TRANSFORM (Multicenter Experience With Rapid Deployment Edwards INTUITY Valve System for Aortic Valve Replacement) US clinical trial: Performance of a rapid deployment aortic valve

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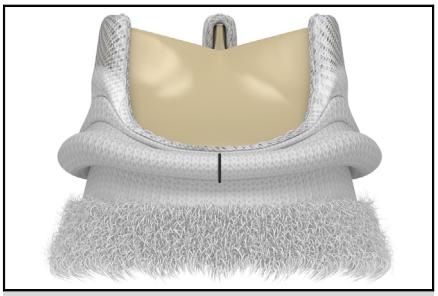
ABSTRACT

Background: The TRANSFORM (Multicen**t**er Experience With **R**apid Deployment Edw**a**rds I**N**TUITY Valve **S**ystem **for** Aortic Valve Replace**m**ent) trial (NCT01700439) evaluated the performance of the INTUITY rapid deployment aortic valve replacement (RDAVR) system in patients with severe aortic stenosis.

Methods: TRANSFORM was a prospective, nonrandomized, multicenter (n = 29), single-arm trial. INTUITY is comprised of a cloth-covered balloon-expandable frame attached to a Carpentier-Edwards PERIMOUNT Magna Ease aortic valve. Primary and effectiveness endpoints were evaluated at 1 year.

Results: Between 2012 and 2015, 839 patients underwent RDAVR. Mean age was 73.5 ± 8.3 years. Full sternotomy (FS) was used in 59% and minimally invasive surgical incisions in 41%. Technical success rate was 95%. For isolated RDAVR, mean crossclamp and cardiopulmonary bypass times for FS were 49.3 ± 26.9 minutes and 69.2 ± 34.7 minutes, respectively, and for minimally invasive surgical 63.1 ± 25.4 minutes and 84.6 ± 33.5 minutes, respectively. These times were favorable compared with Society of Thoracic Surgeons database comparators for FS: 76.3 minutes and 104.2 minutes, respectively, and for minimally invasive surgical, 82.9 minutes and 111.4 minutes, respectively ($P < .001$). At 30 days, all-cause mortality was 0.8%; valve explant, 0.1%; thromboembolism, 3.5%; and major bleeding, 1.3%. In patients with isolated aortic valve replacement, the rate of permanent pacemaker implantation was 11.9%. At 1 year, mean effective orifice area was 1.7 cm^2; mean gradient, 10.3 mm Hg; and moderate and severe paravalvular leak, 1.2% and 0.4%, respectively.



Deployed Intuity valve.

Central Message

INTUITY eliminates complete concentric annular suturing providing an option for rapid surgical deployment and may facilitate smaller incision surgery.

Perspective

Minimally invasive aortic valve replacement may confer patient benefits but is underused because of technical challenges and in part because of longer clamp times. Likewise, ischemia is also prolonged during complex concomitant aortic valve replacement cases. The TRANSFORM (Surgical Treatment of Aortic Stenosis With a Next Generation, Rapid Deployment Surgical Aortic Valve) trial demonstrated that the INTUITY valve eliminates the need for complete concentric annular suturing and provides an option for rapid surgical aortic deployment valve.

See Editorial Commentary page 252.

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Abbreviations and Acronyms

AT	= as-treated
AVR	= aortic valve replacement
CPBT	= cardiopulmonary bypass time
EOA	= effective orifice area
LPY	= late patient-years
LVOT	= left ventricular outflow tract
NYHA	= New York Heart Association
OPC	= objective performance criteria
PVL	= paravalvular leak
RDAVR	= rapid deployment aortic valve replacement
STS	= Society of Thoracic Surgeons
SVD	= structural valve deterioration
TRANSFORM	= Multicenter Experience With **R**apid Deployment Edw**a**rds **INTUITY** Valve **S**ystem **for** Aortic Valve Replace**m**ent
XCT	= crossclamp time

Scanning this QR code will take you to a video for the article.

Conclusions: INTUITY RDAVR performed effectively in this North American trial. It may lead to a relative reduction in aortic crossclamp time and cardiopulmonary bypass time and has excellent hemodynamic performance. Pacemaker implantation rate observed was somewhat greater than European trials and requires further investigation. (J Thorac Cardiovasc Surg 2017;153:241-51)

The incidence and diagnosis of severe aortic stenosis has increased as the result of the aging population and a heightened awareness of mortality.[1] Surgical aortic valve replacement has been the standard of care since the development of prosthetic aortic valves. Numerous design modifications have led to excellent long-term clinical outcomes.[2,3] Both mechanical and tissue valves offer durable performance, but because of concerns relating to chronic anticoagulation, most patients currently prefer tissue valves. Transcatheter aortic valve replacement has been refined over the past several years, increasing treatment choices.[4-6] Recent trials have shown encouraging results in intermediate-risk patients,[7,8] and new trials currently are planned for lower risk patient populations. In response to the value proposition of beating-heart transcatheter aortic valve replacement, rapid deployment aortic valve replacement (RDAVR) was developed to lessen the duration of myocardial ischemia and cardiopulmonary bypass. To be considered successful, however, RDAVR also must meet or exceed attributes of conventionally implanted valves with regard to (1) hemodynamic performance, (2) adaptability to patient anatomy (sizes and shapes), (3) long-term durability, and (4) absence of incremental risk. Moreover, rapid deployment valves should facilitate aortic valve replacement (AVR) through smaller incisions. The INTUITY Valve System (Edwards Life Sciences LLC, Irvine, Calif) relies on the same balloon-expandable deployment system used in the SAPIEN Transcatheter Heart Valve (Edwards Life Sciences LLC) while incorporating the design and well-proven durability of the Carpentier-Edwards PERIMOUNT Magna Ease Pericardial Aortic Bioprosthesis (Edwards Life Sciences LLC).[3]

METHODS

The TRANSFORM (Mul**t**icenter Experience With **R**apid Deployment Edw**a**rds **INTUITY** Valve **S**ystem **for** Aortic Valve Replace**m**ent) trial evaluated the performance of the new INTUITY Valve System. TRANSFORM was a prospective, nonrandomized, multicenter, single-arm clinical trial (ClinicalTrials.gov identifier: NCT01700439). Inclusion criteria included subjects who were 18 years or older and required a planned AVR with or without a concomitant procedure. Exclusion was based on preoperative and intraoperative criteria. Preoperative exclusion criteria included, among others, pure aortic insufficiency, emergency surgery, preexisting prosthetic valve or ring, requirement for multiple valve surgery, hypertrophic obstructive cardiomyopathy, and the presence of a surgical aortic root aneurysm or endocarditis (active or within 3 months of index operation). Intraoperative exclusion criteria included anomalous coronary artery or coronary ostial position, extensive annular or root calcification, and significant calcification of the anterior mitral leaflet or interventricular septum.

TRANSFORM was conducted by the use of Good Clinical Practices in accordance with 21 CFR Part 812 (Investigational Device Exemption), 21 CFR Part 50 (Protection of Human Subjects), CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), and the Health and Insurance Portability and Accountability Act. The clinical protocol, consent form, and protocol amendments were approved by an institutional review board or ethics committee at each investigational site.

