Minimally Invasive Aortic Valve Replacement in Contemporary Practice: Clinical and Hemodynamic Performance from a Prospective Multicenter Trial

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Abstract

Background The advent of transcatheter aortic valve replacement (AVR) has led to an increased emphasis on reducing the invasiveness of surgical procedures. The aim of this study was to evaluate clinical outcomes and hemodynamic performance achieved with minimally invasive aortic valve replacement (MI-AVR) as compared with conventional AVR.

Methods Patients who underwent surgical AVR with the Avalus bioprosthesis, as part of a prospective multicenter non-randomized trial, were included in this analysis. Surgical approach was left to the discretion of the surgeons. Patient characteristics and clinical outcomes were compared between MI-AVR and conventional AVR groups in the entire cohort ($n = 1077$) and in an isolated AVR subcohort ($n = 528$). Propensity score adjustment was performed to estimate the effect of MI-AVR on adverse events.

Results Patients treated with MI-AVR were younger, had lower STS scores, and underwent concomitant procedures less often. Valve size implanted was comparable between the groups. MI-AVR was associated with longer procedural times in the isolated AVR subcohort. Postprocedural hemodynamic performance was comparable. There were no significant differences between MI-AVR and conventional AVR in early and 3-year all-cause mortality, thromboembolism, reintervention, or a composite of

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- minimally invasive
- surgical techniques

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those endpoints within either the entire cohort or the isolated AVR subcohort. After propensity score adjustment, there remained no association between MI-AVR and the composite endpoint (hazard ratio: 0.86, 95% confidence interval: 0.47–1.55, $p = 0.61$).
Conclusion Three-year outcomes after MI-AVR with the Avalus bioprosthetic valve were comparable to conventional AVR. These results provide important insights into the overall ability to reduce the invasiveness of AVR without compromising outcomes.

Introduction

Surgical aortic valve replacement (AVR) remains the gold standard in young, low-risk patients, while the long-term durability of transcatheter aortic valve replacement (TAVR) has yet to be established in this population.[1] However, the advent of TAVR has led to an increased emphasis on reducing the invasiveness of surgical procedures.

While minimally invasive aortic valve replacement (MI-AVR) has been around for more than two decades,[2,3] only a minority of isolated AVR patients are treated in this manner.[4] The perceived limitation of MI-AVR is that it is technically more challenging and hence may lead to inferior outcomes compared with a full sternotomy, which provides more space to operate and resolve procedural complications. Moreover, it is important to provide insights into the feasibility, safety, and performance of new bioprostheses in the setting of MI-AVR, as the design of the prosthesis may impact the ease of implantation. To compare the risks and benefits of MI-AVR versus conventional AVR in contemporary practice with the Avalus bioprosthesis, we stratified the safety and hemodynamic performance results from the PERIcardial SurGical AOrtic Valve ReplacemeNt (PERIGON) Pivotal Trial accordingly.

Patients and Methods

Study Design

The PERIGON Pivotal Trial (www.clinicaltrials.gov, NCT02088554) is a prospective, single-arm study of the Avalus bioprosthesis (Medtronic, Minneapolis, Minnesota, United States), a stented bovine pericardial aortic valve. The trial is being conducted at 36 sites in Europe, Canada, and the United States. The study design was previously described in detail.[5,6] Patients with moderate or severe symptomatic aortic stenosis or chronic severe regurgitation and a clinical indication for surgical AVR, with or without a concomitant procedure, were enrolled. The concomitant procedures were limited to coronary artery bypass grafting, left atrial appendage ligation, patent foramen ovale closure, ascending aortic aneurysm or dissection repair not requiring circulatory arrest, and subaortic membrane resection not requiring myectomy.

The study was designed and conducted in accordance with the Declaration of Helsinki and good clinical practice. Institutional review board or ethics committee approval was obtained at each site, and all patients provided written informed consent. An independent clinical events committee adjudicated all deaths and valve-related adverse events. The original study protocol did not include adjudication of deep sternal/thoracic wound infections by this committee. Therefore, potential infections were screened from adverse event data and subsequently adjudicated by two of the authors (BJJV, MDV) using the definition of The Centers for Disease Control and Prevention.[7] An independent data and safety monitoring board provided study oversight. An independent core laboratory (MedStar, Washington, DC) evaluated echocardiograms.

In the current study, patients were compared according to the surgical approach performed, specifically MI-AVR (i.e., hemisternotomy or right thoracotomy) versus conventional AVR (full sternotomy). In previous manuscripts concerning the PERIGON Pivotal Trial, an extra category of "other" surgical approach was reported. For this analysis, the patients with "other" surgical approach were recategorized to either median or hemisternotomy based on approach descriptions by one of the authors (MDV). Patients who had had a prior open-heart surgery were excluded. The full cohort included both patients who underwent AVR with a concomitant procedure and those who underwent isolated AVR. The isolated AVR subcohort included only patients who received no concomitant procedures.

Follow-Up and Endpoints

Clinical and echocardiographic (transthoracic) evaluations were performed annually after the first year of follow-up. The current study compared patient and procedural characteristics, early outcomes (i.e., within 30 days postimplant), and 3-year outcomes between the MI-AVR and conventional AVR groups. Early outcomes included death and valve-related thromboembolism, major hemorrhage, major paravalvular leak, reintervention, deep sternal/thoracic wound infections, and permanent pacemaker implantation. The 3-year outcomes analysis included all-cause, cardiac, and valve-related mortality, thromboembolism, valve thrombosis, all hemorrhage, major hemorrhage, all paravalvular leak, endocarditis, nonstructural valve dysfunction, reintervention, and explant. In addition, a composite outcome of all-cause death, thromboembolism, or reintervention at 3 years was evaluated.

