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**ORIGINAL ARTICLE**

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# Haemodynamic benefits of rapid deployment aortic valve replacement via a minimally invasive approach: 1-year results of a prospective multicentre randomized controlled trial[†]

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## Abstract

**OBJECTIVES**: Aortic valve replacement (AVR) via minimally invasive surgery (MIS) may provide clinical benefits in patients with aortic valve disease. A new class of bioprosthetic valves that enable rapid deployment AVR (RDAVR) may facilitate MIS. We here report the 1-year results of a randomized, multicentre trial comparing the outcomes for MIS-RDAVR with those for conventional AVR via full sternotomy (FS) with a commercially available stented aortic bioprosthesis.

**METHODS**: A total of 100 patients with aortic stenosis were enrolled in a prospective, multicentre, randomized comparison trial (CADENCE-MIS). Key exclusion criteria included AVR requiring concomitant procedures, ejection fraction of <25% and recent myocardial infarction or stroke. Patients were randomized to undergo MIS-RDAVR via upper hemisternotomy (EDWARDS INTUITY) or AVR via FS with a commercially available stented valve. Procedural, early and late clinical outcomes were assessed for both groups. Haemodynamic performance was evaluated by an echocardiography CoreLaboratory.

**RESULTS**: Technical success was achieved in 94% of MIS-RDAVR patients. MIS-RDAVR was associated with significantly reduced cross-clamp times compared with FS (41.3 ± 20.3 vs 54.0 ± 20.3 min, $P < 0.001$). Clinical and functional outcomes were similar at 30 days and 1 year postoperatively for both groups. While both groups received a similarly sized implanted valve (22.9 ± 2.1 mm MIS-RDAVR vs 23.0 ± 2.1 mm FS-AVR; $P = 0.91$), MIS-RDAVR patients had significantly lower peak gradients 1 year postoperatively (16.9 ± 5.3 vs 21.9 ± 8.6 mmHg; $P = 0.033$) and a trend towards lower mean gradients (9.1 ± 2.9 vs 11.5 ± 4.3 mmHg; $P = 0.082$). In addition, MIS-RDAVR patients had a significantly larger effective orifice area 1 year postoperatively (1.9 ± 0.5 vs 1.7 ± 0.4 $cm^2$; $P = 0.047$). Paravalvular leaks, however, were significantly more common in the MIS-RDAVR group ($P = 0.027$).

**CONCLUSIONS**: MIS-RDAVR is associated with a significantly reduced cross-clamp time and better valvular haemodynamic function than FS-AVR. However, paravalvular leak rates are higher with MIS-RDAVR.

**Keywords:** Aortic valve replacement • Heart valve, Bioprosthesis • Haemodynamics • Minimally invasive

## INTRODUCTION

Aortic valve replacement (AVR) through minimally invasive surgery (MIS) techniques may provide both clinical and cosmetic benefits for patients with aortic valve disease, and can be safely performed without increased risk of major complications or death [1]. Historically, AVR via a full sternotomy (FS) has been the gold standard for patients with aortic stenosis (AS) since the 1960s. Despite the possible benefits of MIS-AVR, such procedures are associated with longer cardiopulmonary bypass times (CPBTs) and aortic cross-clamp times (XCTs) [2]. The prolonged operative times are a marker for increased technical complexity, which may explain the relatively low rate of MIS-AVR procedures currently

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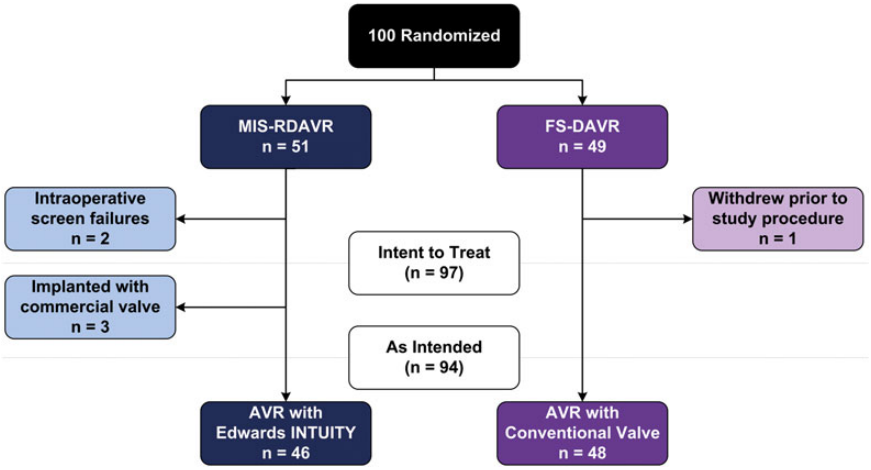


**Figure 1:** Consolidated Standards of Reporting Trials (CONSORT) diagram. (Reproduced from Ref. [9] with permission from Elsevier.) MIS: minimally invasive surgery; RDAVR: rapid deployment aortic valve replacement; FS: full sternotomy; AVR: aortic valve replacement.

performed by cardiac surgeons. Longer CPBTs and XCTs correlate with higher rates of morbidity and mortality in both low- and high-risk patients, particularly those requiring concomitant procedures [3, 4].