INTUITY Valve System

The INTUITY Valve System (Figure 1, *A*) is a Carpentier-Edwards PERIMOUNT Magna Ease Pericardial Aortic Bioprosthesis (Model 3300TFX) modified with an attached precrimped, cloth-covered balloon-expandable stainless-steel frame. The delivery system is composed of a malleable tubular handle into which an integrated balloon catheter is inserted. After the prosthesis is positioned, the balloon expands the valve frame (Figure 1, *B*) within the left ventricular outflow tract (LVOT), establishing a seal between the aortic annulus and the frame. The stented trileaflet valve is composed of glutaraldehyde-preserved bovine pericardium mounted on a flexible cobalt chromium wire form. The outer frame is covered with woven PTFE, and the annulus frame is covered with polyethylene terephthalate. The valve is available in sizes 19, 21, 23, 25, and 27 mm.

Operative Procedure

The following steps were used to deploy the INTUITY Valve System. Three equidistant guide sutures were placed in the nadir of the annulus

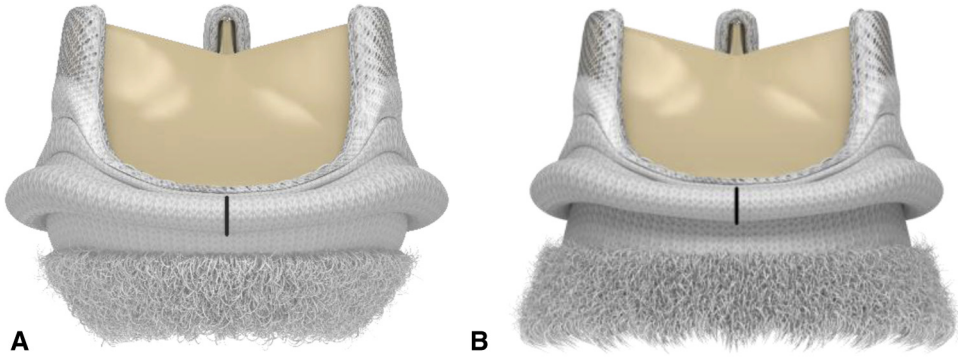


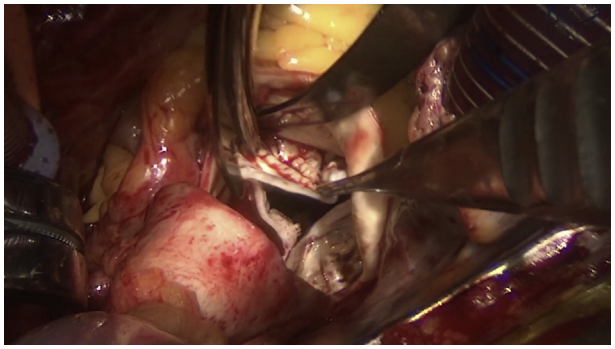
FIGURE 1. Edwards INTUITY aortic valve. A, Valve before deployment; B, after deployment.

and through the sewing cuff of the valve implant. The guide sutures facilitated lowering the INTUITY valve and seating it on the annulus. The holder/expansion device was attached to the valve. After the balloon catheter was inserted through the valve, it was inflated to a prespecified pressure based on valve size. This expanded the frame and secured the valve within the annulus and LVOT. After proper valve seating was verified, the guide sutures were tied and cut. Device technical success was defined as successful implantation of the INTUITY valve within 2 attempts. If a second implant attempt failed, no additional attempts were permitted per protocol, and a conventional surgical valve was used. Video 1 shows an aortic valve replacement with implantation of the INTUITY valve, showing the unique features of this rapid deployment system via an upper mini-sternotomy approach.

Statistical Methods

Statistical analysis was completed with SAS version 7 (SAS Institute, Inc, Raleigh, NC). Adjudication of adverse events was conducted by an independent Clinical Events Committee and trial safety was monitored by a Data Monitoring Committee. Trial endpoints were based on definitions published in the *Guidelines for Reporting Mortality and Morbidity after Cardiac Valve Interventions* by Akins et al.[9] Primary safety endpoints were thromboembolism, valve thrombosis, paravalvular leak (PVL), bleeding events, and endocarditis. The objective performance criteria (OPC) major PVL is an endpoint expressly required by the US Food and Drug Administration for valve approval. Because it is clinically defined, it could underreport PVL discovered on echocardiography in the absence of signs or symptoms. Accordingly, the rates of echocardiography core laboratory-adjudicated PVL (0/1+/2+/3+/4+) also are reported. Primary effectiveness endpoints were New York Heart Association (NYHA) functional class, effective orifice area (EOA), and mean pressure gradient. Secondary safety endpoints were mortality, reoperation, nonstructural valve dysfunction, structural valve deterioration (SVD), device-related conduction defects, and significantly abnormal laboratory values. Secondary effectiveness endpoints were device technical success, procedural success, cardiopulmonary bypass time (CPBT), crossclamp time (XCT), quality of life (SF-12v2 Survey), peak pressure gradient, and EOA index.

Trial safety outcomes are reported as early (≤30 postoperative day) or late (>30 postoperative day) events. The linearized rate is the number of late events divided by the total late patient-years (LPYs) number as 95% upper confidence intervals. One-year Kaplan-Meier estimates were computed on all primary and secondary safety outcomes. Echocardiographic studies were evaluated by a central echocardiographic core lab. PVL was defined as per Valve Academic Research Consortium-2 criteria.[10]



VIDEO 1. Surgical upper mini-sternotomy aortic valve replacement implantation of the INTUITY valve, demonstrating the unique features of this rapid deployment system. Video available at: http://www.jtcvsonline.org/article/S0022-5223(16)31292-2/addons.

RESULTS

Between September 2012 and December 2015, 889 patients were enrolled at 29 investigational sites. Among patients enrolled, 839 were implanted with the INTUITY Valve System. Follow-up was 96.3% complete at 1 year (Figure 2) and included 912.2 patient-years and 844.5 LPY.

Demographics and Baseline Characteristics

Mean age was 73.5 ± 8.3 years, with 24.6% being 80 years or older and 64.5% male. Thirty-two percent (270 of 836) presented with NYHA Class III or IV symptoms. Baseline characteristics and cardiovascular

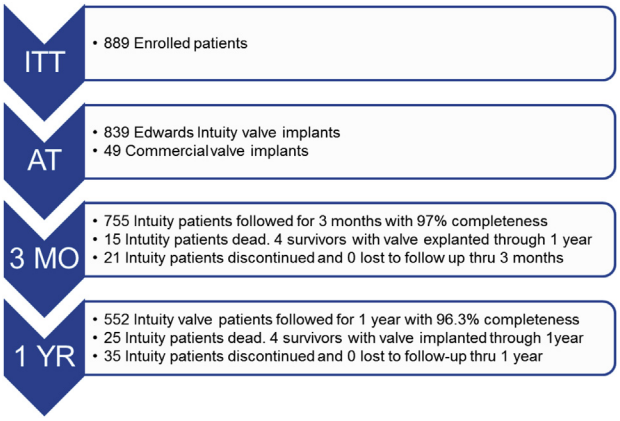


FIGURE 2. Patient flowchart and follow-up.

comorbidities are listed in Appendices E1-E3. More than 25% had important noncardiac conditions that included smoking (58.0%), obesity (46.7%), diabetes (33.1%), and cancer (30.0%). Two thirds of patients (559 of 839) had preoperative conduction abnormalities.

