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STRUCTURAL

Prospective Multicenter Evaluation of the Direct Flow Medical Transcatheter Aortic Valve System

12-Month Outcomes of the Evaluation of the Direct Flow Medical Percutaneous Aortic Valve 18F System for the Treatment of Patients With Severe Aortic Stenosis (DISCOVER) Study

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ABSTRACT

OBJECTIVES The aim of this study was to assess the 1-year outcome after transcatheter aortic valve replacement (TAVR) of the Direct Flow Medical (DFM) valve in patients with severe symptomatic aortic stenosis who were contraindicated or high risk for surgery.

BACKGROUND The DFM transcatheter heart valve is a new-generation, nonmetallic aortic valve with a pressurized support structure and conformable double-ring annular sealing delivered through an 18-F sheath. The device allows repositioning, retrieval, and assessment of valve performance before permanent implantation.

METHODS A prospective multicenter European registry was set up to determine the safety and performance of the valve in 100 consecutive patients (10 centers). Echocardiographic and angiographic data were evaluated by an independent core laboratory, and adverse events were adjudicated by a clinical events committee using Valve Academic Research Consortium criteria.

RESULTS Patients were 83.1 ± 5.9 years of age and had a logistic EuroSCORE of 22.5 ± 11.3% and a Society of Thoracic Surgeons score of 9.7 ± 8.7%. Correct valve positioning was obtained in 99% of cases with a combined 30-day safety endpoint at 10%, including major stroke in 5.0%, major vascular complications in 2.0%, and death in 1%. At 12 months, 95% of patients were in New York Heart Association functional class I or II. Freedom from any death was 90%, and freedom from any death or major stroke was 85%. Echocardiography demonstrated none/trace to mild aortic regurgitation in 100% of patients and an unchanged mean aortic gradient of 12.2 ± 6.6 mm Hg and effective orifice area of 1.6 ± 0.4 cm^2.

CONCLUSIONS At 1 year, the DFM transcatheter heart valve had durable hemodynamics. This study demonstrates that the low rate of early complications and the low risk of significant aortic regurgitation translated into midterm clinical benefit. (J Am Coll Cardiol Intv 2016;9:68–75) © 2016 by the American College of Cardiology Foundation.

Transcatheter aortic valve replacement has been used to successfully treat high-risk patients with symptomatic aortic stenosis (1,2). The ability to fully reposition or remove the valve after deployment avoids potential misplacement that can result in coronary obstruction, mitral valve injury, severe aortic regurgitation, and valve embolization (3,4).

The Direct Flow Medical (DFM) transcatheter aortic valve system has a nonmetallic design with a pressurized support structure that allows precise positioning, retrieval, and assessment of valve performance before final release. The DFM valve is delivered through a flexible, 18-F sheath, which ensures excellent trackability and minimizes vascular complications. The 18-F sheath is used for all valve sizes.

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The DISCOVER (Evaluation of the Direct Flow Medical Percutaneous Aortic Valve 18F System for the Treatment of Patients with Severe Aortic Stenosis) study is a prospective, nonrandomized, multicenter European study to evaluate the early and long-term performance of the DFM valve in an extreme-risk patient population. Early safety and efficacy of this technology have been previously reported (5). Most notably, the device minimized the occurrence of moderate/severe aortic regurgitation. As aortic regurgitation may negatively affect prognosis, the DFM technology may be expected to improve long-term outcomes. Here, we report the 12-month outcomes of the DISCOVER study to address mainly 2 questions. First, is the reduction in aortic regurgitation stable at midterm? Second, is the reduction in occurrence of moderate/severe aortic regurgitation associated with improved survival?

METHODS

Patients who were older than 70 years of age with symptomatic severe aortic valve stenosis were evaluated for enrollment. All patients were required to have a logistic EuroSCORE of ≥20% or other high surgical risk features with agreement for transcatheter aortic valve replacement by both the cardiologist and cardiothoracic surgeon at the clinical site. Inclusion and exclusion criteria were reviewed by an independent patient review committee and were previously reported (5). Echocardiographic and angiographic images were evaluated by an independent core laboratory (MedStar, Washington, DC). Aortic regurgitation was assessed by Valve Academic Research Consortium (VARC) II criteria (6).