Echocardiographic outcomes included mean aortic gradient, calculated with the simplified Bernoulli equation using the mean velocities measured across the bioprosthesis, and effective orifice area (EOA), which was calculated with the continuity equation.

Statistical Analyses

Categorical patient and procedural characteristics are reported as frequencies and percentages, and continuous

characteristics are reported as mean ± standard deviation. *p*-Values were calculated using the *t*-test (continuous variables) or the chi-squared or Fisher's exact test (categorical variables). Early and 3-year outcome event rates (and 95% confidence intervals [CIs]) were calculated using the Kaplan–Meier method, and *p*-values were calculated with the log-rank test. Cox proportional hazards models, adjusted for propensity score to account for baseline differences, were fit to examine differences in safety between the MI-AVR and conventional AVR groups in each cohort. Propensity scores were estimated for the isolated AVR cohort using multivariable logistic regression models adjusted for the following potential confounders: age, male sex, body surface area, New York Heart Association (NYHA) class III/IV, Society of Thoracic Surgeons (STS) mortality risk, diabetes, hypertension, peripheral vascular disease, renal dysfunction, stroke/cerebrovascular accident (CVA), coronary artery disease, left ventricular hypertrophy, atrial fibrillation, and isolated/mixed aortic stenosis. Analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina, United States). *p*-Value < 0.05 was considered statistically significant.

Results

Entire Cohort

In the present study, 224 (20.8%) patients underwent MI-AVR, and 853 (79.2%) patients underwent conventional AVR. Among 36 participating trial sites, 6 centers reported a minimally invasive approach in 50% or more of their enrolled subjects. These centers enrolled 59% of all minimally invasive patients in this study (►**Fig. 1**). The baseline characteristics of the two groups are listed and compared in ►**Table 1**. Patients treated with MI-AVR had a lower age, STS score, and prevalence of coronary artery disease, and a higher prevalence of left ventricular hypertrophy. The procedural characteristics of the two groups are listed in ►**Table 2**. In the overall cohort, the primary indication for AVR was pure aortic stenosis in the majority of patients. The prevalence of aortic regurgitation and mixed aortic disease was higher in the MI-AVR group. Moreover, patients in the MI-AVR group had shorter cardiopulmonary bypass (98.0 ± 30.1 vs. 106.1 ± 42.6 min, $p = 0.001$) and aortic cross-clamp (71.8 ± 21.7 vs. 81.3 ± 33.5 min, $p < 0.001$) times, and the Cor-Knot device (LSI Solutions, Victor, New York, United States) was more often used (28.6 vs. 10.2%, $p < 0.001$). The proportion of concomitant procedures was higher in the conventional AVR group (57.3 vs. 26.8%, $p < 0.001$), including the proportion of concomitant coronary artery bypass grafting procedures (41.0 vs. 0.9%, $p < 0.001$). The distribution of valve sizes was similar between both groups. Within the MI-AVR group, 156 (69.6%) patients underwent hemisternotomy, and 68 (30.4%) patients underwent right anterior thoracotomy (RAT).

All-cause mortality was not significantly different between the MI-AVR and conventional AVR groups at 30 days (1.3% [0.4–3.6%] vs. 0.8% [0.4–1.6%], respectively; $p = 0.47$) and at 3-year follow-up (6.0% [3.3–9.7%] vs. 6.9% [5.3–8.8%], $p = 0.69$). This difference remained nonsignificant for cardiac and valve-related mortality. As reported in ►**Tables 2** and **3**, all valve-related adverse events were also not significantly different between the surgical approaches at early and 3-year follow-up, except for all hemorrhage, which was more frequently present in the MI-AVR group (13.1% [8.9–18.1%] vs. 7.6% [5.9–9.6], $p = 0.018$). This difference was not statistically significant for major hemorrhage (7.2% [4.2–11.2%]) vs. 4.6% [3.3–6.2%], $p = 0.14$).

Deep sternal/thoracic wound infections occurred in 6 patients after conventional AVR and in 1 patient after MI-AVR (0.70 vs. 0.45%, $p = 1.00$). In addition, two patients who underwent RAT developed an inguinal wound infection.

Isolated AVR

The baseline characteristics of the isolated AVR cases are also reported in ►**Table 1**. One hundred sixty-four (31.1%) patients underwent MI-AVR, and 364 (68.9%) patients underwent conventional AVR. The prevalence of coronary

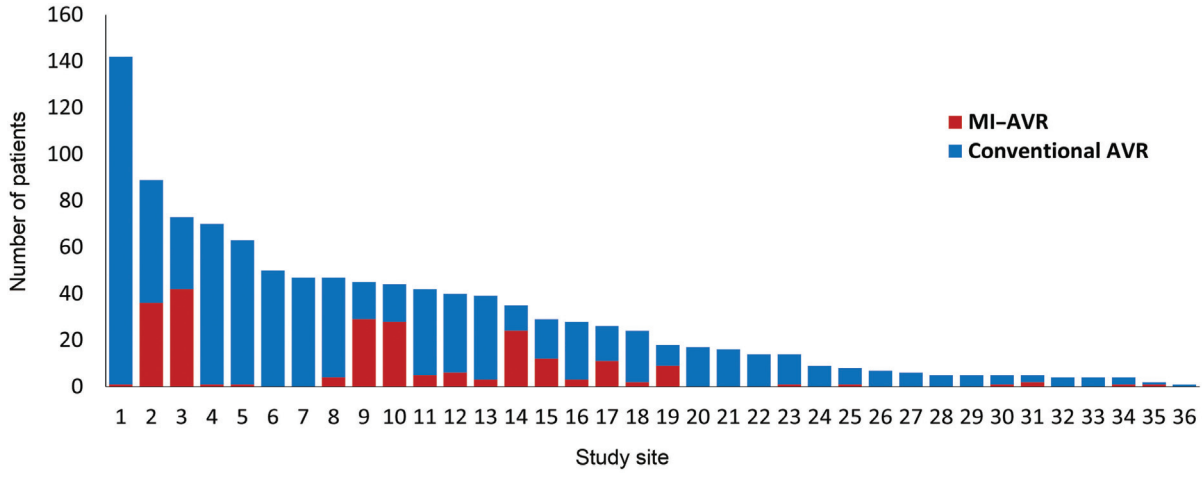


Fig. 1 Distribution of surgical approach across the participating centers of the PERIcardial SurGical AOrtic Valve ReplacemeNt (PERIGON) Pivotal Trial. MI-AVR, minimally invasive aortic valve replacement.