Operative Data

The as-treated (AT) surgical approach and procedure performed are listed in Table 1. For all enrolled patients (intent to treat), 62% underwent isolated AVR (524 of 839). Of those who had isolated AVR, full sternotomy (FS) was performed in 40% (221 of 548), and a minimally invasive incision was used in 60% (327 of 548). The valve generation and size distribution are listed in Table 2. Device technical success (ie, successful implant of INTUITY within 2 attempts) was achieved in 839 of 889 (94.4%) patients. Of 839 successful implants, 773 (92%) were achieved on the first attempt and 66 (7.9%) on the second. Conversion to a nontrial valve because of implant failure occurred in 5.5% of patients (49 of 888).

For isolated RDAVR in all enrolled patients, mean XCT and CPBT for FS were 49.3 ± 26.9 minutes and 69.2 ± 34.7 minutes, respectively, and for minimally invasive surgery 63.1 ± 25.4 minutes and 84.6 ± 33.5 minutes, respectively. These times were favorable compared with Society of Thoracic Surgeons (STS) database comparators for FS: 76.3 minutes and 104.2 minutes, respectively, and for minimally invasive surgery, 82.9 minutes and 111.4 minutes, respectively ($P < .001$). XCT and CPBT stratified by procedure and surgical approach are listed in Appendices E4 and E5 with comparisons to unadjusted summary statistics from the STS Adult Cardiac Surgery Database.

TABLE 1. Surgical approach and procedure (as-treated INTUITY, n = 839)

Approaches and procedures	% (n/N*)
Approach	
Full sternotomy	59.0 (495/839)
Upper mini-sternotomy	32.8 (275/839)
Right anterior thoracotomy	8.2 (69/839)
Procedure	
Isolated AVR	62.5 (524/839)
AVR + CABG	24.9 (209/839)
AVR + CABG + other	3.6 (30/839)
CABG	28.5 (239/839)
1 graft	12.0 (101/839)
2 grafts	10.1 (85/839)
3 grafts	4.6 (39/839)
4+ grafts	1.1 (9/839)
Unknown	0.6 (5/839)
Atrial ablation	5.5 (46/839)
Atrial septal defect repair	1.3 (11/839)
Aortic aneurysm/dissection repair	0.1 (1/839)
Other concomitant procedure	9.9 (83/839)

AVR, Aortic valve replacement; *CABG*, coronary artery bypass grafting. *N is the number of patients with available operative data. Subjects could have more than one concomitant procedure.

TABLE 2. Valve model and size distribution (as-treated INTUITY, n = 839)

	Valve model		
Valve size	Gen I	Gen II	All models
19 mm	10.1% (11/109)	5.2% (38/730)	5.8% (49/839)
21 mm	27.5% (30/109)	19.5% (142/730)	20.5% (172/839)
23 mm	30.3% (33/109)	33.2% (242/730)	32.8% (275/839)
25 mm	25.7% (28/109)	29.7% (217/730)	29.2% (245/839)
27 mm	6.4% (7/109)	12.5% (91/730)	11.7% (98/839)

Trial Safety Outcomes

Intent-to-treat all-cause early mortality was 0.9% (8/889) and 3.8% (34/889) at 1 year. The remaining safety outcomes are presented AT. Early all-cause AT mortality was reported in 7 patients (0.8%; 7/839); 6 died before hospital discharge. Four of the 7 deaths were adjudicated by the Clinical Events Committee as potentially both cardiovascular and valve-related (0.5%; 4/839); these included perioperative bleeding, gastrointestinal catastrophe, heparin-induced thrombocytopenia, and unexplained on day 26. Cardiovascular only-adjudicated deaths (n = 2) were caused by stroke and gastrointestinal catastrophe. An early multiorgan failure death was adjudicated as neither cardiovascular nor valve related. Mortality in patients requiring 2 attempts at implant was 1.2% (1/82). Late all-cause mortality was reported in 25 patients (3.0% per LPY). Eight of the 25 deaths were adjudicated to potentially valve-related (1.1% per LPY) without a known cause of death and of these, 5 were also adjudicated as cardiovascular. At 1 year, Kaplan-Meier freedom from all-cause mortality was 96.4% (Figure 3).

Table 3 lists the early and late event rates and 1 year Kaplan-Meier estimates for primary safety endpoints. These are depicted graphically in Figure 4. Major bleeding was reported in 28 patients that included 11 early (1.3%, 11 of 839) and 21 late events (2.5% per LPY). Only 1 late major bleeding event was adjudicated as valve-related (0.1% per LPY). Most bleeding events resolved without clinical sequelae and occurred while the subjects were receiving anticoagulant treatment either for a concomitant condition or when recommended to reduce the risk of thromboembolism.

Moderate and severe OPC PVL was observed in 1.2% and 0.4%, respectively. Major OPC PVL, defined as PVL of any severity that led to a therapeutic intervention or caused a serious adverse event,[9] was reported in 9 patients. Two occurred early (0.2%, 2 of 839) and 7 late (0.8% per LPY). Two patients were reoperated on within 30 days of the index operation and 7 patients on postoperative days 102, 126, 140, 412, 413, 442, and 712. Freedom from major OPC PVL was 99.3%. Two cases

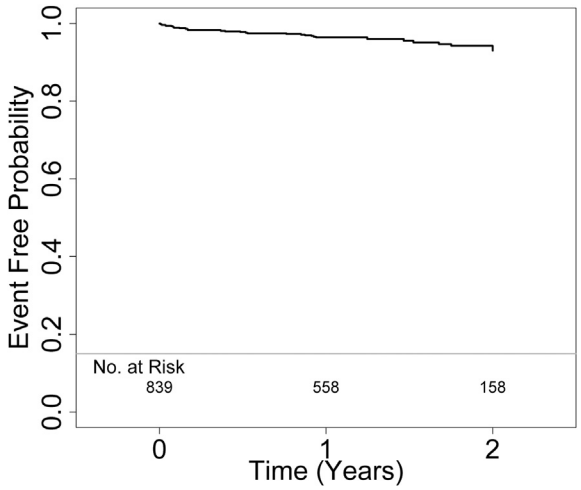


FIGURE 3. Kaplan-Meier freedom from all-cause mortality.

of late hemolysis and no cases of endocarditis were reported.

Table 4 shows early and late event rates and 1-year Kaplan-Meier estimates for all-cause mortality, reoperations, device-related conduction defects, nonstructural valve dysfunction, and SVD. Ten reinterventions (5 percutaneous repairs and 5 surgical explants) of the INTUITY were performed in 9 subjects. Explants occurred early in 1 (0.1%, 1 of 839) and late in 4 (0.5% per LPY) patients. All reoperations were performed for aortic regurgitation. At 1 year, Kaplan-Meier freedom from reintervention was 99.3%.

