Journal of the American College of Cardiology Vol. 57, No. 15, 2011

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.11.044

2-Year Follow-Up of Patients Undergoing Transcatheter Aortic Valve Implantation Using a Self-Expanding Valve Prosthesis

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Objectives The purpose of this study was to evaluate the safety, device performance, and clinical outcome up to 2 years for patients undergoing transcatheter aortic valve implantation (TAVI).

Background The role of TAVI in the treatment of calcific aortic stenosis evolves rapidly, but mid- and long-term results are scarce.

Methods We conducted a prospective, multicenter, single-arm study with symptomatic patients undergoing TAVI for treatment of severe aortic valve stenosis using the 18-F Medtronic CoreValve (Medtronic, Minneapolis, Minnesota) prosthesis.

Results In all, 126 patients (mean age 82 years, 42.9% male, mean logistic European System for Cardiac Operative Risk Evaluation score 23.4%) with severe aortic valve stenosis (mean gradient 46.8 mm Hg) underwent the TAVI procedure. Access was transfemoral in all but 2 cases with subclavian access. Retrospective risk stratification classified 54 patients as moderate surgical risk, 51 patients as high-risk operable, and 21 patients as high-risk inoperable. The overall technical success rate was 83.1%. Thirty-day all-cause mortality was 15.2%, without significant differences in the subgroups. At 2 years, all-cause mortality was 38.1%, with a significant difference between the moderate-risk group and the combined high-risk groups (27.8% vs. 45.8%, $p = 0.04$). This difference was mainly attributable to an increased risk of noncardiac mortality among patients constituting the high-risk groups. Hemodynamic results remained unchanged during follow-up (mean gradient: 8.5 ± 2.5 mm Hg at 30 days and 9.0 ± 3.4 mm Hg at 2 years). Functional class improved in 80% of patients and remained stable over time. There was no incidence of structural valve deterioration.

Conclusions The TAVI procedure provides sustained clinical and hemodynamic benefits for as long as 2 years for patients with symptomatic severe aortic stenosis at increased risk for surgery. (J Am Coll Cardiol 2011;57:1650–7)

Transcatheter aortic valve implantation (TAVI) is evolving rapidly with an exponential growth of procedures performed worldwide. The large unmet clinical need addressed by TAVI relates to the suboptimal treatment options in the past for patients with symptomatic aortic valve stenosis but increased risk for surgical aortic valve replacement. Medical treatment was often the only remaining option for these patients without significant impact on symptoms and prognosis (1). The enthusiasm surrounding TAVI is the result of a simple but convincing concept, which remarkably matured

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Manuscript received August 31, 2010; revised manuscript received October 14, 2010, accepted November 9, 2010.

over the past few years. Improvements included an important reduction in the size of device profiles, more careful patient selection and screening processes, as well as identification of predictors of success (2). However, clinical outcome data are mostly restricted to procedural and short-term follow-up (3–7), whereas long-term and randomized clinical trial data are lacking. We are reporting herein the 2-year follow-up results of the 18-F Medtronic CoreValve (Medtronic, Minneapolis, Minnesota) prosthesis safety and efficacy study, which is the longest follow-up reported so far for this commercially available technology.

Methods

Study design. The study was conducted as a prospective, multicenter study to evaluate safety and performance of the 18-F CoreValve prosthesis in patients undergoing TAVI for treatment of severe aortic valve stenosis. Primary endpoints were major adverse cardiovascular and cerebrovascular events (MACCE) at 30 days as well as technical and procedural success. Clinical and echocardiographic evaluation was performed at baseline and after the procedure at 1, 6, and 12 months, and annually thereafter.

Patient inclusion criteria were defined as presence of severe aortic stenosis (0.6 cm^2/m^2), aortic annulus diameter ranging from 20 to 27 mm as determined by echocardiography, ascending aorta diameter ≤45 mm at the sinotubular junction, age ≥75 years, or surgical risk with logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation) ≥15, or 1 to 2 high-risk comorbidities such as cirrhosis of the liver, pulmonary insufficiency (forced expiratory volume in 1 s <1 l), previous cardiac surgery, pulmonary hypertension (systolic pulmonary pressure >60 mm Hg), porcelain aorta, right ventricular failure, or history of mediastinal radiation therapy.