Several retrospective studies have demonstrated that MIS-AVR is associated with faster recovery time, reduced surgical trauma and blood loss, decreased postoperative pain and disability, shorter ventilation times, reduced intensive care unit and hospital length of stays, as well as better long-term survival rates when compared with FS-AVR surgery [2, 5–7]. Even patients with pulmonary dysfunction may benefit from using a minimal access approach [8]. Despite these potential advantages, MIS-AVR is currently performed in a small proportion of patients [9].

Recent advancements in valve design have resulted in a new class of bioprosthetic valves that enable rapid deployment AVR (RDAVR) and may facilitate the use of MIS approaches [10–12]. Nitinol-based sutureless valves allow the valve frame to self-expand and anchor to the annulus through a thermoresponsive mechanism [13, 14]. Recently, published data have demonstrated low complication rates, good efficacy and expedited procedural times and excellent haemodynamic performance for this new class of devices [9, 15, 16].

The CADENCE-MIS trial was a prospective, multicentre, randomized trial comparing outcomes in patients undergoing MIS-RDAVR using the EDWARDS INTUITY Valve System (Model 8300A, Edwards Lifesciences, Irvine, CA, USA) with those undergoing FS-AVR with a commercially available bioprosthetic valve. The objective of this study was to compare early and mid-term outcomes in these two groups of patients, with a particular focus on haemodynamic data.

## MATERIALS AND METHODS

### Study population

The CADENCE-MIS trial is a prospective, randomized (1 : 1), multicentre trial conducted in five German hospitals. The study design and methods have been previously described by Borger *et al.* [9]. Inclusion criteria consisted of isolated aortic valve surgery for AS with or without aortic insufficiency, low-to-moderate surgical risk (i.e. logistic EuroSCORE <20) and New York Heart Association (NYHA) class II or greater. Exclusion criteria consisted of pure aortic insufficiency, planned concomitant procedures, previous cardiac surgery, true bicuspid aortic valve (i.e. Sievers type 0), ejection fraction of <25% and recent myocardial infarction or stroke. A total of 100 patients were enrolled between May 2012 and February 2013; 51 were randomized to undergo MIS-RDAVR through an upper hemisternotomy using the EDWARDS INTUITY Valve System and 49 were randomized to FS-AVR with a conventional stented bioprosthetic valve of the investigator's preference. Four of the five study centres had no previous clinical experience with the Intuity valve. The study protocol was reviewed and approved by the Ethics Committee of each participating centre and all patients provided written informed consent.

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. Two patients who were randomized to undergo MIS-RDAVR were subsequently excluded because of intraoperative screening failure due to extensive calcification of the aortic root and unavailability of the appropriate sized device in 1 patient each. In addition, 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 remaining 97 patients in the intent-to-treat groups, 49 subjects were intended to receive an EDWARDS INTUITY valve via MIS-RDAVR and 48 patients were intended to receive a control valve via FS. During surgery, 3 subjects of the MIS-RDAVR group were converted to FS with a conventional valve because of inability of positioning in 2 patients and an annular tear in 1 patient (Fig. 1). These 3 patients were excluded from all further analyses (i.e. all further reported analyses are 'as-intended').

### Rapid deployment aortic valve replacement

RDAVR with the EDWARDS INTUITY Valve System was performed through a minimal access incision (i.e. upper hemisternotomy), as previously described [9]. After a standard aortotomy, the diseased aortic valve leaflets were excised and annular calcium was debrided using conventional surgical techniques. The debrided annulus was carefully sized to identify the appropriate sized valve. 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

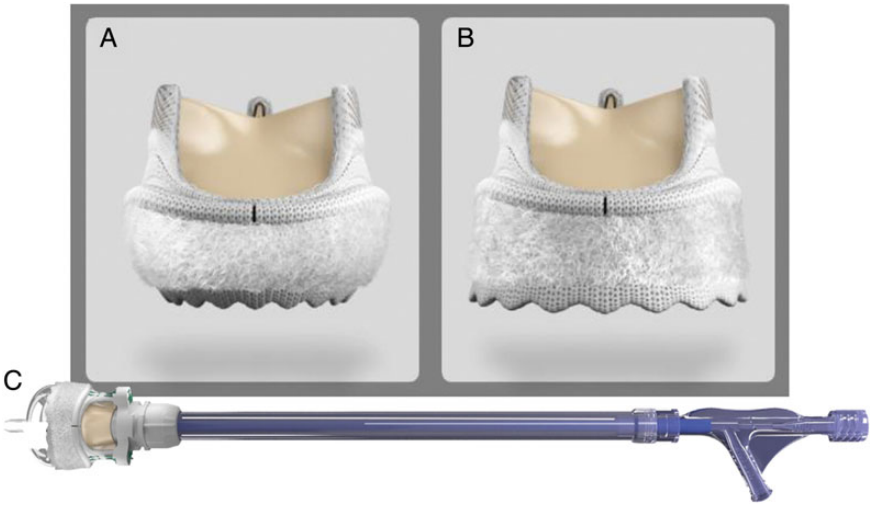


**Figure 2:** The EDWARDS INTUITY valve. The subannular skirt frame in the (**A**) precrimped and (**B**) deployed configuration. (**C**) Complete valve deployment system. (Reproduced from Ref. [9] with permission from Elsevier.)