Echocardiographic PVL as assessed by the core laboratory at 1 year was 1+ (trivial or none) in 91.5% (475/519), 2+ (mild) in 6.9% (36/519), 3+ (moderate) in 1.2% (6/519), and 4+ (severe) in 0.4% (2/519). New permanent pacemaker implantation was required during index hospitalization in 11.9% (57 of 481) of patients undergoing isolated AVR. Of those patients having postoperative pacemaker implant, 73.3% had preexisting complete right bundle branch block and 19.65% had preexisting sinus bradycardia. No cases of SVD were reported.

Trial Effectiveness Outcomes

At 1 year, 77.1% (421 of 549) of patients were in NYHA Class I, 19.6% (107 of 546) in NYHA Class II, 2.7% (15 of 546) in NYHA Class III, and 0.5% (3 of 546) in NYHA Class IV. Overall, NYHA Class improved in 73.1% (399 of 546), remained unchanged in 23.6% (129 of 456), and became worse in 3.3% (18 of 546). INTUITY valve hemodynamic data (EOA and mean gradient) are listed in Table 5. Health-related quality of life was assessed using the Short Form-12v2. At 1 year, significant improvement was observed compared with baseline in both physical health (41.8 $\pm$ 10.2 to 47.6 $\pm$ 9.7, $P < .0001$) and mental health dimensions (51.3 $\pm$ 9.9 to 54.3 $\pm$ 8.6, $P < .0001$).

DISCUSSION

The TRANSFORM trial evaluated the performance of the new INTUITY Valve System, which was designed for RDAVR in patients with severe aortic stenosis. TRANSFORM was a prospective, nonrandomized, multicenter, single-arm clinical trial. The INTUITY Valve System combines the well-proven Carpentier-Edwards PERIMOUNT Magna Ease Pericardial Aortic Bioprosthesis with a cloth-covered balloon-expandable stainless-steel frame. Patients had a mean age of 73.5 years, 24.6% were 80 years and older, and they had a mean STS predicted risk of mortality of 2.5% and logistic EuroSCORE II of 3.3%, which were consistent with low operative risk. FS was used in 40% and upper mini-sternotomy or right anterior thoracotomy in 60%; both approaches were associated with a technical success rate of 95%.

In this study, minimally invasive incisions were used twice as frequently as the 20% observed rate in the large, multicenter registry of the German Society for Thoracic and Cardiovascular Surgery.[11] The mean XCT and CPBT for FS and upper mini-sternotomy/right anterior thoracotomy compared favorably with STS Adult Cardiac Surgery Database comparators. The rate of surgical complications at 30 days was exceptionally low, with all-cause mortality, 0.8% (7 of 839); reoperation, 0.2% (2 of 839); valve explant, 0.1% (1 of 839); thromboembolism, 3.5% (29 of 839); and major bleeding, 1.3% (11 of 839). The rate of major PVL was 0.2% (2 of 839). The rate of new permanent pacemaker implantation was 11.9%. At 1 year, most patients had improved symptomatically, with 77.2% (424 of 549) in NYHA Class I, and 19.5% (107 of 549) in

TABLE 3. Primary safety endpoints: As-treated analysis

	Early events		Late events		Freedom from event
Adverse event or outcome	N	n, m, n/N	n, m, %/LPY	95% UCL	(SE) at 1 y
Thromboembolism	839	29, 29 (3.5)	22, 22 (2.6)	3.7	0.939 (0.009)
Valve thrombosis	839	0, 0 (0.0)	0, 0 (0.0)	0.2	1.000 (0.000)
Endocarditis	839	0, 0 (0.0)	0, 0 (0.0)	0.2	1.000 (0.000)
All bleeding	839	13, 13 (1.5)	37, 43 (5.1)	6.5	0.941 (0.009)
Major bleed	839	11, 11 (1.3)	19, 21 (2.5)	3.5	0.962 (0.007)
All PVL	839	9, 9 (1.1)	15, 15 (1.8)	2.7	0.977 (0.005)
Major PVL	839	2, 2 (0.2)	7, 7 (0.8)	1.5	0.993 (0.003)

n, Number patients; *m*, number of events; *LPY*, late patient-years; *UCL*, upper confidence limit; *SE*, standard error; *PVL*, paravalvular leak.

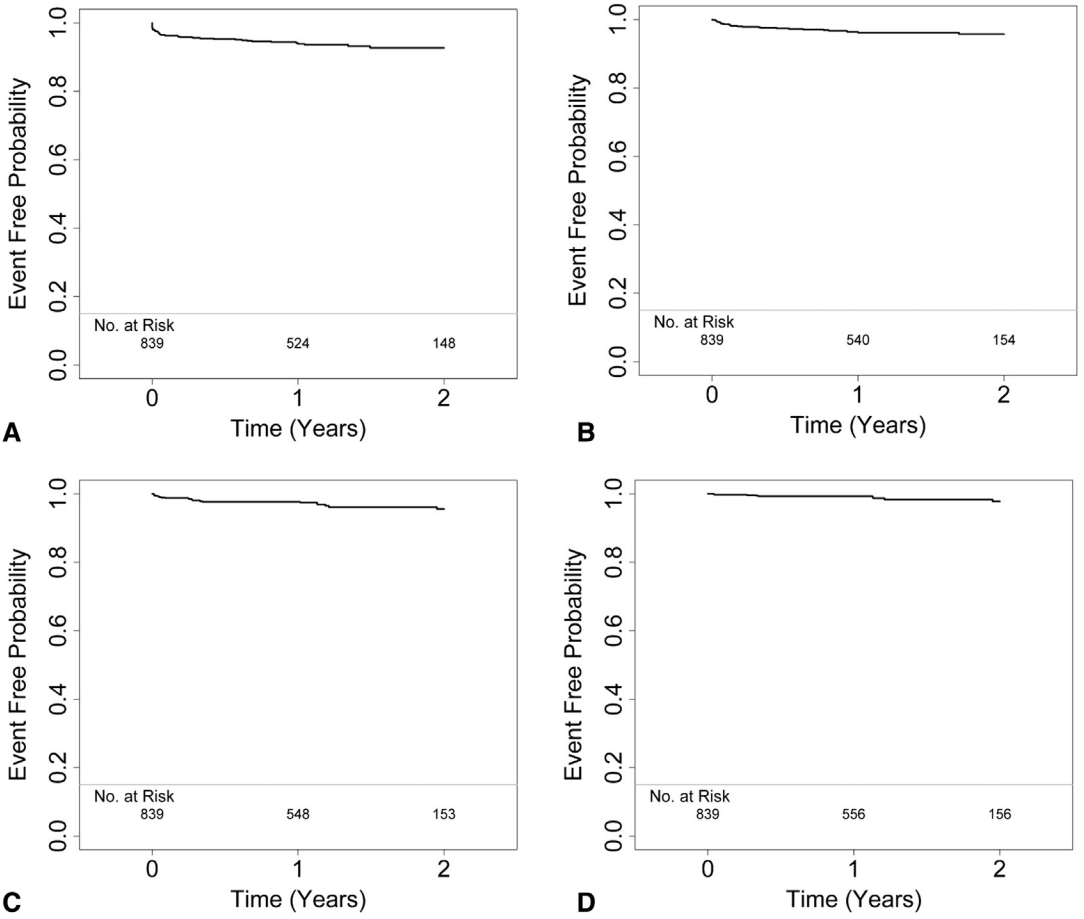


FIGURE 4. Kaplan-Meier Freedom from thromboembolism (A), bleeding (B), PVL (C), Major PVL (D).