To identify patients who would be considered high-risk and moderate-risk for surgical aortic valve replacement, a retrospective risk stratification using commonly accepted surgical criteria was performed by 2 independent cardiovascular surgeons with recognized expertise in aortic valve surgery. The surgeons were blinded to procedural details and outcomes but

Abbreviations and Acronyms

- **AR** = aortic regurgitation
- **EOA** = effective orifice area
- **EuroSCORE** = European System for Cardiac Operative Risk Evaluation
- **HRinop** = high-risk inoperable
- **HRop** = high-risk operable
- **MACCE** = major adverse cardiovascular and cerebrovascular event(s)
- **MR** = moderate risk
- **NYHA** = New York Heart Association
- **TAVI** = transcatheter aortic valve implantation
- **TIA** = transient ischemic attack

Table 1 Baseline Clinical Patient Characteristics

	Total (n = 126)	Moderate-Risk (n = 54)	High-Risk		
			Operable (n = 51)	Inoperable (n = 21)	Combined (n = 72)
Age, yrs	81.9 ± 6.4	83.4 ± 4.9	82.2 ± 7.0	77.3 ± 6.8	80.8 ± 7.2
Male	42.9% (54)	37.0% (20)	43.1% (22)	57.1% (12)	47.2% (34)
EuroSCORE	23.43 ± 13.80	16.14 ± 8.53	29.91 ± 14.84	26.45 ± 13.66	28.90 ± 14.50
Dyslipidemia	57.9% (73)	53.7% (29)	56.9% (29)	71.4% (15)	61.1% (44)
Hypertension	79.4% (100)	75.9% (41)	82.4% (42)	81.0% (17)	81.9% (59)
Diabetes mellitus	26.2% (33)	20.4% (11)	29.4% (15)	33.3% (7)	30.6% (22)
Current smoker	32.5% (41)	22.2% (12)	39.2% (20)	42.9% (9)	40.3% (29)
Coronary heart disease	65.9% (83)	53.7% (29)	74.5% (38)	76.2% (16)	75.0% (54)
History of atrial fibrillation	39.7% (50)	37.0% (20)	37.3% (19)	52.4% (11)	41.7% (30)
Previous myocardial infarction	19.0% (24)	11.1% (6)	21.6% (11)	33.3% (7)	25.0% (18)
Previous CABG	26.2% (33)	9.3% (5)	41.2% (21)	33.3% (7)	38.9% (28)
Previous coronary angioplasty	23.8% (30)	18.5% (10)	23.5% (12)	38.1% (8)	27.8% (20)
Peripheral vascular disease	19.0% (24)	13.0% (7)	21.6% (11)	28.6% (6)	23.6% (17)
Previous stroke or TIA	22.2% (28)	20.4% (11)	23.5% (12)	23.8% (5)	23.6% (17)
Pulmonary hypertension	31.7% (40)	11.1% (6)	41.2% (21)	61.9% (13)	47.2% (34)
Renal failure	43.7% (55)	35.2% (19)	51.0% (26)	47.6% (10)	50.0% (36)
On dialysis	7.3% (4/55)	5.3% (1/19)	7.7% (2/26)	10.0% (1/10)	8.3% (3/36)
Chronic lung disease	23.0% (29)	18.5% (10)	21.6% (11)	38.1% (8)	26.4% (19)
Porcelain aorta	7.9% (10)	1.9% (1)	3.9% (2)	33.3% (7)	12.5% (9)
Previous pacemaker	7.9% (10)	7.4% (4)	9.8% (5)	4.8% (1)	8.3% (6)
History of congestive heart failure	55.6% (70)	38.9% (21)	64.7% (33)	76.2% (16)	68.1% (49)
NYHA functional class I	5.6% (7)	9.3% (5)	2.0% (1)	4.8% (1)	2.8% (2)
NYHA functional class II	19.8% (25)	24.1% (13)	21.6% (11)	4.8% (1)	16.7% (12)
NYHA functional class III	54.0% (68)	57.4% (31)	56.9% (29)	38.1% (8)	51.4% (37)
NYHA functional class IV	20.6% (26)	9.3% (5)	19.6% (10)	52.4% (11)	29.2% (21)

Values are mean ± SD, % (n), or % (n/N).
CABG = coronary artery bypass graft surgery; EuroSCORE = European System for Cardiac Operative Risk Evaluation; NYHA = New York Heart Association; TIA = transient ischemic attack.