Table 1 Baseline characteristics according to surgical approach

	Entire cohort ($n = 1,077$)			Isolated SAVR ($n = 528$)		
	MI-AVR ($N = 224$)	Conventional SAVR ($N = 853$)	*p*-Value	MI-AVR ($N = 164$)	Conventional SAVR ($N = 364$)	*p*-Value
Age (y)	67.6 ± 10.2	70.8 ± 8.4	<0.001	67.7 ± 9.7	70.3 ± 8.9	0.003
Male	159 (71.0%)	646 (75.7%)	0.15	121 (73.8%)	253 (69.5%)	0.32
Body surface area (m^2)	2.0 ± 0.2	2.0 ± 0.2	0.17	2.0 ± 0.2	2.0 ± 0.2	0.16
Body mass index (kg/m^2)	29.3 ± 5.2	29.5 ± 5.5	0.66	29.3 ± 5.3	29.6 ± 5.8	0.64
NYHA class III/IV	84 (37.5%)	366 (42.9%)	0.14	59 (36.0%)	145 (39.8%)	0.40
STS risk of mortality (%)	1.5 ± 1.1	2.0 ± 1.3	<0.001	1.4 ± 1.1	1.7 ± 1.2	0.008
Diabetes	55 (24.6%)	232 (27.2%)	0.43	38 (23.2%)	92 (25.3%)	0.60
Hypertension	168 (75.0%)	650 (76.2%)	0.71	117 (71.3%)	253 (69.5%)	0.67
Peripheral vascular disease	14 (6.3%)	65 (7.6%)	0.48	6 (3.7%)	23 (6.3%)	0.21
Renal dysfunction/ insufficiency	29 (12.9%)	85 (10.0%)	0.20	19 (11.6%)	23 (6.3%)	0.039
Stroke/CVA	4 (1.8%)	40 (4.7%)	0.06	1 (0.6%)	22 (6.0%)	0.002
Chronic obstructive lung disease	25 (11.2%)	102 (12.0%)	0.74	19 (11.6%)	50 (13.7%)	0.50
Coronary artery disease	49 (21.9%)	413 (48.4%)	<0.001	38 (23.2%)	86 (23.6%)	0.91
Left ventricular hypertrophy	123 (54.9%)	321 (37.6%)	<0.001	84 (51.2%)	140 (38.5%)	0.006
Percutaneous coronary intervention	22 (9.8%)	121 (14.2%)	0.09	14 (8.5%)	40 (11.0%)	0.39
Atrial fibrillation	19 (8.5%)	90 (10.6%)	0.36	12 (7.3%)	33 (9.1%)	0.51

Abbreviations: CVA, cerebrovascular accident; MI-AVR, minimally invasive aortic valve replacement; NYHA, New York Heart Association; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons.
Categorical characteristics are expressed as number (percentage) and continuous characteristics as mean ± standard deviation.

artery disease was not significantly different between groups in this subcohort, but the conventional AVR group had a higher prevalence of previous CVA and a lower prevalence of renal dysfunction. In accordance with the entire cohort, the MI-AVR group was younger, had a lower STS risk of mortality, and had a higher prevalence of left ventricular hypertrophy. For the isolated cases, cardiopulmonary bypass (96.8 ± 29.1 vs. 85.1 ± 29.1 min, $p < 0.001$) and aortic cross-clamp (70.8 ± 21.5 vs. 63.8 ± 22.8 min, $p = 0.001$) times were shorter in the conventional AVR group (►**Table 2**). Differences in the primary indication of AVR, the use of Cor-Knot sutures, and distribution of valve size in the isolated AVR cohort were similar to those observed in the overall cohort. Within the MI-AVR group, 105 (64.0%) patients underwent hemisternotomy, and 59 (36.0%) patients underwent RAT.

In accordance with the results of the overall cohort, the unadjusted postoperative mortality and morbidity were not significantly different between the surgical approaches at early and late follow-up (►**Tables 2** and **3**, ►**Fig. 2**). After propensity score adjustment, there was no association between MI-AVR with the composite endpoint of all-cause mortality, thromboembolism, or reintervention through 3 years (hazard ratio [HR]: 0.86, 95% CI: 0.47–1.55, $p = 0.61$). The adjusted effect of MI-AVR on mortality (HR: 0.89, 95% CI: 0.34–2.30, $p = 0.80$) and other valve-related adverse events separately was also not significant (►**Fig. 3**), again, except for all hemorrhage (11.9% [7.4–17.7%] vs. 6.1% [3.9–9.0%], $p = 0.039$). Similar to the findings in the entire cohort, there was no significant difference in major hemorrhage ($p = 0.40$). Furthermore, there was no significant difference in EOA and mean gradient between the MI-AVR and conventional AVR groups at discharge up to 3 years (►**Fig. 4**).