NYHA Class II. Valve hemodynamic performance was excellent at 1 year, with an overall mean EOA of 1.7 cm^2 and mean gradient of 10.3 mm Hg. Taken in the aggregate, these data demonstrate excellent performance profiles of the INTUITY Valve System.

Prolonged XCTs correlate with worse clinical outcomes, but the relationship is complicated and difficult to resolve statistically. In studies that applied unadjusted analysis, longer XCT was associated with increased operative mortality and morbidity. In report of Nissinen and colleagues[12] on 3280 patients undergoing a variety of cardiac operations, the receiver operating characteristic of 30-minute increments of XCT revealed that the area under the curve was significantly correlated with all-cause mortality and stroke at 30 days. Moreover, the authors proposed a critical threshold value for XCT of 150 minutes, where observed mortality was 1.8% versus 12.2% (odds ratio 8.78, 95% confidence interval 4.64-16.61); however, numerous confounding factors account for increases in both XCT and operative mortality, such as high predicted operative risk, technical complexity, and intraoperative complications.

For example, Doenst and colleagues[13] studied 27,215 patients undergoing cardiac operations stratified by preoperative left ventricular ejection fraction. Multivariate regression analysis revealed that XCT was an independent predictor of mortality for patients with a left ventricular ejection fraction greater than 40% (odds ratio 1.01 per minute of XCT, 95% confidence interval 1.01-1.02) but not for patients less than 40%. The authors attributed this to the high mortality rate observed in patients with extremely short XCTs (ie, 30 minutes or less). Nonetheless, other investigators have reported an independent association between XCT and operative mortality and morbidity.[14,15]

TABLE 4. Secondary endpoints: As treated

Outcome	30 d	Freedom from event at 1 y (SE)
All-cause mortality	0.8% (7 of 839)	0.964 (0.007)
Valve-related mortality	0.5% (4 of 839)	0.985 (0.005)
Reoperation	0.2% (2 of 839)	0.993 (0.003)
Valve explant	0.1% (1 of 839)	0.996 (0.002)
Stroke	2.6% (22 of 839)	
Valve thrombosis	0.0%	1.000 (0.000)

SE, Standard error.

TABLE 5. Primary effectiveness endpoints (EOA, mean gradients) at 1 year

	EOA and mean gradients at 1 y					
	19 mm, n mean (min, max)	21 mm, n mean (min, max)	23 mm, n mean (min, max)	25 mm, n mean (min, max)	27 mm, n mean (min, max)	Total, n mean (min, max)
EOA, cm^2	36, 1.1 ± 0.1 (1.0, 1.3)	113, 1.3 ± 0.1 (1.0, 1.8)	157, 1.7 ± 0.2 (1.2, 2.1)	127, 1.9 ± 0.2 (1.4, 2.9)	58, 2.2 ±0.2 (1.3, 2.5)	491, 1.7 ± 0.3 (1.0, 2.9)
Mean gradient, mm Hg	36, 13.9 ± 3.9 (7.2, 25.1)	15, 11.6 ± 3.6 (5.5, 23.5)	165, 10.4 ± 3.5 (3.6, 24.6)	132, 9.1 ± 3.2 (3.1, 19.6)	61, 8.3 ± 3.7 (3.6, 28.7)	509, 10.3 ± 3.8 (3.1, 28.7)

EOA, Effective orifice area.

The INTUITY Valve System has been associated with a reduction in XCT and CPBT. In a recently published randomized controlled trial, Borger and colleagues[16] reported that INTUITY (n = 46) led to a 24% reduction in XCT compared with a group treated with a conventionally implanted bioprosthesis (n = 48; 41.3 ± 20.3 minutes vs 54.0 ± 20.3, $P < .001$). The current study generalizes this finding to a larger surgeon cohort by demonstrating that INTUITY was associated with lower XCTs and CPBTs compared with unadjusted summary statistics reported in the STS Database. Moreover, if the causal relationship between XCT and adverse events becomes stronger as the XCT exceeds some critical value, then it may be reasonable to assume the benefit of INTUITY will be greater as the degree of surgical complexity rises. Hence, as more patients are referred for AVR plus coronary bypass grafting, or tricuspid valve surgery, or atrial fibrillation surgery, the value proposition of the INTUITY Valve System may be more compelling. Compared with the STS Database, INTUITY was associated with clinically meaningful reductions in mean XCT in patients undergoing AVR plus coronary bypass grafting ×1, 2, or 3.

The INTUITY Valve System performed effectively with clinically acceptable rates of PVL. In the TRANSFORM trial, a central echocardiographic core laboratory was used to evaluate all echocardiographic studies. At 1 year, the rate of moderate and severe PVLs was 1.2% (6 of 519) and 0.4% (2 of 519). This result compares favorably with clinically overt PVL rates reported in the literature for surgical AVR.[17-21]

In the current study, the overall rate of new permanent pacemaker implantation in patients with isolated AVR was 11.9% (57 of 481); the rates reported in the surgical literature range between 3.0% and 11.8%.[22] The current implantation rate is in contrast to the observed rate of approximately 5% as reported in the European INTUITY studies for isolated AVR, whereas the remaining endpoints were similar overall.[16] This may be related to the high prevalence (roughly two-thirds) of preoperative conduction abnormalities observed in the current study. Among 342 patients undergoing isolated AVR, Dawkins and colleagues[23] reported preoperative atrial fibrillation in 12%, left anterior hemi block in 10%, left bundle branch block in 7%, and right bundle branch block in 5%. Moreover, they observed that patients with preoperative conduction abnormalities were significantly more likely to require a new permanent pacemaker compared with those without, 16% versus 6% ($P = .004$). Likewise, in sutureless valves, a greater rate of pacemaker implantation (11-fold) has been observed in the presence of preoperative right bundle branch block.[24] Whether INTUITY's balloon-expandable frame imparts greater radial force within the LVOT compared with a conventional valve and, therefore, predisposes to a greater likelihood of pacemaker implantation in patients with baseline conduction abnormalities warrants additional study.

The INTUITY Valve System leverages the well-proven hemodynamic performance and durability of the Carpentier-Edwards PERIMOUNT Magna Ease Pericardial Aortic Bioprosthesis. Recently, Johnston and colleagues[25] reported on 12,569 patients who underwent AVR with the PERIMOUNT valve at the Cleveland Clinic during a 27.5-year period. In patients younger than 60 years, the Kaplan-Meier estimates for SVD at 10 and 20 years were 5.6% and 45%, respectively, and, in patients 60 to 80 years old, a remarkable 1.5% and 8.1%, respectively. Unlike conventional surgical valves, the presence of a balloon-expandable stainless-steel frame within the LVOT may promote circularity and create ideal flow characteristics at the valve inlet. This unique design feature of the INTUITY Valve System may lessen the risk of prosthesis-patient mismatch, particularly in those patients with a small aortic root.[26]

Study Limitations

The TRANSFORM trial was a single-arm study without an active comparator group. Thus, it is susceptible to selection and channeling biases. Because ''roll-in'' cases were not excluded, the reported outcomes reflect the potentially negative impact of the surgeons' learning curve. During the enrollment phase of the study, considerable emphasis was placed on procedural training and the sharing of best practices among the investigators. Nonetheless, the possibility of performance bias cannot be excluded. The clinical endpoints were objectively defined a priori, and the outcomes were determined independently by a Clinical Events

Committee and an echocardiographic core laboratory. Thus, potential detection and measurement biases were mitigated but not completely eliminated. The current report is limited to trial safety and effectiveness at 1 year, with 912.2 patient-years follow-up. Hence, additional follow-up is required to establish long-term safety and effectiveness. The study did not standardize intraoperative valve evaluation for core laboratory review, which limits our ability to compare with subsequent formal valve evaluations and could potentially account for unappreciated significant PVL in the OR. In addition, our normative comparison was to the STS database. Although not a ''matched'' comparison, it is the only dataset available and provides insight to the current practice of AVR by the greatest proportion of US surgeons; the possibility exists that the trial surgeons were more experienced with aortic valve surgery and that the lower operating room times observed were affected by this fact.

