

# Stentless Versus Stented Bioprosthetic Aortic Valves

## A Consensus Statement of the International Society of Minimally Invasive Cardiothoracic Surgery (ISMICS) 2008

John Pepper, FRCS,\* Davy Cheng, FRCPC,† Rex Stanbridge, FRCS,‡ Francis D. Ferdinand, MD,§ W. R. Eric Jamieson, FRCSC,¶ Paul Stelzer, MD,|| Geoffrey Berg, FRCS,\*\* Guido Sani, MD,†† and Janet Martin, PharmD‡‡

**Objective:** The purpose of this consensus conference was to determine whether stentless bioprosthetic valves improve clinical and resource outcomes compared with stented valves in patients undergoing aortic valve replacement, and to outline evidence-based recommendations for the use of stentless and stented bioprosthetic valves in adult aortic valve replacement.

**Methods:** Before the consensus conference, the best available evidence was reviewed in that systematic reviews, randomized trials, and nonrandomized trials were considered in descending order of validity and importance. At the consensus conference, evidence-based statements were created, and consensus processes were used to determine the ensuing recommendations. The American Heart

Association/American College of Cardiology system was used to label the level of evidence and class of recommendation.

**Results and Recommendations:** Seventeen randomized studies published in 23 articles involving 1317 patients, and 14 nonrandomized trial published in 18 articles involving 2485 patients were included in the meta-analysis and consensus conference. All randomized trials inserted the stentless bioprosthetic valves in the subcoronary configuration. The consensus panel agreed upon the following statements and recommendations in patients undergoing aortic valve replacement:

1. Stentless and stented valves both provide an excellent valve substitute for aortic valve disease (class I, level A).
2. In certain situations, the early superior hemodynamic performance of stentless bioprosthesis offers advantages over stented valves (class IIa, level A).

Because there were no randomized control trial comparing subcoronary stentless prosthetic valve and root replacement, the following recommendations are derived from expert opinion:

1. In the absence of aortic root disease and with an annulus greater than or equal to 21 mm, either stentless or stented valves are acceptable alternatives for the majority of patients when a current (second or third) generation bioprosthesis is indicated (class I, level C).
2. In the presence of an aortic annulus <21 mm, the use of a freestanding bioprosthetic root can be considered as an alternative to enhanced diameter stented bioprosthesis or a root enlargement procedure (class I, level C).

**Key Words:** Consensus statements, Aortic valve surgery, Stentless valve surgery, Stentless valve surgery.

(*Innovations* 2009;4:49–60)

Accepted for publication February 15, 2009.

From the \*Department of Cardiothoracic Surgery, Imperial College, Royal Brompton Hospital, London, UK; †Department of Anesthesia and Perioperative Medicine, Evidence-Based Perioperative Clinical Outcomes Research Group (EPiCOR), London Health Sciences Centre, The University of Western Ontario, London, ON, Canada; ‡St. Mary's Hospital, London, UK; §Division of Thoracic and Cardiovascular Surgery, The Lankenau Hospital, Wynnewood, PA USA; ¶St. Paul's Hospital, University of British Columbia, Vancouver, BC, Canada; ||Department of Cardiothoracic Surgery, Mount Sinai Medical Center, Mount Sinai School of Medicine, New York, NY USA; \*\*Golden Jubilee National Hospital, Clydebank, UK; ††Department of Surgery, Siena University School of Medicine, Siena, Italy; and ‡‡High Impact Technology Evaluation Centre, London Health Sciences Centre, London, ON, Canada.

Support for the meta-analysis and a consensus conference was provided by the International Society for Minimally Invasive Cardiothoracic Surgery (ISMICS), which has received unrestricted educational grants from industries that produce surgical technologies.

Address correspondence and reprint requests to: John R. Pepper, FRCS, Department of Cardiothoracic Surgery, Imperial College, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK. E-mail: J.Pepper@rbht.nhs.uk.

**Disclosure:** Geoffrey A. Berg, FRCS, Consultant for Vascutek Ltd. Francis D. Ferdinand, MD, Investigator for Sorin Group, St. Jude Medical, Edwards Lifesciences. WR Eric Jamieson, FRCSC, Consultant for Sorin, St. Jude Medical, Medtronic; Speakers Bureau/Honoraria for Edwards Lifesciences, Sorin Group, On-X Life Technologies, St. Jude Medical; Principal Investigator for St. Jude Medical, Edwards Lifesciences, On-X Life Technologies, Medtronic Inc, Rib-X Pharmaceuticals, Sorin Group, Medtronic, CIHR; Randomized Controlled Trials for On-X, St. Jude Medical.

Copyright © 2009 by the International Society for Minimally Invasive Cardiothoracic Surgery  
ISSN: 1556-9845/09/0402-0049

Aortic stenosis remains the most prevalent acquired heart valve pathology in an aging population. The ideal aortic valve substitute should be simple to implant, provide a hemodynamic profile identical to a normal native valve with unlimited durability and have a low thrombogenic potential to preempt the need for ongoing anticoagulants. Current valve substitutes are typically xenograft valves often complicated with residual gradient across the prosthesis.

This will result in incomplete regression of left ventricular hypertrophy after aortic valve replacement and is associated with higher risk of death.<sup>1</sup>

Stentless biologic aortic valves with increased effective orifice area have been developed in response to the need to overcome the obstructive limitations associated with stented biologic aortic valves. Previous meta-analyses in this area have not included the most recent trials and evaluated only selected outcomes<sup>2-5</sup>; therefore, a consensus conference was organized to systematically evaluate the relative advantages and disadvantages of stentless and stented biologic aortic valves based on best currently available evidence. To date all published randomized control trials (RCTs) of stentless bioprosthesis valves have been inserted in the subcoronary configuration.

## METHODS

### Purpose of the Consensus Conference

A consensus conference was held to clarify if stentless bioprosthetic valves improve clinical and resource outcomes compared with stented valves in patients undergoing aortic valve replacement? The primary objectives were to evaluate the evidence for stentless versus stented valve replacement in term of perioperative morbidity, mortality, and long-term outcomes; perioperative hemodynamic performance and cardiac function; and resource utilization. The secondary objective was to identify the gaps in the needed evidence and to suggest a future research agenda.

### Funding

Support for this consensus conference was provided by the International Society for Minimally Invasive Cardiothoracic Surgery (ISMICS), which has received unrestricted educational grants from industries that produce surgical technologies. Although ISMICS receives industry funding, no specific industry was linked with this consensus conference and support did not involve direct funding from manufacturers of devices related to aortic valves. Editorial independence was granted to the members of the expert panel, with the expectation that the resulting consensus statements would be clearly based on the best available evidence with explicit methodology. When evidence was lacking, opinions were consented to create statements.

### Selection of Panel Members

Members of the consensus panel were invited to participate by the chair (J.P.) and facilitator of the consensus process. Members included representation from four countries: seven board certified cardiothoracic surgeons, each with experience in valvular surgery, one cardiothoracic anesthesiologist/evidence-based researcher, and one methodologist with expertise in health technology assessment and meta-analysis.

### Defining the Clinical Question

Before the consensus conference, the consensus panel was asked to define the clinical question, which involved defining the scope and depth of each of the following considerations: patient population of interest, intervention of interest, valid comparator group(s), and outcomes of interest.<sup>6</sup>

The clinical question was developed collaboratively with input from all consensus panel members and was finally stated as follows:

“Do stentless bioprosthetic valves improve clinical and resource outcomes compared with stented valves in patients undergoing aortic valve replacement?”