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 in 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. After the valve was properly seated, the balloon catheter was expanded with a 10-s inflation at the appropriate pressure for the corresponding valve size. The delivery system was then removed, guiding sutures were tied and the aortotomy was closed in a routine fashion. Following 46 EDWARDS INTUITY valves were successfully implanted: 19 mm ($n = 2$), 21 mm ($n = 15$), 23 mm ($n = 16$), 25 mm ($n = 9$) and 27 mm ($n = 4$).

## Aortic valve replacement with a conventional bioprosthetic valve

All control patients underwent AVR surgery via an FS approach. 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 via FS: Hancock II (Medtronic, Minneapolis, MN, USA; $n = 3$), Mitroflow (Sorin Biomedica Cardia Srl, Saluggia, Italy; $n = 3$), Trifecta (St. Jude Medical, St. Paul, MN, USA; $n = 10$) or Perimount Magna Ease (Edwards Lifesciences; $n = 32$). The valve size distribution was as follows: 19 mm ($n = 2$), 21 mm ($n = 16$), 23 mm ($n = 15$), 25 mm ($n = 12$), 27 mm ($n = 2$) and 29 mm ($n = 1$).

## Postoperative care and follow-up

Patients were given maintenance anticoagulant therapy, except when contraindicated, for 3-month post-valve implant in accordance with the published guidelines [17]. Some patients received further anticoagulation in cases of atrial fibrillation; appropriate anticoagulation monitoring was performed by the treating physician on an individual basis. Clinical and echocardiographic data (transthoracic) were collected per protocol at baseline, discharge, 30 days, 3 months and 1 year postoperatively. Echocardiograms were reviewed by an independent echocardiography CoreLaboratory (RadCore Labs/Cardiocore, LLC, Torrance, CA, USA). Safety end-points and adverse events, as per the guidelines for reporting mortality and morbidity after cardiac valve interventions [18], were adjudicated by an independent Clinical Events Committee (CEC) whose members were independent of both the study sponsor and the investigators.

## End-points

Primary end-points of this trial were XCT and CPBT. Secondary end-points were assessed at each follow-up period and included all-cause and valve-related mortality, paravalvular leakage (PVL), resternotomy, cardiac reoperation, major bleeding events, prosthetic valve endocarditis, myocardial infarction, deep sternal wound infection, thromboembolism (stroke, transient ischaemic attack, non-cerebral embolic event and study valve thrombosis), permanent pacemaker implantation, respiratory failure, renal failure and study valve explant.

All-cause mortality included all deaths from any cause after a valve intervention, whereas valve-related mortality was any death caused by structural valve deterioration, non-structural dysfunction, valve thrombosis, embolism, bleeding event or operated valve endocarditis; death related to reintervention on the operated valve or sudden, unexplained death. Major PVL was defined as a paravalvular leak, exclusive of that associated with thrombosis or infection, that (i) leads to intervention or reoperation (with or without symptoms), (ii) graded moderate or greater (with or without symptoms and with or without intervention/reoperation), (iii) results in death, or that is moderate-sized or greater when diagnosed by autopsy. Major bleeding event was defined as any episode of major internal or external bleeding that causes death, hospitalization or permanent injury (e.g. vision loss) or necessitates transfusion of three or more units of RBCs. Permanent pacemaker implantation was any implantation of a permanent pacemaker or internal cardioverter/defibrillator that was not planned prior to the aortic valve implant procedure.

Additional secondary end-points included technical success, which was defined as successful delivery and deployment of the study valve within two attempts and leaving the operating room with the study valve in place. Procedural success was defined as technical success plus the absence of the following complications

