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STRUCTURAL

5-Year Outcomes After Transcatheter Aortic Valve Implantation With CoreValve Prosthesis

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ABSTRACT

OBJECTIVES The purpose of this analysis was to assess 5-year outcomes of transcatheter aortic valve implantation (TAVI) using the current technology of the self-expanding CoreValve prosthesis (Medtronic Inc., Minneapolis, Minnesota).

BACKGROUND There is a paucity of evidence on long-term durability of currently available transcatheter heart valves.

METHODS Starting in June 2007, all consecutive patients with severe aortic stenosis undergoing TAVI with the third-generation 18-F CoreValve device in 8 Italian centers were prospectively included in the ClinicalService Project. For the purposes of this study, we included only consecutive patients with 5-year follow-up data available (n = 353) treated from June 2007 to August 2009. All outcomes were reported according to VARC (Valve Academic Research Consortium)-1 criteria.

RESULTS All-cause mortality rates at 1, 2, 3, 4, and 5 years were 21%, 29%, 38%, 48%, and 55.0%, respectively. Cardiovascular mortality rates at 1, 2, 3, 4, and 5 years were 10%, 14%, 19%, 23%, and 28.0%, respectively. The overall neurological event rate at 5 years was 7.5%, of which more than two-thirds occurred early after the procedure. During follow-up, there were 241 rehospitalizations for cardiovascular reasons in 164 (46%) patients. Among all rehospitalizations, acute heart failure was the most frequently reported (42.7%), followed by requirement of permanent pacemaker implantation (17.4%). On echocardiography, mean transaortic gradients decreased from 55.6 ± 16.8 mm Hg (pre-TAVI) to 12.8 ± 10.9 mm Hg (5-year post-TAVI) ($p < 0.001$). Late prosthesis failure occurred in 5 cases (1.4%); among these, redo TAVI was successfully carried out in 2 patients (0.6%) presenting with symptomatic prosthesis restenosis. The remaining 3 cases of prosthesis failure did not undergo further invasive interventions. Ten patients (2.8%) showed late mild stenosis with a mean transaortic gradient ranging from 20 to 40 mm Hg. No other cases of structural or nonstructural valvular deterioration were observed. Valve thrombosis or late valve embolization were not reported.

CONCLUSIONS TAVI with the currently adopted CoreValve generation was associated with sustained clinical outcomes up to 5-year follow-up, with a low rate (1.4%) of significant prosthetic valve degeneration. The procedure appears to be an adequate and lasting resolution of aortic stenosis in selected high-risk patients. (J Am Coll Cardiol Intv 2015;8:1084–91)

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Transcatheter aortic valve implantation (TAVI) has become an accepted and less invasive treatment alternative for high-risk surgical patients with severe aortic stenosis. Short- and medium-term outcomes have been encouraging (1–5). However, data on long-term clinical outcomes, valve durability, and structural integrity remain scarce (6–8). Although the 5-year outcomes of balloon-expandable Edwards-SAPIEN prosthesis (Edwards Lifesciences, Irvine, California) were recently reported (6), the longest follow-up with the CoreValve (Medtronic Inc., Minneapolis, Minnesota) device thus far is 3 years, as reported by 2 different groups (7).

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The paucity of evidence on long-term durability of currently available transcatheter heart valves is one of the main issues that prevents TAVI from being used in younger and lower-risk patients. The objective of this analysis was to assess 5-year outcomes of TAVI using the current technology of the self-expanding CoreValve prosthesis.

METHODS

PATIENT POPULATION. Starting in June 2007, all consecutive patients with severe aortic stenosis undergoing TAVI with the third-generation 18-F CoreValve device in 8 Italian centers were prospectively included in the ClinicalService Project (NCT01007474). Details of the ClinicalService Project's design have been previously described (9). Briefly, this is a nation-based clinical data repository and medical care project aimed at describing and improving the use of implantable devices in Italian clinical practice. The project was approved by each site's institutional review board or medical director and conforms to the principles outlined in the Declaration of Helsinki. Each patient signed an informed consent for data collection and analysis. Clinical and echocardiographic follow-up were performed according to each center's clinical practice by clinical visits or telephone contacts. All events were site reported. For the purposes of this study, we included in this analysis only consecutive patients with 5-year follow-up data available.