1. Perioperative morbidity, mortality ( $\leq 30$  days) and long-term outcomes (6 months, 1, 3, 5, 10 years).
2. Perioperative hemodynamic performance and cardiac function ( $\leq 30$  days) and long term (6 months, 1, 3, 5, 10 years).
3. Resource utilization.

### Identifying Relevant Evidence

After the clinical questions had been defined, all published and unpublished evidence with acceptable study designs was sought to maximally inform this clinical question. Acceptable study designs included any randomized or nonrandomized comparative trial comparing stentless versus stented aortic valve replacement. A full systematic review and meta-analysis of the evidence was performed before the conference. The complete methodology and results of the systematic review has been described in another article in this issue of the *Innovations*.<sup>7</sup> Potentially relevant trials were circulated to the consensus panel for review to determine agreement upon the inclusion criteria and whether any relevant trials were missed. Information related to baseline characteristics and outcomes was extracted independently by two authors (D.C., J.M.) from each study that met prospectively defined inclusion criteria. The appropriate data were synthesized by valid meta-analytic techniques to provide more precise aggregate outcome estimates. Trials that did not meet inclusion criteria were qualitatively summarized in tables to ensure all relevant data were addressed in the systematic review by the panel. The results of the systematic review and meta-analysis were used to populate evidence tables and graphs to form the basis for discussions and support the decision-making of the consensus panel. Comprehensive evidence for all potential benefits, risks, and resource considerations of stentless versus stented aortic valve replacement was sought.

### Reviewing and Presenting the Evidence

Before the consensus conference, each member of the consensus panel received a copy of the identified randomized and nonrandomized clinical trials and relevant background literature related to the clinical question. During the consensus conference meeting, the panelists were divided into groups and asked to address the following subquestions with the best available evidence from the meta-analysis:

1. Do stentless bioprosthetic valves improve perioperative morbidity (prosthesis patient mismatch, valve complications, cerebral vascular accident (CVA), acute myocardial infarction, atrial fibrillation, A-V heart block, permanent pacemaker, thromboembolic events, heart failure, renal failure, wound infection, bleeding complications, and endocarditis), mortality ( $\leq 30$  days), and long-term outcomes (6 months, 1, 3, 5, 10 years)?
2. Do stentless bioprosthetic valves improve perioperative hemodynamic performance and cardiac function (effective orifice area index [EOAI], left ventricular mass

index [LVMI], mean and peak aortic valve pressure gradient, ejection fraction, and symptomatic improvement) at ≤30 days, 6 months, 1, 3, 5, 10 years?

3. Do stentless bioprosthetic valves improve resource utilization (cardiopulmonary bypass time, operating room time, ventilation duration, ICU, and hospital length of stay)?

## Applying the Evidence to Generate Recommendations

### Levels of Evidence and Grade of Recommendations

The best evidence used to inform each clinical subquestion was classified according to the taxonomy suggested by American Heart Association (AHA)/American College of Cardiology (ACC), as outlined in Table 1. This classification categorizes the evidence base on study design and susceptibility to bias, wherein higher levels of evidence and grades are labeled to highlight their lesser likelihood for bias and increased confidence in “closeness to the truth.”<sup>8–11</sup> Several systems of grading recommendations and labeling strength of the evidence exist. The AHA/ACC system was chosen for consistency with other guidelines ([http://www.acc.org/clinical/manual/manual\\_index.htm](http://www.acc.org/clinical/manual/manual_index.htm) accessed April 19, 2004) (Tables 1 and 2). As recommended by guidelines, classification of the evidence and labeling recommendations is best done by the group panel using a democratic voting process after group discussion of the strength of the evidence.<sup>12,13</sup>

Members of the panel considered the highest possible level of evidence to inform their clinical subquestion, (eg, systematic reviews, meta-analyses and randomized trials (level A evidence, see Table 1) were considered superior to nonrandomized clinical trials). If there was insufficient level A evidence to inform the question, members reviewed nonrandomized comparative trials (level B evidence, see Table 1). Only when level A and level B evidence was not available were

**TABLE 1.** Levels of Evidence

Level of evidence A	Data derived from multiple randomized clinical trials.
Level of evidence B	Data derived from a single randomized trial, or non-randomized studies.
Level of evidence C	Consensus opinion of experts.

**TABLE 2.** Classes of Recommendations

Class I	Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.
IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Conditions for which there is evidence and/or general agreement that the procedure/treatment is NOT useful/effective and in some cases may be harmful.

noncomparative trials consulted to inform decisions (level C evidence, not formally included in the systematic review) along with expert opinion. When evidence from published or unpublished clinical trials to address the question was nonexistent, the consensus panel members were consulted. In each case, the best available level of evidence was explicitly stated and interpreted in light of its methodologic strengths and weaknesses before a statement of recommendation was made. As in previous consensus conferences, it was agreed that recommendations with higher levels of evidence should be interpreted with more confidence than recommendations based on lower levels of evidence, and that recommendations should be explicitly classified as per the ACC/AHA system (Table 2). After this review, each subgroup prepared a proposed draft statement.

### Consensus Process and the Role of Evidence Versus Opinion

After each subgroup presented a proposed draft statement for their assigned subquestions to the entire consensus panel for further discussion of the strength, consistency, and clinical significance of the evidence, revisions were made until there was final agreement on each consensus statement along with its assigned level of evidence and class of recommendation.

When limited evidence was found to inform a clinical subquestion, it was explicitly recognized that scientific information would need to be supplemented by the interpretations and opinions of the experts. Legitimate conflicts over values and interpretations were resolved by discussion to achieve consensus. Therefore, the consensus was not always unanimous, but was always representative of the majority of panel members. This is particularly true for the subquestions informed only by lower levels of evidence and expert opinion, where controversy was not resolved by clear evidence.

In summary, this consensus process sought to be primarily evidence based, whereas allowing for opinions when the evidence was incomplete, and requiring that the basis for the statement be labeled by a declarative level of evidence. Bringing selected experts together in a consensus process allowed for breadth of perspectives and representation of interpretations for a multidimensional and carefully considered judgment of the evidence along with its certainties and uncertainties.

## RESULTS AND RECOMMENDATIONS

### Included Evidence

A systematic review and meta-analysis of the randomized and nonrandomized evidence was performed prior to the conference by the authors<sup>7</sup> and was the basis for the formation of the recommendations.

Seventeen randomized studies published in 23 articles involving 1317 patients were included in the meta-analysis. Fourteen nonrandomized trials published in 18 articles involving 2485 patients were included in the meta-analysis. One registry was identified, but not included in the analysis because it was unknown whether the patients in the registry would overlap with the published studies. It is important to note that case series and noncomparative trials were excluded from this analysis.

## Baseline Characteristics

In the randomized trials, baseline mean age was 72 versus 73 years for the stentless and stented valve groups, respectively. In nonrandomized trials the baseline mean age was significantly lower in the stentless valve group (68 years) versus the stented valve group (71 years; weighted mean difference [WMD]—3 years, 95% CI –4 to –0.4 years;  $P = 0.02$ ). Baseline ejection fraction, mean gradient, peak gradient, EOAI, LVMI, and concomitant CABG surgery were not statistically significant between stentless and stented groups for randomized trials and nonrandomized trials. Annulus size was larger in the stentless valve group compared with the stented valve group for randomized studies (WMD 0.5 mm, 95% CI 0.2–0.8,  $P = 0.002$ ). Valve size was larger for the stentless group compared with stented group in randomized studies (WMD 0.15 mm, 95% CI 0.9–2.0mm,  $P < 0.0001$ ), and for nonrandomized studies (WMD 1.2 mm, 95% CI –1.2 to +3.5 mm,  $P = 0.33$ ; Fig. 1A,B). All randomized trials inserted the stentless bioprosthetic valves in the subcoronary configuration.