The primary endpoint was freedom from all-cause mortality at 30 days. Secondary endpoints included VARC II–defined patient safety and device success (6). Clinical events and study safety were adjudicated by an independent committee (Online Appendix 1). All operators were trained on a simulated bench model and in an animal laboratory before the first attempted implantation. The study was designed with a preplanned roll-in training cohort of 3 patients per site. These patients were also included in the current analysis.

DEVICE DESCRIPTION. The DFM valve is a nonmetallic percutaneous bovine pericardial valve (**Figure 1**) with an expandable Dacron polyester double-ring design that encircles and captures the native valve annulus. This technology ensures anchoring of the bioprosthesis and minimizes potential paravalvular leakage. A complete description of the valve and implantation technique was previously published (5,7).

ABBREVIATIONS AND ACRONYMS

DFM = Direct Flow Medical

VARC = Valve Academic Research Consortium

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The bioprosthesis used in the study was provided in a 25-mm size for annular diameters of 19 to 24 mm and a 27-mm size for annular diameters of 22 to 26 mm. Valve sizing recommendations were based on computed tomography dimensions and perimeter-derived diameters in particular. The valvuloplasty balloon that was selected had a diameter 2 to 3 mm smaller than the valve size but never exceeding the annulus diameter. Patients with a coronary artery height <15 mm were treated using a valve size smaller than the aortic bulbus to allow adequate perfusion and access to coronary arteries. During the course of the study, DFM received the CE mark for the 29-mm valve to accommodate those patients with native annulus diameters between 26 and 28 mm.

STATISTICS. Summary statistics are provided for baseline characteristics and all outcome variables. No hypothesis testing was performed. Percentages and counts are provided for categorical data and mean ± SD, and ranges for continuous data. Time-to-event endpoints (e.g., survival analyses) were analyzed using the Kaplan-Meier method. To ensure the appropriateness of pooling the results across clinical sites in this small study of 100 patients, an analysis of variance was performed across the 9 centers.

RESULTS

PATIENT POPULATION. A total of 100 patients with severe symptomatic aortic stenosis were enrolled at 9 clinical sites in 4 European countries (Online Appendix). The baseline demographics have been described previously (5) and are illustrated and compared with those of the CoreValve (Medtronic, Minneapolis, Minnesota) high-risk pivotal study (8) and the PARTNER (Placement of AoRTic TraNscathetER Valve Trial Edwards SAPIEN Transcatheter Heart Valve) high-risk randomized study (1) in **Table 1**.

In summary, the mean age of the patients was 83.1 ± 5.9 years, and 50% were female. The mean gradient was 45.8 ± 9.7 mm Hg, and the effective orifice area was 0.65 ± 0.17 cm^2. The logistic EuroSCORE was 22.5 ± 11.3%, and the Society of Thoracic Surgeons score was 9.7 ± 8.7%. The mean left ventricular ejection fraction was 56.7 ± 8.9%; 58% of the patients had coronary artery disease, 23% had previous coronary artery bypass surgery, 27% had chronic renal insufficiency, and 13% had severe COPD.

FIGURE 1 The Direct Flow Medical Percutaneous Aortic Valve

The Direct Flow Medical valve prosthesis consists of bovine pericardial leaflets and an inflatable nonmetallic scaffold, allowing the valve to be repositioned and retrieved if necessary.

30-DAY OUTCOMES. The 30-day outcome was described previously (5) and is illustrated in **Table 2**. In summary, correct valve positioning was obtained in 99% of patients and device success in 91%. The combined 30-day safety endpoint was observed in 10%, including major stroke in 5.0%, major vascular complication in 2.0%, and death in 1.0%. A new pacemaker was implanted in 17.0% of patients.

12-MONTH OUTCOMES. One-year clinical follow-up was obtained in all patients. The main results are described in **Table 2** and compared with those of the CoreValve high-risk pivotal study (8) and the PARTNER high-risk randomized study (1). **Figure 2** demonstrates the clinical outcomes observed at 1 year. Overall survival was 90%, cardiovascular survival was 93%, and freedom from death and major stroke was 85% at 1 year.