CONCLUSIONS

The INTUITY RDAVR system performed effectively in this North American trial. This system has excellent hemodynamic performance, and it potentially reduces aortic XCT and CPBT while facilitating minimally invasive approaches for surgical AVR. This may confer benefits to the patient, such as decreased mortality and morbidity, reduced length of intensive care unit and total hospital stay, and increased patient satisfaction. By leveraging the well-proven hemodynamic performance and durability of the Carpentier-Edwards PERIMOUNT Magna Ease Pericardial Aortic Bioprosthesis, the INTUITY Valve System is expected to have similar hemodynamic characteristics and long-term durability and performance. Overall pacemaker implantation rate observed, although in the range of the reported literature, was greater than in INTUITY European trials and will require further investigation.

Conflict of Interest Statement

G.R.B. reports a consultancy and is a Principal Investigator. K.A. is a consultant for Edward Lifesciences, speaker for Edwards Lifesciences, and is a Principal Investigator. E.A.G. developed the device and receives IP royalties from Edwards Lifesciences and Medtronic. M.A.M. received a research grant from Edwards Lifesciences, is a consultant to Edwards Lifesciences, a Proctor, and received honoraria. J.F.S. is on the advisory board of Medtronic & Sorin; F.N.S. is an investigator for Edwards Lifesciences. H.J.P. is a consultant and has commercial Interest(s) in W L Gore, Medtronic. M.A.B. is consultant for Edwards Lifesciences and has received Speaker Honoraria from Edwards Lifesciences. P.M.M. is a consultant and received IP royalties from Edwards Lifesciences LLC. F.G.D. is an employee of Edwards Lifesciences, with equity ownership. M.J.M. is the co-Principal Investigator for Partner 3 Trial for Edwards Lifesciences (uncompensated). W.R.C. is a Principal Investigator. All other authors have nothing to disclose with regard to commercial support.

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Key Words: aortic valve replacement, rapid deployment valves, sutureless valves, calcific aortic stenosis, minimally invasive surgery

Discussion

Dr P. Kappetein *(Rotterdam, The Netherlands)*. Mr Chairman, ladies and gentlemen. Thank you for inviting me to discuss this paper, and I have to congratulate Dr Chitwood and colleagues on performing a trial on a new surgical device for aortic valve replacement. This by itself is great news, as in recent years much of the investments of the valve companies were focused on transcatheter heart valves. Sutureless heart valves have the potential to make valve implantation easier and faster. At the same time, they need to offer the same hemodynamic performance, adaptability to patient anatomy, no increase in adverse events, and offer the same long durability as standard surgical heart valves.

I had the advantage of having read the article, and in the introduction section you write that sutureless heart valves were developed to lessen the duration of myocardial ischemia and cardiopulmonary bypass time. However, if lessening the duration of myocardial ischemia and bypass time is so important that it justifies the implantation of a new device without a proven track record of durability and a price that at least is twice as high as a standard surgical bioprosthesis, I am surprised that we perform a minimally invasive procedure with 14-minute longer crossclamp time and 16-minute longer cardiopulmonary bypass time compared with a full sternotomy.

So the first question to you: is a reduction in crossclamp time really that important? Does the reduction in operative time also justify the greater price of the device? And if we want to do a minimally invasive procedure, can we not achieve the same reduction in time by using a Cor-Knot suture?

Dr Chitwood. Thank you very much, Dr Kappetein, for your comments. Clearly, minimally invasive operations take longer, no matter who is doing the operation. Both the minimally invasive anterior thoracotomy and a hemisternotomy approach take longer than a full sternotomy operation. I think any reduction in cross clamp time is important. In the TRANSFORM trial, the times that were reduced were significantly both for the full sternotomy operations as well as for minimally invasive procedures.

Can I tell you whether a reduction in 20 minutes makes any difference in long-term survivability? No, I can't. In patients with concomitant operations who required multiple bypasses, however, we showed that the significant reduction in time was significant and most likely important. Moreover, this time is important especially if multiple valve procedure or other combination operations were done. The reduction in cardiopulmonary bypass and crossclamp times should be very beneficial when you are doing a 4-vessel coronary bypass operation, possibly a Maze procedure, all combined with an aortic valve replacement.

As far as the price, it has not been determined what the price will be, and we are hoping that Centers for Medicare and Medicaid Services in the United States will give us an add-on that will provide extra reimbursement for this device. Clearly, the price of any of the advanced valves, whether transcatheter aortic valve replacement or any of the minimally invasive rapid deployment valves, is going to be an issue.

Dr Kappetein. With the Cor-Knot device, could you not achieve the same result?

Dr Chitwood. This device is a time-saving secret, because the Cor-Knot device does decrease in aortic and mitral valve implantation times. It does add about $800 per operation. There is doubt that will ever be a randomized study evaluating a rapid deployment valve versus a surgical valve deployed with the Cor-Knot device. Definitely, the Cor-Knot device is an enabling technology.

Dr Kappetein. Thank you. My next question is thus: the total of permanent pacemaker implants is 14%, which is much greater than one would expect. The paper by Vinod Thourani, "Contemporary Real-World Outcomes of Surgical Aortic Valve Replacement in 141,905 Low-Risk, Intermediate-Risk, and High-Risk Patients," published in the *Annals* last year, showed that the incidence of heart block was only 4%. In most other series, the incidence of postoperative pacemaker varies between 2% and 7%.

In the Methods section, you describe that the trial endpoints were based on definitions published in the guidelines for reporting mortality and morbidity after cardiac valve intervention by Akins et al. In the current study, however,

a completely new concept was introduced of valve-related and nonvalve-related pacemaker implantation. This is not described in the Akins paper, nor in the Valve Academic Research Consortium-2 definitions. By this new concept, the pacemaker rate decreases immediately from 14% to 1.3%, which all of a sudden is much lower than any other previously published series.

Although everyone knows from the transcatheter valve studies that the radial force of transcatheter aortic valve replacement devices is responsible for a greater pacemaker rate and that with greater radial force the pacemaker rate is increased, do you really think that the valve is not responsible for the greater pacemaker rate and should you not revisit your definition?

Dr Chitwood. Well, I think you noticed in the presentation that I only used the raw pacemaker insertion data. I didn't use any other objective performance criteria type of variation.