## Heterogeneity

For a number of outcomes, heterogeneity across studies was observed in the meta-analysis. Random effects statistical analysis was used to account for the heterogeneity found between trials for these outcomes.

## Assigning Level of Evidence and Strength of Recommendation

The discussion and resulting evidence-based statements with assignment of levels of evidence and class of recommendation are given below for each clinical subquestion, and for the overarching clinical question. The aggregate results for RCTs (level A) from the meta-analysis are preferentially reported here; however, when RCTs were unavailable, aggregate results from non-RCTs evidence (level B) will be reported. Readers may consult the original meta-analysis publication for comprehensive reporting of both randomized and nonrandomized trials for all endpoints.<sup>7</sup> For discrete outcomes, odds ratios and their 95% confidence intervals (OR, 95% CI) are reported. For continuous outcomes, the weighted mean difference (WMD, 95% CI) or standardized mean difference (SMD, 95% CI) is reported.

### Question 1: Do Stentless Bioprosthetic Valves Improve Perioperative Morbidity and Mortality at $\leq 30$ Days and Long Term (6 Months, 1, 3, 5, 10 Years)?

Valve complications were generally poorly reported in the randomized trials. Valve regurgitation occurred in 4.4% and 6.4% of patients (OR 0.36, 95% CI 0.11 to 1.17; 4 RCT, level A; Fig. 2A) valvular dysfunction occurred in 1.4% and 2.6% of patients (OR 0.55, 95% CI 0.13–2.35; 2 RCT, level A), and reoperation for valvular complications occurred in 0.7% versus 1.9% of patients (OR 0.47, 95% CI 0.11–1.95; 4 RCT, level A; Fig. 2B) and were not significantly different between stentless and stented valve groups, respectively. Stroke or neurologic complications did not differ between stentless (3.6%) and stented (4.0%) valve groups (OR 0.73,

95% CI 0.37–1.44; 10 RCT, level A; Fig. 2C). The risk of thromboembolic events was reported in only one randomized trial (1.6% stentless versus 7.3% stented), and it suggested possible reduction in risk (OR 0.20, 95% CI 0.04–1.00; 1 RCT, level B). No difference was found for overall composite estimates of complications for stentless versus stented groups (13.0% versus 13.8%; OR 0.97, 95% CI 0.52–1.83; 4 RCT, level A; Fig. 2D). Endocarditis (early and late) did not differ significantly between stentless and stented groups. Similarly, no difference was found for risk of atrial fibrillation, myocardial infarction, atrioventricular block, permanent pacemaker insertion, intra-aortic balloon pump, heart failure, renal dysfunction, ventricular arrhythmia, wound infection, bleeding complications, reoperation for bleeding, and reoperation for any reason.

Mortality for stentless versus stented valve groups did not differ at any time point, including at 30 days (OR 1.36, 95% CI 0.68–2.72; 9 RCT, level A), 1 year (OR 1.01, 95% CI 0.55–1.85; 6 RCT, level A), and at 2 to 10 years follow up (OR 0.82, 95% CI 0.50–1.33; 3 RCT, level A; Fig. 2E). Aggregate event rates for all-cause mortality at 30 days were 3.7% versus 2.9%, at 1 year were 5.5% versus 5.9% and at 2 to 10 years were 17% versus 19% for stentless versus stented valve groups, respectively.

## Consensus Statements

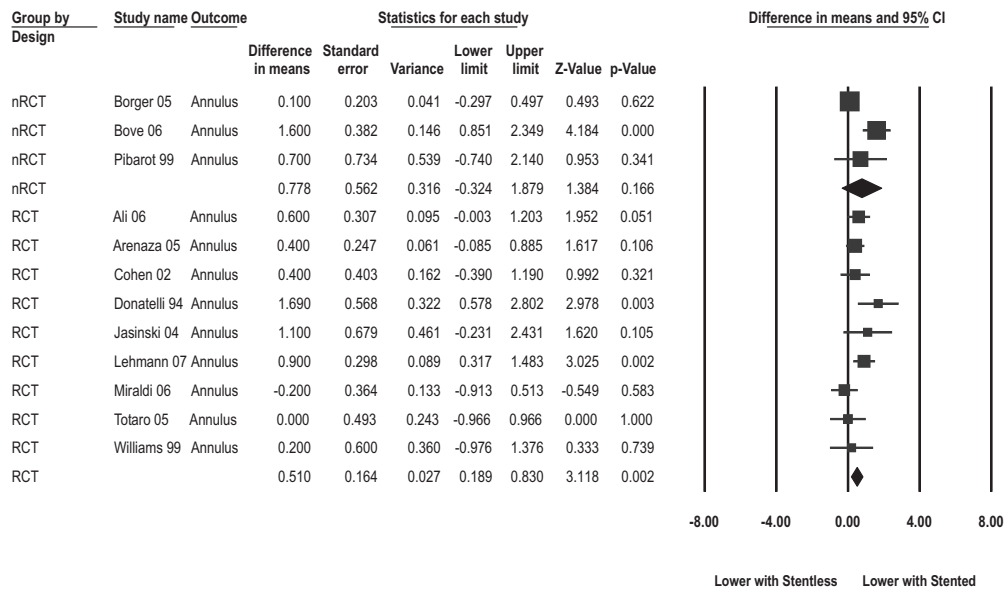
1. There was no difference in mortality ( $\leq 30$  days, 1 year and at a mean of 2–3 years) for stentless versus stented aortic valve replacement (level A).
2. There were no differences in perioperative morbidity ( $\leq 30$  days) including IABP, perioperative bleeding, insertion of permanent pacemaker, atrial fibrillation, acute myocardial infarction, and CVA for stentless versus stented aortic valve replacement (level A).
3. There were no differences in structural and nonstructural dysfunction between stentless and stented bioprosthetic valves (level B).

### Question 2: Is There a Difference in Perioperative Hemodynamic Performance and Cardiac Function ( $\leq 30$ Days) and Long Term (6 Months, 1, 3, 5, 10 Years)?

Risk of prosthesis patient mismatch was not significantly different between stentless and stented valve groups (11.0% versus 31.3%, OR 0.30, 95% CI 0.05–1.66; 4 RCT, level A; Fig. 3A). EOAI was significantly greater for patients receiving stentless aortic valve compared with stented valves at 30 days, 2 to 6 months and at 1 year (WMD 0.26 cm<sup>2</sup>/m<sup>2</sup>, 95% CI 0.10–0.41 cm<sup>2</sup>/m<sup>2</sup>; 6 RCT, level A; Fig. 3B).

