

Minimally Invasive Versus Open Mitral Valve Surgery A Consensus Statement of the International Society of Minimally Invasive Coronary Surgery (ISMICS) 2010

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Objective: The purpose of this consensus conference was to deliberate the evidence regarding whether minimally invasive mitral valve surgery via thoracotomy improves clinical and resource outcomes compared with conventional open mitral valve surgery via median sternotomy in adults who require surgical intervention for mitral valve disease.

Methods: Before the consensus conference, the consensus panel reviewed the best available evidence up to March 2010, whereby systematic reviews, randomized trials, and nonrandomized trials were considered in descending order of validity and importance. The accompanying meta-analysis article in this issue of the Journal

provides the systematic review of the evidence. Based on this systematic review, evidence-based statements were created for pre-specified clinical questions, and consensus processes were used to derive recommendations. The American Heart Association/American College of Cardiology system was used to label the level of evidence and class of each recommendation.

Results and Conclusions: Considering the underlying level of evidence, and notwithstanding the limitations of the evidence base (retrospective studies with important differences in baseline patient characteristics, which may produce bias in results of the evidence syntheses), the consensus panel provided the following evidence-based statements and overall recommendation:

In patients with mitral valve disease, minimally invasive surgery may be an alternative to conventional mitral valve surgery (Class IIb), given that there was comparable short-term and long-term mortality (level B), comparable in-hospital morbidity (renal, pulmonary, cardiac complications, pain perception, and readmissions) (level B), reduced sternal complications, transfusions, post-operative atrial fibrillation, duration of ventilation, and intensive care unit and hospital length of stay (level B). However, this should be considered against the increased risk of stroke (2.1% vs 1.2%) (level B), aortic dissection (0.2% vs 0%) (level B), phrenic nerve palsy (3% vs 0%) (level B), groin infections/complications (2% vs 0%) (level B), and, prolonged cross-clamp time, cardiopulmonary bypass time, and procedure time (level B). The available evidence consists almost entirely of observational studies and must not be considered definitive until future adequately controlled randomized trials further address the risk of stroke, aortic complications, phrenic nerve complications, pain, long-term survival, need for reintervention, quality of life, and cost-effectiveness.

Key Words: Minimally invasive, Mitral valve surgery, Consensus statement.

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Uptake of minimally invasive cardiac surgery continues to grow. The potential benefits of minimally invasive surgery include reduced pain and perioperative clinical complications, reduced length of stay, along with improved cosmetic results and patient satisfaction.^{1,3}

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Given the progression in popularity of minimally invasive mitral valve surgery (mini-MVS), and the increasing experience with the technique, mini-MVS has been adopted as standard of care by some, but not all, centers. Whether the purported benefits of mini-MVS translate into clinically important outcomes remains controversial, and there are conflicting opinions about whether minimally invasive surgery is ready for routine uptake in place of conventional open mitral valve surgery (conv-MVS) in selected patients or in the majority of patients who require surgical intervention for mitral valve disease. This article is intended to be read in light of the evidence provided in the accompanying systematic review published in this issue of the Journal.

METHODS

Purpose of the Consensus Conference

This consensus conference was held to clarify, for clinical practitioners and health care planners or administrators, the role of mini-MVS relative to conv-MVS in adults requiring surgical intervention for mitral valve disease. The growing practice of performing mitral valve surgery through the minimally invasive approach confirms the need for evidence-based recommendations, with careful deliberation of the balance of benefits versus risks. A secondary objective of this consensus conference was to identify the gaps in the evidence and suggest a future research agenda for mini-MVS.

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 did not involve direct funding from any device manufacturers. As in previous ISMICS consensus conferences, editorial independence was granted to the members of the expert panel, and the expectation was that the resulting consensus statements would be based on the best available evidence, with explicit acknowledgment of which recommendations were informed by evidence versus where opinion was required to create statements (when evidence was lacking).

Selection of Panel Members

Members of the consensus panel were invited to participate by the chair (V.F.) and facilitators of the consensus process. Members included representation from eight countries: eight cardiovascular surgeons (one from Israel, one from Switzerland, two from Germany, two from France, and two from the United States), one cardiac anesthesiologist, and one methodologist with expertise in health technology assessment and meta-analysis (Canada).

Defining the Clinical Question

Before the consensus conference, the consensus panel was asked to specify the clinical question, which involved defining each of the following considerations: patient population of interest, intervention of interest, valid comparator

group(s), and outcomes of interest.⁴ The clinical question was developed collaboratively with input from all consensus panel members and was finally stated as follows:

“Does minimally invasive mitral valve surgery via thoracotomy (mini-MVS) improve clinical and resource outcomes compared with conventional open mitral valve surgery through median sternotomy (conv-MVS) in adults requiring intervention for mitral valve disease?” Specifically, does mini-MVS compared with conv-MVS improve:

1. Perioperative and long-term morbidity and mortality
2. Pain, functionality, and quality of life (QOL)
3. Perioperative and long-term resource utilization.

Identifying Relevant Evidence

After the clinical questions had been defined, all published and unpublished evidence (presented at major meetings) with prespecified acceptable study designs was sought to inform this clinical question. Acceptable study designs included any randomized or nonrandomized comparative trial providing clinical or resource information for mini-MVS versus conv-MVS in adults requiring surgical intervention for mitral valve disease. Because there was no available comprehensive systematic review that included all relevant evidence to answer our clinical question, we conducted a full systematic review and meta-analysis of the evidence before the conference. The complete methodology and results of the systematic review has been described in another article in this issue of the Journal and should be consulted before reading the consensus statements provided here.⁵ In short, before the consensus conference, comprehensive searches of Cochrane, MEDLINE, EMBASE, and abstract databases were conducted to identify all randomized and nonrandomized comparative trials comparing mini-MVS with conv-MVS, and which reported clinical- or resource-related outcomes. Potentially relevant studies were circulated to the consensus panel for review and to assess agreement with the prespecified inclusion criteria and to determine whether any relevant trials were missed. Information related to baseline characteristics and outcomes was extracted by one author and verified by a second author. When appropriate, data were synthesized by valid meta-analytic techniques to provide more precise aggregate outcome estimates across multiple studies reporting the same outcome. Data that were not appropriate for statistical synthesis across trials were summarized qualitatively in tables and text to ensure all relevant data were addressed in the systematic review. The results of the systematic review and meta-analysis were used to populate evidence tables and forest plots to form the basis for discussions and support decision making for the consensus panel.

