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A Randomized Multicenter Trial of Minimally Invasive Rapid Deployment Versus Conventional Full Sternotomy Aortic Valve Replacement

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Background. **Minimally invasive surgical procedures (MIS) may offer several advantages over conventional full sternotomy (FS) aortic valve replacement (AVR). A novel class of aortic valve prostheses has been developed for rapid-deployment AVR (RDAVR). We report a randomized, multicenter trial comparing the outcomes for MIS-RDAVR with those of conventional FS-AVR.**

Methods. **A total of 100 patients with aortic stenosis were enrolled in a prospective, multicenter, randomized comparison trial (CADENCE-MIS). Exclusion criteria included ejection fraction below 25%, AVR requiring concomitant procedures, and recent myocardial infarction or stroke. Patients were randomized to undergo MIS-RDAVR through an upper hemisternotomy (n = 51) or AVR by FS with a conventional stented bioprosthesis (n = 49). Three patients were excluded before the procedure, and 3 more patients who were randomized to undergo RDAVR were excluded because of their anatomy. Procedural, early clinical outcomes, and functional outcomes were assessed for the remaining 94 patients. Hemodynamic performance was assessed by an echocardiography core laboratory.**

Results. **Implanted valve sizes were similar between groups (22.9 ± 2.1 vs 23.0 ± 2.1 mm, $p = 0.9$). MIS-RDAVR was associated with significantly reduced aortic cross-clamp times compared with FS-AVR (41.3 ± 20.3 vs 54.0 ± 20.3 minutes, $p < 0.001$), although cardiopulmonary bypass times were similar (68.8 ± 29.0 vs 74.4 ± 28.4 minutes, $p = 0.21$). Early clinical outcomes were similar between the two groups, including quality of life measures. The RDAVR patients had a significantly lower mean transvalvular gradient (8.5 vs 10.3 mm Hg, $p = 0.044$) and a lower prevalence of patient–prosthesis mismatch (0% vs 15.0%, $p = 0.013$) 3 months postoperatively compared with the FS-AVR patients.**

Conclusions. **RDAVR by the MIS approach is associated with significantly reduced myocardial ischemic time and better valvular hemodynamic function than FS-AVR with a conventional stented bioprosthesis. Rapid deployment valves may facilitate the performance of MIS-AVR.**

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Aortic valve replacement (AVR) through a full sternotomy (FS) has been the gold standard for aortic stenosis treatment for the past 5 decades. AVR through minimally invasive surgical procedures (MIS) was first reported by Cosgrove and Sabik in 1996 [1]. MIS-AVR aims to reduce trauma and to achieve decreased postoperative pain and ventilation time, less blood loss, faster recovery, and better aesthetic outcomes [2–7].

Despite the advantages associated with reduced trauma, MIS-AVR has been slow to gain clinical application momentum, at least in part because of the technically more demanding nature of accessing the aortic valve through a smaller access portal, which may in turn lead to prolonged procedural times [8]. Prolonged cross-clamp time during cardiac surgical procedures

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correlates with major postoperative morbidity and mortality in both low- and high-risk patients [9, 10]. Therefore, enhanced MIS procedural efficiency and reduced procedural times may be of importance for improved clinical outcomes postoperatively. Recent advancements in bioprosthetic valve design have introduced new technologies to facilitate MIS approaches.

Valves with self-anchoring technologies or rapid deployment mechanisms have recently been developed [11, 12]. Nitinol-based sutureless valves allow the valve frame to self-expand and anchor to the annulus through a thermoresponsive mechanism [13, 14]. Rapid deployment AVR (RDAVR) represents another new development in this area and consists of positioning the valve with a precrimped subannular skirt frame into the annulus, then balloon deploying the frame [15]. A randomized comparison between patients undergoing AVR with an MIS-facilitating valve and those undergoing conventional AVR through a FS has yet to be reported.

We describe a prospective, multicenter, randomized trial comparing outcomes in patients undergoing MIS-RDAVR with those undergoing FS-AVR with commercially available valves.

Patients and Methods

Study Population

CADENCE-MIS is a multicenter, randomized, controlled trial comparing MIS-RDAVR through an upper hemisternotomy with Edwards Intuity valve with FS-AVR with a conventional stented valve of the investigator's preference. Between May 2012 and February 2013, 100 patients with aortic stenosis were enrolled. The operations were performed by 12 cardiac surgeons in 5 centers in Germany.