The mean gradient remained significantly lower at 2 to 6 month follow-up (WMD –4 mm Hg, 95% CI –7 to –1 mm Hg; 9 RCT, level A), at 1 year follow-up (WMD –3 mm Hg, 95% CI –6 to –1 mm Hg; 7 RCT, level A; Fig. 3C) and up to 3 year follow-up (WMD –3 mm Hg, 95% CI –3 to –2 mm Hg; 1 RCT, level B). Similarly, peak gradient was lower and maintained at 2 to 6 month follow-up (WMD –8 mm Hg, 95% CI –13 to –3 mm Hg; 7 RCT, level A), 1 year follow-up

### A Annulus size (mm): Stentless versus Stented Valve for AVR



### B Valve Size (mm): Stentless versus Stented Valve for AVR

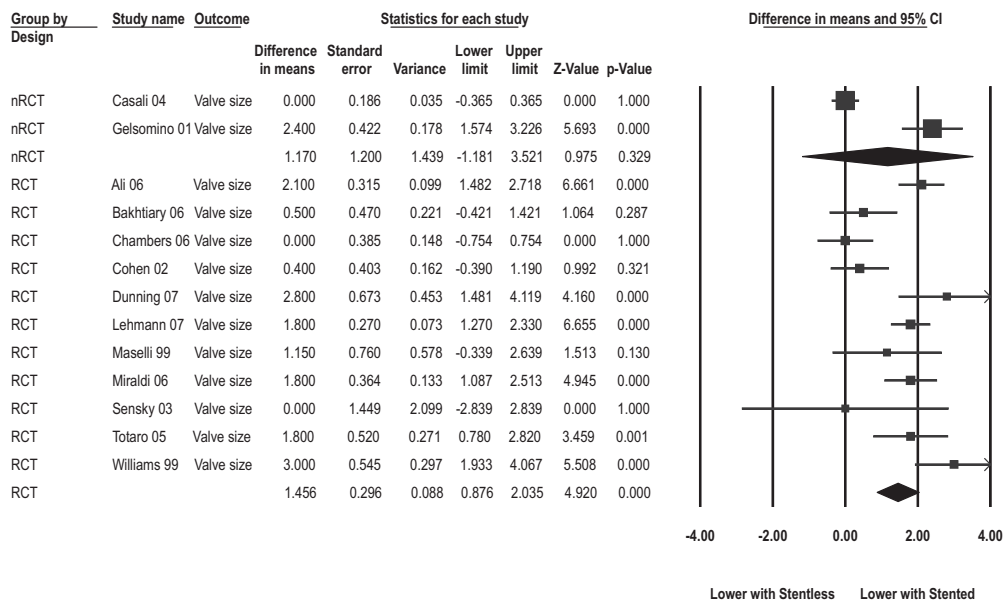


FIGURE 1. (A) Annular size comparison in RCT. (B) Valve size comparison in RCT.

(WMD -8 mm Hg, 95% CI -14 to -3 mm Hg; 6 RCT, level A; Fig. 3D) and at 3 to 8 years' follow-up (WMD -10 mm Hg, 95% CI -16 to -5 mm Hg; 2 RCT, level A).

Although the LVMI was generally lower in the stentless group versus the stented valve group, the aggregate estimates of mean difference did not reach significance during any time period of follow-up (1 month, 2 to 6 months, 1 year, at 8 years). Percent ejection fraction was also not significantly different

between stentless and stented groups at any time point (1 month, 6 months, 1 year, 3 years).

The coronary flow measured by magnetic resonance imaging was found to be higher in the stentless group compared with the stented group (343 ± 137 versus 221 ± 66 mL/min). Also, coronary flow reserve was higher for stentless valves (3.4 ± 0.3) than for stented valves (2.3 ± 0.1).<sup>14</sup>

**Consensus Statements**

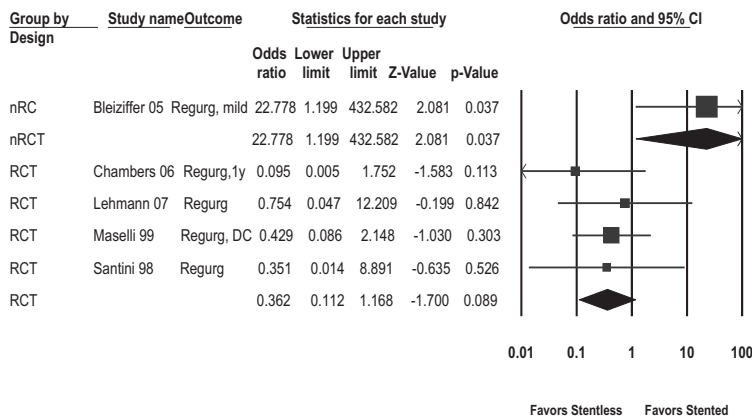
1. The mean/peak Ao gradient and EOAI showed a greater improvement in patients with stentless bioprosthetic valves at 6 months compared with stented bioprosthetic valves (level A).
  - a. There is a benefit for stentless valves for EOAI at 30 days ( $P = 0.04$ ) and 6 months ( $P = 0.033$ ) but not at 1 year ( $P = 0.101$ ; level A; EOAI in the normal range  $\geq 0.85\text{cm}^2/\text{m}^2$ ).
  - b. In stentless valves EOAI identified no mismatch. In stented valves the EOAI varied from mild mismatch ( $>0.75$ ) to normal ( $\geq 0.85$ ; level A).

2. A trend toward improvement remained at 1 year in mean Ao gradient, EOAI, and LVMI, but only peak Ao gradient was significantly lower in stentless versus stented bioprosthetic valves (level A).
3. Stentless and stented bioprosthetic valves showed similar improvement in LVEF at 1 month and at 6 months (level A).
4. Coronary flow reserve was greater with the stentless compared with stented bioprosthetic valve at hospital discharge and 6 months (level B).

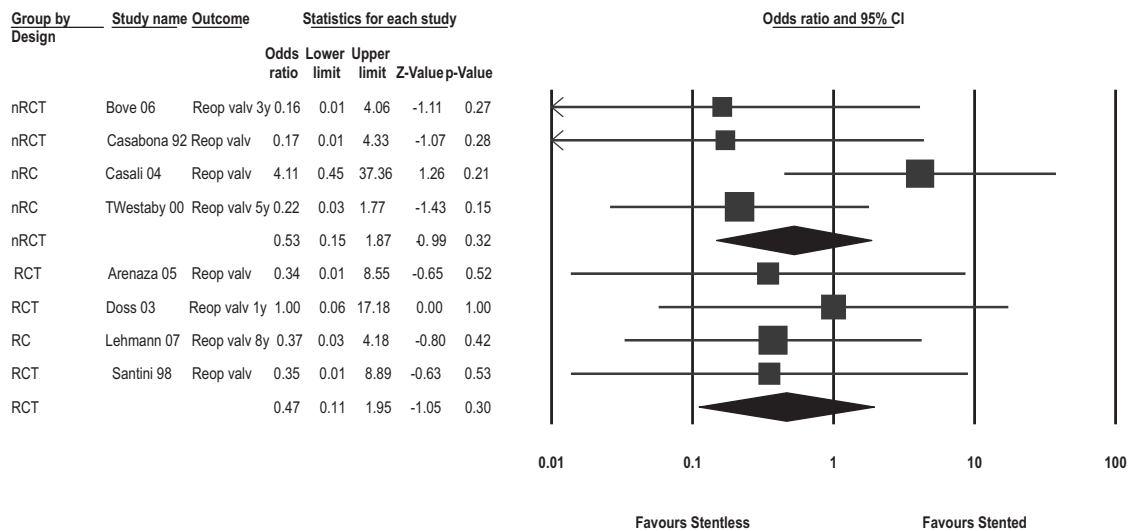
**Question 3: Do Stentless Bioprosthetic Valves Improve Resource Utilization?**