Table 2 30-Day and 2-Year Clinical Follow-Up

	30-Day Follow-Up							2-Year Follow-Up						
			High-Risk			p Value				High-Risk			p Value	
	Total (n = 126)	Moderate Risk (n = 54)	Operable (n = 51)	Inoperable (n = 21)	Combined (n = 72)	MR–HRcomb	HRop–HRinop	Total	Moderate Risk	Operable	Inoperable	Combined	MR–HRcomb	HRop–HRinop
All-cause mortality	15.2% (19)	11.3% (6)	15.7% (8)	23.8% (5)	18.1% (13)	0.38	0.74	38.1% (48)	27.8% (15)	41.2% (21)	57.1% (12)	45.8% (33)	0.04	0.22
Cardiac mortality	10.4% (13)	9.4% (5)	7.8% (4)	19.0% (4)	11.1% (8)	0.93	0.41	23.0% (29)	18.5% (10)	17.6% (9)	47.6% (10)	26.4% (19)	0.30	0.01
Myocardial infarction	5.6% (7)	5.7% (3)	3.9% (2)	9.5% (2)	5.6% (4)	1.00	0.57	6.3% (8)	5.6% (3)	3.9% (2)	14.3% (3)	6.9% (5)	1.00	0.12
Stroke	9.6% (12)	11.3% (6)	7.8% (4)	9.5% (2)	8.3% (6)	0.60	1.00	13.5% (17)	14.8% (8)	9.8% (5)	19.0% (4)	12.5% (9)	0.71	0.43
TIA	2.4% (3)	1.9% (1)	2.0% (1)	4.8% (1)	2.8% (2)	1.00	0.50	4.0% (5)	3.7% (2)	3.9% (2)	4.8% (1)	4.2% (3)	1.00	1.00
Emergent cardiac reintervention	8.8% (11)	9.4% (5)	7.8% (4)	9.5% (2)	8.3% (6)	0.63	0.62	8.7% (11)	9.3% (5)	7.8% (4)	9.5% (2)	8.3% (6)	0.86	1.00
Structural valve deterioration	0	0	0	0	0	1.00	1.00	0	0	0	0	0	1.00	1.00
Endocarditis	0	0	0	0	0	1.00	1.00	0.8% (1)	0	0	4.8% (1)	1.4% (1)	1.00	0.29

Values are % (n).
HRcomb = high-risk combination; HRinop = high-risk inoperable; HRop = high-risk operable; MR = moderate-risk; TIA = transient ischemic attack.

were provided with baseline case report forms, logistic EuroSCORE, and available source documentation for each patient. All patients provided written informed consent before the procedure. The study was approved by the local ethics committees at each institution.

Device and procedure. Design characteristics of the CoreValve prosthesis as well as the procedural characteristics have been described elsewhere (2,3). Briefly, the current 18-F generation of the CoreValve prosthesis consists of a trileaflet bioprosthetic porcine pericardial tissue valve, which is mounted and sutured in a self-expanding nitinol stent frame. The device is implanted retrogradely. The currently commercially-available third-generation device analyzed in this study is offered in 2 different sizes (26- and 29-mm prosthesis) for different annulus dimensions ranging from 20 to 27 mm. As of May 2007, only the 26-mm prosthesis was available and implanted.

Definitions. The MACCE were defined as the composite of all-cause death, myocardial infarction, emergent cardiac surgery or percutaneous reintervention, and stroke. Myocardial infarction was defined as elevation of creatine kinase twice the upper limit of normal in the presence of elevated creatine kinase-myocardial band above the upper limit of normal, with electrocardiographic evidence of ischemia and a compatible clinical history. Stroke was defined as a new prolonged (>24 h) or permanent neurological deficit and radiographic imaging demonstrating an acute ischemic cerebrovascular event. Technical success was defined as successful device implantation without valve misplacement or malfunction at the index procedure. Procedural success was defined as successful device implantation without occurrence of MACCE during index hospitalization. Structural valve deterioration was defined as any change in function of the study valve resulting from an intrinsic abnormality of the valve that causes stenosis or regurgitation.

Statistical analysis. Categorical variables are presented as frequencies and percentages and were compared by chi-square test or Fisher exact test. Continuous variables are presented as mean ± SD, and were compared by unpaired Student *t* test. Survival and other time-to-event analyses at 2 years were performed by Kaplan-Meier analysis. A p value <0.05 was considered statistically significant.

Results

Baseline characteristics and procedural results. A total of 126 patients were enrolled between 2006 and 2008 at 9 sites in Europe and Canada. Baseline patient characteristics are listed in Table 1. The risk classification grouped the study population into 54 patients with moderate-risk (MR [42.9%]), 51 patients with high but operable risk (HRop [40.5%]), and 21 patients with high inoperable risk (HRinop [16.7%]). The mean EuroSCORE was 23%, and was almost twice as high for high-risk patients as compared with moderate-risk patients (28.9% vs. 16.1%, respectively).