At 1 year, 96% of patients were in New York Heart Association functional class I or II (**Figure 3**). No patient was in New York Heart Association functional class IV. Hospitalizations for valve-related symptoms of heart failure occurred in 9.4% patients between 31 and 182 days post-procedure and 8.7% of patients between 6 and 12 months. There were no cases of valve dysfunction (endocarditis, thrombosis, migration, or embolization). There was 1 repeat procedure due to a low implantation

of the valve. The patient underwent successful surgical aortic valve replacement during the index hospitalization.

The rate of permanent pacemaker implantation between 30 days and 12 months was 4.0%.

CAUSES OF DEATH. From inclusion to 12-month follow-up, 10 deaths were recorded. Causes of death during the course of the study are summarized in Table 3. They were mainly noncardiovascular, with 2 cases of sudden death, 1 of unknown cause, and 1 cerebral hemorrhage.

ECHOCARDIOGRAPHIC HEMODYNAMICS. Patients underwent core laboratory evaluation of echocardiograms and experienced a significant and persistent reduction in transvalvular gradients. Because some echocardiographic data were missing, a paired analysis was also performed. The mean gradient decreased from 45.8 ± 9.7 mm Hg at baseline to 12.6 ± 5.8 mm Hg at 30 days and remained stable at 12 months with a mean gradient of 12.2 ± 6.6 mm Hg (Figure 4). The effective orifice area (Figure 5) at baseline was 0.65 ± 0.17 cm^2, increased to 1.50 ± 0.48 cm^2 at 30 days, and was stable at 12 months (1.57 ± 0.42 cm^2).

AORTIC REGURGITATION. The severity of central and paravalvular aortic regurgitation was graded as none or mild in all patients with evaluable echocardiographic assessment at 12 months using both VARC-1 and American College of Cardiology/American Heart

TABLE 1 Baseline Characteristics and Echocardiographic Findings of the Patients in the Direct Flow Medical Study and Comparison With the PARTNER B and CoreValve Pivotal Study

	DISCOVER (N = 100)	CoreValve HR* (N = 394)	PARTNER HR* (N = 348)
Age, yrs	83.1 ± 5.9	83.2 ± 7.1	83.6 ± 6.8
Male	50/100 (50.0)	211/394 (46.4)	201/348 (57.8)
STS score	9.7 ± 8.7	7.3 ± 3.0	11.8 ± 3.3
Logistic EuroSCORE	22.5 ± 11.3	17.6 ± 13.0	29.3 ± 16.5
NYHA functional class			
II	38/100 (38.0)	56/394 (14.2)	20/348 (5.7)
III or IV	58/100 (58.0)	338/394 (85.8)	328/3,487 (94.3)
Previous atrial fibrillation or atrial flutter	30/100 (30.0)	161/393 (41.0)	80/196 (40.8)
Coronary artery disease	57/98 (58.2)	297/394 (75.4)	260/347 (74.9)
Previous myocardial infarction	9/100 (9.0)	101/394 (25.6)	92/343 (26.8)
Previous intervention			
CABG	23/100 (23.0)	117/394 (29.7)	147/345 (42.6)
PCI	31/99 (31.3)	133/394 (33.8)	116/341 (34.0)
Cerebrovascular disease	5/99 (5.1)†	101/394 (25.6)	95/324 (29.3)
Peripheral vascular disease	23/98 (23.5)	163/391 (41.7)	148/344 (43.0)
COPD	13/100 (13.0)	52/390 (13.3)	151/348 (43.4)
Chronic kidney disease (stage 4/5)	27/100 (27.0)‡	48/387 (12.4)	38/343 (11.1)
Permanent pacemaker	13/100 (13.0)	92/394 (23.4)	69/345 (20.0)
Extensive calcified aorta	6/100 (6.0)	24/394 (4.9)	2/348 (0.6)
Echocardiographic findings			
Aortic valve area, cm^2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2
Mean aortic valve gradient, mm Hg	45.8 ± 9.7	47.3 ± 14.6	42.7 ± 14.6
Mean LVEF	56.7 ± 8.9	54.5 ± 14.4	52.5 ± 13.5
Moderate or severe mitral regurgitation§	5/85 (5.9)	ND	66/344 (19.8)

Values are mean ± SD or n/N (%). *CoreValve HR is the CoreValve high-risk pivotal trial (8); PARTNER HR is the PARTNER high-risk patients (1). †Previous carotid or cerebrovascular intervention. ‡Chronic kindney disease not limited to stage 4/5. §Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; ND = no data; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons.