Cross-clamp time was significantly longer by 23 minutes (WMD 23 minutes, 95% CI 18–27 minutes; 14 RCT,

**A Valve Regurgitation: Stentless versus Stented Valve for AVR**

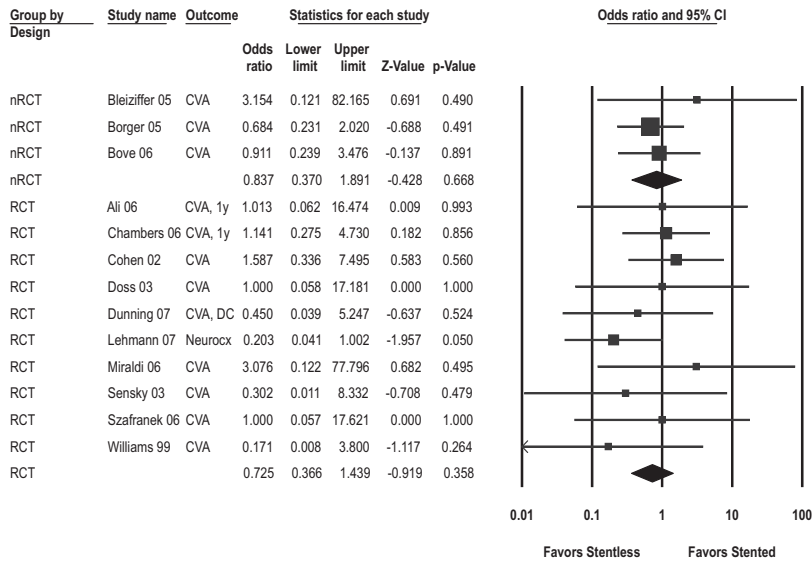


**B Reoperation for Valve Complications: Stentless versus Stented Valve for AVR**

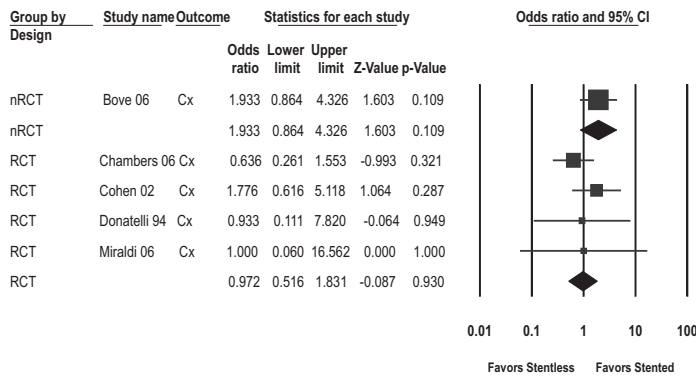


**FIGURE 2.** (A) Complication of Valvular regurgitation in Stentless and Stented bioprosthetic valve replacement. (B) Reoperation for valve complication in Stentless and Stented bioprosthetic valve replacement. (C) Postoperative CVA in Stentless and Stented bioprosthetic valve replacement. (D) Any postoperative complications in Stentless and Stented bioprosthetic valve replacement. (E) 2–10 yr mortality follow-up in Stentless and Stented bioprosthetic valve replacement.

**C Stroke or TIA: Stentless versus Stented Valve for AVR**



**D Any Complication: Stentless versus Stented Valve for AVR**



**E Death at 2 - 10 years: Stentless versus Stented Valve for AVR**

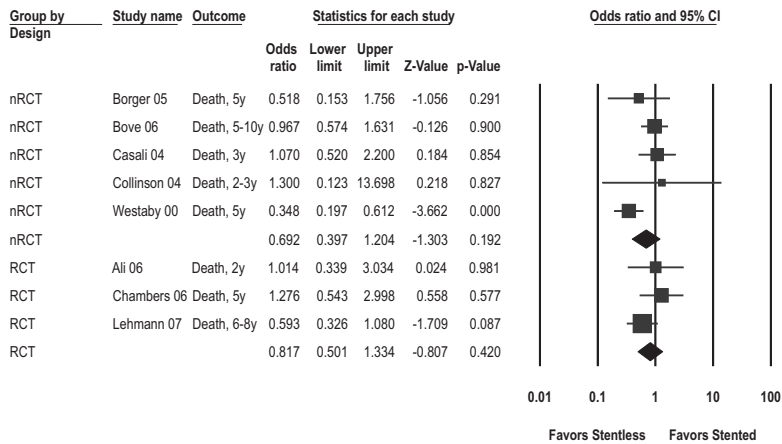
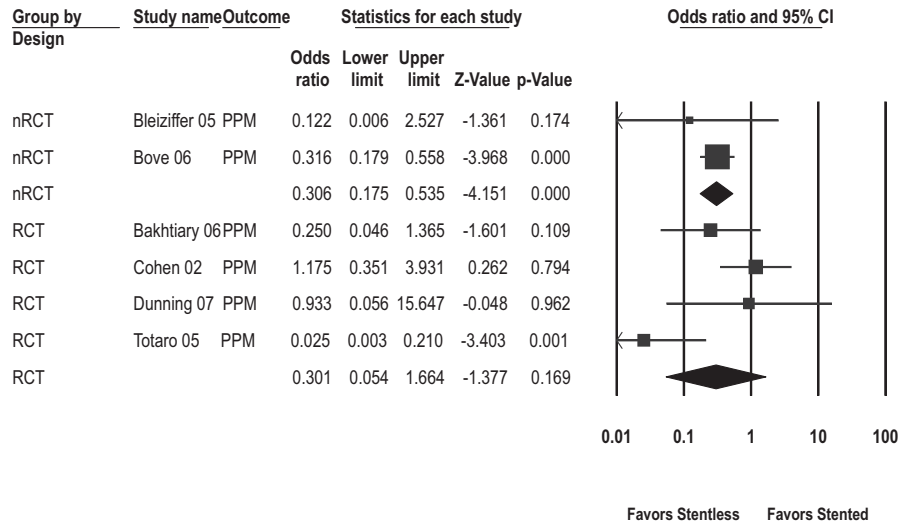
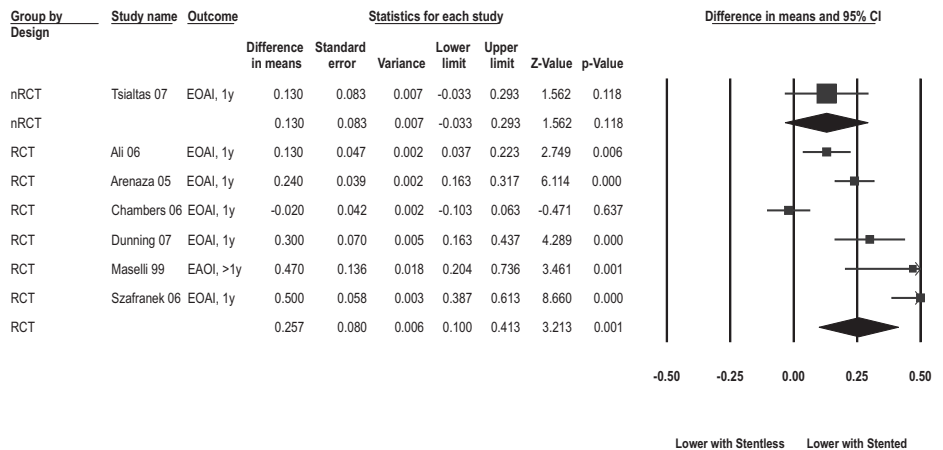


FIGURE 2. (Cont.)