**Table 1:** Demographics and baseline characteristics by the randomized group

| Variable | EDWARDS INTUITY (*N* = 46) | Control (*N* = 48) | *P*-value |
|---|---|---|---|
| Age (years) | 73.0 ± 5.3 | 74.2 ± 5.0 | 0.30 |
| BMI (kg/m$^2$) | 29.4 ± 5.1 | 28.8 ± 5.1 | 0.48 |
| Female | 19/46 (41%) | 27/48 (56%) | 0.15 |
| NYHA ≥Class III | 31/46 (67%) | 29/48 (60%) | 0.48 |
| Diabetes | 15/46 (33%) | 11/48 (23%) | 0.29 |
| COPD | 6/46 (13%) | 7/48 (15%) | 0.83 |
| Angina | 16/46 (345%) | 18/48 (38%) | 0.78 |
| Myocardial infarction | 3/46 (7%) | 4/48 (8%) | 0.74 |
| Cardiac rhythm abnormalities/conduction disturbances[a] | 11/46 (24%) | 14/48 (29%) | 0.56 |
| Permanent pacemaker or ICD | 2/46 (4%) | 6/48 (13%) | 0.16 |
| Myocarditis | 0/46 (0%) | 0/48 (0%) | – |
| Hyperlipidaemia or hypercholesterolaemia | 33/46 (72%) | 23/48 (48%) | 0.019 |
| Rheumatic fever | 0/46 (0%) | 0/48 (0%) | – |
| History of smoking | 22/46 (48%) | 12/48 (25%) | 0.021 |
| Alcohol/drug abuse | 0/46 (0%) | 0/48 (0%) | – |
| Blood diatheses | 0/46 (0%) | 0/48 (0%) | – |
| Prior cardiovascular surgery | 0/46 (0%) | 0/48 (0%) | – |
| Calcium metabolic disorders | 1/46 (2%) | 0/48 (0%) | 0.30 |
| Cancer | 4/46 (9%) | 3/48 (6%) | 0.65 |
| Obesity (BMI ≥30) | 22/46 (48%) | 14/48 (29%) | 0.063 |
| Liver disease | 2/46 (4%) | 0/48 (0%) | 0.14 |
| Renal failure/insufficiency | 7/46 (15%) | 7/48 (15%) | 0.93 |
| Dialysis | 0/46 (0%) | 0/48 (0%) | – |
| Creatinine (mg/dl) | 1.0 ± 0.3 | 1.0 ± 0.3 | 0.97 |
| Bicuspid aortic valve (Sievers 1) | 19/46 (41%) | 17/48 (35%) | 0.67 |
| Logistic EuroSCORE | 6.4 ± 3.7 | 6.7 ± 3.6 | 0.45 |
| EuroSCORE II | 38: 1.7 ± 0.9 | 40: 1.8 ± 1.0 | 0.48 |
| STS score (%) | 1.6 ± 0.7 | 47: 1.7 ± 0. | 0.21 |

Continuous variables are expressed as mean ± standard deviation.
Categorical variables were expressed as percentages and number of patients.
BMI: body mass index; STS: The Society of Thoracic Surgeons; NYHA: New York Heart Association; COPD: chronic obstructive pulmonary disease; ICD: internal cardioverter/defibrillator.
[a]Includes sinus tachycardia, sinus bradycardia, bradycardia–tachycardia, atrial fibrillation/supraventricular tachycardia, atrial flutter, ventricular tachycardia and other cardiac rhythm abnormality.

within 10 days or discharge, whichever is first: requiring device reoperation, new permanent pacemaker implantation or death. Furthermore, quality-of-life outcome measures (EQ-5D, SF-12 and KCCQ) and NYHA classification were evaluated. Haemodynamic secondary outcomes were transvalvular peak and mean gradients, effective orifice area (EOA) and patient–prosthesis mismatch (defined as EOA <0.65 cm/m$^2$). All haemodynamic parameters were determined by the echocardiography CoreLaboratory in accordance with published guidelines [19].

## Data management and statistical analysis

As study sponsor, Edwards Lifesciences managed the collection and monitoring of data. However, surgeon investigators assumed primary responsibility for the interpretation and reporting of data. Results depicted within this study are reflective of an 'as intended' analysis. The 'as intended' analysis does not include those subjects that were randomized to the EDWARDS INTUITY group, but received a commercial valve (*n* = 3). Details for these 3 patients are mentioned separately above.

Continuous variables are summarized as mean and standard deviation (SD) and categorical variables were expressed as percentages and number of patients in each category throughout the report. Complications are summarized for the early (≤30 days after the index procedure) and medium-term (>30 days and up to 1 year) periods. Statistical inferences comparing continuous variables were made using a Wilcoxon–Mann–Whitney test and comparisons of categorical variables were made using Pearson's $\chi^2$ test (or Fisher's exact test when cell counts were low). Two-sided tests were utilized and a type I error significance level of 0.05 was considered. All data are based on a data extract date of 15 July 2015.

# RESULTS

## Baseline patient characteristics

Baseline patient characteristics for the two groups of patients are presented in Table 1. The risk of perioperative death, as calculated by the logistic EuroSCORE, [20] was similar in both groups (6.3 ± 3.7 vs 6.7 ± 3.6 for MIS-RDAVR versus FS-AVR). In general, the two groups had a similar risk profile with the exception of hypercholesterolaemia and history of smoking, which were significantly higher in the MIS-RDAVR group. There was no significant difference in the proportion of patients with bicuspid aortic valve (i.e. Sievers type 1) disease.