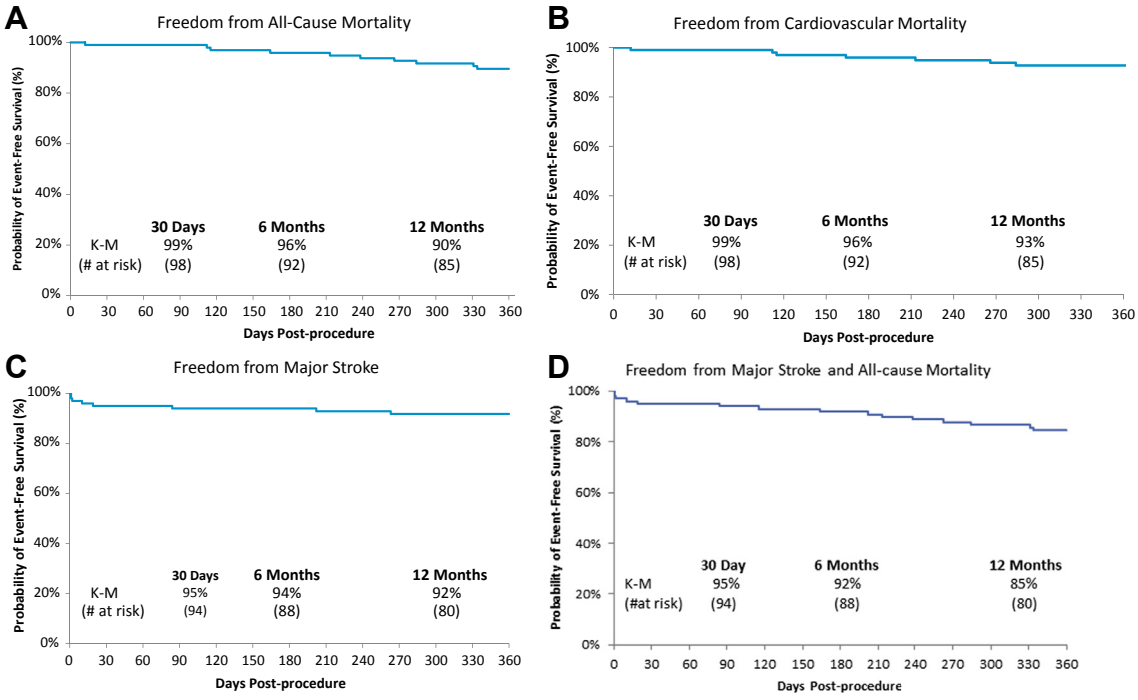
TABLE 2 Clinical Outcome at 1 Month and 1 Year in the DFM Study and Comparison With PARTNER High-Risk Patients and CoreValve High-Risk Pivotal Study*