Subanalysis-Isolated MI-AVR Cohort

The RAT group was significantly younger, had lower STS scores, and less left ventricular hypertrophy compared with the hemisternotomy group. The Cor-Knot was more frequently used in the RAT group (61 vs. 11%, $p < 0.0001$). Early and late safety endpoints, valve-related event rates, and hemodynamic performance did not differ between the groups (see ►**Supplementary Tables 1–3**, available online only).

Within the MI-AVR group, the Cor-Knot was used in 49 patients (30%), and manually tied sutures ("No Cor-Knot") were used in 115 patients (70%). The baseline characteristics were comparable apart from a higher frequency of NYHA class III/IV in the No Cor-Knot group. Cardiopulmonary bypass and aortic cross-clamp times were not significantly different between the Cor-Knot group and the No

Table 2 Procedural characteristics and early outcomes

	Entire cohort ($n = 1,077$)			Isolated SAVR ($n = 528$)		
	MI-AVR	Conventional SAVR	*p*-Value	MI-AVR	Conventional SAVR	*p*-Value
	($N = 224$)	($N = 853$)		($N = 164$)	($N = 364$)	
Total cardiopulmonary bypass time, min	98.0 ± 30.1	106.1 ± 42.6	0.001	96.8 ± 29.1	85.1 ± 29.1	<0.001
Total aortic cross-clamp time, min	71.8 ± 21.7	81.3 ± 33.5	<0.001	70.8 ± 21.5	63.8 ± 22.8	0.001
Use of Cor-Knot	64 (28.6%)	87 (10.2%)	<0.001	49 (29.9%)	18 (4.9%)	<0.001
Primary indication			<0.001			0.002
Aortic stenosis	169 (75.4%)	746 (87.5%)		132 (80.5%)	330 (90.7%)	
Aortic regurgitation	20 (8.9%)	38 (4.5%)		10 (6.1%)	16 (4.4%)	
Mixed	35 (15.6%)	69 (8.1%)		22 (13.4%)	18 (4.9%)	
Minimally invasive approach						
Hemisternotomy	156 (69.6%)	NA		105 (64.0%)	NA	
Right anterior thoracotomy	68 (30.4%)	NA		59 (36.0%)	NA	
Concomitant procedures						
CABG	2 (0.9%)	350 (41.0%)	<0.001	NA	NA	NA
Implantable cardiac device	0 (0.0%)	1 (0.1%)	>0.99	NA	NA	NA
Left atrial appendage closure	20 (8.9%)	65 (7.6%)	0.52	NA	NA	NA
Patent foramen ovale closure	3 (1.3%)	10 (1.2%)	0.74	NA	NA	NA
Subaortic membrane resection not requiring myectomy	10 (4.5%)	11 (1.3%)	0.002	NA	NA	NA
Ascending aorta aneurysm repair not requiring circulatory arrest	10 (4.5%)	71 (8.3%)	0.05	NA	NA	NA
Ascending aorta dissection repair not requiring circulatory arrest	1 (0.4%)	0 (0.0%)	0.21	NA	NA	NA
Other	33 (14.7%)	117 (13.7%)	0.70	NA	NA	NA
Valve size						
Mean valve size (mm)	23.4 ± 2.1	23.5 ± 2.0	0.32	23.3 ± 2.1	23.3 ± 2.1	>0.99
17 mm	0 (0.0%)	1 (0.1%)		0 (0.0%)	1 (0.3%)	
19 mm	10 (4.5%)	31 (3.6%)		8 (4.9%)	18 (4.9%)	
21 mm	48 (21.4%)	156 (18.3%)		37 (22.6%)	73 (20.1%)	
23 mm	78 (34.8%)	310 (36.3%)		61 (37.2%)	144 (39.6%)	
25 mm	65 (29.0%)	270 (31.7%)		40 (24.4%)	97 (26.6%)	

(*Continued*)

Table 2 (*Continued*)

	Entire cohort ($n = 1,077$)			Isolated SAVR ($n = 528$)		
	MI-AVR	Conventional SAVR	*p*-Value	MI-AVR	Conventional SAVR	*p*-Value
	($N = 224$)	($N = 853$)		($N = 164$)	($N = 364$)	
27 mm	23 (10.3%)	75 (8.8%)		18 (11.0%)	27 (7.4%)	
29 mm	0 (0.0%)	10 (1.2%)		0 (0.0%)	4 (1.1%)	
Early outcomes[a,b]						
All-cause mortality	1.3% (0.4–3.6%) ($n = 3$)	0.8% (0.4–1.6%) ($n = 7$)	0.47	0.6% (0.1–3.1%) ($n = 1$)	0.8% (0.2–2.3%) ($n = 3$)	0.80
Thromboembolism	1.8% (0.6–4.3%) ($n = 4$)	1.3% (0.7–2.2%) ($n = 11$)	0.57	1.8% (0.5–4.9%) ($n = 3$)	0.8% (0.2–2.3%) ($n = 3$)	0.31
Major hemorrhage[c]	1.4% (0.4–3.6%) ($n = 3$)	0.7% (0.3–1.5%) ($n = 6$)	0.35	0.6% (0.1–3.1%) ($n = 1$)	0.8% (0.2–2.3%) ($n = 3$)	0.79
Major paravalvular leak	0.0% (NA) ($n = 0$)	0.1% (0.0–0.6%) ($n = 1$)	0.61	0.0% (NA) ($n = 0$)	0.3 (0.0–1.5%) ($n = 1$)	0.50
Reintervention	0.4% (0.0–2.3%) ($n = 1$)	0.4% (0.1–1.0%) ($n = 3$)	0.83	0.6% (0.1–3.1%) ($n = 1$)	0.3% (0.0–1.5%) ($n = 1$)	0.56
Implanted cardiac device[d]	3.1% (1.4–6.1%) ($n = 7$)	4.0% (2.8–5.5%) ($n = 34$)	0.56	3.0% (1.1–6.5%) ($n = 5$)	5.0% (3.0–7.5%) ($n = 18$)	0.33