### A Prosthesis Patient Mismatch: Stentless versus Stented Valve for AVR



### B EOAI at 1 year: Stentless versus Stented Valve for AVR



**FIGURE 3.** (A) Prosthesis-Patient Mismatch in Stentless and Stented bioprosthetic valve replacement. (B) EOAI at 1 yr in Stentless and Stented bioprosthetic valve replacement. (C) Mean valvular gradient in Stentless and Stented bioprosthetic valve replacement. (D) Peak valvular gradient in Stentless and Stented bioprosthetic valve replacement.

level A; Fig. 4A) and bypass time was significantly greater by 24 minutes (WMD 24, 95% CI 19–30 minutes; 13 RCT, level A) in the stentless group compared with the stented valve group. Time in the operating room was not significantly different with one RCT. Other resource-related outcomes, including ventilation time (WMD –11 hours, 95% CI –42 to +22 hours), ICU length of stay (WMD –0.1 day, 95% CI –1 to +1 day; 5 RCT, level A; Fig. 4B), and total hospital length of stay (WMD –0.2 day, 95% CI –2 to +2 days; 7 RCT, level A; Fig. 4C) did not differ between groups.

**Consensus Statements**

1. The ischemic and CPB times are significantly longer for implantation of a stentless bioprosthetic valve (~20 minutes; level A).

2. No difference has been shown in total time in the operating room (level B), ICU and hospital LOS (level A).

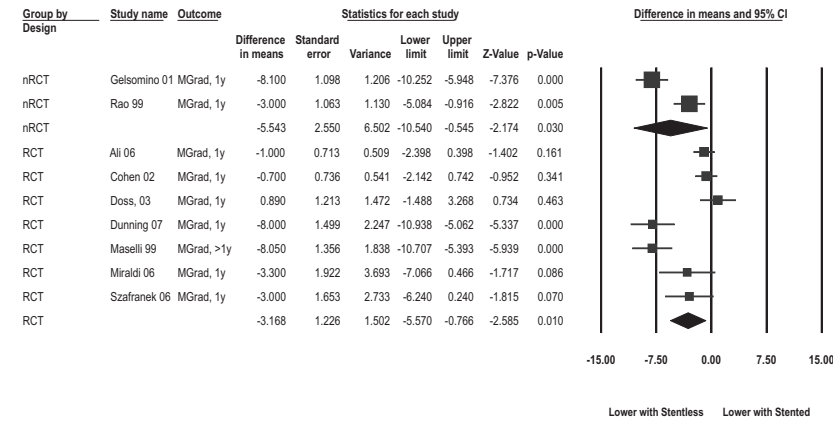
**Consensus Conference Recommendations**

To date all published RCTs of stentless bioprostheses valves have been inserted in the subcoronary configuration. The consensus panel agreed upon the following statements and recommendations in patients undergoing aortic valve replacement (Table 3):

1. Stentless and stented valves both provide an excellent valve substitute for aortic valve disease (class I, level A).
2. In certain situations, the early superior hemodynamic performance of stentless bioprostheses offers advantages over stented valves (class IIa, level A).



**C** Mean Gradient, 1 year: Stentless versus Stented Valve for AVR



**D** Peak Gradient, 1 year: Stentless versus Stented Valve for AVR

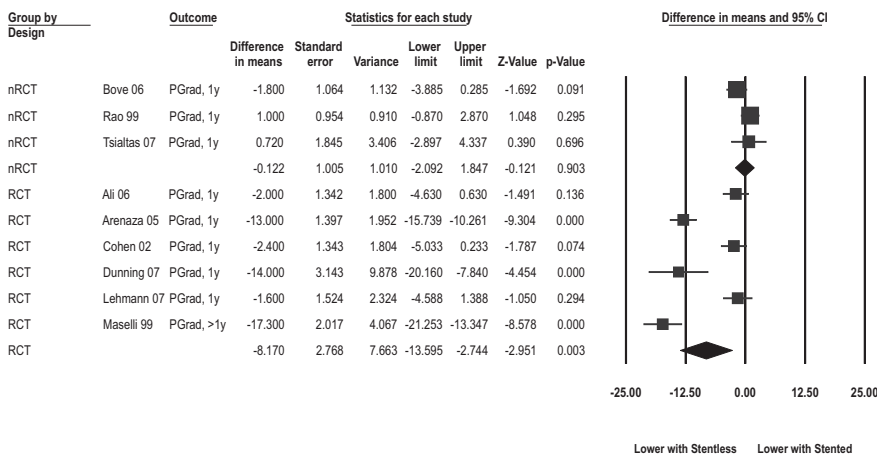


FIGURE 3. (Cont.)

Because there were no RCT comparing subcoronary stentless prosthetic valve and root replacement, the following recommendations are derived from expert opinion:

1. In the absence of aortic root disease and with an annulus greater than or equal to 21 mm, either stentless or stented valves are acceptable alternatives for the majority of patients when a current (second or third) generation bioprosthesis is indicated (class I, level C).
2. In the presence of an aortic annulus <21 mm, the use of a freestanding bioprosthetic root can be considered as an alternative to enhanced diameter stented bioprosthesi or a root enlargement procedure (class I, level C).

**DISCUSSION**

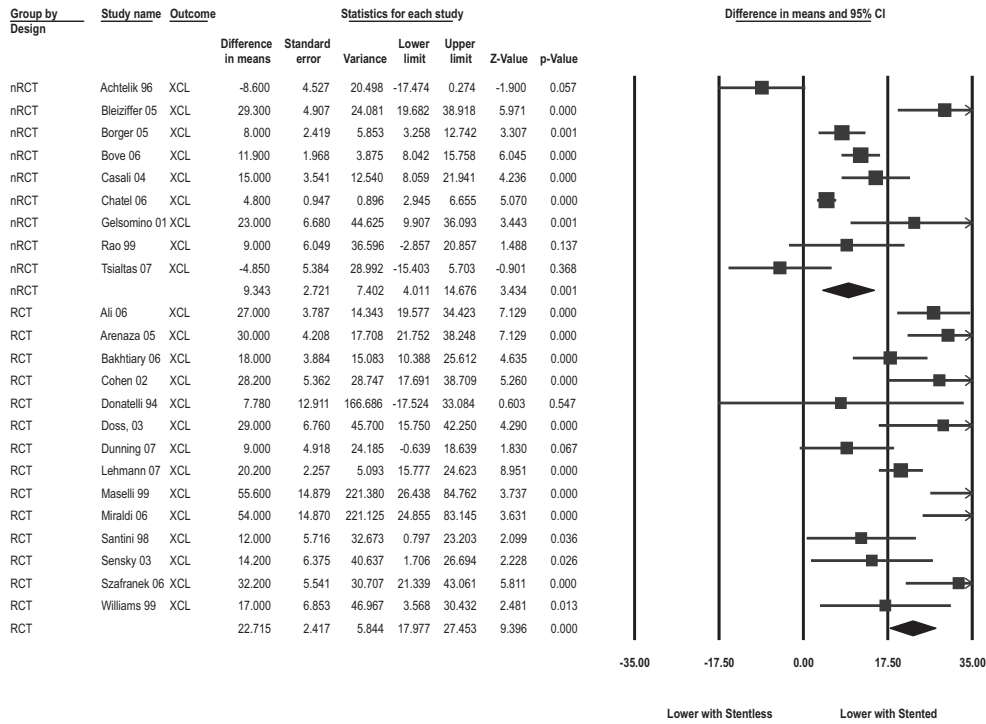
All randomized trials inserted the stentless bioprosthetic valves in the subcoronary configuration. Although none of the important clinical outcomes (prosthesis patient mismatch, valve complications, CVA, acute myocardial infarction, atrial fibrillation, A-V heart block, permanent pacemaker, thromboembolic events, heart failure, renal failure,

wound infection, bleeding complications, endocarditis, and mortality) were significantly impacted by the insertion of stentless versus stented valves, there were a number of intermediate hemodynamic and cardiac parameters (mean/peak Ao gradient, EOAI, and LVMI) that were improved with stentless valves. On the other hand, the ischemic and CPB times are significantly longer for implantation of a stentless bioprosthetic valve (~20 minutes) with no impact in total operating room time, ICU and hospital LOS.