Within the high-risk group, the inoperable high-risk group had a higher incidence of New York Heart Association (NYHA) functional class IV (19.6% HRop vs. 52.4% HRinop) and pulmonary hypertension (41.2% HRop vs. 61.9% HRinop). All patients in the moderate-risk group underwent the procedure through the femoral access route whereas 2 patients in the high-risk group underwent the procedure through the left subclavian approach.

The overall technical and procedural success rates were 83.1% and 72.6%, respectively. High-risk patients compared with moderate-risk patients had similar rates of technical success (84.7% vs. 80.8%), whereas procedural success was lower in the high-risk group than in the moderate-risk group (69.4% vs. 76.9%). Post-procedural implantation of permanent pacemakers due to atrioventricular conduction abnormalities was required for 26.2% of all patients.

Follow-up. MACCE. Follow-up availability was 99.2% (125 of 126) at 30 days and 87.3% (110 of 126) at 2 years. The overall MACCE rate at 30 days amounted to 26.4%, with an all-cause mortality of 15.2% and a rate of stroke of 9.6% (Table 2). At 2 years, the overall MACCE rate increased to 47.4%, with a significantly higher MACCE rate in the high-risk inoperable group (69.4%) compared with the moderate-risk group (40.3%) (Fig. 1). All-cause mortality increased from the 30-day to 2-year follow-up period from 15.2% to 38.1% in the overall population, with a significant difference between the moderate- and high-risk groups (27.8% vs. 45.8%, p = 0.04) (Fig. 2). Cardiac mortality rates at 2 years were similar among patients of the moderate- and high-risk operable groups (18.5% vs. 17.6%) (Fig. 3).

ECHOCARDIOGRAPHIC OUTCOME. Comparing baseline and 30-day echocardiographic follow-up data, there was a significant reduction of the mean transvalvular gradient from 46.8 ± 15.9 mm Hg to 8.5 ± 4.0 mm Hg in the overall population, with similar results in all subgroups (Fig. 4). The hemodynamic status remained essentially unchanged between the 30-day and 2-year follow-up period, with a mean pressure gradient of 9.0 ± 3.4 mm Hg at 2 years. Aortic regurgitation of any kind was present in 58% of patients at baseline compared with 41% and 37% at 30 days and 2 years after the intervention, respectively. There was no severe aortic regurgitation (3+/4+) at any time (Fig. 5). There was no report of structural valve deterioration, frame fractures, or valve migrations up to 2 years, and only 1 case of endocarditis.

FUNCTIONAL OUTCOME. Figure 6 shows the change in clinical status based on the NYHA functional classification at various times for the overall population as well as for the subgroups compared with the baseline status. At 30 days, 80% of all patients with technical success improved by at least 1 NYHA level, 15% remained unchanged, and 5% worsened. This clinical improvement was apparent in all subgroups, with the greatest benefit among patients in the high-risk groups. At 2 years, 74% of patients still reported functional improvement, 16% reported the same status as before the intervention, and 10% had worsened.

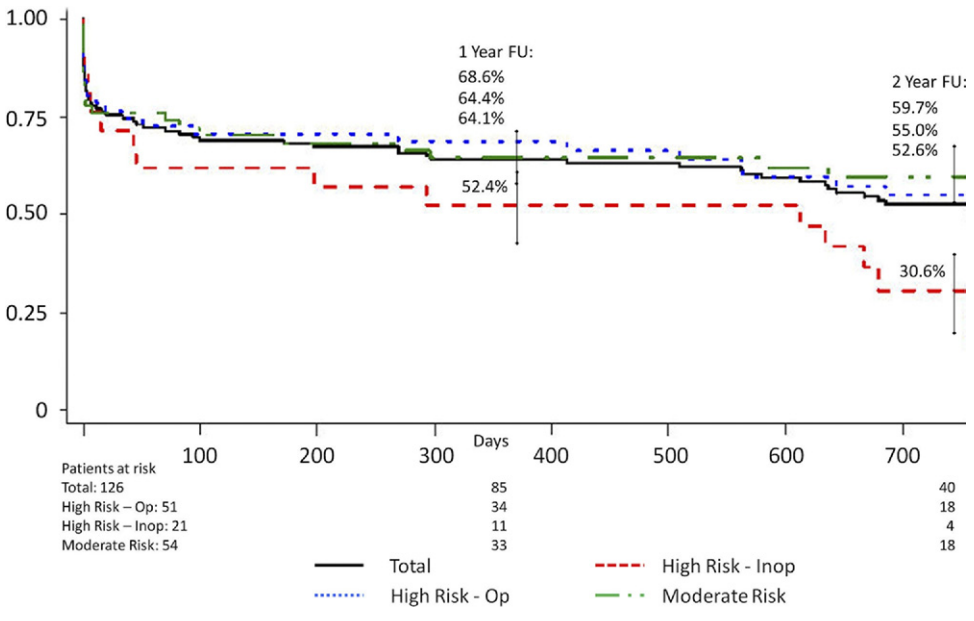

Figure 1 Freedom From MACCE

Kaplan-Meier estimates of freedom from major adverse cardiac and cerebrovascular events (MACCE) up to 2-year follow-up (FU). **Black line** indicates total group; **blue line** indicates high-risk operable (Op); **red line** indicates high-risk inoperable (Inop); and **green line** indicates moderate risk.