**Table 2:** Clinical outcomes

| Outcome | 30 days | | | 1 year | | |
|---|---|---|---|---|---|---|
| | EDWARDS INTUITY % (*n*/*N*) | Control % (*n*/*N*) | *P*-value | EDWARDS INTUITY % (*n*/*N*) | Control % (*n*/*N*) | *P*-value |
| Mortality | 4% (2/46) | 2% (1/48) | 0.53 | 6% (3/46) | 6% (3/48) | 0.96 |
| Cardiac reoperation for any reason (including explant) | 13% (6/46) | 10% (5/48) | 0.69 | 15% (7/46) | 13% (6/48) | 0.70 |
| Resternotomy | 13% (6/46) | 10% (5/48) | 0.69 | 15% (7/46) | 10% (5/48) | 0.49 |
| New permanent pacemaker | 4% (2/46) | 2% (1/48) | 0.53 | 4% (2/46) | 2% (1/48) | 0.53 |
| Thromboembolism | 7% (3/46) | 6% (3/48) | 0.96 | 8% (4/46) | 8% (4/48) | 0.95 |
| Major bleeding event | 17% (8/46) | 8% (4/48) | 0.19 | 17% (8/46) | 10% (5/48) | 0.33 |
| Cardiac tamponade | 4% (2/46) | 6% (3/48) | 0.68 | 4% (2/46) | 6% (3/48) | 0.68 |
| CVA or permanent stroke | 4% (2/46) | 4% (2/48) | 0.97 | 4% (2/46) | 4% (2/48) | 0.97 |
| Endocarditis | 0% (0/46) | 0% (0/48) | – | 0% (0/46) | 0% (0/48) | – |
| Myocardial infarction | 0% (0/46) | 2% (1/48) | 0.33 | 0% (0/46) | 4% (2/48) | 0.16 |
| Deep sternal wound infection | 2% (1/46) | 2% (1/48) | 0.98 | 2% (1/46) | 2% (1/48) | 0.98 |
| Respiratory failure | 4% (2/46) | 0% (0/48) | 0.14 | 4% (2/46) | 4% (2/48) | 0.97 |
| Renal failure | 7% (3/46) | 0% (0/48) | 0.072 | 7% (3/46) | 2% (1/48) | 0.29 |

*P*-values comparing the rates of events between EDWARDS INTUITY and control group are based on Pearson's $\chi^2$ tests.
CVA: cerebrovascular accident.

## Procedural outcomes

Technical success in MIS-RDAVR patients was 93.9% (46/49). Of these 46 patients, 44 patients were successfully implanted with the EDWARDS INTUITY valve on the first attempt (96%).

Compared with the FS-AVR patients, MIS-RDAVR patients had a significantly reduced XCT (41.3 ± 20.3 vs 54.0 ± 20.3 min; $P < 0.001$). However, CPBT was not significantly different between groups (68.8 ± 29.0 vs 74.4 ± 28.4 min for MIS-RDAVR versus FS-AVR, respectively; $P = 0.21$).

Similar sized valves were implanted in both groups (22.9 ± 2.1 mm MIS-RDAVR vs 23.0 ± 2.1 mm FS-AVR; $P = 0.91$).

## Clinical outcomes

As noted in Table 2, early (≤30 days after the index procedure) and medium-term (>30 days and up to 1 year) clinical outcomes were similar between groups.

***Mortality.*** There were a total of 7 deaths during follow-up: 3 in the MIS-RDAVR, 3 in the FS-AVR groups and 1 excluded patient (intended to undergo MIS-RDAVR but instead underwent FS-AVR). Of the deaths that occurred in the MIS-RDAVR group, 1 patient died 2 days postoperatively due to cardiogenic shock, 1 died 14 days post-procedure due to pericardial tamponade and 1 died on postoperative day 315 due to pneumonia and sepsis. Both early deaths were adjudicated by the CEC as procedure-related, whereas the first event was also adjudicated as study valve-related. In the FS-AVR group, 2 patients died because of unknown reasons on postoperative days 15 and 202. These deaths were adjudicated as procedure-related, with the second one adjudicated as potentially valve-related. The third subject died due to major neurological bleeding on postoperative day 74.

No episodes of endocarditis were observed during the trial in either patient group. All other medium-term clinical outcomes were similar between the two study groups (Table 2).

***Paravalvular leak.*** A total of 21 patients experienced PVL at discharge (from 84 adequate echocardiographic examinations) and a total of 19 patients experienced PVL at 1 year ($n = 76$ echocardiographic examinations). Moderate or severe PVL was present in none of the patients in the MIS-RDAVR group at discharge and in 1 subject at 1 year (3%), with 1 further patient undergoing reoperation for PVL prior to 1-year follow-up (see below). In the control group, none of the patients developed moderate or severe PVL up to 1-year follow-up. While the frequency of any grade of PVL was not significantly different between study groups at discharge (11/41 MIS-RDAVR vs 10/43 FS-AVR; $P = 0.81$), the difference at 1 year was statistically significant (13/36 MIS-RDAVR vs 6/40 FS-AVR; $P = 0.027$; Table 3). There was no statistically significant difference in 1-year PVL rates in patients with and without bicuspid aortic valve disease ($P = 0.29$), and no significant interaction effect of bicuspid aortic valve disease × patient group (i.e. Intuity versus control, $P = 0.61$).

***Valve explants.*** Within those patients who underwent cardiac reoperation, 2 valve explants occurred during follow-up, both occurring in the MIS-RDAVR group. One early explant was performed 3 h after the index surgery due to haemodynamic instability and major bleeding. The patient subsequently died 2 days postoperatively. The other explant occurred on postoperative day 344 due to major PVL and haemolysis. After 30 days of safety follow-up, this patient was excluded from the study.

## Haemodynamic outcomes

Table 4 summarizes the haemodynamic outcomes for both groups of patients. EOA at 1 year was significantly increased in the MIS-RDAVR group in comparison with the FS-AVR group (1.9 ± 0.5 vs 1.7 ± 0.4 $cm^2$; $P = 0.047$). MIS-RDAVR patients had a significantly decreased peak transvalvular gradient when compared with FS-AVR patients (16.9 ± 5.3 vs 21.9 ± 8.6 mmHg; $P = 0.033$), as well as a trend towards lower mean transvalvular gradients (9.1 ± 2.9 vs 11.5 ± 4.3 mmHg; $P = 0.082$).