	DISCOVER (N = 100)		CoreValve HR (N = 390)		PARTNER HR (N = 348)	
Outcome	1 Month	1 Year	1 Month	1 Year	1 Month	1 Year
Death						
From any cause	1 (1.0)	10 (10.0)	13 (3.3)	55 (14.2)	12 (3.4)	84 (24.2)
From a cardiac cause	1 (1.0)	7 (7.0)	ND	ND	11 (3.2)	47 (14.3)
Any stroke	7 (7.0)	10 (10.0)	19 (4.9)	34 (8.8)	16 (4.7)	20 (6.0)
Minor stroke	2 (2.0)	2 (2.0)	4 (1.0)	11 (3.0)	3 (0.9)	3 (0.9)
Major stroke	5 (5.0)	8 (8.0)	15 (3.9)	23 (5.8)	13 (3.8)	17 (5.1)
Death or major stroke	5 (5.0)	15 (15.0)	23 (5.9)	64 (16.3)	24 (6.9)	92 (26.5)
Myocardial infarction	1 (1.0)	2 (2.0)	ND	ND	0	1 (0.4)
Any vascular complication	13 (13.0)	14 (14.0)	ND	ND	59 (17.0)	62 (18.0)
Major vascular complication	2 (2.0)	3 (3.0)	23 (5.9)	24 (6.2)	38 (11.0)	39 (11.3)
Acute kidney injury	1 (1.0)‡	3 (3.0)‡	23 (6.0)	23 (6.0)	4 (1.2)	12 (3.9)
Major bleeding	9 (9.0)	10 (10.0)	109 (28.1)	114 (29.5)	32 (9.3)	49 (14.7)
Endocarditis	0	0	ND	ND	0	2 (0.6)
New-onset atrial fibrillation	11 (11.0)	13 (13.0)	45 (11.7)	60 (15.9)	30 (8.6)	42 (12.1)
New pacemaker	17 (17.0)	21 (21.0)	76 (19.8)	85 (22.3)	13 (3.8)	19 (5.7)

Values are n (%) or mean ± SD. *CoreValve HR is the CoreValve high-risk pivotal trial (8); PARTNER HR is the PARTNER high-risk patients (1). ‡Includes acute kidney injury stage 3 only.

ND = no data.

FIGURE 2 Kaplan-Meier Estimates of Freedom From Mortality and/or Mayor Stroke Through 1 Year



(A) Freedom from all-cause mortality. **(B)** Freedom from cardiovascular mortality. **(C)** Freedom from major stoke. **(D)** Freedom from major stroke and all-cause mortality. K-M = Kaplan Meier method.

Association criteria. Specifically, paravalvular aortic regurgitation was none or trace in 84% of patients at 30 days and 79% at 12 months. Total aortic regurgitation was none or trace in 68% and mild or less in 100% of patients at 12 months (Figures 6 and 7). A figure with paired echocardiographic data obtained at 30 days and 1 year follow-up can be found in the Online Figure 1.

FIGURE 3 New York Heart Association Functional Class

New York Heart Association functional class at baseline and 12-month follow-up.

DISCUSSION

The study demonstrates excellent 1-year clinical outcomes with the DFM transcatheter valve system

TABLE 3 Cause of Death in the DISCOVER Study

No. of Days Post-procedure	Cause of Death
12	Pneumonia
112	Sudden death
115	Gastrointestinal bleed
164	Sudden death
213	Unknown cause
238	Multiple organ failure
266	Cerebral hemorrhage
284	Chronic obstructive pulmonary disease
331	Cancer
334	Vascular dementia

in high- and extreme-risk patients. This is the first prospective multicenter trial evaluating second-generation transcatheter aortic valve replacement technology and demonstrating near elimination of paravalvular aortic regurgitation. This was a significant limitation with first-generation technology that resulted in worse survival rates in patients with more than mild AR (9).

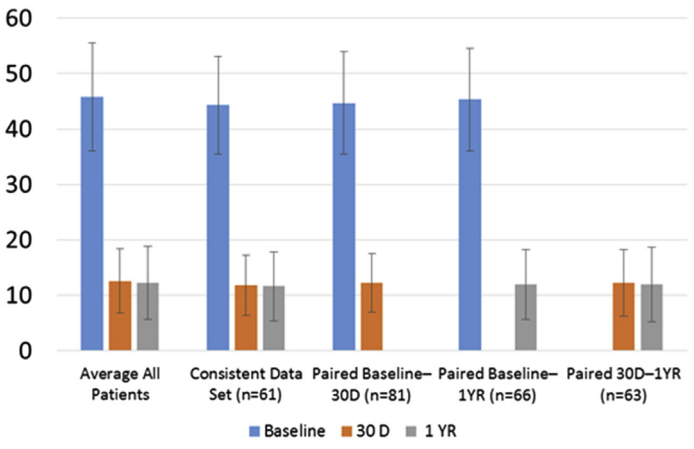
The DFM valve has a conformable ring design that minimizes aortic regurgitation. At 1 year, 100% of patients had mild or less aortic regurgitation, and 68.2% had none or trace. This is in contrast to the results obtained with balloon-expandable and self-expanding devices, for which the reported incidence of moderate to severe AR ranged from 6% to 27%, respectively (9–13). The most recent data from the PARTNER trial comparing the SAPIEN with the SAPIEN XT valve (Edwards Lifesciences, Irvine, California) demonstrated a 20.9% and 29.2% incidence of moderate or severe AR at 1 year (12). The ability to reposition the valve assists in minimizing the risk of paravalvular regurgitation.

