)	Yes	Yes
Adverse events were reported.	Yes	Yes	Yes	Yes	Yes
The results support the conclusions of the study.	Yes	Yes	Preliminary results of large study	Yes	Yes
Competing interests and sources of support for the study are reported.	Yes	No	Yes	Yes	Yes

Table 3C Critical Appraisal of Propensity-Matched Studies

Austin, 2008,[11] identifies five criteria to be considered in appraising a propensity-matched study.

1. The strategy for selecting the pairs is explicitly stated and justified, with citations.
2. Whether sampling is with or without replacement is documented.
3. The distribution of baseline characteristics between treated and untreated subjects in the matched sample is explicitly described.
4. The baseline balance in the matched sample is assessed using methods not influenced by sample size, are sample specific, and do not refer to a hypothetical population.
5. Analytic methods for estimating outcome difference and treatment effect are appropriate for matched data.

Criterion	Biancari, 2015[25]	Gilmanov, 2014[22]	Pollari, 2014[23]	D'Onofrio, 2013[24]
1	Yes	No	No	Yes
2	No	No	No	Yes
3	Yes	Yes	Yes	Yes
4	No	No	No	No
5	No	No	Some	Yes

APPENDIX 4: Main Study Findings and Author's Conclusions

Table 4A: Summary of Findings of Included Studies

First Author, Publication Year, Country, Study Name	Main study findings	Author's Conclusions
Meta-analysis		
Phan, 2014[12]	N=1037 (All valves; Perceval S N=502). Weighted mean age 77.3 years, female 61%, EuroSCORE 11.7, LVEF 58.9%. Proportion MS 20.1% [range 0 to 72%], MT 16.8% [0 to 100%], CS 64% [0 to 100%]. CABG 28.4% [0 to 50%]. Weighted mean ACC duration 45 [range 22 to 70] min, CPB 73 [46 to 111] min. Isolated SU-AVR ACC 33 min, CPB 57 min. MI SU-AVR ACC 59 min, CPB 92 min. 30-day mortality (10 studies) 2.1% (95% CI 1.1 to 3.3%). 1-year mortality (11 studies) 4.9% (95% CI 2.7% to 7.7%). Reoperation for bleeding (10 studies) 1.2% (95% CI 0 to 4.1%), stroke 1.5% (0.4% to 3.1%), endocarditis 2.2% (0.8% to 4.1%), PVR 3.0%% (1.0% to 5.8%), pacemaker 5.6% (3.5% to 8.0%), renal failure 1.2% (0 to 4.1%). Mean AVG at discharge (8 studies) 11.13 mmHg (95% CI 9.8 to 12.4 mmHg), at 12 months (6 studies) 9.6 mmHg (8.7 to 10.6 mmHg). Peak AVG at discharge 19.6 mmHg (16.5 to 22.7 mmHg), at 12 months 17.3 mmHg (16.1 to 18.4 mmHg). Mean AVA at discharge (5 studies) 1.77 cm^2 (1.6 to 2.0 cm^2), at 12 months 1.73 cm^2 (1.5 to 1.9 cm^2).	"The evaluation of current observational evidence suggests that sutureless aortic valve implantation is a safe procedure associated with shorter cross-clamp and CPB duration, and comparable complication rates to the conventional approach in the short term." (p1)[12]
Single arm, non-comparative		
Mazine, 2015.[17] Six centres, Canada. June 2011 to May 2013.	N=215. Mean age 78.9 years, female 54%, EuroSCORE II 7.2%, STS 6.9%. NYHA III/IV 56%. Proportion MS 9%, MT 11%, CS 80%. CABG 40%, multi-valve surgery 11%.	"Sutureless AVR using the Perceval S prosthesis is safe and reproducible and results in short operative times. Echocardiographic results are encouraging,