Abbreviations: MI-AVR, minimally invasive aortic valve replacement; SAVR, surgical aortic valve replacement; CABG, coronary artery bypass graft; NA, not available.
Categorical characteristics are expressed as number (percentage) and continuous characteristics as mean ± standard deviation.
[a]Early outcomes are those that occurred within 30 days postimplant. Data are the Kaplan–Meier event rate, 95% confidence interval, and number of patients with an event.
[b]*p*-Value from log-rank test through 30 days.
[c]Only anticoagulant-related hemorrhage events are included.
[d]Implanted cardiac devices include permanent pacemaker, defibrillator, and cardiac resynchronization device.

Table 3 Summary of adverse events according to surgical approach at 3 years follow-up[a]

	Entire cohort ($n = 1,077$)			Isolated SAVR ($n = 528$)		
	MI-AVR	Conventional SAVR	*p*-Value[b]	MI-AVR	Conventional SAVR	*p*-Value[b]
	($N = 224$)	($N = 853$)		($N = 164$)	($N = 364$)	
All-cause mortality	6.0% (3.3–9.7%) ($n = 13$)	6.9% (5.3–8.8%) ($n = 56$)	0.69	3.8% (1.6–7.6%) ($n = 6$)	5.8% (3.6–8.5%) ($n = 20$)	0.38
Cardiac-related mortality	4.1% (2.0–7.3%) ($n = 9$)	3.3% (2.2–4.7%) ($n = 26$)	0.47	3.1% (1.2–6.7%) ($n = 5$)	3.2% (1.7–5.5%) ($n = 11$)	0.99
Valve-related mortality	0.9% (0.2–3.1%) ($n = 2$)	1.1% (0.6–2.1%) ($n = 9$)	0.85	1.3% (0.3–4.2%) ($n = 2$)	0.6% (0.1–2.0%) ($n = 2$)	0.41
Thromboembolism	3.7% (1.8–6.9%) ($n = 8$)	4.8% (3.5–6.5%) ($n = 39$)	0.54	3.8% (1.6–7.6%) ($n = 6$)	5.3% (3.3–8.1%) ($n = 18$)	0.52
Valve thrombosis	0.0% (NA) ($n = 0$)	0.3% (0.1–0.9%) ($n = 2$)	0.47	0.0% (NA) ($n = 0$)	0.6% (0.1–2.0%) ($n = 2$)	0.34
All hemorrhage[c]	13.1% (8.9–18.1%) ($n = 27$)	7.6% (5.9–9.6%) ($n = 61$)	0.018	11.9% (7.4–17.7%) ($n = 18$)	6.1% (3.9–9.0%) ($n = 21$)	0.039
Major hemorrhage[c]	7.2% (4.2–11.2%) ($n = 15$)	4.6% (3.3–6.2%) ($n = 37$)	0.14	5.9% (2.9–10.4%) ($n = 9$)	4.1% (2.3–6.6%) ($n = 14$)	0.40
All paravalvular leak	0.0% (NA) ($n = 0$)	0.7 (0.3–1.5%) ($n = 6$)	0.21	0.0% (NA) ($n = 0$)	0.3 (0.0–1.5%) ($n = 1$)	0.50
Endocarditis	2.4% (0.9–5.1%) ($n = 5$)	3.2% (2.1–4.6%) ($n = 25$)	0.57	3.2% (1.2–6.8%) ($n = 5$)	3.2% (1.7–5.5%) ($n = 11$)	0.99
Nonstructural valve dysfunction	0.0% (NA) ($n = 0$)	0.7% (0.3–1.5%) ($n = 6$)	0.21	0.0% (NA) ($n = 0$)	0.3% (0.0–1.5%) ($n = 1$)	0.50
Reintervention	2.3% (0.9–5.1%) ($n = 5$)	2.0% (1.2–3.2%) ($n = 16$)	0.73	3.2% (1.2–6.8%) ($n = 5$)	2.3% (1.1–4.3%) ($n = 8$)	0.56
Explant	2.3% (0.9–5.1%) ($n = 5$)	2.0% (1.2–3.2%) ($n = 16$)	0.73	3.2% (1.2–6.8%) ($n = 5$)	2.3% (1.1–4.3%) ($n = 8$)	0.56

Abbreviations: MI-AVR, minimally invasive aortic valve replacement; SAVR, surgical aortic valve replacement; NA, not available.
[a]Data are the Kaplan–Meier event rate, 95% confidence interval, and number of patients with an event.
[b]*p*-Value from log-rank test through 3 years.
[c]Only anticoagulant-related hemorrhage events are included.