The all-cause mortality rate at 12 months after DFM implantation was 10%. These results compare favorably with the most recent multicenter prospective, nonrandomized CoreValve trial in extreme-risk patients (13) that demonstrated a 1-year mortality rate of 24% in the extreme-risk group. The logistic EuroSCORE was similar in both studies: 22.5% versus 22.6%. This study also reported a combined death and major stroke rate of 26% versus the DISCOVER trial rate of 15% at 12 months. The PARTNER 2B trial of extreme-risk patients reported a 23.7% and 22.5% mortality rate at 12 months in the SAPIEN and SAPIEN XT cohorts, respectively (12).

Valvular hemodynamics were well maintained at 1 year. Both the transvalvular gradient and effective orifice area were maintained from the post-procedure evaluation out to 1 year. This demonstrates that, owing to its design and the polymerization of the rings, the frame maintains its radial strength and anatomic position. This is consistent with results from a previous prototype version of this valve that was durable at 5-year follow-up (14).

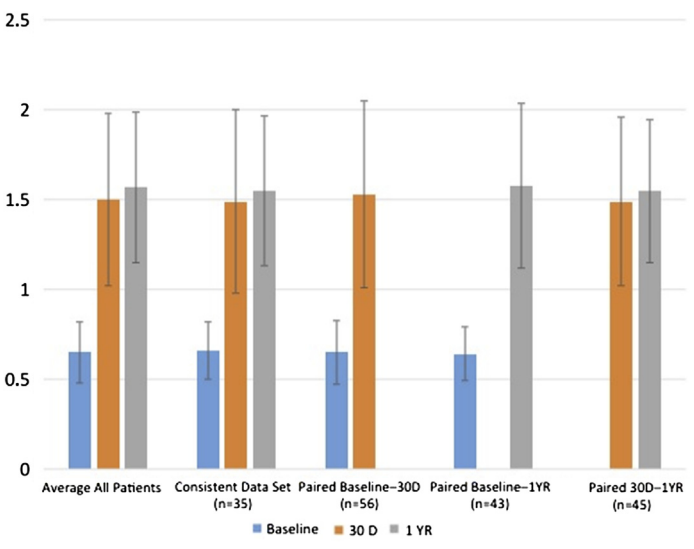
The current study reflects the outcomes from the first 100 patients ever treated with the current iteration of this valve and delivery system. The operators had no previous experience with the current system, and only 1 physician (J.S.) had experience with the first-generation prototype device (14). The total procedure time was 91 ± 47 min for the first 25 patients and decreased with experience to 72 ± 21 min for the last 25 implants (**Figure 8**). This demonstrates that despite the unique technology and deployment technique (7) of a nonmetallic frame, this device has an acceptably short learning curve.

FIGURE 4 Transvalvular Aortic Mean Pressure Gradient



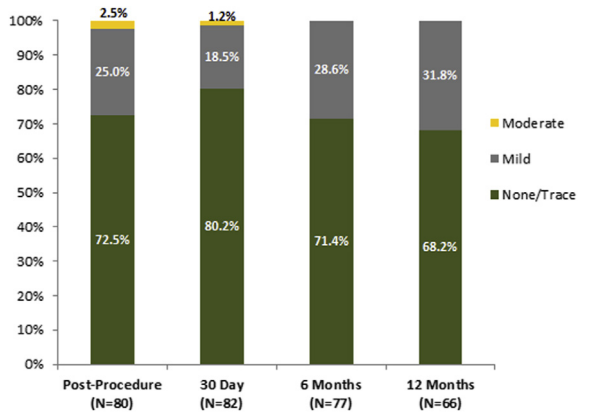
Evolution of transvalvular aortic mean pressure gradient (mm Hg) at baseline and follow-up (global and paired data).