Table 4A: Summary of Findings of Included Studies

First Author, Publication Year, Country, Study Name	Main study findings	Author's Conclusions
	Implantation success 100%. Isolated SU-AVR mean ACC duration 40.5±11.6 min. CPB 56.6±16.6 min. Combined SU-AVR ACC 69.6±28.8 min, CPB 88.7±38.4 min. MS/MT SU-AVR ACC 43.4±12.1 min, CPB 58.2±15.8 min. Perioperative mortality 4%. Bleeding requiring reoperation 5%, explantation 0, stroke 3%, MI 0.5%, endocarditis 0, PVR 11% (none moderate/severe), pacemaker 17%, renal replacement therapy 2%. ICU length of stay 3.7±3.9 days, hospital length of stay 11.4±7.6 days. Mean predischarge AVG 13.3±6.4 mmHg. Peak AVG 24.5±10.8 mmHg. Mean AVA 1.56±0.37 cm^2.	with low gradients and no paravalvular aortic insufficiency. However, in this series, sutureless AVR was associated with a high risk of permanent pacemaker implantation." (p64)[17]
König, 2014.[18] Cologne, Germany. September 2013 to February 2013.	N=14. Mean age 78 years, female 86%, additive EuroSCORE 7.4%. CABG 35.7%. Isolated SU-AVR ACC duration (N=9) 37.3±6.8 min, CPB 58.4±11.0 min. Combined SU-AVR ACC 51.6±5.6, CPB 74.8±7.1 min. 30-day mortality 0. Reoperation for bleeding 7.1%, stroke 7.1%, PVR 7.1%, pacemaker 28.6%. ICU length of stay 3.0±2.7 days (one patient excluded). Predischarge mean AVG 13±3.3 mmHg, peak AVG 24.8±5.2 mmHg.	"The sutureless SP bioprosthesis seems to represent a good alternative to conventional stented bioprostheses, especially in older patients with a high risk profile, and particularly if concomitant surgical procedures are planned." (p19)[18]
Michelena, 2014.[19] Rochester and New York, US. (US FDA IDE trial)	N=8. Age range 72 to 91 years, female 50%, STS mortality 2% to 9%. CABG 2 patients.	Preliminary report. No conclusions.

Table 4A: Summary of Findings of Included Studies

First Author, Publication Year, Country, Study Name	Main study findings	Author's Conclusions
	ACC duration 21 to 133 min, CPB duration 28 to 159 min. 30 day mortality, none. Reoperation for bleeding 1 patient, stroke none, PVR none, pacemaker 3. Hospital length of stay 4 to 16 days. Predischarge mean AVG 9 to 22 mmHg, AVA 1.2 to 2.5 cm^2.	
Rubino, 2014.[20] Leuven, Belgium†; Oulu, Finland; Nürnberg, Germany†, Catania, Italy; Stockholm, Sweden. September 2007-September 2013	Rubino, 2014. N=314. Mean age 77.9 years, female 60.2%, EuroSCORE II 9.0%, NYHA Class III/IV 80.6%. MS 41.7%, MT 2.9%, CS 55.4%. CABG 29.9%. Successful implants 313 (99.7%). Isolated SU-AVR ACC 39±15 min, CPB 66±23. Combined SU-AVR 52±26, CPB 88±32 min. 30 day mortality 3.2% (1.4% isolated AVR, 7.4% with CABG). Reoperation for bleeding 2.5%, redo with sutured AVR 1.0% (2 patients PVR, 1 dislodgement), stroke 1.9%, intraoperative PVR 12.7%, pacemaker 8.0%, new dialysis 1.6%. ICU length of stay 3.2±3.4 days. Hospital length of stay 13.4±6.5 days. Median length of follow-up 0.9 years (0.1 to 3 years). 1-year 90.5%, 2-year 87%. Freedom from valve-related mortality 99.0%, from reoperation 98.3%, from stroke, 98.1%, from endocarditis 99.2%.	"The sutureless Perceval S valve is associated with excellent early survival in high-risk patients, particularly among those undergoing an isolated procedure." (p865)[20] "A longer follow-up is needed to define the structural and clinical durability of this bioprosthesis. Further data are needed on the potential benefits of this approach in patients requiring coronary revascularization or any other cardiac procedure." (p870)[20]
Shrestha, 2014.[16] Pooled results for 3 European registration studies. (PERCEVAL Pilot, Pivotal, and Cavalier) April 2007 to February	See Appendix 5 for preliminary results for all patients, and study design. For subgroup who underwent AVR and a concomitant procedure (N=243 of total 770), mean age 79.7 years, female 61%, mean EuroSCORE 12.1%.	"These trials confirm the safety and efficacy of the Perceval sutureless aortic valve, especially in elderly patients requiring AVR+concomitant procedures. In this patient group, sutureless