Reviewing and Presenting the Evidence

Before the consensus conference, each member of the consensus panel reviewed the selected randomized and nonrandomized studies related to the clinical questions. During the consensus conference meeting, the panelists were asked to address the following subquestions with the best available evidence:

1. When compared with conv-MVS, does mini-MVS reduce perioperative morbidity (stroke, myocardial infarction, ar-

- rhythmias, regurgitation, heart failure, transfusion, bleeding, reoperation for bleeding, renal failure, and infection) and mortality over the short term and long term?
2. When compared with conv-MVS, does mini-MVS improve functionality, satisfaction, and QOL?
 3. When compared with conv-MVS, does mini-MVS affect overall resource utilization (procedure time, length of stay, and overall costs)?

Applying the Evidence to Create Recommendations

Levels of Evidence and Grade of Recommendations

The methods were similar to previous consensus conferences hosted by ISMICS, (6–11) and the methodologic details are provided here for reader convenience. The evidence used to inform each clinical subquestion was classified according to the taxonomy suggested by AHA (American Heart Association)/American College of Cardiology (ACC), as outlined in Table 1. This classification categorizes the evidence based 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.”^{4,12–15} 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; accessed April 19, 2004) (Tables 1 and 2). As recommended by guidelines,¹⁶ classification of the evidence and labeling recommendations should involve a group panel using a democratic voting process after adequate group discussion of the strength of the evidence.

Members of the panel considered the highest possible level of evidence to inform the clinical subquestions. Systematic reviews, meta-analyses, and randomized trials (level A evidence, Table 1) were considered preferentially to non-randomized clinical trials (level B evidence). When evidence from published or unpublished studies (from major meetings) to address the question was not available, expert opinion from the consensus panel members was required (level C evidence). In each case, the best available level of evidence was explicitly stated and subsequently interpreted in light of strengths and weaknesses before a statement of recommendation was made. It was generally agreed that recommendations with higher levels of evidence without heterogeneity should be interpreted with more confidence than recommendations based on lower levels of evidence or with heterogeneity, and that recommendations should be explicitly classified as per the ACC/AHA system (Table 2).

TABLE 1. Levels of Evidence

Level A	Data derived from multiple randomized clinical trials
Level B	Data derived from a single randomized trial, or non-randomized studies
Level 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

Consensus Process and the Role of Evidence Versus Opinion

After reviewing the available evidence during the consensus meeting, the consensus panel created draft statements for the subquestions. Further discussion of the strength, consistency, clinical significance, and relevance of the evidence occurred before final revisions and final agreement was made to the consensus statement (along with its appropriate Level of Evidence and Class of Recommendation) for each of the subquestions.

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 differences in interpretation and value were resolved by discussion and majority consensus. Therefore, it is important to note that consensus was not always unanimous per se. This is particularly true for subquestions informed only by lower levels of evidence or heterogeneous evidence, where controversy was not allayed by clear evidence and where expert opinion was required to make a judgment.

After each subquestion had been addressed, the entire consensus panel reviewed the recommendations and their assigned grades of recommendations and proposed levels of evidence to address the overarching question of whether mini-MVS should be recommended as an alternative to conv-MVS in today's practice environment.

In summary, this consensus process sought to be evidenced based whenever evidence was available, while allowing for opinions to inform the judgment when the evidence was incomplete. The basis for the statement was labeled by a declarative level of evidence in order to understand whether the basis was evidence or opinion. Bringing experts together for a consensus process based as far as possible on evidence allowed for a carefully considered judgment of the evidence-based recommendations along with their certainties and uncertainties, but still remains imperfect given the limitations of the evidence and the need for filling in the gaps.

RESULTS

A systematic review and meta-analysis of the evidence performed by members of the consensus panel was used as the basis for the discussion of the evidence and formation of the recommendations. All available randomized and nonran-

domized comparative trials of isolated mini- versus conv-MVS were included in the systematic review.⁵

The systematic review with meta-analysis identified two randomized trials and 33 nonrandomized studies for a total of 35 studies comparing mini-MVS versus conv-MVS.¹¹ There was broad representation from a variety of countries in the included studies. Average age of patients at baseline was 55 years, 42% of whom were women. At baseline, mean ejection fraction was 55%, and approximately 7% of patients had diabetes, 22% had atrial fibrillation, 4% had previous myocardial infarction, and 3% had previous stroke. On average, 3.7% of patients required conversion from planned mini-MVS to conv-MVS, and it was not clear whether the individual studies excluded converted patients. We were unable to consider the impact of converted patients because of the lack of information about their outcomes in the studies.

There were some differences in baseline characteristics between groups when the studies were combined. Mini-MVS patients were slightly younger by 1.6 years than conv-MVS patients, and this difference was statistically significant [weighted mean difference (WMD) -1.57 , 95% confidence interval (CI) -2.72 to -0.42 years]. In addition, mini-MVS patients were less likely to have renal dysfunction, chronic obstructive pulmonary disease, or elevated pulmonary artery pressures at baseline. These differences were generally driven by patient selection in the nonrandomized studies in this meta-analysis.¹¹ Please refer to the accompanying systematic review in this issue of the Journal for the baseline characteristics table.

For the following outcomes, heterogeneity across studies was observed in the meta-analysis for chest tube drainage, deep infection or dehiscence, bypass time, cross-clamp time, ventilation time, procedure time, length of stay, and time to return to normal activity. Nevertheless, much of the heterogeneity was less concerning because it was driven by uncertainty about the size of effect and not the direction of effect and therefore did not put into question the presence of significant benefit (when detected). The presence of heterogeneity was considered for each respective outcome during the consensus conference. 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 from meta-analysis of randomized controlled trials (RCTs, level A) would have been preferred; however, because randomized trials were generally unavailable, aggregate results from nonrandomized evidence (non-RCTs, level B) were therefore required for most outcomes. Readers may consult the original publication for comprehensive reporting of both randomized and nonrandomized trials for all endpoints. For discrete outcomes, risk ratios (RRs) and their 95% CIs are reported. For continuous outcomes, the WMD (95% CI) is reported.