The MIS-RDAVR group showed stable mean and peak gradients over time, whereas gradients slightly worsened over time in the FS-AVR group.

**Table 3:** Paravalvular leak rates as determined by CoreLaboratory

| | Discharge | | 30 days | | 1 year | |
|---|---|---|---|---|---|---|
| | EDWARDS INTUITY *n/N* (%) | Control *n/N* (%) | EDWARDS INTUITY *n/N* (%) | Control *n/N* (%) | EDWARDS INTUITY *n/N* (%) | Control *n/N* (%) |
| 0 None | 30/41 (73%) | 33/43 (77%) | 27/34 (79%) | 24/36 (67%) | 23/36 (64%) | 34/40 (85%) |
| +1 Trivial/trace | 10/41 (24%) | 7/43 (16%) | 6/34 (18%) | 11/36 (31%) | 9/36 (25%) | 6/40 (15%) |
| +2 Mild | 1/41 (2%) | 3/43 (7%) | 1/34 (3%) | 1/36 (3%) | 3/36 (8%) | 0/40 (0%) |
| +3 Moderate | 0/41 (0%) | 0/0 (0%) | 0/34 (0%) | 0/0 (0%) | 1/36 (3%) | 0/0 (0%) |
| +4 Severe | 0/0 (0%) | 0/0 (0%) | 0/0 (0%) | 0/0 (0%) | 0/0 (0%) | 0/0 (0%) |
| *P*-value | 0.81 | | 0.25 | | 0.027 | |

**Table 4:** Haemodynamic outcomes

| Parameter | Trial arm | Baseline *n*: mean ± SD | Discharge *n*: mean ± SD | 30 days *n*: mean ± SD | 3 months *n*: mean ± SD | 1 year *n*: mean ± SD | *P*-value |
|---|---|---|---|---|---|---|---|
| BSA-corrected LV mass (g) | Control | 38: 135.2 ± 37.9 | N/A | 31: 115.4 ± 30.5 | 37: 105.3 ± 31.8 | 29: 102.1 ± 28.9 | 0.33 |
| | EDWARDS INTUITY | 33: 123.9 ± 35.4 | N/A | 26: 118.2 ± 33.2 | 35: 104.1 ± 26.7 | 24: 108.5 ± 31.0 | |
| EOA ($cm^2$) | Control | 43: 0.7 ± 0.2 | 36: 1.9 ± 0.7 | 31: 2.0 ± 0.7 | 39: 1.8 ± 0.6 | 29: 1.7 ± 0.4 | 0.047 |
| | EDWARDS INTUITY | 38: 0.7 ± 0.2 | 38: 1.9 ± 0.6 | 30: 1.9 ± 0.5 | 36: 1.9 ± 0.5 | 27: 1.9 ± 0.5 | |
| Mean gradient (mmHg) | Control | 45: 45.4 ± 20.0 | 44: 10.8 ± 3.4 | 37: 9.7 ± 3.9 | 40: 10.3 ± 4.8 | 40: 11.5 ± 4.3 | 0.082 |
| | EDWARDS INTUITY | 42: 44.0 ± 15.9 | 40: 10.3 ± 5.4 | 33: 8.8 ± 4.2 | 39: 9.1 ± 4.2 | 40: 9.1 ± 2.9 | |
| Peak gradient (mmHg) | Control | 45: 75.4 ± 27.9 | 44: 21.0 ± 6.9 | 37: 17.8 ± 6.5 | 40: 18.9 ± 8.2 | 40: 21.9 ± 8.6 | 0.033 |
| | EDWARDS INTUITY | 42: 69.6 ± 23.7 | 40: 19.0 ± 9.5 | 33: 16.5 ± 7.8 | 39: 17.0 ± 7.6 | 40: 16.9 ± 5.3 | |

BSA-corrected LV mass (per CoreLaboratory) is used in place of LV mass index.
SD: standard deviation; LV: left ventricular; EOA: effective orifice area.

Patient–prosthesis mismatch was present in 3.7% of MIS-RDAVR patients and 10.3% of FS-AVR patients 1 year postoperatively ($P = 0.34$).

## DISCUSSION

Based on the structural design and documented long-term outcomes of the Carpentier-Edwards Perimount valve, [21] the EDWARDS INTUITY Valve System was developed with the goal of enabling RDAVR in patients with AS. The objective of the CADENCE-MIS trial was to evaluate the safety and performance of the Intuity Valve System when compared with conventional FS-AVR surgery, with a particular focus on myocardial ischaemic and bypass times. We hypothesized that the EDWARDS INTUITY device would facilitate MIS-AVR surgery, as measured by operative times. In addition, early and medium-term haemodynamic outcomes were measured and compared between study groups, which is the focus on the current study.