Patients were eligible for study enrollment if they were over 18 years of age and required isolated AVR because of aortic stenosis with or without aortic insufficiency. Other inclusion criteria included low to moderate surgical risk score (ie, logistic EuroSCORE <20) and New York Heart Association (NYHA) class II or greater. Exclusion criteria included the following: pure aortic insufficiency, planned concomitant procedures, previous cardiac surgical procedures, congenital true bicuspid (ie, Sievers type 0) aortic valve, emergency operations, ejection fraction below 25%, and recent myocardial infarction (≤90 days), or stroke or transient ischemic attack (≤6 months). The study protocol was reviewed and approved by the ethics committee of each participating center, and all patients provided written informed consent.

Patients were randomized to undergo MIS-RDAVR through an upper hemisternotomy (n = 51) with Edwards Intuity or FS-AVR with a conventional stented valve (n = 49) of the investigator's preference. Randomization was performed after all preoperative investigations were completed and the investigator confirmed that the study participant met all the inclusion criteria and no exclusion criteria. Figure 1 outlines the Consolidated Standards of Reporting Trials (CONSORT) diagram of the enrolled, intent-to-treat, and as-intended groups of the CADENCE-MIS trial. Two patients who were randomized to undergo RDAVR were subsequently excluded because of intraoperative screening failure (extensive calcification of the aortic root and unavailability of appropriate sized device in 1 patient each), and 1 patient randomized to the FS-AVR group withdrew from the study before the procedure. As a result, AVR was performed in a total of 97 patients (Leipzig, n = 38; Bochum, n = 32; Hamburg, n = 14; Berlin, n = 8; Jena, n = 5).

From the 97 patients remaining in the intent-to-treat group, 3 who were randomized to MIS-RDAVR eventually received a conventional valve because of problems with their anatomy. These 3 patients received a commercially available bioprosthesis by means of MIS and therefore could not be accurately categorized into the MIS-RDAVR or FS-AVR category. We therefore removed these patients from the subsequent analysis, resulting in an as-intended population of MIS-RDAVR (n = 46) and FS-AVR (n = 48) patients. These remaining 94 patients form the basis of the following analyses.

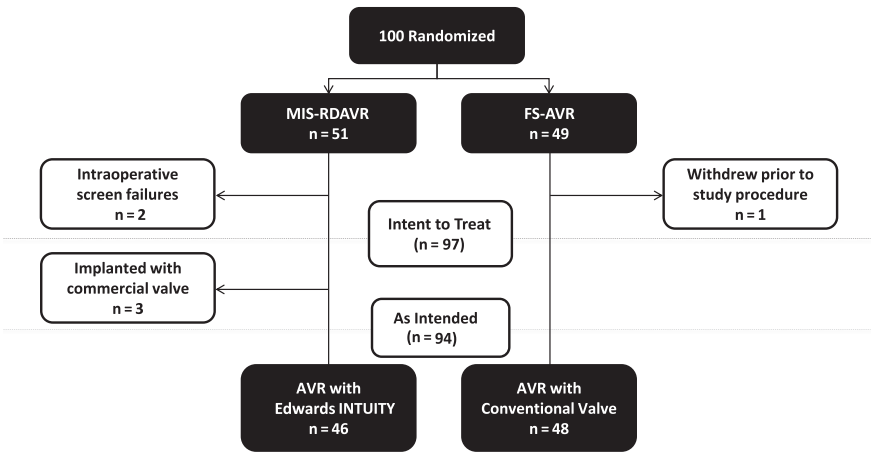

Fig 1. Consolidated Standards of Reporting Trials diagram. (FS-AVR = full sternotomy aortic valve replacement; MIS-RDAVR = minimally invasive surgery – aortic valve replacement.)

Surgical Approach

The MIS approach was performed as described previously [7, 16]. Briefly, an upper hemisternotomy was performed into the third or fourth intercostal space. The distal ascending aorta was directly cannulated. A two-stage venous cannula was inserted into the right atrium, or percutaneous cannulation was performed through the right femoral vein. FS was performed with a standard skin incision and median sternotomy, along with standard cannulation of the ascending aorta and right atrium.

Normothermic or mild hypothermic cardiopulmonary bypass (CPB) was used, and ante-grade crystalloid or cold or warm blood cardioplegia was administered in both groups of patients. A transverse aortotomy was performed 1 cm above the sinotubular junction in all patients. Carbon dioxide was continuously flooded into the pericardial well during aortic cross-clamping.