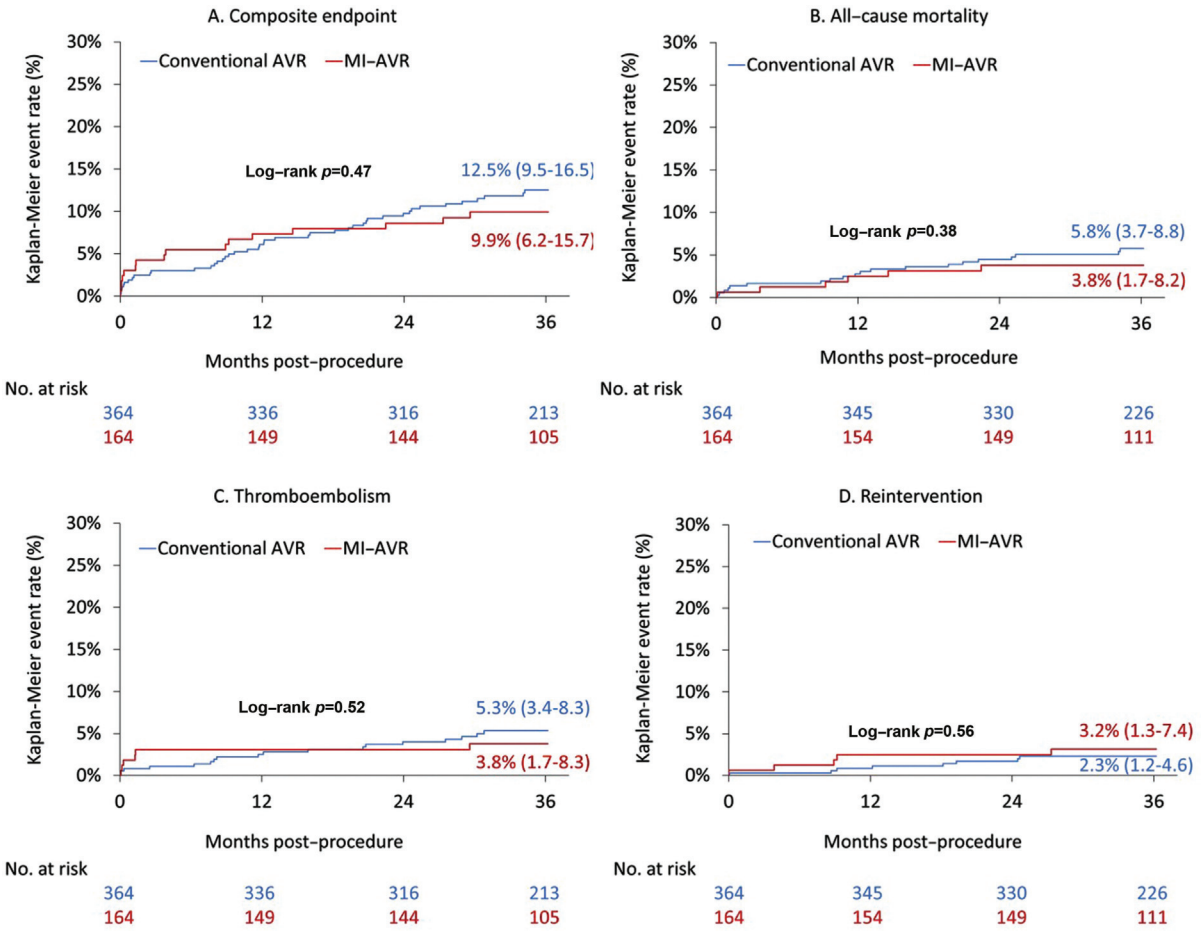


Fig. 2 Three-year outcomes according to surgical approach in the isolated surgical aortic valve replacement (AVR) cohort. Shown are unadjusted Kaplan–Meier event rates with 95% confidence intervals (CIs) for (**A**) the composite outcome of all-cause mortality, thromboembolic events, and reintervention; (**B**) all-cause mortality; (**C**) thromboembolism; and (**D**) reintervention. MI-AVR, minimally invasive AVR.

Endpoint	No. of events MI-AVR (N=164)	No. of events Conventional AVR (N=364)	Hazard ratio (95% CI)	*p* Value
All-cause death	6	20	0.89 (0.34-2.30)	0.80
Thromboembolism	6	18	0.77 (0.30-2.00)	0.59
Reintervention	5	8	1.06 (0.34-3.35)	0.92
Endocarditis	5	11	0.99 (0.33-2.97)	0.99
Composite endpoint*	16	44	0.86 (0.47-1.55)	0.61

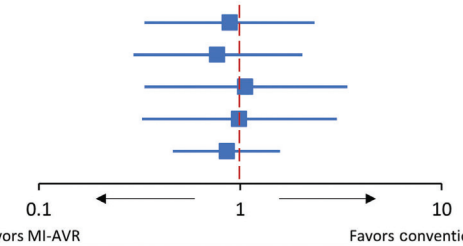
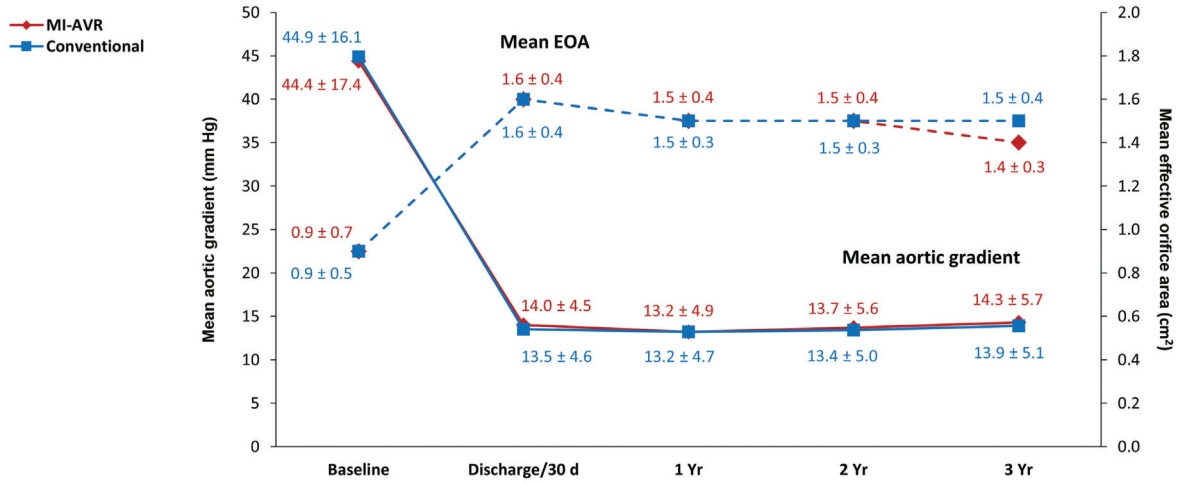


Fig. 3 Factors associated with 3-year outcomes in a propensity-score adjusted multivariable model. Impact of surgical approach on outcomes at 3 years in the isolated surgical aortic valve replacement (AVR) cohort. Propensity-score-adjusted multivariable models were fit to examine differences in outcomes between the minimally invasive aortic valve replacement (MI-AVR) and conventional AVR groups. *The composite outcome comprised all-cause death, thromboembolism, and reintervention. CI, confidence interval.