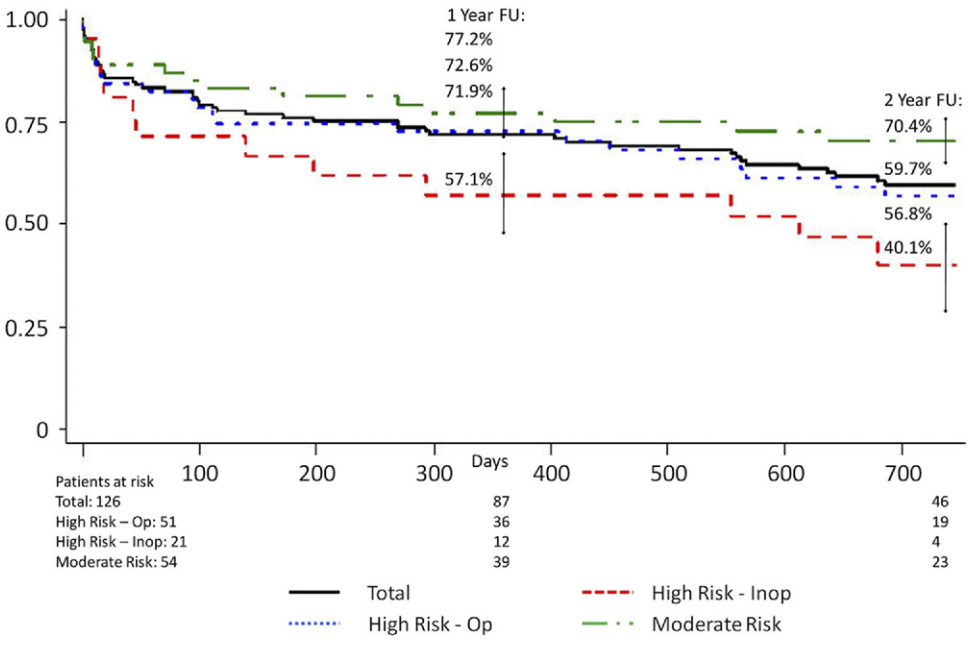

Figure 2 **Freedom From All-Cause Mortality**

Kaplan-Meier estimates of freedom from all-cause mortality up to 2-year FU. **Black line** indicates total group; **blue line** indicates high-risk Op; **red line** indicates high-risk Inop; and **green line** indicates moderate risk. Abbreviations as in Figure 1.