RDAVR

The diseased aortic valve leaflets were excised, care being taken not to cause any defects in the aortic annulus. The debrided annulus was sized to identify the appropriate Edwards Intuity valve (Edwards Lifesciences, LLC, Irvine, CA). The Edwards Intuity valve is a stented trileaflet bovine pericardial bioprosthesis with a balloon-expandable, cloth-covered skirt frame at the inflow aspect (Fig 2). Three equidistant figure-of-eight or mattress guiding sutures were placed through the annulus at the nadir of each sinus and then passed through the corresponding black marks on the nadir portion of the valve suture ring. The valve was positioned into the aortic annulus by use of the guide sutures and three tourniquets, with the stent and polyester sealing cloth being seated directly below the aortic annulus. A thoracoscope was occasionally inserted through the holding device to confirm proper positioning [17]. Once the valve was properly seated, the balloon-expandable frame was deployed with a 10-second balloon inflation. The guiding sutures were tied, and the aortotomy was closed.

AVR With a Conventional Valve

After leaflet and annular calcium debridement, valve sizing was performed with standard manufacturers' sizers, with selection of the size that would comfortably fit within the aortic annulus. The following conventional stented valves were implanted by FS: Hancock II (Medtronic, Minneapolis, MN; n = 3), Mitroflow (Sorin Biomedica Cardia Srl, Sallugia, Italy; n = 3), Trifecta (St. Jude Medical, St. Paul, MN; n = 10), or Perimount Magna Ease (Edwards Lifesciences; n = 32).

Postoperative Care and Follow-Up

Patients were given maintenance anticoagulant therapy, except when contraindicated, for 3 months after operation in accordance with published guidelines [18]. Appropriate anticoagulation monitoring was performed by the treating physician on an individual basis. Clinical and echocardiographic follow-up evaluations were performed 30 days, 3 months, and 1 year after implantation. Echocardiograms were reviewed by an independent core laboratory (RadCore Labs, LLC, Torrance, CA). Safety endpoints and adverse events were adjudicated by an independent clinical events committee whose members were independent of both the study sponsor and the investigators. Aggregate data were reviewed by an independent data safety monitoring board.

Endpoints

Primary endpoints of this trial were cross-clamp time and CPB time. Safety endpoints included cardiac reoperation, thromboembolism, renal failure, paravalvular leak (PVL), permanent pacemaker implantation, resternotomy, major bleeding events, endocarditis, myocardial infarction, deep sternal wound infection, cerebrovascular accident or permanent stroke, and respiratory failure. Additional secondary endpoints included hemodynamic performance, quality of life outcome measures (EQ-5D), and NYHA classification.

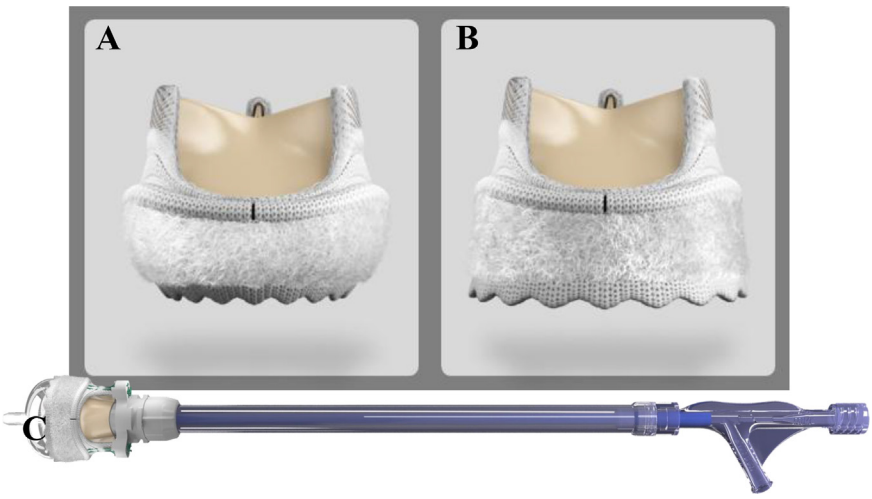

Fig 2. Edwards Intuity valve showing the subannular skirt frame in (A) precrimped configuration, (B) deployed configuration, and (C) complete valve deployment system.

Data Management

Data monitoring and collection was performed by the study sponsor (Edwards Lifesciences). Continuous variables are summarized as mean and standard deviation, and categoric variables are summarized as percentage and number of patients in each category throughout the report. Adverse events are summarized for the early outcomes (ie, those occurring ≤30 days after the index procedure).