Table 4A: Summary of Findings of Included Studies

First Author, Publication Year, Country, Study Name	Main study findings	Author's Conclusions
2013.	MS 6%, CS 94%. CABG 75%, CABG+others 7%, septal myectomy 9%, others 9%. Mean procedural times: CPB 78.9±32.3 min, ACC 50.7±22.8 min. 30-day mortality 2.1%. To 30 days: re-exploration for bleeding 3.8%, valve explantations 2.1% (1 patients for bleeding, 4 for PVR), stroke 1.3%, MI 0.8%, endocarditis 0.4%, pacemaker 5.9%, heart failure 1.3%. Mean follow-up 444 days. 2-year overall survival 86.4%. Explantations 4 (1.35%/patient years), no valve thrombosis, valve dislodgement, migration or deterioration. Hemodynamics: 1 year post-op (N=161) mean AVG 8.9±4.6 mmHg, peak AVG 17.5±8.2 mmHg, AVA 1.6±0.5 cm^2. NYHA Class I/II at 1 years 91.9%.	valves may be advantageous compare to transcatheter valve implantations as concomitant procedures other than percutaneous coronary artery angioplasty are not always possible in the latter." (p1294)[16]
Comparative non-randomized studies		
Biancari, 2015.[25] Oulu, Finland, Catania, Italy, Nurnberg, Germany, Leuven, Belgium, Stockholm, Sweden, Triest, Italy. June 2007 to April 2014.	(*Order of presentation: SU-AVR versus TAVI, N=144*) Mean age 79.4 versus 79.0 years, female 61.1% versus 62.5%, mean EuroSCORE II 4.1% versus 3.6%, NYHA III/IV 75.0% versus 72.9%. Device success (successful procedure with no major adverse events) 79.9% versus 77.8%. In-hospital mortality 1.4% versus 6.9%. Reoperation for major bleeding 4.2% versus 0, stroke 0 versus 2.1%, PVR (>mild) 2.8% versus 53.5%, pacemaker implantation 11.2% versus 15.4%, de novo dialysis 2.1% vs 0.	"… SU-AVR may provide favorable early results when compared with a population treated with TAVI. The use of sutureless Perceval bioprosthesis is associated with a rather low incidence of significant paravalvular regurgitation and excellent immediate postoperative survival. SU-AVR is a valid alternative to TAVI in intermediate risk patients." (p6)[25]
Muneretto, 2015.[21] Brescia, Mantova and	(*Order of presentation: Su-AVR versus AVR versus TAVI, N=55 versus 53 versus 55*)	"… we could not detect an advantage in survival

Table 4A: Summary of Findings of Included Studies

First Author, Publication Year, Country, Study Name	Main study findings	Author's Conclusions
Seriate, Italy. October 2010 to February 2013.	Mean age 79 versus 79 versus 81 years, female 68.9% versus 52.7% versus 56.3%, mean EuroSCORE 16% versus 21.3% versus 20.4%. NYHA III/IV 88.7% versus 71% versus 56.4%. MS 18.9% versus 49.1%. Mean ACC duration 30.9±13.6 versus 65.4±27.7 min. CPB 47±18.5 versus 89.4±20.4 min. In-hospital/30 day mortality 0 versus 0 versus 1.8%. Bleeding requiring surgery 7.5% versus 10.9% versus 0, postoperative MI 0 versus 0 versus 1.8%, stroke 0 versus 1.8% versus 0, atrioventricular block/pacemaker 2% versus 1.8% versus 25.5%, AR (Grade II+) 1.9% versus 0 versus 9%, acute renal failure 7.5% versus 12.7% versus 9%. Mortality to 24 months: 9.4% versus 14.5% versus 12.7%. 24-month survival (Kaplan-Meier) 83.8% versus 89.5% versus 83%. Cardiac death 3.7% versus 0 versus 5.4%, major bleeding 0 versus 1.8% versus 3.6%, stroke 1.9% versus 1.8% versus 1.8%, late MI none. 24-month follow-up mean AVG 10.8±6.8 versus 11.4±6 versus 8.4±4.2 mmHg, peak AVG 19.5±12.5 versus 23.8±11.7 versus 15.3±7.5 mmHg.	when a sutureless was utilized compared with a conventional AVR." (p95)[21] "This preliminary study suggests that the use of TAVI in patients with an intermediate to high risk profile is associated with a higher rate of perioperative complications and decreased survival at the 24 month follow-up compared with the use of conventional surgery or sutureless valves." (p90)[21]
Gilmanov, 2014.[22] Massa and Rozzano, Italy. August 2004 (surgical), 2011 (SU-AVR) to January 2014.	(*Order of presentation: SU-AVR versus AVR,* N=133) Mean age 75.3 versus 73.6 years, female 44.4% versus 42.9%. EuroSCORE 5.83% versus 5.46%. NYHA III/IV 29.3% versus 30.1%. MT 100% versus 100%. Median ACC 56 min [IQR 48 to 72.5 min] versus 88 [77 to 110 min] Median CPB 90 [78 to 108.5 min] versus 88 min [77 to 100	"In the present limited cohort of patients, sutureless prostheses reduced operative times for aortic valve replacement and the duration of mechanically assisted ventilation and might have influenced early and mid-term survival." (p1585)[22]