**Strengths and Limitations**

A notable strength of this consensus statement is its reliance on the evidence base, with comprehensive consideration of benefits, risks, and resource-related issues. The methodology undertaken and recommendations provided by this consensus conference are in agreement with current recommendations for developing consensus statements and guidelines.<sup>12,13</sup> Clinicians tend to overestimate the effectiveness of new interventions, especially if the intervention in question rests within the realm of their expertise, unless they objectively take into account a systematic review of the

### A Cross Clamp Time (min): Stentless versus Stented Valve for AVR



### B ICU Length of Stay (days): Stentless versus Stented Valve for AVR

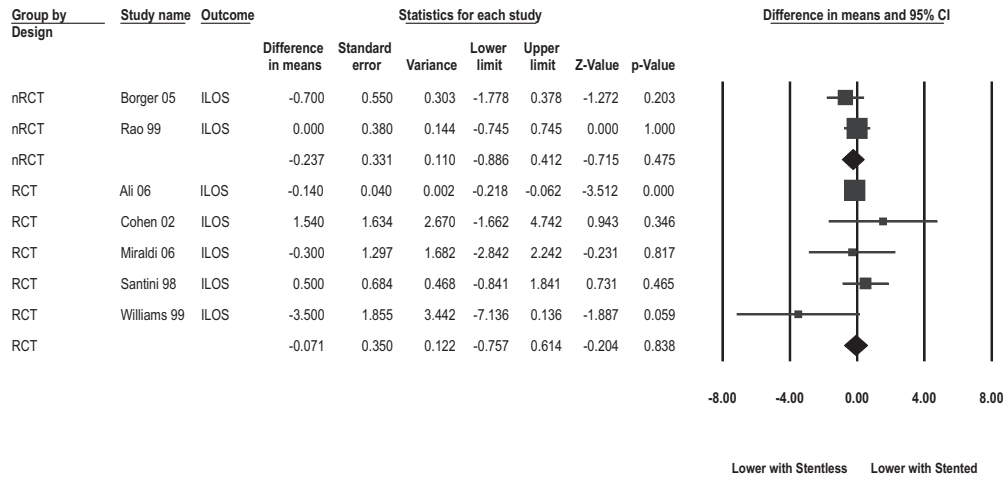


FIGURE 4. (A) Cross-clamp time in Stentless and Stented bioprosthetic valve replacement. (B) ICU LOS in Stentless and Stented bioprosthetic valve replacement. (C) Hospital LOS in Stentless and Stented bioprosthetic valve replacement.

evidence.<sup>15</sup> There is a tendency for group decision-making processes to experience “regression to the mean” or a group-think effects, whereby compromises are made in recommendations to come closest to pleasing all members of the panel,

even for issues that start off greatly polarized. To mitigate these risks, experts in evidence-based methodology and health technology assessment from within and outside of the surgical field were invited to facilitate the discussion and to

### C Hospital Length of Stay (days): Stentless versus Stented Valve for AVR

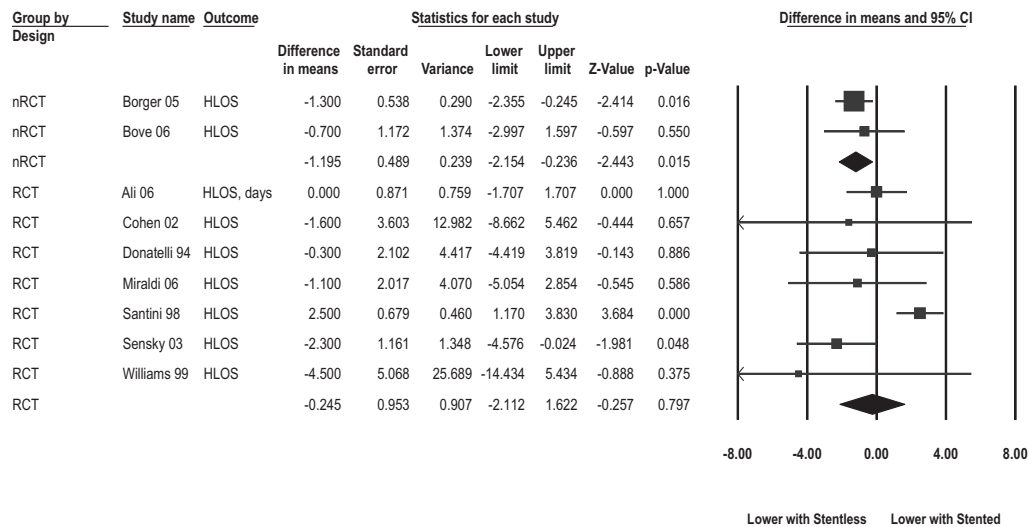


FIGURE 4. (Cont.)

ensure the best available evidence was the focus for discussion rather than opinions or political charges. This process has been similar to other ISMICS consensus conferences conducted in recent years.<sup>16-19</sup>

A few important limitations in the current literature were observed by the panel and were carefully balanced when addressing the question if stentless valve improves clinical and resource utilizations in compared with stented valve:

1. Insufficient data reported follow-up for assessment of long term performance inclusive of durability between stentless and stented bioprosthetic valve.

TABLE 3. Consensus Recommendations for Stentless Versus Stented Bioprosthetic Aortic Valves

Class of Recommendations and Level of Evidence	ISMICS Consensus Recommendations Stentless Versus Stented Valves
Class I, level A	Stentless and stented valves both provide an excellent valve substitute for aortic valve disease.
Class IIa, level A	In certain situations, the early superior hemodynamic performance of stentless bioprosthesis offers advantages over stented valves.
Class I; level C	In the absence of aortic root disease and with an annulus $\geq 21$ mm, either stentless or stented valves are acceptable alternatives for the majority of patients when a current (second or third) generation bioprosthesis is indicated.
Class I; level C	In the presence of an aortic annulus $< 21$ mm, the use of a freestanding bioprosthetic root can be considered as an alternative to enhanced diameter stented bioprosthesis or a root enlargement procedure.

2. Overlapping databases found with discrepancy in outcomes in some publications.
3. Publications often do not follow STS/AATS/EACTS guidelines (96') in reporting morbidity outcomes.
4. Drop out in trials were not explicitly accounted for in most studies.
5. There was a bias toward survivor and healthy patients with regard to echocardiographic studies.
6. Important subgroups of patients were not adequately studied, ie, ventricular dysfunction, elderly, abnormal BMI, and small aortic roots.
7. Insufficient published reports on clinical relevant outcomes such as AMI, renal failure, neurologic injury, quality of care, and prosthesis patient mismatch.
8. Insufficient published data on third generation (diameter enhanced) stented bioprostheses compared with stentless bioprosthetic valves.
9. Insufficient published data to differentiate the relative outcomes across subtypes of stentless compared with subtypes of stented bioprosthetic valves.