Results

Patient Characteristics

Baseline patient characteristics were similar between the MIS-RDAVR and FS-AVR groups (Table 1). The two groups had a similar risk profile, with the exception of hypercholesterolemia and history of smoking, which were higher in the MIS-RDAVR group.

Procedural Outcomes

Successful placement of the valve was performed in 93.9% of MIS-RDAVR patients, with 3 being converted to MIS-AVR with a conventional valve because of difficulties with annular sizing (2 patients) and because of an annular tear (1 patient) (Table 2).Within successful RDAVR implants, 95.7% of the implantations were performed in the first attempt. Significant cross-clamp time reduction was observed for the MIS-RDAVR group compared with the FS-AVR group, resulting in a 12.7-minute difference ($p < 0.0001$) (Table 2). Shorter CPB time was also observed in the MIS-RDAVR group, although the difference was not statistically significant. When data from the 3 patients who were randomized to receive an Intuity valve but who subsequently received a commercial valve were included (ie, intention-to-treat analysis), the difference in cross-clamp time remained statistically significant (46.5 ± 29.7 vs 54.0 ± 20.3 minutes for MIS-RDAVR vs FS-AVR, $p = 0.01$). However, the CPB times were similar (75.6 ± 43.0 vs 74.4 ± 28.4 minutes, $p = 0.47$).

Early Clinical Outcomes

Comparable early (≤30 day) clinical outcomes were observed between the MIS-RDAVR and the FS-AVR groups (Table 3). No significant differences in safety outcomes including reoperation, thromboembolic events, myocardial infarction, renal failure, pacemaker implantation, or PVL (>1+) were observed.

There were two deaths in the MIS-RDAVR group. One patient experienced sudden bleeding 3 hours postoperatively, resulting in pericardial tamponade and reoperation under cardiopulmonary resuscitation. The exact source of bleeding was not determined. However, it was noted on intraoperative transesophageal echocardiography that the Intuity valve was tilted in the aortic annulus and that a new PVL was present. The Intuity valve was presumed to have been deformed during manual compressions and was therefore replaced with a conventional valve. The patient experienced low cardiac output and died of multisystem organ failure 2 days later. The other patient was readmitted to the hospital 2 weeks postoperatively with shock caused by an intrapericardial hematoma with tamponade, and also intrahepatic portal vein thrombosis confirmed by computed tomography. His condition deteriorated further during release of the pericardial tamponade, at which time no bleeding source was identified. In view of the patient's hemodynamic instability and a history of previous percutaneous coronary intervention to the left anterior descending (LAD) coronary artery, it was decided to perform a saphenous vein graft bypass to the LAD. The patient experienced progressive low cardiac output syndrome and died the next day of cardiogenic shock. One death in the FS-AVR group occurred as a result of sepsis and multisystem organ failure of undetermined cause. The Clinical

Table 1. Baseline Patient Characteristics

Characteristic	MIS-RDAVR (n = 46)	FS-AVR (n = 48)	*p* Value
Age[a]	73.0 ± 5.3 (61–83)	74.2 ± 5.0 (61–84)	0.304
Female	41.3 (19)	56.3 (27)	0.147
BMI, kg/m^2,[a]	29.4 ± 5.1 (20–42)	28.8 ± 5.0 (20–47)	0.538
Obesity, BMI ≥30	47.8 (22)	29.2 (14)	0.063
STS score, %[a]	1.6 ± 0.7 (0.6–4)	1.7 ± 0.6 (0.9–3)[b]	0.207
NYHA class ≥III	67.4 (31)	60.4 (29)	0.482
Creatinine, mg/dL[a]	1.0 ± 0.3 (0.7–2)	1.0 ± 0.3 (0.6–2)	0.970
Hypercholesterolemia	71.7 (33)	48.9 (23)	0.025
History of smoking	47.8 (22)	25.5 (12)	0.026
Chronic obstructive pulmonary disease	13.0 (6)	12.5 (6)	0.937
Renal insufficiency	15.2 (7)	14.9 (7)[c]	0.965
Diabetes	32.6 (15)	22.9 (11)	0.294
Liver disease	4.3 (2)	0.0 (0)[c]	0.148
Conduction disturbance	23.9 (11)	27.7 (13)[c]	0.680

[a] Mean ± standard deviation (range). [b] Data unavailable for 2 patients. [c] Data unavailable for 1 patient.

BMI = body mass index; FS-AVR = full sternotomy aortic valve replacement; MIS-RDAVR = minimally invasive surgery – aortic valve replacement; NYHA = New York Heart Association; STS = The Society of Thoracic Surgeons.