Table 4A: Summary of Findings of Included Studies

First Author, Publication Year, Country, Study Name	Main study findings	Author's Conclusions
	min]. In-hospital mortality 0.8% versus 1.5%. Reexploration for bleeding versus 6.8% 3.8%, conversion to median sternotomy 2.3% versus 3.0%, perioperative MI 1.5% versus 0 patients, stroke 1.5% versus 0, pacemaker 4.5% versus 2.3%, infection 3.8% versus 3.8%. ICU length of day median 1 day versus 1 day. Hospital length of stay median 6 days versus 6 days. Mean follow-up 15.3±8 versus 53.6±29 months. 10-month Kaplan-Meier survival 96% versus 95%. Freedom from reoperation at follow-up 98.5% versus 97%. Mean AVG at follow-up 11±7 mmHg versus 12±8 mmHg.	
Pollari, 2014,[23] Nürnberg and Münster, Germany. March 2010 to April 2013.	(*Order of presentation: SU-AVR versus AVR*, N=88) Mean age 75.5 versus 74.5 years, female 61% versus 52.4%, EuroSCORE 12.1% versus 10.9%, mean NYHA 2.9 versus 3.1. Combined operation 22% versus 17.1%. Mean ACC duration 47±16 versus 59±23 min, CPB 71±11 versus 92±33 min. Isolated SU-AVR ACC 47±16 min versus 49±16 min. 30-day mortality 2.4% versus 3.7%. Re-exploration for bleeding 2.4% versus 6.1%, stroke/ TIA 3.7% versus 7.3%, pacemaker 6.1% versus 8.5%. ICU length of stay 2±1.2 das versus 2.8±1.3 days. Hospital length of stay 10.9±2.7 days versus 12.4±4.4 days. Follow-up 13 months. Overall survival 97.6% versus 96.2%, freedom from valve-related death 100% versus 98.7%, freedom	"A shorter procedural time in the sutureless group is associated with better clinical outcomes and reduced hospital costs." (p611)[23] "… despite the promising preliminary results, a longer follow-up is warranted before a definite conclusion can be drawn." (p617)[23]

Table 4A: Summary of Findings of Included Studies

First Author, Publication Year, Country, Study Name	Main study findings	Author's Conclusions
	from stroke 98.8% versus 97.5%, freedom from endocarditis 100% versus 98.7%, freedom from reoperation 100% versus 98.7%.	
D'Onofrio, 2013,[24] Italy. Reanalysis of data from D'Onofrio, 2012, with three-way comparison. January 2009 to March 2012.	(*Order of presentation: Both surgical groups versus TAVI, N=143 each*) Mean age 73.5 versus 77.6 years, female 50.3% versus 62.9%, EuroSCORE 18.3% versus 20.2%. NYHA III/IV 54.5% versus 65%. Postoperative outcomes (*Order of presentation: SU-AVR versus SAVR versus TA-TAVI*, N=31 versus 112 versus 143) 30-day mortality 0 versus 1.8% versus 7%. MI 0 versus 0.9% versus 3.5%,stroke 0 versus 0 versus 2.8%, AR (mild+) 19.4% versus 1.0% versus 28.7%, pacemaker 3.2% versus 0.9% versus 4.9%, renal replacement therapy 3.2% versus 0 versus 4.9%. Mean AVG at discharge: 11.1±3.3 versus 16.5±5.8 versus 10.7±10.7 mmHg.	"SAVR [surgical AVR] was associated with lower 30-day mortality than TA-TAVR [TA-TAVI]. SAVR was also associated with a lower risk of postoperative aortic regurgitation compared with TA-TAVR. We did not find other significant differences in outcomes among matched patients treated with SAVR, SU-AVR, and TA-TAVR." (p1065)[24]