Question 1: Does Mini-MVS Compared With Conv-MVS Improve Perioperative Morbidity and Mortality?

Postoperative all-cause mortality was not significantly different between mini-MVS and conv-MVS in hospital or at

30 days (1.2% vs 1.5%, RR 1.03, 95% CI 0.75–1.42; 20 studies, level B). There was no difference between the RCTs and non-RCTs for this outcome, given that there were no deaths reported in either of the two RCTs.

Clinical outcomes that were improved with mini-MVS compared with conv-MVS included bleeding, units of red blood cells (RBCs), platelets and fresh frozen plasma transfused, postoperative atrial fibrillation, and (of course) sternal wound complications. Volume of bleeding, generally measured by chest tube drainage, was reduced with mini-MVS compared with conv-MVS by ~ 300 mL (WMD -255 mL, 95% CI -437 to -95 mL; 12 studies; level B). Volume of RBCs transfused was reduced by nearly two units (WMD 1.9 units, 95% CI -2.5 to -1.2 units, level B) for mini-MVS versus conv-MVS. However, the number of patients transfused RBCs was not significantly reduced. The volume of fresh frozen plasma transfused was reduced with mini-MVS versus conv-MVS, although the reduction was <0.5 unit (WMD -0.4 units, 95% CI -0.8 to -0.08 units, level B). The number of patients receiving platelet transfusion was reduced with mini-MVS versus conv-MVS, although the absolute reduction was small (16% vs 19%; RR 0.80, 95% CI 0.73–0.88; two studies, level B). The reasons for reduced bleeding are most likely associated with a smaller incision and less dissection of tissue and thus a smaller wound surface. Diffuse bleeding should therefore be less. There may, however, be a potential bias in that patients were also younger, and the threshold for transfusion may thus be different as lower hematocrit levels may have been accepted in younger patients. Transfusion data by age were unfortunately not available to test this hypothesis.

Mini-MVS was associated with a reduction in postoperative atrial fibrillation compared with conv-MVS (absolute risk reduction 4%). Whether this may be due to the reduced systemic inflammatory approach associated with the less traumatic minimally invasive approach remains to be proven. Reduction in atrial fibrillation with minimally invasive cardiac surgery has also been shown for other minimally invasive procedures including off-pump bypass surgery compared with on-pump bypass surgery.^{17,18} The reason for this difference in the new onset of atrial fibrillation remains uncertain. Perhaps, femoral vein cannulation is less likely to trigger fibrillation than direct right atrial cannulation, which is associated with more atrial manipulation. Limited dissection and manipulation of the heart and limited pericardiotomy may also play a role. Size of the left atrium as well as age differences may also be confounding factors. In addition, the studies did not clearly denote the number of patients who received concomitant surgical ablation for atrial fibrillation, and it is possible that this was performed more commonly in the conv-MVS group.

Although atrial fibrillation was significantly reduced (absolute risk reduction 4%) with mini-MVS compared with conv-MVS (RR 0.87; 95% CI 0.77 to 0.99; eight studies, level B), it is important to note that no reduction in pacemaker insertion was found (perhaps due to low power, as few studies consistently reported this outcome). It is also important to note that the finding of lesser postoperative atrial

fibrillation seems counterintuitive to the finding of increased risk of stroke in the mini-MVS group (see below).

Some adverse clinical outcomes were increased with mini-MVS compared with conv-MVS, including stroke (defined as neurologic deficits >24 hours), aortic dissection, phrenic nerve palsy, and groin wound/vasculature complications. The absolute risk increase of stroke for mini-MVS versus conv-MVS was 0.9% overall (2.1% vs 1.2%, RR 1.79, 95% CI 1.35–2.38; 13 studies, level B). In the two RCTs in the meta-analysis, stroke was not measured (or not reported). To select for higher quality nonrandomized studies to explore whether study design impacted the estimate of stroke risk, subanalysis of propensity-matched studies was performed. Subanalysis of two propensity comparison studies also showed significant increase of stroke of 1% with mini-MVS compared with conv-MVS (1.9% vs 0.9%, RR 2.02, 95% CI 1.40–2.94; two studies, level B). The results of these higher quality propensity-adjusted studies were consistent with the remainder of the retrospective unmatched cohort studies reporting on this outcome. Further exploration of the potential reasons for increased risk of stroke was performed by subanalyzing studies that reported using endoaortic clamp separately from those that reported using exclusively the transthoracic clamp.

The increased risk of stroke in the mini-MVS group compared with conv-MVS was numerically greater in the subgroup of mini-MVS studies that used endoaortic clamp exclusively (RR 1.72, 95% CI 0.91–3.23; $P = 0.09$; five studies, level B) or in studies that reported using endoaortic clamping in a proportion of included patients (RR 1.84, 95% CI 1.33–2.55; $P = 0.0002$; three studies, level B). In those studies in which transthoracic clamping was used exclusively, the risk was not increased, although this subgroup was underpowered (RR 0.80, 95% CI 0.07–8.92; $P = 0.9$; four studies, level B). In the studies using exclusively transthoracic clamping, there were only two strokes reported (one in each group). Because there was no heterogeneity across the trials for the outcome of stroke ($I^2 = 0\%$), we cannot conclude from these data that the difference in risk of stroke is related to the use of the endoaortic approach for clamping. More importantly, because these results are derived from observational studies, a causal link between mini-MVS and stroke cannot be definitively determined because important differences between patients in each group at baseline and/or differences in their treatment other than the type of surgery received may have biased the results. Clearly, this finding of potential for increased risk of stroke remains an important result to be explored further through trial designs adequate in size and duration to answer the question.

Potential reasons for the increased risk of stroke remain unknown, and have not been specifically studied. Some opinions (not yet supported by evidence) that may be important to consider for future hypothesis generation to guide future studies might include the following:

- Incomplete de-airing associated with the minimally invasive approach.
- Retrograde aortic flow with the potential of retrograde embolism from a calcified thoracic aorta or aortic arch.