PROCEDURE. Design features of the CoreValve prosthesis and technical details of the procedure have been previously described (10,11). The CoreValve prosthesis, available in the 26- and 29-mm sizes, was implanted using the transfemoral and subclavian approaches with an 18-F delivery catheter. All procedures were performed under local anesthesia (with or without additional sedation and/or analgesia) or general anesthesia and endotracheal intubation, under fluoroscopic guidance.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
HR = hazard ratio
IQR = interquartile range
IRR = incidence rate ratio
MR = mitral regurgitation
TAVI = transcatheter aortic valve implantation

STATISTICAL ANALYSIS AND DEFINITIONS. Descriptive statistics were summarized as mean ± SD for normally distributed continuous variables or otherwise as median and 25th to 75th percentile (interquartile range [IQR]), whereas for categorical variables, absolute and relative frequencies are reported. Survival analysis has been carried out with the Kaplan-Meier method, reporting incidence of event at each year. Landmark analyses at 30 days and 5 years were also performed, and incidence of the outcomes was assessed with the Kaplan-Meier method at both landmark points. Univariate Cox Regression has been used to identify univariate predictors of events from the major baseline and procedural characteristics; all of the variables with a univariate $p < 0.15$ have been subsequently tested in a multivariate Cox regression to identify independent predictors of the event. Results of the Cox regression are reported as hazard ratio (HR) together with 95% confidence interval (CI). To identify predictors of heart failure hospitalizations, univariate Poisson regression models were carried out, and then all resulting variables with a p value <0.15 were put into the multivariable model to identify independent predictors. The Akaike information criterion was used to identify the best subset of predictors. Incidence rate ratio (IRR), together with 95% CI, is reported as a result of the Poisson regression.

For statistical analysis, SAS version 9.3 for Windows (SAS Institute Inc., Cary, North Carolina) was used. All outcomes were reported according to VARC (Valve Academic Research Consortium)-1 criteria (12).

Scientific. Dr. Ettori has served as a medical proctor for Medtronic. Dr. Latib has served on the advisory board of Medtronic; and has served as a consultant for Direct Flow Medical. Dr. Colombo is a minor shareholder in Direct Flow. Dr. Bruschi has served as a consultant for Medtronic and Direct Flow. Dr. Attizzani has served as a consultant for St. Jude Medical, Medtronic, and Edwards Lifesciences; and has served as a proctor for Medtronic and Edwards Lifesciences. All other authors have reported that they have no relationships with industry to disclose.

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TABLE 1 Baseline Characteristics (n = 353)

Clinical Variables	
Age, yrs	81.5 ± 6.3
Males	44.5 (157/353)
Logistic EuroScore, %	21.5 (15–31)
STS score, %	
Mean	9.5 ± 10.0
Median	5.8 (4–11)
Creatinine, mg/dl	1.2 (1–2)
Chronic renal failure	11.1 (37/333)
NYHA functional class III to IV	70.0 (247/353)
Hypertension	75.6 (267/353)
Diabetes mellitus	30.3 (107/353)
Prior ischemic event	7.4 (26/353)
Prior stroke	5.1 (18/353)
Permanent AF	1.4 (5/353)
Prior MI	21.8 (77/353)
Prior PCI	30.0 (106/353)
Prior SAVR	1.1 (4/353)
PVD	27.2 (96/353)
COPD*	25.8 (91/353)
Prior CABG	15.3 (54/353)
Prior PPM	11.2 (37/331)
Echocardiographic Variables	
Mean aortic gradient, mm Hg	55.6 ± 16.8
Aortic regurgitation ≥ moderate	33.8 (112/331)
Mitral regurgitation ≥ moderate	41.7 (143/343)
LVEF, %	50.6 ± 12.3
LVEF <35%	13.0 (46/353)
LVEF 35%–55%	48.7 (172/353)
sPAP >60 mm Hg	9.1 (32/353)

Values are mean ± SD, % (n/N), or median (25th–75th percentile). *Defined as long-term use of bronchodilators or steroids for lung disease.

AF = atrial fibrillation; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PPM = permanent pacemaker; PVD = peripheral artery disease; SAVR = surgical aortic valve replacement; sPAP = systolic pulmonary artery pressure; STS = Society of Thoracic Surgery.

RESULTS

POPULATION. A total of 353 patients (mean age 81.5 ± 6.3 years) treated consecutively with TAVI with CoreValve from June 2007 to August 2009 formed the analysis group. Baseline demographic, clinical, and echocardiographic characteristics are listed in Table 1. All patients had severe symptomatic aortic stenosis (mean transaortic pressure gradients 55.6 ± 16.8 mm Hg). Predicted 30-day mortality 21.5% (IQR: 15% to 31%) by Logistic EuroSCORE and 5.8% (IQR: 4% to 11%) by Society of Thoracic Surgery (STS) mortality score. The majority of patients (n = 247; 70.0%) were in New York Heart Association (NYHA) functional class III or IV before the procedure.