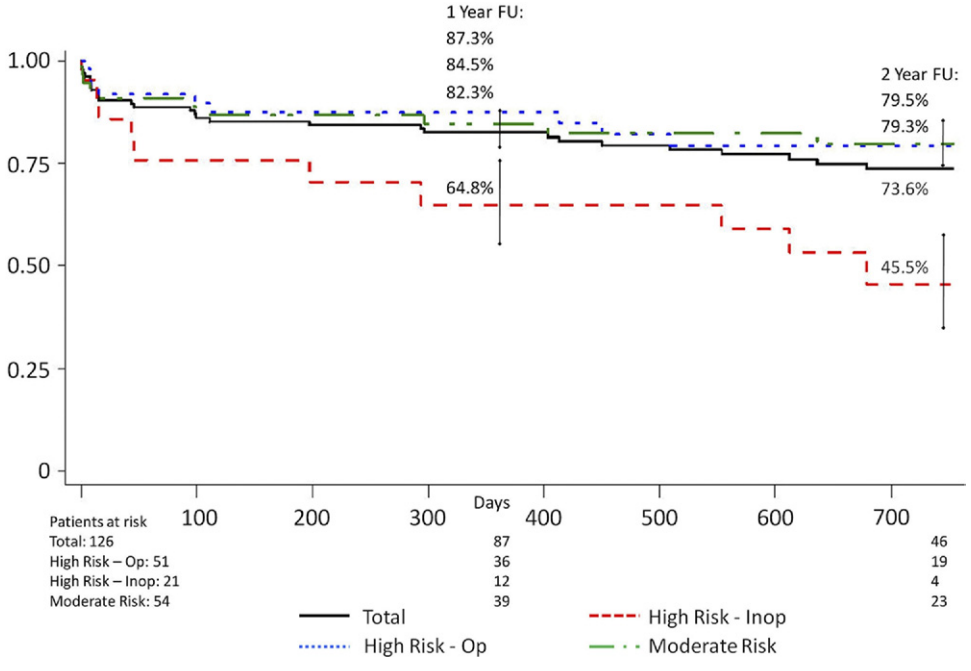

Figure 3 **Freedom From Cardiac Mortality**

Kaplan-Meier estimates of freedom from cardiac mortality up to 2-year FU. **Black line** indicates total group; **blue line** indicates high-risk Op; **red line** indicates high-risk Inop; and **green line** indicates moderate risk. Abbreviations as in Figure 1.

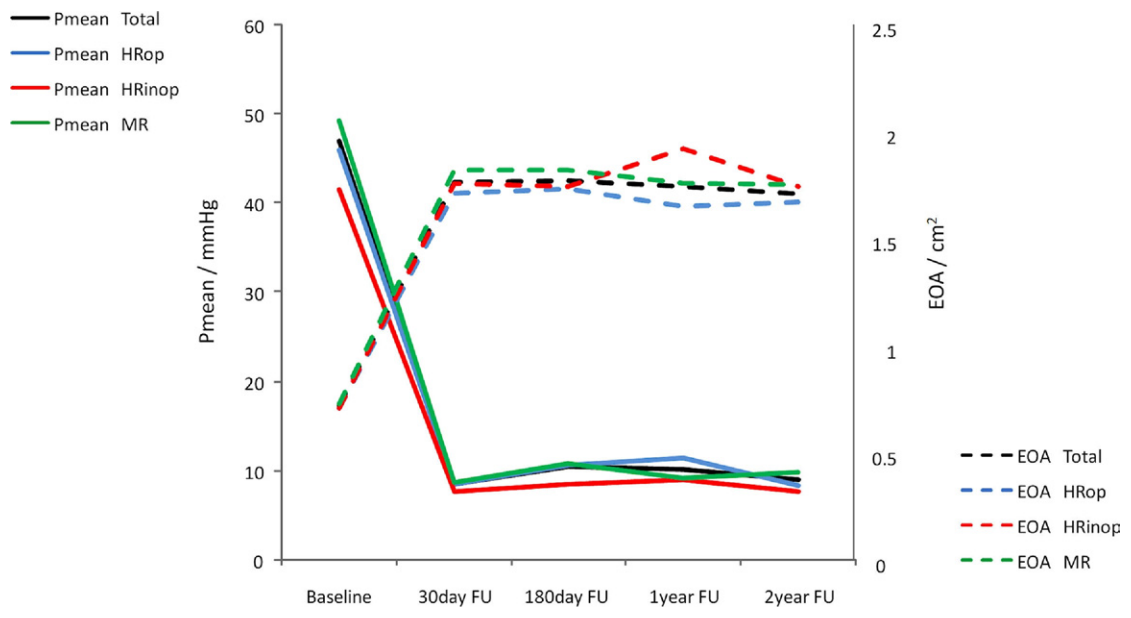

Figure 4 **Mean Gradient and EOA Area**

Mean pressure gradient (Pmean) and effective orifice area (EOA) assessed by echocardiography. **Solid black line** is Pmean total; **solid blue line** is Pmean high-risk operable (HRop); **solid red line** is Pmean high-risk inoperable (HRinop); **solid green line** is Pmean moderate risk (MR). **Dashed black line** indicates EOA total; **dashed blue line** indicates EOA HRop; **dashed red line** indicates EOA HRinop; **dashed green line** indicates EOA MR. FU = follow-up.

Discussion

This study provides evidence of the durability of both the safety and the efficacy of TAVI using the self-expanding Medtronic CoreValve prosthesis for the treatment of patients with severe aortic valve stenosis. Two years after implantation and independent of pre-procedural risk features, there was no evidence of structural valve deterioration or significant changes of the hemodynamic status of the