- Use of CO₂ insufflation during mini-MVS to reduce the amount of detectable bubbles using transcranial Doppler.
- Failure to use an aortic root vent may potentially increase the risk of air emboli, leading some to recommend leaving the aortic root vent until the heart is fully beating and no more bubbles are seen on transesophageal echocardiography (TEE).
- To prevent retrograde embolism, it has been suggested that retrograde flow should be avoided in patients with an athermanous aorta or arterial cannulation may be performed via the axillary artery.
- Perhaps, prolonged cross-clamp time and cardiopulmonary bypass (CPB) time associated with mini-MVS contributes to the increased risk of stroke.

None of these factors has yet been proven to be the reason for increased risk of stroke, and these hypotheses require appropriate study.

Aortic dissections and iatrogenic aortic injuries were both increased with mini-MVS versus conv-MVS. Risk of aortic dissection, considered alone, was 0.2% versus 0% for the two groups, respectively (RR 6.04, 95% CI 1.06 to 34.47; six studies, level B). Similarly, when aortic dissections and injuries were considered as a composite endpoint, there was a significant increased risk with mini-MVS versus conv-MVS, although the absolute event rate was small (0.4% vs 0%, 5.68, 95% CI 1.23 to 26.17; eight studies, level B). It was not possible to determine the reasons for aortic dissections and iatrogenic aortic injuries from the information provided in the studies. No studies have been done to specifically inform this risk. Perhaps, increased incidence of aortic injury can be attributed to the learning curve associated with a change in aortic clamping techniques. If not monitored well, the endoaortic balloon can obstruct the truncus and lead to temporary malperfusion of the brain, and for this reason, it has been recommended to monitor both right and left radial artery pressures. Perhaps, retrograde cannulation of the femoral artery leads to increased risk of aortic injury which, with retrograde aortic flow, can predispose to aortic dissection. Some have suggested, therefore, that meticulous use of the Seldinger technique is important, and if there is any resistance for the guide wire, subclavian artery access should be chosen. These suggestions remain to be studied.

Risk of phrenic nerve palsy was higher with mini-MVS versus conv-MVS by an absolute increase of 3% (3% vs 0%, RR 7.6, 95% CI 1.3 to 44.7; three studies, level B). Some of the patients in the studies that reported phrenic nerve palsy experienced respiratory compromise and prolonged ventilation,^{19,20} whereas other patients experienced only diaphragm elevation¹ and/or were not described in sufficient detail to determine the clinical significance of the nerve palsy. It has been suggested that phrenic nerve palsy may result from extensive pull on the pericardial retraction sutures that are sometimes used for enhancing exposure of the left atrium. As a result, some have suggested that it is important to (1) cut the pericardium not too close to the phrenic nerve (≥ 3 cm away) and (2) not to place the retraction sutures close to the nerve and avoid excessive pull. Another potential source of phrenic nerve injury may be the use of a cryoprobe for concomitant

ablation therapy, as the probe can come in close proximity to the nerve and cause temporary palsy. Again, studies are needed to clarify these hypotheses.

Not surprisingly, sternal wound infections were significantly decreased with mini-MVS versus conv-MVS (0% vs 0.3%; RR 0.34, 95% CI 0.12 to 0.95; seven studies, level B). This is a result that is consistent with expectations, as the mini-MVS approach was by definition via a thoracotomy rather than via sternotomy, whereas the conv-MVS approach was by definition only via median sternotomy in this meta-analysis. As a corollary, the conv-MVS approach resulted in an absolute increase in the risk of groin infections/complications by 2% compared with conv-MVS (2% vs 0%, RR 5.62, 95% CI 1.26 to 25.135 studies, level B).

Other perioperative clinical outcomes did not differ between mini-MVS and conv-MVS, including renal complications (renal dialysis and renal dysfunction), pulmonary complications (pneumonia, pneumonitis, pleural effusion, and pneumothorax), cardiac outcomes (acute myocardial infarction, ventricular arrhythmias, mitral insufficiency, tamponade, pericardial effusion, heart failure, and thromboembolic events), reoperation for bleeding.

Statement

1. No difference was found in mortality (1.2% vs 1.5%) between mini-MVS and conv-MVS during the perioperative period and up to 30 days postoperatively (level B).
2. Risk of stroke was increased (2.1% vs 1.2%, number needed to harm = 111) with mini-MVS versus conv-MVS (level B).
3. Risk of aortic dissection was increased (0.2% vs 0%) with mini-MVS versus conv-MVS (level B).
4. Risk of phrenic nerve palsy was increased (3% vs 0%) with mini-MVS versus conv-MVS (level B).
5. Risk of groin infections/complications was increased (2% vs 0%) with mini-MVS versus conv-MVS (level B).
6. Risk of sternal complications was decreased (0% vs 0.3%) with mini-MVS versus conv-MVS (level B).
7. Volume of blood product transfusion was reduced (1.5 vs 3.5 RBC units) with mini-MVS versus conv-MVS (level B), but reoperation for bleeding was not different between groups (level B).
8. Risk of postoperative atrial fibrillation was reduced (18% vs 22%) with mini-MVS versus conv-MVS (level B).
9. There was comparable risk of other in-hospital morbidities (renal, pulmonary, cardiac, and readmission rates) for mini-MVS and conv-MVS (level B).
10. Longer term outcomes, including readmissions, need for reoperation, and survival at 1 to 8 years, were similar between mini-MVS and conv-MVS (level B); however, very few studies reported these outcomes.

Question 2: Does Mini-MVS Reduce Pain and Improve Functionality, Satisfaction, and QOL Compared With Conv-MVS?

Pain measured via VAS was not significantly reduced for mini-MVS versus conv-MVS (WMD -0.07 points, 95% CI

-0.25 to $+0.11$ points; five studies, level B) when measured postoperatively on day 1 through to discharge. Use of analgesics also did not differ between groups. However, few studies reported any outcomes related to pain and failure to find a difference may be due to underreporting. Nonetheless, it is interesting to note that in the studies where VAS was reported, the difference between groups (mean difference) and range of plausible differences (95% CI) was very small.