When we went back and looked at all the INTUITY studies in Europe, the pacemaker rate was 5.8% versus 14% in the TRANSFORM trial. Then we went back and looked at the preoperative electrocardiograms for any type of dysrhythmia, we found a very high level, with 45% having a right bundle block. So we need to do a deep dive to look at why the European data were different. In the Perceval valve study done by Laborde and colleagues, the pacemaker rate was around 11%.

Any valve that has a skirt below the annulus has a risk of creating radial pressure on the atrioventricular (AV) node or bundle. I agree pacemaker implantation rates are always a concern. When a recent meta-analysis looked at pacemaker insertion rates after a traditional surgical valve implantation, the incidence was about 7%; therefore, there is clearly more work to be done in this area with more investigation of the data, and we are doing this at present.

Dr Kappetein. The last point is the conversion to a standard prosthesis due to implant failure, which occurred in 5.5% of patients. Did this occur after the valve container already was opened, which means that the cost will even be greater, or can one already know beforehand that implantation of the valve is not possible as soon as the aorta is opened?

Dr Chitwood. This is related to both situations. Most of these, more than 60%, were from either a sizing or a seating problem and in 10% there were pop-ups after implantation. Basically the valve was seated and it popped back up, with the surgeon not feeling comfortable continuing with a third implantation. Surgeons were allowed at least 2 attempts at implantation. Therefore, most of these pop-ups were from difficult sizing.

We think that we have solved the sizing problem, because in the European group we found that sizing was a bit better. We determined that when one downsizes the valve greater than 2 mm there clearly are more paravalvular leaks. In contradistinction, if you upsize too much, then one may have problems with pop-ups. Therefore, right sizing is the key, and we now have better information of how to do that correctly.

Dr Kappetein. Congratulations on a great study and with excellent results, and thank you for the privilege.

Dr H. Najm *(Cleveland, Ohio)*. I enjoyed your presentation. My question is relevant to the anatomy of the aortic root and suitability of this valve to it, and it also properly relates to the 49 patients who were disqualified from this valve. Would this valve be suitable for those patients with a small or calcified sinutubular (ST) junction, because I know it is difficult to negotiate that skirt through a smaller ascending aorta, and the other question is would the bicuspid aortic valves be suitable for this and could you have had lower rates of paravalvular leaks if they were only implanted in tricuspid aortic valves as opposed to bicuspid aortic valves?

Dr Chitwood. I will answer the last question first. We did not find that there was a difference in implanting in the presence of bicuspid aortic valves as far as leaks. Also, the narrow ST junction can be a problem, especially when it is calcified. Surgeons in this study used different aortotomies; each surgeon could use the aortotomy that he normally used. Unless the ST junction is calcified totally, one can cut across the ST junction with a hockey stick–shaped incision. There didn't seem to be a problem seating in that circumstance; however, when you have a highly calcified ST junction or mitral valve anterior leaflet calcium, seating really becomes a problem.

Dr Najm. Would you do it in a double-valve replacement?

Dr Chitwood. I would. We did not include this parameter in the study, but I certainly would in combination with a mitral valve repair. The skirt is short enough that if you did a mitral valve replacement combined with an INTUITY aortic valve replacement, I think it would work fine.

Dr A. El Gamel *(Hamilton, New Zealand)*. Using some of these valves, how much decalcification do you need? Do you do complete decalcification as surgical? And also do you check under the valve with a telescope or a mirror after deployment that the valve is intact with the ring?

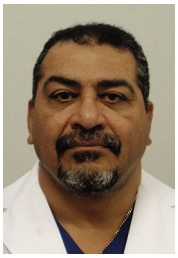
Dr Chitwood. Early on, we thought it would be like a SAPIEN-type valve in that you would do less debridement. The notion then was to leave some calcium so that the valve would hang in place. We found that as we moved ahead with this study that a standard surgical debridement was best, and so we did not leave excess calcium.

In answer to your question about using an endoscope to confirm seating, I like cameras. I do a lot of photography, and I started out doing this. It was not part of the protocol.

Actually, Michael Borger started doing this in Leipzig a long time ago. He would pass a 5-mm endoscope camera below the annulus to see if the valve was really seated well. However, most of our investigators did not use a scope. It was not part of the protocol, and it did not seem to make any difference in results.

Dr El Gamel. Is there a learning curve number?

Dr Chitwood. There is a learning curve for everything. Yes, there is a learning curve, but it relates to sizing. We basically found that when we did a really deep dive on how to best size these, we did decrease the learning curve. At first we were not debriding as much as we did later. So there was a minimal learning curve, and we modified our technique as we moved ahead.



Dr S. Damle *(Lincoln, Neb)*. Regarding the 5% of patients in whom this valve couldn't be placed, was there a consequence such as longer bypass time, conversion to sternotomy, et cetera?

Dr Chitwood. The 5.8% of patients, the 49 patients?

Dr Damle. Yes, the 49 patients in whom trouble seating the valve led to a conversion to a regular valve, likely longer crossclamp time, were there any consequences in the 30 days or one year for those patients?

Dr Chitwood. No, not in survival or complications, and it did not result in more conversions from a mini-thoracotomy to a full sternotomy. Most of these were related to a seating problem. I don't have the data, but you would expect that if one tried two attempts that this time would ablate some of the benefit of having a shorter cross clamp time. So I would expect those times would be just a bit longer. We did not see any adverse effects in those patients. We cautioned surgeons about continuing to work with this valve if they felt it couldn't be implanted. Then they should switch to a conventional surgical valve implantation.

Dr T. Rosengart *(Houston, Tex)*. Ease of use is an important component of any valve quality profile. In this case, ease of use may encourage increased adoption of minimally invasive approaches, which would be advantaged by facilitated valve implantation techniques. Dr Chitwood, do you agree that that's an important component of this valve, and if so, how do you incorporate that ultimately into the adoption process?

Dr Chitwood. Well, I think type of valve will enhance the adoption of less invasive techniques. We thought a number of years ago that if we could have some sort of rapid deployment device there would be a benefit for minimally invasive operations, because we knew that a standard minimally invasive aortic valve replacement, especially through a mini-thoracotomy, would take significantly longer than through a full sternotomy. Therefore, both shortening the crossclamp time and easing deployment are very important, especially when you are operating through a very small incision. Therefore, this type of prosthesis could enhance the adoption of minimally invasive techniques.

My belief is everything is going toward minimally invasive techniques if possible. We will have to see if this happens.

Dr C. Muneretto *(Brescia, Italy)*. Congratulations, Dr Chitwood. I enjoyed very much your presentation. As far as the incidence of AV block is concerned, you pointed out that in your study AV block was significantly more frequent compared with the European experience. It is well known that AV block may not only be related to the valve design but may be also related to the surgical technique, as, for example, the deepness of the device driving suture, rapid deployment device oversizing, and incomplete annular calcification removal.

On the basis of the high incidence of AV block in your experience, do you plan to re-evaluate some aspects of your surgical techniques?

Dr Chitwood. No, we really didn't. Everyone used their own technique, but clearly the skirt positioned below the annulus could have something to do with block. The thing that really confounds me is why are these results different than our European studies using the same valve? Why are we different? Maybe Europeans don't have as high an incidence of right bundle branch block, but I don't think that is the case. So we are going back and looking at this issue in detail.