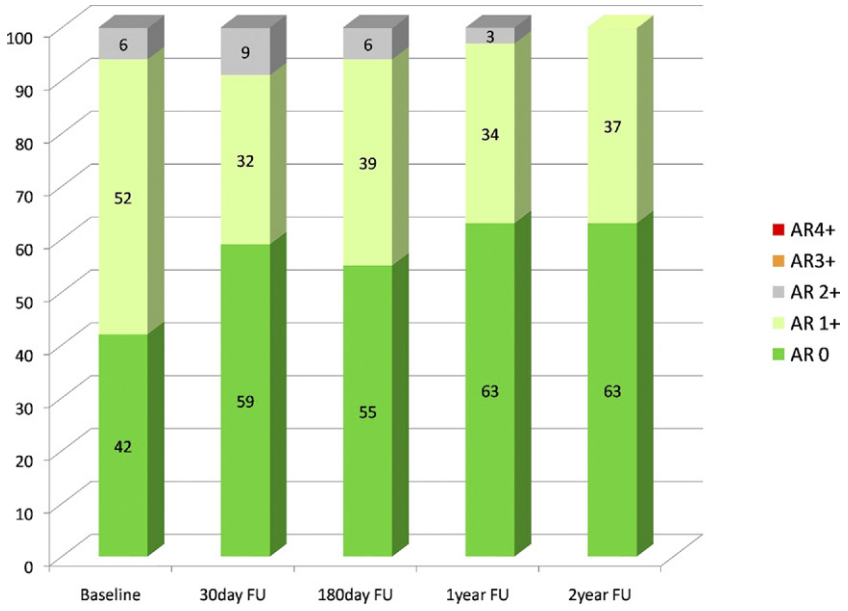

Figure 5 **Aortic Valve Regurgitation**

Pre-procedural and post-procedural aortic valve regurgitation assessed by echocardiography. AR = aortic regurgitation; FU = follow-up.

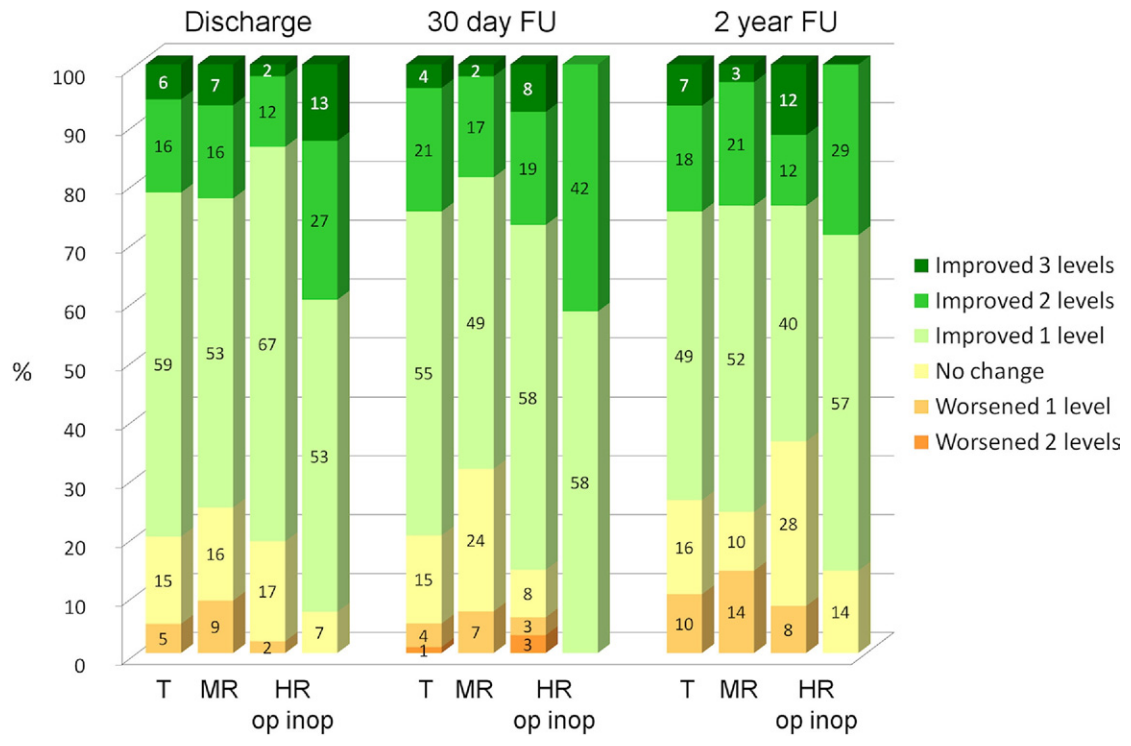

Figure 6 **Functional Clinical Outcome**

Functional status expressed by New York Heart Association (NYHA) classification at discharge, and at 30-day and 2-year follow-up (FU) compared with baseline. **Dark green** = improved 3 levels; **medium green** = improved 2 levels; **light green** = improved 1 level; **light yellow** = no change; **medium yellow** = worsened 1 level; **dark yellow** = worsened 2 levels. HR = high risk; inop = inoperable; MR = moderate risk; op = operable; T = total.

prostheses. There was only 1 case of prosthetic valve endocarditis at 2 years of follow-up (0.8% = 0.4% annual risk), which is well within the range of surgical series of bioprosthetic aortic valve replacement, with a reported annual risk of approximately 0.6% (8). Accordingly, technical performance of the device appears to be durable so far.