New York Heart Association class was slightly improved after 1 year for mini-MVS compared with conv-MVS (mean class 1.32 vs 1.52, WMD -0.26 , 95% CI -0.27 to -0.25 ; two studies, level B), but the difference was small and based on two studies. The clinical relevance of this small incremental improvement between groups is uncertain.

There was no significant difference in freedom from reoperation between groups at 1 year (RR 1.03, 95% CI 0.97 to 1.10; 1 study, level B) based on one study only. However, at 8 years, there was significant improvement in freedom from reoperation for mini-MVS compared with conv-MVS (RR 1.04, 95% CI 1.01 to 1.08; one study, level B) based on one study only.

Return to normal activity was significantly faster for mini-MVS versus conv-MVS (6.3 vs 12.3 weeks, WMD -4.96 weeks, 95% CI -6.39 to -3.52 weeks; three studies, level B). There was significant heterogeneity across the studies for this outcome.

Time to return to normal activity was significantly improved with mini-MVS versus conv-MVS (WMD -5 weeks, 95% CI -6.4 to -3.5 weeks; three studies, level B). QOL was reported in only one observational study and showed no differences in the degree of improvement in QOL postoperatively between groups.

Mean incision length was 6.3 cm, and it was 16 cm shorter, on average, in the mini-MVS group compared with conv-MVS in the few studies that reported comparative data for this outcome (WMD -16 cm, 95% CI -19 to -13 cm, level B). One study measured patient dissatisfaction with the scar postoperatively and showed that significantly fewer patients were dissatisfied with the scar in the mini-MVS group versus conv-MVS (0% vs 19%, RR 0.05, 95% CI 0 to 0.79; 1 study, level B).

Statement

1. There was no difference in reported pain perception between mini-MVS and conv-MVS during the perioperative period and up to 30 days (level B).
2. Patient dissatisfaction with the scar postoperatively was reduced (0% vs 19%) with mini-MVS versus conv-MVS (level B); however, only one study reported this outcome.
3. New York Heart Association class improvement at 1 year was similar (mean class 1.32 vs 1.52) with mini-MVS and conv-MVS (level B).
4. Time to return to normal activity was significantly improved (6 vs 12 weeks) with mini-MVS compared with conv-MVS (level B).

5. There was a similar need for reoperation at 1 year between mini-MVS and conv-MVS (level B); however, few studies reported this outcome.
6. No difference was found for QOL between mini-MVS and conv-MVS (level B); however, only one study reported this outcome.

Question 3: When Compared With Conv-MVS, Does Mini-MVS Affect Overall Resource Utilization (Operating Room Time, Length of Stay, and Overall Costs)?

Although cross-clamp time, CPB time, and procedure time were increased with mini-MVS compared with conv-MVS, the ventilation time, and intensive care unit (ICU) and hospital length of stay were reduced. Cross-clamp time was increased by 21 minutes (WMD 21.41, 95% CI 10.14 to 32.69 minutes, level B), when all studies were considered in aggregate. In exploratory subanalyses, the increased cross-clamp time among observational studies was found mainly for repair but not for replacement. At least one study has reported a learning curve effect with earlier experience in mini-MVS requiring longer than later experience with mini-MVS, although in later experience, they still required a longer procedure time with the minimally invasive approach compared with conventional surgery.²¹ However, subanalysis of RCTs showed shorter cross-clamp time with mini-MVS versus conv-MVS (56 ± 16 minutes vs 60 ± 19 minutes, WMD -4.0 minutes, 95% CI -7.2 to -0.7 minutes), which is opposite to what the observational studies suggested. Cross-clamp time may be related directly to the experience of the centres. However, this hypothesis was not tested in our meta-analysis.

CPB time was significantly increased with mini-MVS versus conv-MVS (WMD 33.0, 95% CI 18.9 to 47.1 minutes; 27 studies, level B), when all studies were considered in aggregate. There was significant heterogeneity across studies for this outcome, and subanalysis of the two RCTs showed significantly reduced CPB time with mini-MVS versus conv-MVS (WMD -4 minutes, 95% CI -7 to -1 minutes), which is opposite to what the nonrandomized studies reported. The reasons for the discrepancy between randomized and nonrandomized studies remain uncertain. Often, the patient is put on CPB immediately after femoral cannulation even before the thoracotomy is made. This of course adds to the overall CPB time in mini-MVS.

Procedure time was significantly increased for mini-MVS compared with conv-MVS (WMD 0.79 hours, 95% CI 0.41 to 1.16 hours; 13 studies, level B) when all studies were considered together. There was significant heterogeneity among the studies for this outcome, but the heterogeneity was mostly due to the degree of increased procedure time rather than to differences in direction of effect. The single RCT that reported this outcome showed no significant difference in procedure time between groups (WMD 0.24, 95% CI -0.31 to $+0.79$ hours, one RCT, level B), although the trend was in the same direction and the study was likely underpowered.

Ventilation time was significantly reduced for mini-MVS compared with conv-MVS (12.6 vs 19.9 hours, WMD -2.07 hours, 95% CI -3.39 to -0.75 hours, 18 studies, level

B). The one RCT that reported this outcome showed no difference in the length of ventilation between mini- and conv-MVS (WMD -3.0 , 95% CI -7.4 to $+1.4$ hours, level B) but may have been underpowered to detect a significant difference.

Length of stay in ICU was significantly reduced for mini-MVS versus conv-MVS (WMD -0.50 days, 95% CI -0.68 to -0.32 days, 18 studies, level B). No RCTs reported this outcome, and the heterogeneity among observational studies was generally not of concern given that the direction of effect was similar for most studies. Similarly, length of hospital stay was reduced with mini-MVS versus conv-MVS (WMD -1.60 days, 95% CI -2.09 to -1.11 days, 26 studies, level B). There was significant heterogeneity among the studies for this outcome, but the direction of effect was similar for most studies. Differences in patient discharge protocols and bed availability may account for differences in degree of reduction in length of stay. Subanalysis of the two RCTs reporting this outcome showed only a small numeric reduction in hospital length of stay that did not reach significance (WMD -0.04 days, 95% CI -0.8 to $+0.7$ days).