Cor-Knot group (97.0 ± 23.5 vs. 96.7 ± 31.2 [$p = 0.94$] and 70.2 ± 17.9 vs. 71.1 ± 23.0 min [$p = 0.80$], respectively) (see ►**Supplementary Tables 4–5**, available online only). There were no significant differences in the early and late safety endpoints, including all-cause mortality, thromboembolism, paravalvular leak, endocarditis, and reintervention, as shown in ►**Table 4**.

Discussion

In a cohort of 1,077 patients who underwent AVR with the Avalus bioprosthesis, we found that the incidence of postoperative mortality and morbidity was comparable between the MI-AVR and conventional AVR groups up to 3 years of follow-up.



No. of patients with echocardiographic data					
Mean aortic gradient					
MI-AVR	162	159	149	305	108
Conventional AVR	350	350	330	139	246
Mean effective orifice area					
MI-AVR	149	146	140	132	98
Conventional AVR	330	312	318	288	241

Fig. 4 Postprocedural hemodynamics according to surgical approach through 3 years of follow-up. Shown are the mean gradient (solid lines) and the effective orifice area (EOA; dashed lines) for the minimally invasive aortic valve replacement [MI-AVR] group and conventional aortic valve replacement [AVR] group during follow-up.

While minimally invasive techniques for AVR were first described in the 1990s,[2,3] there remains a lack of consensus about their application in clinical practice.[8] Previous attempts to explore the safety of MI-AVR have been hampered by the poor quality of evidence in the literature. In a Cochrane review of randomized controlled trials that compared limited versus full sternotomy in 2017, only 511 patients were included from 7 clinical trials.[9] In addition, a recent meta-analysis by Chang et al suggested that the comparison of early mortality is subject to publication bias.[10] Despite these methodological concerns, neither of these reviews nor the present study found a significant difference in mortality or other major adverse events between MI-AVR and conventional surgical AVR. The strengths of the present study are its prospective multicenter design, the size of the study population, the robustness of follow-up, adjudication of valve-related safety endpoints by an independent clinical events committee, as well as consistent assessment of hemodynamic performance by an independent core laboratory.

As part of the protocol of the PERIGON Pivotal Trial, surgical approach was left to the discretion of the participating surgeon. This gives insight into the decision-making of experienced surgeons in contemporary practice, and it appears that conventional AVR is still deemed a more appropriate approach for older patients who require concomitant procedures. Because of this evident confounding by indication, a secondary analysis was performed on a narrowed down cohort that included only patients who underwent isolated AVR, although there remained a difference in age, prevalence of left ventricular hypertrophy, and previous stroke. However, both before and after propensity score adjustment, there were no relevant differences in mortality or other valve-related adverse events at 3 years of follow-up, except for all hemorrhage, which was more frequently observed in the MI-AVR group. However, the clinical value of this difference remains unclear since there was no difference in major hemorrhage that was broadly defined in the PERIGON Pivotal Trial as any bleeding episode that resulted in death, hospitalization, reoperation, centesis, or a decrease in hemoglobin to < 7 g/dL that required > 3 U blood transfusion or that caused > 1 L blood loss.

Due to the limited room to maneuver with MI-AVR, it can be hypothesized that the optimal valve size may not always be implanted. However, in our study, MI-AVR was not associated with inferior hemodynamic performance in the isolated AVR subcohort, as the average implanted valve size and postoperative echocardiographic parameters (i.e., mean gradient and EOA) were not significantly different between the two groups. This corresponds to the work of Furukawa et al, who also found no relevant difference in the prosthesis size implanted.[11] In addition, there were no differences in paravalvular leakage and cardiac device implantation at 30 days between the surgical approaches, demonstrating that the Avalus valve can be safely used in a MI-AVR setting.

As clinical outcomes and hemodynamic performance were comparable in the isolated AVR subcohort, the use of MI-AVR over conventional AVR presents a trade-off between less scarring and longer procedural times. To shorten the MI-AVR procedure and hence make it more attractive for surgeons to adopt these techniques, it has been recommended that sutureless valves be used.[10] However, as shown in the PERSIST-AVR trial, the average reduction in cardiopulmonary bypass and aortic cross-clamp times was only 20 minutes with sutureless versus sutured valves.[12] This

Table 4 Summary of adverse events according to the use of Cor-Knot at 3 years follow-up[a]