The procedural success rate of only 73% compared with reported rates of 90% to 97% in more recent studies (2,5–7,9) is related to learning phase factors as well as a very conservative definition used in this study requiring MACCE-free in-hospital survival, without which the technical success rate was 83%. Similarly, the 30-day mortality rate of 15.2% in this study appears to be high in the light of more recent TAVI studies, which report 30-day mortality rates of 6% to 10% (5–7,9). In addition to the learning curve issues and various improvements described, that might be related to a tendency to treat patients with less comorbidity today than in the early phase of TAVI, as is reflected in this paper.

Between 30-day and 2-year follow-up, we observed a 2- to 3-fold increase in all-cause mortality, which is in line with a previous publication by Gurvitch et al. (10) of patients undergoing TAVI using a balloon-expandable prosthesis. In this publication, a follow-up of 3 years is reported, with a 2-year survival of 74% of patients who survived the first 30 days after the procedure, and an overall 2-year survival of 64%. Our data demonstrate that this mortality is strongly influenced by pre-procedural risk characteristics. Patients classified high-risk before the intervention had twice the risk of major adverse events up to 2 years compared with patients in the moderate-risk group, underlining the importance of pre-existing comorbidities. Although there was no difference in cardiac deaths between the moderate-risk and the high-risk operable groups, there was a significant difference in all-cause mortality due to more noncardiac events in the high-risk population, indicating that high-risk patients do not have a higher likelihood of dying for procedural or valve-related reasons but for reasons originating from their pre-existing comorbidities. Clinical improvement among survivors was remarkable and durable, particularly in high-risk subgroups.

The occurrence of strokes during a TAVI procedure is reported with an incidence of 2% to 4% in more recent publications (5–7,9), which appears acceptable in light of the high-risk patient population and compares favorably with surgical studies of aortic valve replacement. The reported 30-day stroke rate of 9.6% in our study is the result of the definition of stroke accounting for any defects on imaging studies (3 patients did not have any clinical deficits by neurological examination, but had

small defects on imaging studies). Therefore, it is difficult to compare this rate with other reports using different definitions. Future studies will certainly benefit from the consensus on standardized outcome definitions that are currently prepared by the Valve Academic Research Consortium representing several academic research organizations, surgical and cardiological professional societies, members of the U.S. Food and Drug Administration, and independent experts. However, embolic cerebral events remain an important issue that is stimulating the development of various protection concepts entering clinical investigation.

Study limitations. This is a multicenter, prospective study with independent monitoring and event adjudication, but the lack of randomization limits the ability to compare these data with established treatment standards. In addition, small subgroup sizes might affect interpretation of the data. When comparing the mortality result with the calculated EuroSCORE, which was standard at the time of patient enrollment and, therefore, the only score used in this study, one has to consider that today this score is known to be of limited value to characterize the risk for patients undergoing valve replacement and captures only a limited number of risk-predicting characteristics (e.g., porcelain aorta is not considered) (11). Therefore, new scores and algorithms for the combined field of transcatheter and surgical aortic valve replacement should be developed to accurately describe the pre-procedural patient risk to be able to select the best treatment option for the specific patient. Finally, follow-up of this study will continue up to 4 years, and additional long-term studies are needed before durability of these new devices can be confirmed according to surgical standards.

Acknowledgments

Participating centers (in order of numbers of included patients, given in parentheses) are as follows: HELIOS Heart Center, Siegburg, Germany (n = 42); University of Leipzig Heart Centre, Leipzig, Germany (n = 19); Montreal Heart Institute, Montreal, Ontario, Canada (n = 18); University Hospitals Leicester, Leicester, United Kingdom (n = 14); Erasmus University Medical Center, Rotterdam, the Netherlands (n = 12); University of Ottawa Heart Institute, Ottawa, Ontario, Canada (n = 11); Amphia Hospital, Breda, the Netherlands (n = 4); Royal Brompton Hospital, London, United Kingdom (n = 4); and University of Alberta Cardiac Surgery, Edmonton, Alberta, Canada (n = 2).

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Key Words: aortic valve stenosis ■ long-term follow-up ■ transcatheter aortic valve implantation.