The overall impact on total costs remains uncertain. Although some centers have suggested cost savings with mini-MVS, this finding was not universal. It was not possible to combine costs reported in various studies across disparate countries, and synthesis of cost estimates was not possible because of heterogeneity. The incremental cost-effectiveness for mini- versus conv-MVS remains unstudied.

Statements

1. Cross-clamp time was longer (95 vs 74 minutes) for mini-MVS compared with conv-MVS (level B).
2. Cardiopulmonary bypass time was longer (144 vs 112 minutes) for mini-MVS compared with conv-MVS (level B).
3. Procedure time was longer (4.5 vs 3.7 hours) for mini-MVS versus conv-MVS (level B).
4. Ventilation time was shorter (13 vs 20 hours) for mini-MVS versus conv-MVS (level B).
5. Postoperative ICU stay (1.6 vs 2.4 days) and hospital stay (7 vs 9 days) were shorter for mini-MVS versus conv-MVS (level B).
6. Costs were reported in few studies, but with varied definitions and settings, generalizable conclusions regarding costs or cost-effectiveness were not possible.

Consensus Summary for Overarching Question

After discussion of each of the substatements for the three subquestions, the consensus panel discussed what should be the overall role of mini-MVS compared with conv-MVS in the current practice environment, to address the overarching question: does mini-MVS improve clinical and resource outcomes compared with conv-MVS? Because there are no studies that have examined a policy of routine mini-MVS versus conv-MVS as standard of care, the maximal level of evidence for this recommendation is level B. But, because the evidence was less well established for key clinical outcomes, and because there was some inconsistency of

opinion across the consensus panel, the recommendation was designated as Class IIb. In addition, there was much discussion about the limitations of the evidence and the fact that there have been no prospective randomized trials to establish the comparative effectiveness of the mini- versus conv-MVS. The current evidence base relies on retrospective reviews of experiences from a variety of centers, with varied levels of expertise, and there may be significant risk of publication bias as authors will be less likely to publish adverse outcomes when publishing their center's experience (and many centers have not published their experience at all). Notwithstanding these limitations, the panel discussed the fact that the review of the evidence was comprehensive and attempted to be objective in ascertaining all outcomes from all studies. The current evidence should guide our decision making, with full acknowledgment of the limitations and the need for future research to guide consensus updates in the future. Given this discussion, the panel suggested the following overarching recommendation:

Recommendation

In patients with mitral valve disease, minimally invasive surgery may be an alternative to conventional mitral valve surgery (Class IIb), given that there was:

1. Comparable short-term and long-term mortality (level B)
2. Comparable in-hospital morbidity (renal, pulmonary, cardiac complications, pain perception, and readmissions) (level B)
3. Avoidance of sternal complications (0 vs 0.3%), units transfused (1.5 vs 3.5 RBC units), postoperative atrial fibrillation (18% vs 22%), duration of ventilation, and ICU and hospital length of stay (level B).

However, this should be considered against the increased risk of:

4. Stroke (2.1% vs 1.2%) (level B)
5. Aortic dissection (0.2% vs 0%) (level B)
6. Phrenic nerve palsy (3% vs 0%) (level B)
7. Groin infections/complications (2% vs 0%) (level B)
8. Prolonged cross-clamp time, cardiopulmonary bypass time, and procedure time (level B).

DISCUSSION

Overall, the recommendations suggest that mini-MVS may have advantages with respect to reduced risk of bleeding, atrial fibrillation, and sternal infection but may increase the risk of stroke and groin infections/complications. For most other endpoints, no difference was found for either technique. However, the reliance on retrospective studies reduces the confidence in our findings, and some of the results may represent conservative estimates (especially if complicated patients crossed over to and were accounted for as conv-MVS, which is more likely to happen in retrospective studies where the original intent of the intended procedure may not be documented).

Statement on Future Research

This consensus statement must be interpreted in light of the fact that all recommendations were level B. Because only

two small randomized trials of mini-MVS have been published, and because there were insufficient events in these randomized trials to determine whether any differences might exist, none of the recommendations is based on level A evidence. Future evidence may change or further refine the statements within this consensus statement. Based on discussion of the limitations of the evidence base and key gaps in the available literature, the following areas were suggested by the consensus panel as priority areas for future research.

Trial Design

Future trials should be designed to compare mini-MVS versus conv-MVS rather than focusing on noncomparative case series only. Without a comparison to conventional open surgery, it is difficult to know whether mini-MVS is better, same, or worse than standard open mitral valve surgery with regard to the endpoints discussed here. Rates of repair versus replacement were inadequately studied in the existing studies and should be clarified in future comparative studies. Some series from experienced centers have shown repair rates exceeding 90% with minimally invasive techniques. However, these were noncomparative case series and provide insufficient proof of comparative outcomes and have been singularly underpowered to assess uncommon risks such as stroke.

Because of the potential implications of increased risk of stroke and because the retrospective nature of current studies raise questions of bias (which may change the results for worse or for better, and the balance of effect of bias remains unknown), adequately powered randomized trials are required to determine whether the risk of stroke truly differs between groups. Without randomized trials with baseline homogeneity in patient characteristics between groups, it will not be known whether this finding is real or whether it may be an artifact of differential patient selection and different intensities of reporting or follow-up in the observational studies included in the meta-analysis. Such a serious outcome requires a fair evaluation through randomized trials to definitively answer the question for future patients. The authors are aware that mini-MVS has been adopted as the standard of care in many centers and is also driven by patient desire that may provide a challenging environment for recruitment. Nonetheless, a randomized trial is possible despite these challenges and has been overcome in other areas of surgery where procedures have been adopted before developing an adequate evidence base.

In designing future randomized trials, careful attention to study design should be given. The process of randomization should be objective and concealed so that patients in each arm will be comparable and decisions to enroll patients are made under equipoise rather than having control over which patients are included in each arm of the study. Primary analysis of randomized studies, or any comparative analysis, should be made by intention-to-treat, with subsequent subanalysis of patients who crossover. This is equally important for prospective randomized studies as it is for nonrandomized retrospective studies, because patients who are intended to undergo mini-MVS and who are subsequently crossed over to

open surgery tend to have worse outcomes when compared with patients who were originally intended to undergo open surgery (without crossover). If these crossover patients are analyzed in the open surgery group, their results will unfairly bias the open surgical group. Therefore, for retrospective studies, extra effort should be applied to ascertaining whether patients in the open surgery group wrongly include patients who were originally intended to undergo minimally invasive surgery but were crossed over.