Technical success rate was achieved in 94% of patients randomized to receive the EDWARDS INTUITY valve, whereas procedural success rate was 90%. The statistically significant reduction in XCT for the MIS-RDAVR group can lead one to conclude that the MIS approach is facilitated with the Intuity device since previous studies have demonstrated that MIS is associated with a 16% increase in XCT when compared with conventional FS-AVR [22]. Other studies have also confirmed short implant and myocardial ischaemic times for the Intuity valve [16, 23]. Our findings are particularly striking given that some of the study centres performed a small number of Intuity implants, and that these implants were the first clinical experience in these centres. It is likely that XCT and CPB times for Intuity implantation would be even lower with increasing clinical experience, as noted by Schlomicher *et al.* [23].

Early and medium-term clinical outcome rates were similar in both cohorts. In particular, the observed rates for new permanent pacemaker implantation, thromboembolism and endocarditis were low for both groups of patients [13, 14, 24, 25]. Our observed rate of permanent pacemaker implantation for the EDWARDS INTUITY valve (i.e. 4%) is low in comparison with other commercially available RD valves [i.e. Perceval S (Sorin Biomedica Cardio Srl) and ATS 3f Enable (ATS Medical, Inc., Minneapolis, MN, USA)], with a reported rate of ∼7% for both [13, 14].

Despite the lack of significant differences in PVL rates at discharge, a significantly higher proportion of MIS-RDAVR patients had PVL 1 year postoperatively. Only 1 patient required valve explant for PVL and haemolysis during follow-up, whereas the other cases of PVL have remained clinically non-significant thus far. The rate for minor PVL (i.e. 1+ or 2+) was 21% before discharge and 33% at 1 year. Major PVL (3+ or 4+) was not observed before discharge, but was present in 1 patient (3%) at 1 year postoperatively (in addition to the one valve explant described above). In comparison with our observed PVL rates, major PVL requiring intervention has been reported in 4% of patients undergoing Perceval S implantation [18]. For the ATS 3f Enable valve, PVL rates have been reported as 2.1% for early minor PVL and 2.1% for early major PVL [13, 14]. Previous reports of the EDWARDS INTUITY valve found a 1.4% early major PVL rate, a 36% late minor PVL rate and 0.9–1.2% late major PVL rate at 1 year requiring explant [15, 16].

In view of the above-mentioned studies, the PVL rates in the current study seem to be somewhat increased, particularly for

minor PVL. It should be noted, however, that the current study is the only randomized controlled trial of RD/sutureless valves and the only study that used an echocardiographic CoreLaboratory in order to assess PVL. One can therefore hypothesize that the detection of PVL was more sensitive in the CADENCE-MIS trial. Nonetheless, our observation of a statistically significant increase in PVL rates in the RDAVR group, when compared with conventional FS-AVR patients, is an important issue that will require further follow-up and study. The reason for the increased PVL rates is not known. We did not observe any relation between bicuspid aortic valve disease and PVL in Intuity patients. It should be stressed, however, that the current study was performed with the first generation of the EDWARDS INTUITY valve and that four of the five participating centres had never implanted an Intuity valve prior to joining the study. Whether or not PVL rates are lower with the newer-generation EDWARDS INTUITY Elite valve or with increasing clinical experience remains to be seen.

Haemodynamic performance of the EDWARDS INTUITY valve was better than that of conventional bioprostheses in our study, with significantly lower peak transvalvular gradients and larger EOAs. A possible explanation for this important observation may be the stent skirt frame of the Intuity valve that is seated below the annulus in a flared configuration within the left ventricular outflow tract (LVOT). The stent may limit active constriction of the LVOT during systole which may lead to more laminar blood flow across the prosthesis [15]. In addition, the lack of pledgeted sutures may contribute to more laminar flow across the LVOT/aortic annulus. However, more clinical and benchside data are required to test these hypotheses.

### Study limitations

Although the CADENCE-MIS trial was a prospective, multicentre, randomized trial, it was limited by a small sample size. Due to the limited number of patients per cohort, summary statistics were influenced by potential outliers due to natural variability. Also, the analysis of the smallest valve size was limited to only 3 subjects. A randomized trial comparing MIS-RDAVR with FS-AVR with larger cohorts over a longer period of follow-up needs to be conducted in order to confirm our findings, as well as to more fully assess the long-term durability and haemodynamic performance of these two groups. In addition, further observation of our patients and those from international registries will be required to determine whether PVL rates are indeed increased for the Intuity valve system, and whether minor PVL eventually becomes clinically significant.

## SUMMARY

Patients undergoing RDAVR via MIS with EDWARDS INTUITY have lower myocardial ischaemic times, decreased transvalvular gradients and larger EOA compared with those undergoing FS-AVR with conventional bioprosthetic valves. However, MIS-RDAVR is associated with a significantly increased rate of PVL.

## CONCLUSIONS

RDAVR with the EDWARDS INTUITY valve may facilitate MIS surgery, as demonstrated by the decreased myocardial ischaemic times when compared with FS-AVR. While haemodynamic performance for MIS-RDAVR with EDWARDS INTUITY appears to be significantly better than that for FS-AVR with conventional bioprostheses, PVL rates are a potential concern. Further follow-up is required to determine whether such observations persist over time.

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**Conflict of interest:** Michael A. Borger is consultant to Edwards Lifesciences and receives speaker honoraria from Edwards Lifesciences. Pascal M. Dohmen receives speakers honoraria from Edwards Lifesciences. David M. Holzhey is consultant to Edwards Lifesciences. Justus Strauch is proctor for the EDWARDS INTUITY valve system. Francis Duhay is an employee of Edwards Lifesciences and reports equity ownership in Edwards Lifesciences.