Table 2. Procedural Outcomes

Characteristic	MIS-RDAVR (n = 46)	FS-AVR (n = 48)	*p* Value
Cross-clamp time	41.3 ± 20.3 (35.0; 29.0–45.0)	54.0 ± 20.3 (47.5; 38.5–65.5)	<0.0001
Cardiopulmonary bypass time	68.8 ± 29.0 (58.5; 51.0–71.0)	74.4 ± 28.4 (69.0; 51.5–86.0)	0.208
Operative time	141.9 ± 46.1 (130.0; 110.0–156.0)	146.4 ± 48.4 (145.5; 108.5–166.0)	0.591
Implanted valve size, mm	22.9 ± 2.1 (23; 21–25)	23.0 ± 2.1 (23; 21–25)	0.917

Values expressed as mean ± standard deviation (median and interquartile range in parentheses).

FS-AVR = full sternotomy aortic valve replacement; MIS-RDAVR = minimally invasive surgery – aortic valve replacement.

Events Committee adjudicated all three deaths as related to the cardiac procedure, but not related to the study valve.

One death was observed among the 3 patients omitted from the as-intended analysis. The surgeon had difficulty positioning the Intuity prosthesis in the aortic annulus of this patient. After several failed attempts to seat the valve, a tear in the aortic annulus occurred, and the decision was made to perform MIS-AVR with a conventional valve. The aortic annulus was repaired with felt sutures, and a conventional valve was inserted. The patient experienced right heart failure and low cardiac output syndrome thereafter, and died of multisystem organ failure on postoperative day 5.

Effectiveness Outcomes

An increase in the effective orifice areas (EOA) and corresponding decrease in mean aortic gradient were observed from baseline to 3 months for both the MIS-RDAVR and the FS-AVR group (Table 4). At 3 months, the mean gradient was significantly lower for the Edwards Intuity valve than for the conventional valves (8.5 ± 3.4 vs 10.3 ± 4.8 mm Hg, $p = 0.044$). At 3 months, no severe patient–prosthesis mismatch (<0.65 cm^2/m^2) was observed for the MIS-RDAVR group compared with 6 patients (of 40 evaluable echocardiograms) in the FS-AVR group ($p = 0.013$).

When compared with only those patients who received a Perimount valve (n = 32), the MIS-RDAVR patients had a significantly lower gradient ($p = 0.024$). Similarly, severe patient–prosthesis mismatch was observed more commonly in those with the Perimount valve (14.3% vs 0%) ($p = 0.016$).

NYHA class improvement was observed as early as 30 days, and it continued through the 3-month follow-up period for both groups. At 30 days, 82.4% (28/34) of the MIS-RDAVR group and 74.3% (26/35) of the FS-AVR group improved by one or more NYHA class. At 3 months, 83.3% (35/42) of the MIS-RDAVR group and 73.2% (30/41) of the FS-AVR group showed NYHA class improvement. The EQ-5D remained constant from baseline to 3 months for both groups: baseline EQ-5D scores were 0.9 ± 0.1 and 0.9 ± 0.1, and 3-month EQ-5D scores were 0.9 ± 0.1 and 0.9 ± 0.1 in the MIS-RDAVR and FS-AVR patients, respectively ($p = 0.630$).

Comment

The FS-AVR procedure has been the gold standard for patients with symptomatic aortic stenosis since the 1960s

Table 3. Early (≤30 Days) Clinical Outcomes

Outcome	MIS-RDAVR (n = 46)	FS-AVR (n = 48)	*p* Value
Mortality	4.3% (2)	2.1% (1)	0.5324
Reoperation	2.2% (1)	2.1% (1)	0.9757
Major bleeding	6.5% (3)	8.3% (4)	0.7380
New pacemaker	4.3% (2)	0.0% (0)	0.1442
Cerebrovascular accident	4.3% (2)	2.1% (1)	0.5324
Sternal wound infection	4.3% (2)	6.3% (3)	0.6812
Respiratory failure	4.3% (2)	2.1% (1)	0.5324
Renal failure	4.3% (2)	0.0% (0)	0.1442
Endocarditis	0.0% (0)	0.0% (0)	…
Myocardial infarction	0.0% (0)	2.1% (1)	0.3250
Paravalvular leak[a]			
0 (none)	85.3% (29)	73.7% (28)	0.247
1+ (trace)	11.8% (4)	23.7% (9)	
2+ (mild)	2.9% (1)	2.6% (1)	
≥3+ (moderate/severe)	0.0% (0)	0.0% (0)	

[a] Denominators based on evaluable echocardiograms; MIS-RDAVR (n = 34) and FS-AVR (n = 38).