	Cor-Knot ($N = 49$)	No Cor-Knot ($N = 115$)	p-Value[b]
All-cause mortality	4.2% (1.1–15.7%) ($n = 2$)	3.6% (1.4–9.2%) ($n = 4$)	0.8
Cardiac-related mortality	2.0% (0.3–13.6%) ($n = 1$)	3.6% (1.4–9.2%) ($n = 4$)	0.61
Valve-related mortality	2.0% (0.3–13.6%) ($n = 1$)	0.9% (0.1–6.4%) ($n = 1$)	0.56
Thromboembolism	6.6% (2.2–19.2%) ($n = 3$)	2.6% (0.9–8.0%) ($n = 3$)	0.27
Valve thrombosis	0.0% (NA) ($n = 0$)	0.0% (NA) ($n = 0$)	NA
All hemorrhage[c]	11.6% (4.9–25.9%) ($n = 5$)	12.2% (7.2–20.1%) ($n = 13$)	0.86
Major hemorrhage[c]	4.1% (1.0–15.3%) ($n = 2$)	6.6% (3.2–13.4%) ($n = 7$)	0.61
All paravalvular leak	0.0% (NA) ($n = 0$)	0.0% (NA) ($n = 0$)	NA
Endocarditis	6.2% (2.0–18.0%) ($n = 3$)	1.8% (0.5–7.1%) ($n = 2$)	0.15
Nonstructural valve dysfunction	0.0% (NA) ($n = 0$)	0.0 (NA) ($n = 0$)	NA
Reintervention	6.3% (2.1–18.3%) ($n = 3$)	1.8% (0.4–6.8%) ($n = 2$)	0.15
Explant	6.3% (2.1–18.3%) ($n = 3$)	1.8% (0.4–6.8%) ($n = 2$)	0.15

Abbreviation: NA, not available.
[a]Data are the Kaplan–Meier event rate, 95% confidence interval, and number of patients with an event.
[b]p-Value from log-rank test through 3 years.
[c]Only anticoagulant-related hemorrhage events are included.

time saved comes at the cost of a threefold higher risk of permanent pacemaker implantation, which is associated with decreased survival during long-term follow-up.[13] In addition, despite the longer procedural times compared with conventional AVR, MI-AVR with a stented bioprosthesis was not associated with a higher rate of postoperative mortality and morbidity. Hence, sutureless valves are not a prerequisite to perform MI-AVR safely.

Another theoretical way of shortening MI-AVR procedures is the use of automated suture fasteners. Literature on automated suture fasteners in MI-AVR is scarce. A recent systematic review and meta-analysis by Sazzad et al[14] included three retrospective cohort studies and one small randomized controlled trial. Short-term outcomes showed reduced cardiopulmonary bypass and aortic cross-clamp times and similar early mortality rates. Mid- and long-term outcomes are lacking, leaving a gap of knowledge about potential complications related to extra foreign material, such as thromboembolism, endocarditis, and reintervention. We did not find a difference in bypass or cross-clamp times in the present study, and all safety endpoints were similar at 30 days and 3 years of follow-up.

While the present study suggests that MI-AVR is as safe as conventional AVR in patients who require isolated AVR, it does not support MI-AVR through hemisternotomy or RAT unequivocally. To prove the benefit of these techniques, future studies should focus on time to recovery and quality-of-life outcomes. These "soft" outcomes may help to align patient preferences with the selection of the most appropriate treatment strategy.[8] Furthermore, surgeons should be aware that there is a learning curve associated with the adoption of MI-AVR techniques. Approximately 50 cases are required to achieve a stable operative time,[15,16] although cumulative institutional experience could likely benefit the individual learning curve.

Limitations

Although data were prospectively collected, patients were not randomized to the respective treatment strategies, as reflected in differences in baseline characteristics between the groups. Nevertheless, narrowing inclusion criteria and applying propensity score adjustment did not change the results. In addition, follow-up was relatively short as the average duration was 3 years after the procedure. While hemodynamic performance was consistent between the two groups, the PERIGON trial will continue to follow a subset of patients for up to 12 years of follow-up, and those long-term results will provide further insights into the relative safety and hemodynamic performance of the Avalus valve in a MI-AVR setting.

Conclusion

Three-year outcomes after MI-AVR with the Avalus bioprosthetic valve were comparable to outcomes achieved with a conventional AVR. These results provide important insights into the overall ability to reduce the invasiveness of AVR without compromising outcomes.

Abbreviations

AVR	aortic valve replacement
CABG	coronary artery bypass grafting
CVA	cerebrovascular accident
EOA	effective orifice area
MI-AVR	minimally invasive aortic valve replacement
NYHA	New York Heart Association
PERIGON	PERIcardial SurGical AOrtic Valve ReplacemeNt Pivotal Trial of the Avalus valve
RAT	right anterior thoracotomy
STS	Society of Thoracic Surgeons
TAVR	transcatheter aortic valve replacement

Note
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Authors' Contribution
B.J.J.V. and M.D.V. were involved in writing of the original draft, methodology, and visualization. M.J.R., V.R., R.L., and H.J.P. helped in providing resources, and were involved in writing and review and editing of the manuscript. E.G. was involved in software, validation, formal analysis, data curation, visualization, and in writing, review and editing of the manuscript. J.F.S. III and R.J.M.K. were involved in supervision, conceptualization, resources, writing and review and editing of the manuscript.

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Conflict of Interest
B.J.J.V. declares no conflict of interest; M.D.V. receives research support from Medtronic; M.J.R. is a consultant to Medtronic, Abbott Medical, Boston Scientific, Gore Medical, and Transverse Medical, with fees paid to his department; V.R. is a member of the Surgical Advisory Board for Medtronic and a consultant for Abbott Labs, Gore, and Medtronic. R.L. reports consulting fees, royalties, and stock ownership for Medtronic; he also reports being a consultant for Highlife; H.J.P. is consultant for Medtronic; E.G. is an employee of Medtronic. J.F.S. is the North American Principal Investigator for the PERIGON Pivotal Trial (sponsored by Medtronic). R.J.M.K. receives research support and consultation fees from Medtronic. He is the European Principal investigator of the PERIGON Pivotal Trial (sponsored by Medtronic).
Medical writing was performed by the first and second authors. A writing check for spelling and grammar was performed by Julie Linick, employee of Medtronic.

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