FIGURE 5 Effective Orifice Area



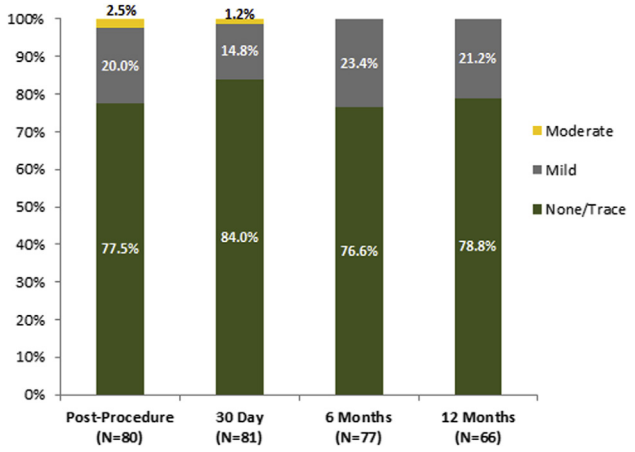
Evolution of effective orifice aortic area (cm^2) at baseline and follow-up (global and paired data).

FIGURE 6 Total Aortic Regurgitation



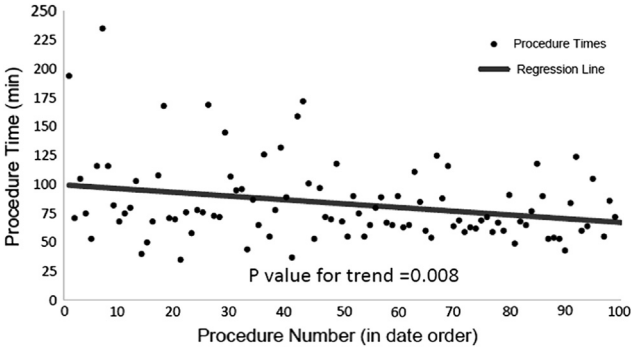
Total aortic regurgitation post-procedure and at follow-up by the core laboratory.

FIGURE 7 Paravalvular Aortic Regurgitation



Paravalvular aortic regurgitation post-procedure and at follow-up by the core laboratory.

FIGURE 8 Evolution of Procedure Time in Date Order



The ability to reposition and evaluate the final result before implantation yielded several important safety advantages. These are highlighted by the fact that there was no case of aortic rupture, valve embolization, or coronary occlusion.

STUDY LIMITATIONS. The main limitation of this study is the relatively small cohort and the fact that it is not a randomized trial that compares the results with those of the first-generation devices. Additional real-world registry outcomes are ongoing in Europe and the pivotal U.S. randomized study SALUS (TranScatheter Aortic Valve RepLacement System Pivotal Trial The Safety and Effectiveness of the Direct Flow Medical Tanscatheter Aortic Valve System) has already started. This study will include 912 extreme surgical risk patients who will be randomized 2:1 with the Medtronic CoreValve. Echocardiographic images were either unavailable or of insufficient quality for all patients to enable analysis by the core laboratory, and this could be a limitation for echocardiographic analysis.

CONCLUSIONS

The low rate of early complications, the low risk of significant aortic regurgitation, and stable hemodynamics at 1 year after implantation of the DFM valve translated into midterm benefit with a low mortality rate of 10% in high-risk patients.

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PERSPECTIVES

WHAT IS KNOWN? Paravalvular leak remains a significant issue after percutaneous aortic valve implantation.

WHAT IS NEW? These preliminary data show that the risk of paravalvular leak is decreased with the DFM valve, which is a conformable and repositionable percutaneous aortic valve.

WHAT IS NEXT? A pivotal U.S. study is ongoing (the SALUS study).

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KEY WORDS aortic stenosids, transcatheter aortic valve replacement, transfemoral transcatheter aortic valve replacement

APPENDIX For supplemental material and a figure, please see the online version of this article.