Future studies should also be of adequate duration to measure the most clinically relevant outcomes—long-term survival, patient functionality and QOL, and freedom from residual mitral insufficiency, and reoperation. Future studies from centers reporting their experience should ensure that any overlap with previous publications is declared.

Definitions

Efforts should be made to standardize definitions of mini-MVS. A variety of techniques have been used under the name of mini-MVS ranging from thoracotomy with small incision and videoscope used to assist vision, to thoracotomy with large incision and direct vision, and to mini-median sternotomy. Some mini-MVS have used totally robotic techniques, whereas others use robot-assisted techniques. Therefore, all future studies should explicitly define the mini-MVS procedure so that reviewers can understand what was done. Clear explanation of the access, cannulation site, occlusion technique, de-airing technique, and level of experience of the operators should be provided.

Outcomes

Because there is inadequate power in the existing small randomized trials (each with short-term follow-up), the majority of outcomes have not been adequately addressed. Although the balance of the evidence suggests that there may be some reduced risk of certain perioperative morbidities (transfusion, atrial fibrillation, mediastinitis, ventilation time, length of stay, and return to normal activity) and some increased risk of other perioperative morbidities (stroke, aortic dissection, phrenic nerve palsy, groin complications, increased cross-clamp and cardiopulmonary bypass time, and increased procedure time), these are based on nonrandomized trials with measurable selection bias. Therefore, all clinically relevant outcomes remain to be definitively proven in future adequately powered randomized trials that control for selection biases. In particular, outcomes that should be given high priority in future randomized trials include pain, QOL, functionality, return to normal function, survival, reoperation, long-term valvular function (with echo follow-up year by year), major adverse coronary events and overall resource utilization.

Strengths and Limitations

This consensus statement is based on a current and comprehensive systematic review of the evidence, with formal consensus processes that limited the role of opinion secondary to that of the evidence base. Care was taken to explicitly label the recommendations with the evidence available to inform it, and when evidence was unavailable, to

apply considered expert judgment to provide perspective for potential users of the statement. With this explicit evidence-based consensus process, it should be clear to the user how the recommendations were derived. The panel acknowledges that many large single center studies that report positive results with mini-MVS were excluded from this analysis because they were noncomparative case series without the ability to inform comparative efficacy versus conventional surgery. Thus, this analysis may not reflect contemporary practice because many experienced centers did not report comparative studies. Only two randomized trials have been published, and both of these date back to the earlier history of mini-MVS. Updated randomized trials involving experienced centers are necessary to elucidate the issue of stroke.

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^{22,23} and guidelines.²⁴ To self-appraise our consensus statement against current standards for valid guidelines, we subjected our consensus process and recommendations to quality assessment checklists and found that most indicators of high-quality were met or exceeded.^{22,24} This is in contrast to the majority of existing guidelines, which rarely meet all of these recommended criteria.²⁴

Although a range of health care professionals and methodological expertise was represented on the consensus panel, some stakeholders were not represented. In particular, patients, administrators, and policymakers, were not invited to participate; however, patient-related outcomes including satisfaction and QOL were sought from published trials to address this perspective. It is unfortunate that patient satisfaction was infrequently reported in the studies. In addition, stakeholders from the manufacturing sector (ie, producers of technologies related to endoscopic and open surgery) were not included in the consensus and review process, to reduce the risk of bias that may result from direct manufacturer involvement.

Clinicians tend to overestimate the effectiveness of new interventions, especially if the intervention in question rests within the realm of their expertise.²⁵ In addition, there is a tendency for group decision-making processes to converge with compromises made to please all members, even for issues that are greatly polarized. To reduce this problem, experts in evidence-based decision-making and health technology assessment were invited to facilitate the discussion and to promote that the best available evidence should be the focus for discussion. Nonetheless, a key limitation was the absence of other surgeons on the consensus panel who are not strong proponents of mini-MVS. Most members were expert surgeons who perform mini-MVS, and this represents a significant limitation of breadth and balance of perspectives.

A further limitation of the evidence base on which these recommendations were made is the inconsistent management of patients who crossed over from mini-MVS to conv-MVS because of difficult morphology, intraoperative bleeding, he-

modynamic collapse, or other complications. In some studies, patients who crossed over were either excluded or accounted for in the conventional group. In many studies, no mention was made of how crossover patients were handled in the analysis. Studies that analyzed crossover patients may provide overestimations of benefit because the risk of crossover to conventional open surgery might not have been accounted for in the mini-MVS group (crossover patients tend to do worse, on average, than all other patients). Of trials that reported crossovers, there was an average of 3.4% of patients who required conversion to open surgery. The outcomes of patients who required conversion were not reported in the studies, and it was therefore not possible to separately analyze these patients. Most of the studies did not clarify how the converted patients were handled in the data analysis, and it is likely that many studies excluded converted patients from their analysis.

Finally, the lack of randomized trials to inform any of the consensus statements is a limitation that deserves discussion here. Although this limitation is common in surgery and is true of many consensus statements,²⁶ it does not provide reason to abandon the consensus statement. Rather, it should serve the purpose of explicitly defining the best available evidence to inform each statement. Even without the availability of an ideal evidence base, decisions must be made. In this case, the decisions need to be weighed with both the potential benefits and risks of mini-MVS. Because the studies were nonrandomized, usually retrospective series, there will be inherent biases in the patient selection. In particular, selection bias may increase the likelihood that patients with differing prognoses will be systematically chosen for mini-MVS rather than conv-MVS. Some of the significant differences found in the meta-analysis may be due to this selection bias. Because the magnitude of impact of this bias cannot be known, readers should bear in mind that the evidence base for statements labeled with level B may be an overestimation or underestimation of the overall magnitude of benefit. The consensus panel incorporated this uncertainty into their discussions and assigned the Class of Recommendation to reflect this uncertainty. It is hoped that future trials will be conducted to address these areas where only lower levels of evidence are available.