FS-AVR = full sternotomy aortic valve replacement; MIS-RDAVR = minimally invasive surgery – aortic valve replacement.

Table 4. Hemodynamic Performance

Characteristic	MIS-RDAVR, Edwards Intuity Valve	FS-AVR, Perimount Valve
EOA, cm^2	Mean ± SD (n)[a]	
Valve size, mm	Discharge	
21	1.8 ± 0.6 (9)	1.6 ± 0.4 (11)
23	1.7 ± 0.4 (16)	1.9 ± 0.5 (14)
25	2.0 ± 0.7 (8)	1.9 ± 0.7 (7)
	3 Month	
21	1.8 ± 0.5 (10)	1.6 ± 0.4 (13)
23	1.9 ± 0.4 (14)	1.6 ± 0.4 (14)
25	2.1 ± 0.5 (8)	2.0 ± 0.6 (10)
Mean gradient, mm Hg	Mean ± SD (n)[a]	
Valve size, mm	Discharge	
21	8.1 ± 4.4 (11)	11.5 ± 4.2 (14)
23	12.0 ± 3.4 (16)	11.2 ± 3.1 (15)
25	8.8 ± 4.4 (8)	11.1 ± 3.9 (10)
	3 Month	
21	7.2 ± 2.3 (10)	11.7 ± 6.6 (13)
23	9.3 ± 3.5 (15)	10.2 ± 3.9 (14)
25	9.1 ± 3.9 (8)	9.9 ± 3.0 (10)

[a] n represents assessed evaluable echocardiogram.

EOA = effective orifice area; FS-AVR = full sternotomy aortic valve replacement; MIS-RDAVR = minimally invasive surgery – aortic valve replacement; SD = standard deviation.

[1]. Since the first reported MIS-AVR in 1996, studies have reported several benefits associated with an MIS approach [2–8, 19, 20]. However, MIS-AVR has not gained widespread application, with only 10% of all AVR procedures in Germany, for example, performed by MIS in 2009 [21].

Three MIS-AVR facilitating devices have achieved CE Mark approval to date and are being implanted with increasing frequency in Europe. The Edwards Intuity Valve System is unique in that no folding or crimping of leaflet tissue is required before implantation. Although the procedural and clinical outcomes of these new MIS enabling technologies have been presented in several single-armed studies, a randomized comparison with conventional FS-AVR has not been reported to date.

Four randomized, prospective studies have compared MIS with FS operations in patients receiving a conventional aortic valve prosthesis [3–5, 22]. These studies all revealed that MIS-AVR is a safe and effective treatment option; however, prolonged operative times have been consistently reported in MIS-AVR patients. A metaanalysis confirmed a weighted mean difference of 7.9 additional minutes of cross-clamp time for MIS-AVR when compared with FS-AVR [8].

In direct contrast to the above findings, our current study revealed a significant cross-clamp time reduction in patients undergoing RDAVR, despite the MIS approach. The cross-clamp time reduction is especially of note when learning curves are taken into account, inasmuch as four of the five centers implanted the Edwards Intuity for the first time during this trial. MIS-RDAVR was associated with a mean cross-clamp time reduction of 12.7 minutes (24% relative reduction) when compared with FS-AVR. Although the clinical importance of a 13-minute cross-clamp time reduction is arguable, our observation strongly supports the hypothesis that rapid deployment valves facilitate the performance of MIS-AVR. Additionally, we found that RDAVR with the Edwards Intuity valve was associated with a high primary implantation success rate of 95.7%, consistent with previous reports [11, 15].

We failed to find any statistically significant differences in clinical outcomes between MIS-RDAVR and FS-AVR in our study. The major bleeding and pacemaker implantation rates for both groups were comparable with the respective reported ranges of 0.2% to 6.5%, and 3.0% to 8.2% in the literature [13, 14, 23–28]. We also observed good functional and quality of life outcomes after the procedure in our study, with no significant differences between the two groups.

The PVL rates we observed, particularly in FS-AVR patients (ie, 23.7% and 2.6% for trace and mild PVL, respectively), may at first glance appear relatively high when compared with retrospective reports in the literature. However, our observed PVL rates are comparable with those observed in prospective, core laboratory-controlled trials. For example, the prevalence of trace or mild PVL in the surgically treated arm of the PARTNER A trial was 25.3%, and the prevalence of moderate or severe PVL was 0.9% 30 days after AVR [29].