ACC = aortic cross-clamping; AR = aortic valve regurgitation; AV = atrioventricular; AVA = aortic valve area; AVG = aortic valve gradient; AVR = aortic valve replacement; CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; CS = conventional sternotomy; EuroSCORE = European System for Cardiac Operative Risk Evaluation; GI = gastrointestinal; MI = myocardial infarction; MS = ministernotomy; MT = minithoracotomy; NYHA = New York Heart Association functional class; PVR = paravalvular leak; SAVR = surgical aortic valve replacement; STS = Society for Thoracic Surgeons risk calculator; SU-AVR = sutureless aortic valve replacement; TA-TAVI = transcatheter aortic valve implantation by the transapical route; TAVI = transcatheter aortic valve implantation. PVR

APPENDIX 5: Registration trial results reported in abstract

A non-systematic search identified abstracts presented at the European Association for Cardio-Thoracic Surgery conference, October 2014, which described interim results for all patients in the PERCEVAL European pivotal trials.[29,30] As a search of conference abstracts was not part of the systematic search, these abstracts were not included as part of the main summary, but are presented here for completeness. Available information on the study design from ClinicalTrials.gov is summarized in Table 5A and results in Table 5B.

The data are to be considered preliminary, lacking full details of study design and conduct and a full description of adverse events. Given the interest in this field, peer reviewed publications may be anticipated shortly.

Table 5A: Characteristics of European Registration studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s) versus Comparator(s)	Clinical Outcomes
PERCEVAL Cavalier. EU registration trial.[31] 26 centres in Austria, Belgium, France, Germany, Netherlands, Poland, Switzerland, United Kingdom Started February 2011.	Prospective, single arm, multi-center trial	N=658 Age ≥65 years with aortic stenosis. Pre-operative assessment suggests need for replacement. Excluded: needing additional procedures except CABG or septal myomectomy	SU-AVR with Perceval S. No comparator.	Improvement in clinical status (NYHA class). Hemodynamic parameters. Adverse events. PVR.
PERCEVAL Pivotal. EU registration trial.[32] 9 centres in Belgium, France, Germany, Switzerland January 2007-September 2011	Prospective, single arm, multi-center trial	N=150 Age ≥75 years with aortic stenosis NYHA Class III/IV. Excluded: needing additional procedures except CABG or septal myomectomy	SU-AVR with Perceval S. No comparator.	Improvement in clinical status (NYHA class). Hemodynamic parameters. Adverse events. PVR.

ACC = aortic cross clamp (duration); AVA = aortic valvular area; AVG = aortic valvular gradient; AVR = aortic valve replacement; CPB = cardiopulmonary bypass (duration); LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PVR = paravalvular regurgitation; SU-AVR = sutureless aortic valve replacement.

Table 5B: Results of European Registration studies

First Author, Publication Year, Country, Study Name	Main study findings
Shrestha, 2014.[29] Pooled results for 3 European registration studies (Perceval Pilot, Pivotal and Cavalier).	N=731. Mean age 78.9 years, mean logistic EuroSCORE 11.04%. Mean procedural times: For AVR alone via sternotomy (n=308), time on CPB, 50.3 min, ACC 30.7 min. For AVR alone via less invasive approach (n=189), time on CPB 64.5 min, ACC 37.3 min. Cumulative follow-up 729 patient-years. Overall survival 1 year 92.1%, 5 years 74.4%. To 30 days: Deaths 3.4%, cardiac deaths 1.4%. Explants 1.4%. PVR 1.4%. Endocarditis 0.3%. Third degree AV block 6%. To 1 year: Deaths 10.4%, cardiac deaths 2.1%. Explants 2.9%. PVR 2.6%. Endocarditis 1.9%. Third degree AV block 7.4%. Hemodynamics: Mean AVG pre-op 42.7 mmHg, 3 years post-op 7.7 mmHg.
Laborde, 2014.[30] PERCEVAL Cavalier. European registration trial for extended CE Mark.	N=658. Mean age 77.8 years, mean logistic EuroSCORE 10.2%. Successful implantation 95.4%. Mean procedural times: For AVR alone via sternotomy (n=232), time on CPB, 53.7 min, ACC 32.6 min. For AVR alone via less invasive approach (n=219), time on CPB 73.4 min, ACC 40 min. To 30 days: Deaths 3.7%, valve-related 0.3%. Explanted valves 1.0%, explanted for PVR 0.5%. Stroke 2.1%. Endocarditis 0.2%.