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## APPENDIX. CONFERENCE DISCUSSION

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***Dr G. Weiss*** *(Vienna, Austria):* I basically only have two short questions, one requiring annulus geometry and the second one pacemaker implantation. We know that the spherical aortic annulus geometry and correct sizing is crucial for achieving a good result after implantation of rapid deployment valves like the EDWARDS INTUITY. Did you include any patients with bicuspid aortic valve diseases in your study population, and if this was the case, did you observe any higher incidence of paravalvular leakage in those patients? What is your personal opinion about using rapid deployment valves for the treatment of bicuspid aortic valve stenosis?

This is my second question. In the manuscript you mentioned a low incidence of new permanent pacemaker implantation of 4%, especially when compared to other commercially available rapid deployment valves, with a reported rate of approximately 7%. Do you think it is related to the valve design or was it just coincidence?

***Dr Borger***: I will answer the first question first. We did not exclude patients with bicuspid aortic valves in this study unless they had the true bicuspid, that is, the Sievers 0 with two commissures that are 180 degrees apart from each other. Whether or not bicuspid aortic stenosis could have been a contributor to a paravalvular leak rate, it is a very good question and we have to analyse the data. We collected information on whether the aortic valves were bicuspid or tricuspid, but we haven't looked at it yet. But we certainly will.

What I can tell you from my own point of view, I do not think that a bicuspid annulus is much of a problem for this valve. As you know, the bicuspid aortic valve annulus is more oval shaped than a tricuspid aortic valve and tends to calcify more. As long as the surgeon takes that into consideration when he is decalcifying the annulus and making sure that he has the right size of the valve for that annulus, even if the annulus is oval-shaped, the annulus is going to become more spherical after stent deployment. Just like, if you perform a conventional aortic valve replacement, the annulus will also become spherical.

Sizing is really the most crucial element of these devices. My main tip to surgeons who want to use one of these valves in a biscupid patient is to be careful on the sizing of the annulus. If you are unsure of the appropriate size, then you should probably think about implanting a conventional valve.

It is also important to note that this study was the first clinical experience in four of the five study centres. Back when we were conducting this trial, we were also saying that you probably don't need to do aggressive decalcification of the annulus. That's not what we say anymore with this valve, that is, we say go ahead and decalcify the annulus like you normally would. Perhaps that's why we have a slightly increased paravalvular leak rate in the Intuity group in our trial.

Regarding your second point for the low rate of pacemaker implantation, I would like to say that it's due to a better design specific to the Intuity. However the scientist part of me says that the extension of the stent below the annulus is just as much as for the Intuity valve as it is for the Perceval valve. The Perceval studies do have a pacemaker implantation rate, that is higher than the one we found for Intuity, but they are also a little bit older patient population. So in the paper from Folliguet, for example, from Paris and Hannover, over 200 patients, their average age was 79 years; ours was 73. So maybe that's the explanation for our low pacemaker rate. I can say for the Intuity that it definitely has a lower pacemaker rate than for the Enable or for some of the transcatheter valves.

***Dr Weiss***: Thank you very much.

***Dr B. Meuris*** *(Leuven, Belgium)*: I think, Michael, indeed you mentioned that this was the first in man for several of these surgeons.

***Dr Borger***: Four of the five centres, yes.

***Dr Meuris***: So you think the paravalvular leaks, is the short learning curve you have to go through and I think it is disappearing now or completely disappears? What is your thought?

***Dr Borger***: Well, the much larger TRITON registry has a low paravalvular leak (PVL) rate then we report but these investigators have only reported moderate or move paravalvular leak and I want to stress, that we only had one patient that had moderate or more paravalvular leak on core lab echocardiography. So I think clinically significant paravalvular leak rates are still very low with the device. We just have to watch what happens with those patients with the trivial to mild paravalvular leak and see if these leaks do become clinically apparent in the future. But getting back to your point, the current trail definitely represents the learning phase for most of the enrolling centres. As stated before, we also performed less aggressive annular decalcification in this trial. In addition, the trial was done with the first generation of the Intuity system, which has been altered significantly in order to improve ease of implantation. I therefore think we will improve our paravalvular leak rates over time.

***Dr J. Seeburger*** *(Leipzig, Germany)*: Michael, you have a lot of experience. When you have the paravalvular leaks, where are they located, what is the predominant location where you find them?

***Dr Borger***: I hope I don't have a big experience with paravalvular leaks. I do have a large experience with this valve, and I think it comes from improper sizing. When you are caught between sizes, that's when it's difficult with this valve. If you know exactly which is the right size from your sizing measurement, i.e., you can get the cylinder portion of the sizer through the annulus but not the flange, then it's an easy decision. But when you're stuck between sizes, if you choose the lower size you increase the risk of a paravalvular leak. Picking the larger size, however, may lead to valve 'pop out' before closing the aorta. Getting back to your question, we have not yet identified any one specific area on the echocardiographic exams where the leaks have occurred. We will have to look into this issue further.