The current study demonstrated excellent hemodynamic performance of the RDAVR bioprosthesis, similar to those reported in the literature [13–15]. At 3 months, the mean gradient and patient–prosthesis mismatch rates for all valve sizes was significantly lower for the RDAVR group than in the FS-AVR group with conventional valves. Furthermore, the trend was consistent when the Edwards Intuity group was compared with the Perimount valve subgroup, an interesting finding given the Perimount platform–based Edwards Intuity valve design. Such an observation may lead one to conclude that the balloon-deployable frame, which is expanded in the inflow aspect of the left ventricular outflow tract, combined with the lack of annular suture material, allows for maximum hemodynamic performance of the prosthesis.

As with all new technologies, some limitations were observed in this trial. In some patients, obtaining proper seating of the Intuity valve within the aortic annulus can be challenging because of resistance between the polyester sealing cuff and the native annulus. However, a newer version of the valve has been developed which has a lower profile polyester cuff and more marked crimping of the stent, resulting in less resistance with the patient's annulus during positioning. In addition, sizing of the aortic annulus is critical to successful deployment of all rapid deployment valves, as displayed by the 2 patients in the current study who required a conventional bioprostheses because of incorrect annular sizing. Further developments in annular sizing devices may result in improved accuracy for such procedures.

Study Limitations

Although the current study has the strength of a randomized controlled design, it is limited by the relatively small cohort, and the summary statistics were subject to influence by potential outliers. A larger randomized, controlled trial comparing MIS-RDAVR with FS-AVR needs to be conducted to confirm these findings. Additionally, this report describes outcomes out to 3 months, and further follow-up is needed to explore the long-term safety and performance outcomes of MIS-RDAVR.

In conclusion, our prospective, randomized, controlled trial demonstrates that MIS-RDAVR is a safe and effective treatment option for patients requiring aortic valve surgical procedures. MIS-RDAVR significantly reduces aortic cross-clamp times compared with FS-AVR with a conventional bioprosthesis, and it is associated with hemodynamically superior outcomes.

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DISCUSSION

DR LOUIS P. PERRAULT (Montreal, Quebec, Canada): Awesome talk, Mike, I think you should be commended for doing a randomized study with that new technology. I just have a question. Here in the abstract, the mortality was 6.1% in the Intuity group. How many patients do you figure it would take to convince everybody that there is no difference? Is it 50 on each side or is 48 enough? And also concerning the other complications?

DR BORGER: The total mortality rate for the group of patients that I presented here was 3%. However, of the 3 patients who were excluded because of difficulty seating the valve from coronary anatomy, 1 of those patients died. If we include those 3 patients in the group, because of the relatively small sample size of the study, then the mortality jumps, not to 6%, but for the entire patient population from 3% up to 4%. So this is a little higher than probably what we wanted to see, but at the same time it is still certainly within the 95% confidence limits of isolated AVR series that are published in the literature to date.

If we assume a mortality rate of about 3%, you'd need to randomize approximately 2,000 patients per group to rule out a difference in mortality with any degree of certainty. Such a sample size is probably not feasible.

However, we have experience with the Edwards Intuity valve in another ongoing trial in Europe, with over 300 patients enrolled to date. The mortality rate in that group is lower than what I've shown here today; that is, less than 2%. So, therefore, my gut feeling is that there is no difference in mortality, and there won't be a difference, no matter how big you make the trial.

DR PERRAULT: Just one other small question. Do you think there is an advantage of the Intuity versus the Perceval in the minimally invasive approach, or other sutureless or rapid deployment valves?

DR BORGER: I've had the opportunity to implant both of those valves at our center, and I can tell you that the Perceval valve is technically a little easier to implant than the Intuity valve because it is easier to seat in the annulus. The leaflets are folded together, and therefore you can clearly see the patient's own annulus before deploying the nitinol stent. The disadvantage is that you have to make your incision at least 1 centimeter higher because of the stent that protrudes into the ascending aorta. If you make your aortotomy too low, you've got a big problem. With the Intuity valve, it is sometimes difficult to see exactly where it is in the native annulus before deploying it, but that should translate into better long-term outcomes because there isn't any folding or crimping of the pericardial tissue.