#### Aortic Root Configuration of Stentless Bioprosthetic Valve

As pointed out in the meta-analysis that all randomized trials inserted the stentless bioprosthetic valves in the sub-coronary configuration, the consensus panel discussed and consented as expert opinions on the following:

- Stentless bioprostheses have been used in a freestanding root configuration for patients with aortic root diseases such as aneurysm, dissection, Marfan syndrome, and native valve endocarditis (level C).
- This particular configuration is also useful for complex redo aortic valve surgery, eg, prosthetic valve endocarditis, reoperative homograft replacement (level C).

- Root configuration for elective AVR without root disease is another alternative for surgeons with experience in aortic root replacement (level C).
- For the surgical treatment of the small aortic root (<21 mm diameter), the stentless bioprostheses in the freestanding root configuration can be considered as an alternative to aortic annulus enlargement (Nicks or Manouagian procedures), or 3rd generation stented (optimal tissue-stent relationship for diameter enhancement, low (<2 mm Hg) or zero pressure glutaraldehyde fixation and treatment for the reduction of calcification), Carpentier Edwards PERIMOUNT Magna, Medtronic Mosaic Ultra, St. Jude Medical Epic Supra, Sorin Mitroflow and Sorin Freedom and Sorin Freedom Solo (level C).

### Indications for Subcoronary Implantation: (Level C)

The subcoronary configuration may be considered for (a) simple native valve endocarditis affecting leaflets only and for (b) small aortic roots where avoidance of a late calcified bioprosthetic root is considered desirable.

### Contraindications for Subcoronary Implantation: (Level C)

1. Severe calcification of the aortic root may be a contraindication to the use of a stentless bioprostheses.
2. The surgeon must give consideration to a disparity between the diameter of the annulus versus the sinotubular junction. If this is >10% a subcoronary configuration is not advised.
3. In the presence of bicuspid valve disease with a dilated aortic root, it may be advisable to buttress the sinotubular junction to prevent subsequent dilatation.
4. As a potential consequence of aging and dilatation of the aortic root, buttressing of the sinotubular junction may also be considered.
5. In the presence of abnormally placed coronary ostia eg, 180 degrees apart, a subcoronary implant is ill advised.

### Statements on Future Research

Future investigation must also evaluate the long-term survival in conventional aortic valve replacement matched in age/gender. This may relate to the timing of aortic valve intervention, in relation to the natural history of the disease and the status of systolic and diastolic function at the time of the intervention; correlated with postoperative hemodynamic, coronary flow evaluation, durability of the bioprostheses and quality of life. The hemodynamic performance should assess both systolic and diastolic performance to at least 10 years. The attainment of a normal cardiac output is dependent upon restoration of diastolic function which may depend upon adequate resolution of left ventricular hypertrophy. The assessment of durability of stentless bioprostheses requires at least 15 years evaluation. Studies should update the existing RCT in long-term follow-up, and benchmark for assessment of transcatheter technology and sutureless prostheses.

### ACKNOWLEDGMENTS

The authors acknowledge Ms. Aurelie Alger and Ms. Elizabeth Chouinard for their professional assistance in organizing the consensus conference; Dr. Guyan Wang, Dr. Kathy Fang, Dr. Myoung Kim, and Dr. Ling Pei for their expert data extraction; Ms. Jennifer Podeszwa-deOliviera and Ms. Karla VanKessel for their services in facilitating the literature searches and retrieval.

### REFERENCES

1. Levy D, Garrison RJ, Savage DD, et al. Prognostic implications of echocardiographically determine left ventricular mass in the Framingham heart study. *N Engl J Med*. 1990;322:1561–1566.
2. Sharma UC, Barenbrug P, Pokharel S, et al. Systematic review of the outcome of aortic valve replacement in patients with aortic stenosis. *Ann Thorac Surg*. 2004;78:90–95.
3. Kunadian B, Vijayalakshmi K, Thornley AR, et al. Meta-Analysis of valve hemodynamics and left ventricular mass regression for stentless versus stented aortic valves. *Ann Thorac Surg*. 2007;84:73–79.
4. Raja SG, MacArthur KJ, Pollock JC. Impact of stentless aortic valves on left ventricular function and hypertrophy: current best available evidence. *J Card Surg*. 2006;21:313–319.
5. Kallikourdis A, Jacob S. Is a stentless aortic valve superior to conventional bioprosthetic valves for aortic valve replacement? *Interact Cardiovasc Thorac Surg*. 2007;6:665–672.
6. Sackett DL, Straus SE, Richardson WS, et al. *Evidence-Based Medicine: How to Practice and Teach EBM*. 2nd ed. London: Churchill Livingstone; 2000.
7. Cheng D, Pepper J, Martin J, et al. Stentless versus stented bioprosthetic aortic valves: a systematic review and meta-analysis of controlled trials. *Innovations*. 2009;4:61–73.
8. Colditz GA, Miller JN, Mosteller F. How study design affects outcomes in comparisons of therapy. I. Medical. *Stat Med*. 1989;8:441–454.
9. Moher D, Pham B, Jones A, et al. Does quality of reports of randomized trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet*. 1998;352:609–613.
10. Milz S, Colditz GA, Mosteller F. How study design affects outcomes in comparisons of therapy. II. Surgical. *Stat Med*. 1989;8:455–466.
11. Schulz KF, Chalmers I, Hayes RJ, et al. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA*. 1995;273:408–412.
12. Shekelle PG, Woolf SH, Eccles M, et al. Clinical guidelines: developing guidelines. *BMJ*. 1999;318:593–596.
13. Shiffman RN, Shekelle P, Overhage M, et al. Standardized reporting of clinical practice guidelines: a proposal from the conference on guideline standardization. *Ann Intern Med*. 2003;139:493–498.
14. Bakhtiyari F, Schiemann M, Dzemali O, et al. Stentless bioprostheses improve postoperative coronary flow more than stented prostheses after valve replacement for aortic stenosis. *J Thorac Cardiovasc Surg*. 2006;131:883–888.
15. Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest*. 1986;89:2–3.
16. Puskas J, Cheng D, Knight J, et al. Off-pump versus conventional coronary artery bypass grafting: a meta-analysis and consensus statement from the 2004 ISMICS consensus conference. *Innov: Technol Tech Cardiothorac Vasc Surg*. 2005;1:2–27.
17. Allen K, Cheng D, Cohn W, et al. Endoscopic vascular harvest in coronary artery bypass grafting surgery: a consensus statement of the International Society of Minimally Invasive Coronary Surgery (ISMICS). *Innov: Technol Tech Cardiothorac Vasc Surg*. 2005;1: 51–60.
18. Diegeler A, Cheng D, Allen K, et al. Transmyocardial laser revascularization: a consensus statement of the International Society of Minimally Invasive Cardiothoracic Surgery (ISMICS) 2006. *Innov: Technol Tech Cardiothorac Vasc Surg*. 2006;1:314–322.
19. Downey R, Cheng D, Kernstine K, et al. Video-assisted thoracic surgery in lung cancer resection: a consensus statement of the International Society of Minimally Invasive Cardiothoracic Surgery (ISMICS) 2007. *Innov: Technol Tech Cardiothorac Vasc Surg*. 2007;2:293–302.