Feasibility and Training

Judgments about whether the affordability, feasibility, and uptake of mini-MVS (as a clinical or research program) depend on the local context and setting. Feasibility issues worth considering include time, skills, staff, training and equipment necessary to adhere to the recommendations, and the ability of local systems of care to implement them. Issues to consider when localizing these recommendations to specific settings include skills development programs, certification programs for mitral valve surgery, and local availability of equipment and supporting technologies. The learning curve for minimally invasive surgery is steep, and it should not be presumed that these evidence-based recommendations should be applied without consideration of individual skills development.

SUMMARY AND CONCLUSIONS

After review and discussion of the best available evidence, the following summary consensus recommendations were delineated.

In patients with mitral valve disease, minimally invasive surgery may be an alternative to conventional mitral valve surgery (Class IIb), given that there was

1. Comparable short-term and long-term mortality (level B)
2. Comparable in-hospital morbidity (renal, pulmonary, cardiac complications, pain perception, and readmissions) (level B)
3. Reduced sternal complications (0% vs 0.3%), transfusions (1.5 vs 3.5 RBC units), postoperative atrial fibrillation (18% vs 22%), duration of ventilation, and ICU and hospital length of stay (level B).

However, this should be considered against the increased risk of:

4. Stroke (2.1% vs 1.2%) (level B)
5. Aortic dissection (0.2% vs 0%) (level B)
6. Phrenic nerve palsy (3% vs 0%) (level B)
7. Groin infections/complications (2% vs 0%) (level B)
8. Prolonged cross-clamp time, cardiopulmonary bypass time, and procedure time (level B).

The available evidence consists almost entirely of observational studies and should not be considered definitive until future adequately controlled randomized trials further address the risk of stroke, aortic complications, phrenic nerve complications, pain, long-term survival, need for reintervention, QOL, and cost-effectiveness.

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REFERENCES

1. Raanani E, Spiegelstein D, Sternik L, et al. Quality of mitral valve repair: median sternotomy versus port-access approach. *J Thorac Cardiovasc Surg*. 2010;140:86–90.
2. Schmitto JD, Mokashi SA, Cohn LH. Minimally-invasive valve surgery. *J Am Coll Cardiol*. 2010;56:455–462.
3. Seeburger J, Borger MA, Doll N, et al. Comparison of outcomes of minimally invasive mitral valve surgery for posterior, anterior, and bileaflet prolapse. *Eur J Cardiothorac Surg*. 2009;36:532–538.
4. Sackett DL, Straus SE, Richardson WS, et al. *Evidence-Based Medicine: How to Practice and Teach EBM*. 2nd ed. London: Churchill Livingstone; 2000.
5. Cheng DCH, Martin J, Lal A, et al. Minimally invasive versus conventional open mitral valve surgery: a meta-analysis and systematic review. *Innovations*. 2011;6:84–103.
6. Ad N, Cheng D, Martin J, et al. Surgical ablation for atrial fibrillation in cardiac surgery: a consensus statement of the International Society of Minimally Invasive Cardiothoracic Surgery (ISMICS) 2009. *Innovations*. 2010;5:74–83.
7. Pepper J, Cheng D, Stanbridge R, et al. Stentless versus stented bio-

- prosthetic aortic valves: a consensus statement of the International Society of Minimally Invasive Cardiothoracic Surgery (ISMICS) 2008.
8. 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. *Innovations*. 2007;2:293–302.
 9. 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. *Innovations*. 2006;1:314–322.
 10. Allen K, Cheng D, Clhn 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) 2005. *Innovations*. 2005;1:51–60.
 11. Puskas JD, 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. *Innovations*. 2005;1:3–27.
 12. Colditz GA, Miller JN, Mosteller F. How study design affects outcomes in comparisons of therapy. I. Medical. *Stat Med*. 1989;8:441–454.
 13. Milz S, Colditz GA, Mosteller F. How study design affects outcomes in comparisons of therapy. II. Surgical. *Stat Med*. 1989;8:455–466.
 14. Moher D, Pham B, Jones A, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet*. 1998;22:609–613.
 15. Schulz KF, Chalmer I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA*. 1995;273:408–412.
 16. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. *BMJ*. 1999;318:593–596.
 17. Cheng DC, Bainbridge D, Martin JE, Novick RJ. Does off-pump coronary artery bypass reduce mortality, morbidity, and resource utilization when compared with conventional coronary artery bypass? A meta-analysis of randomized trials. *Anesthesiology*. 2005;102:188–203.
 18. Anselmi A, Possati G, Gaudino M. Postoperative inflammatory reaction and atrial fibrillation: simple correlation or causation? *Ann Thorac Surg*. 2009;88:326–333.
 19. Chitwood WR Jr, Wxon C, Elbeery J, et al. Video-assisted minimally invasive mitral valve surgery. *J Thorac Cardiovasc Surg*. 1997;114:773–782.
 20. Felger JE, Chitwood WR Jr, Nifong L, Holbert D. Evolution of mitral valve surgery: toward a totally endoscopic approach. *Ann Thorac Surg*. 2001;72:1203–1209.
 21. Shinfeld A, Kachel E, Paz Y, et al. Minimally invasive video-assisted mitral and aortic valve surgery—our initial clinical experience. *Israel Med Assoc J*. 2003;5:482–484.
 22. Hibble A, Kanka D, Pencheon D, Pooles F. Guidelines in general practice: the new Tower of Babel? *BMJ*. 1998;317:862–863.
 23. Appraisal of Guidelines RaEiEACG. Guideline development in Europe. An international comparison. *Int J Technol Assess Health Care*. 2000;16:1039–1049.
 24. Cluzeau FA, Littlejohns P, Grimshaw JM, et al. Development and application of a generic methodology to assess the quality of clinical guidelines. *Int J Qual Health Care*. 1999;11:21–28.
 25. Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest*. 1986;89(2 suppl):2S–3S.
 26. Proceedings of the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: evidence-based guidelines. *Chest*. 2004;126(3 suppl):174S–696S.