DR MARIAN ZEMBALA (Zabrze, Poland): Thank you for your message. A few small remarks. Certainly, mortality is too high to persuade as a valid option, especially in the isolated aortic valve pathology, except when you prove there is a very special risk. That's one. The second question: I would rather use a more homogeneous group of bioprostheses as a control group because then you can compare the hemodynamics. You have Hancock II, you have Perimount in some, and others.

And the third, in our hands, almost 50 sutureless valves: we find them very useful, not only a short cross-clamp time but a very low gradient in a tiny, obese lady certainly has fantastic hemodynamics.

DR BORGER: There are some excellent indications for these new technologies. The hemodynamics are better than what we've seen for most stented bioprostheses, rivaling those observed with homografts and stentless prostheses. And certainly the hemodynamic performance is advantageous in an obese patient or those with a small annulus, where you're worried about patient–prosthesis mismatch. Getting back to your first question about the mortality, again, just to stress that the current study has a small sample size, and the 95% confidence limits of our observed mortality are well within the published range in the literature. Your second point? I'm sorry I missed the second question.

DR ZEMBALA: Homogenicity in the control study, because you have Hancock which is different from Perimount. Perhaps if you build the study it will be used to compare one type of tissue valve like Perimount, which is almost the same technologically.

DR BORGER: We discussed this issue at length when we were designing the trial, and we decided we wanted to leave it at the surgeon's discretion because we didn't want to force them to use another new valve that they may not have been using in the past. That leads me as a segue into the next point, which is that of the five centers that were included in this multicenter trial, only one had previous experience with the Edwards Intuity valve. So I believe it's also important to stress that this represents an early experience study and, despite that, we achieved very respectable outcomes.

DR ZEMBALA: You're absolutely right. When you involve the centers where they have already experience with sutureless valve, the outcome will be much better and the technical error less.

DR CLAUDIO MUNERETTO (Brescia, Italy): Michael, I enjoyed your paper. As far as you caution about advantage and disadvantages obviously between Perceval and Intuity, we have a lot of differences in terms of size of aortotomy and alignment with the valve. For example, allowing the positioning of the valve through

a minithoracotomy for the Perceval, that could be quite hard. Could you comment on that.

DR BORGER: Thank you, Claudio. As I said, the Perceval S valve is a bit easier to implant than the Intuity. And if I'm going to use the right anterolateral minithoracotomy approach, which I just recently started doing, I have actually been using the Perceval S exactly for that reason. As an aside, I think that the upper lateral minithoracotomy is an approach that somebody should embark upon only after having an extensive experience with the upper hemisternotomy and also preferably with the small right minithoracotomy approach for the mitral valve. The tricks and techniques and the long instruments used for the minimally invasive mitral valve operation are very helpful for this aortic valve approach.

And finally, I'd like to mention that much more information will become available in the foreseeable future from another ongoing randomized clinical trial of the Edwards Intuity valve, which is currently taking place in the United States. These data will further help us determine the clinical benefits and possible indications for this promising new technology.

DR JOHN CONTE (Baltimore, MD): I have one quick question about the study design that I can't come to grips with. One of your primary outcomes is time on bypass and ischemia. And certainly with a ministernotomy it's technically going to be much more difficult than with a full sternotomy. So don't you think by the study design of having a full sternotomy in one group and a ministernotomy in the other group, you're going to put the new technology at a disadvantage based on your study design?

DR BORGER: Definitely. And that's why we thought that this would be a robust study design in order to show whether the Intuity valve facilitates the performance of minimally invasive operations. One may argue that we should have designed the trial to have minimally invasive Intuity rapid deployment versus minimally invasive standard conventional bioprostheses, and this issue was discussed at length before the start of the study. However, we also wanted to try to demonstrate with this study that there are some clinical benefits to the minimally invasive approach, particularly with regards to quality of life. Unfortunately, we were unable to demonstrate that.

DR CONTE: I just think as this gets into the literature 5 years from now, people are going to look back and say: Well, this study only showed a 13-minute advantage with the ministernotomy rapid deployment; is it worth the extra $10,000 per valve to do that?

DR BORGER: Well, first of all, I hope it's not $10,000. And second, if you look at the literature, there is a very good systematic review showing that when comparing minimally invasive with conventional aortic valve replacement with a normal bioprosthesis, you have a 9-minute longer ischemic time for the minimally invasive approach. So now we've gone from a 9-minute-longer to a 12-minute-shorter myocardial ischemic time, corresponding to even more than the 24% relative risk reduction that we demonstrated in the current study. I think the take-home message is that this technology definitely facilitates minimally invasive aortic valve replacement.