Dr M. Shrestha *(Hannover, Germany)*. Just a small comment. I had the honor of doing the first-in-human implantation way back in 2010 in Hannover. What we have seen is I agree with Randy Chitwood. I just wanted to answer to Pieter that it is not fair to compare the results of this ID trial with the established valves, because there is a learning curve, and we saw that in Hannover that after you have gone through a learning curve, afterwards that it is really good. So that more people can do minimally invasive aortic valve replacement and especially in combined cases with four coronaries and aortic valve replacement, it does bring down the cross clamp time and the mortality.

Dr Chitwood. Dr Shrestha has used all types of these rapid deployment valves, so he should know. Awesome. Thank you.

APPENDIX E1. Baseline patient characteristics (as-treated INTUITY, n = 839)

Characteristic	
Age, y, N, mean ± SD (min-max)	839: 73.5 ± 8.3 (34-95)
Sex	% (n/N)
Female	35.5 (298/839)
Male	64.5 (541/839)
NYHA classification	% (n/N)
Class I	15.6 (130/836)
Class II	52.2 (436/836)
Class III	30.5 (255/836)
Class IV	1.8 (15/836)
Risk scores, n, mean ± SD (min-max)	
STS risk of mortality (%)	733: 2.5 ± 1.8 (0.4-14.6)
EuroSCORE II (%)	839: 3.3 ± 3.4 (0.5-31.6)
Etiology	% (n/N)
Degenerative	91.5 (768/839)
Rheumatic	0.7 (6/839)
Remote endocarditis	0.0 (0/839)
Other etiology	8.0 (67/839)
Diagnosis for replacement	% (n/N)
Stenosis	68.9 (578/839)
Stenosis with insufficiency	31.1 (261/839)
Intervention	% (n/N)
Percutaneous coronary intervention	16.8 (141/839)
CABG	6.6 (55/838)
Permanent pacemaker or ICD	6.2 (52/839)
Carotid artery intervention	4.2 (35/839)
Limb artery intervention	2.3 (19/839)
Abdominal aorta intervention	1.0 (8/839)
Aortic valve valvuloplasty	0.4 (3/839)
Mitral valve valvuloplasty	0.0 (0/839)
Tricuspid valve valvuloplasty	0.0 (0/839)
Pulmonic valve valvuloplasty	0.0 (0/839)

SD, Standard deviation; *NYHA*, New York Heart Association; *STS*, Society of Thoracic Surgeons; *CABG*, coronary artery bypass grafting; *ICD*, implantable cardioverter defibrillator.

APPENDIX E2. Cardiovascular comorbidities (as-treated INTUITY, n = 839)

Condition	% (n/N)
Aortic stenosis	100 (839/839)
Mitral insufficiency	95.9 (805/839)
Tricuspid insufficiency	95.9 (805/839)
Systemic hypertension	86.4 (725/839)
Cardiac rhythm abnormalities/conduction disturbance	66.6 (559/839)
Coronary artery disease	53.8 (451/839)
Congestive heart failure	48.8 (409/838)
Pulmonary hypertension	40.0 (334/836)
Carotid artery disease	28.0 (235/839)
Peripheral artery/vascular disease	16.8 (141/839)
Myocardial infarction	9.9 (83/839)
Transient ischemic attack	7.0 (59/839)
Cerebrovascular accident	5.5 (46/839)
Cardiomyopathy	5.1 (43/839)
Rheumatic fever	4.5 (38/838)
Mitral stenosis	2.3 (19/839)
Tricuspid stenosis	1.0 (8/838)
Endocarditis	0.2 (2/839)
Myocarditis	0.1 (1/839)

APPENDIX E3. Noncardiovascular risk factors (as-treated INTUITY, n = 839)

Condition	% (n/N)
Smoking	58.0 (486/838)
Current smoker	6.1 (51/838)
Previous smoker	51.9 (435/838)
Musculoskeletal dysfunction	52.2 (438/839)
Obesity (BMI ≥30)	46.7 (392/839)
Diabetes	33.1 (278/839)
Type 1	1.9 (16/837)
Type 2	31.1 (260/837)
Cancer	30.0 (252/839)
Chronic obstructive pulmonary disease	15.5 (130/839)
Renal failure/insufficiency	11.6 (97/839)
Blood diatheses	6.8 (57/839)
Immunosuppression	6.4 (54/839)
Liver disease	3.9 (33/839)
Calcium metabolic disorder	0.6 (5/839)

BMI, Body mass index.

APPENDIX E4. Aortic crossclamp time for enrolled patients (intent to treat)

	Surgical approach			
	Full sternotomy n mean ± SD median (min, max)	**Mini upper sternotomy n mean ± SD median (min, max)**	**Right thoracotomy n mean ± SD median (min, max)**	**All subjects n mean ± SD median (min, max)**
Isolated AVR	221	263	64	548
	49.3 ± 26.9	62.3 ± 25.6	66.4 ± 24.7	57.5 ± 26.9
	44.0 (11.0, 268.0)	55.0 (23.0, 188.0)	60.0 (36.0, 174.0)	52.0 (11.0, 268.0)
AVR + CABG	215	3	N/A	218
	87.1 ± 36.2	79.0 ± 21.0		86.9 ± 36.0
	84.0 (26.0, 228.0)	79.0 (58.0, 100.0)		83.5 (26.0, 228.0)
AVR + other	52	25	7	84
	76.5 ± 60.7	78.0 ± 34.6	94.6 ± 83.8	78.5 ± 56.1
	63.0 (28.0, 455.0)	77.0 (27.0, 188.0)	70.0 (43.0, 282.0)	64.0 (27.0, 455.0)
All subjects	522	291	72	885*
	71.2 ± 41.2	63.9 ± 26.7	70.9 ± 37.5	68.8 ± 36.9
	61.0 (11.0, 455.0)	57.0 (23.0, 188.0)	61.5 (36.0, 282.0)	60.0 (11.0, 455.0)

SD, Standard deviation; *AVR*, aortic valve replacement; *CABG*, coronary artery bypass grafting. *Missing data for 4 patients.

APPENDIX E5. Comparison with STS database*: Bypass time

Surgical group	n, mean ± SD	STS value	*P* value
Isolated AVR, full sternotomy	222, 69.2 ± 34.7	04.23	<.001
Isolated AVR, MIS	327, 84.6 ± 33.5	111.44	<.001
AVR + CABG 1 graft(s)	89, 87.1 ± 34.2	125.95	<.001
AVR + CABG 2 graft(s)	76, 113.3 ± 38.4	144.95	<.001
AVR + CABG 3 graft(s)	38, 140.6 ± 44.0	163.60	.003
AVR + CABG 4+ graft(s)	7, 171.0 ± 44.4	180.49	.592

P values were calculated with 1-sample *t*-tests. *SD*, Standard deviation; *STS*, Society of Thoracic Surgeons; *AVR*, aortic valve replacement; *MIS*, minimally invasive surgery; *CABG*, coronary artery bypass grafting. *Society of Thoracic Surgeons database for the period of July 2011 to December 2012.