TABLE 2 In-Hospital Outcomes (n = 353)

Death from any cause	6.5 (23/353)
Cardiovascular death	4.0 (14/353)
Any stroke	2.3 (8/353)
Major stroke	1.7 (6/353)
Minor stroke	0.6 (2/353)
Life-threatening bleeding	5.9 (21/353)
Major bleeding	20.7 (73/353)
AKI 1	29.0 (85/293)
AKI 2	1.0 (3/293)
AKI 3	0.3 (1/293)
New PPM	23.7 (75/316)*
PVR more than mild	23.6 (81/343)
Antiplatelet therapy at discharge	
SAPT	19.1 (63/330)
DAPT	71.5 (236/330)
OAT	0.9 (3/330)
SAPT + OAT	6.7 (22/330)
DAPT + OAT	0.9 (3/330)
Unknown	0.9 (3/330)

Values are % (n/N). *Denominator represents the number of patients without PPM at baseline.

AKI = acute kidney injury; DAPT = dual antiplatelet therapy; OAT = oral anticoagulant; PPM = permanent pacemaker; PVR = paravalvular regurgitation; SAPT = single antiplatelet therapy.

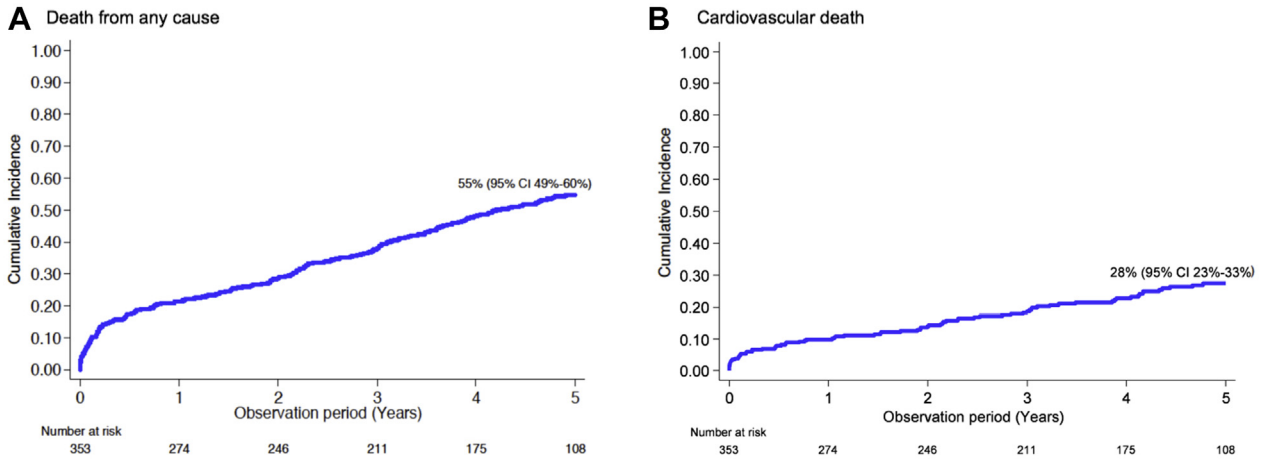
PROCEDURAL AND IN-HOSPITAL OUTCOMES. Transfemoral access was used in 317 patients (89.8%); in 36 patients (10.2%) in whom the transfemoral approach was unfeasible, a trans-subclavian access was employed. The 26- and 29-mm CoreValve ReValving Systems were implanted in 216 (61.4%) and 136 (38.6%) patients, respectively. In-hospital outcomes are listed in Table 2. All-cause and cardiovascular mortality were 6.5% and 4.0%, respectively. A permanent pacemaker was implanted in 23.7% (75 of 316) of patients, in most cases due to permanent or intermittent third-degree atrioventricular block. Life-threatening bleeding occurred in 21 patients (5.9%) and cerebrovascular events in 8 patients (2.3%).

5-YEAR OUTCOMES. Clinical follow-up was available in all patients (100%). A total of 187 (53%) patients died during a median follow-up of 47 months (IQR: 16 to 70 months). All-cause mortality rates at 1, 2, 3, 4, and 5 years were 21%, 29%, 38%, 48%, and 55.0%, respectively (Figure 1A). Cardiovascular mortality rates at 1, 2, 3, 4, and 5 years were 10%, 14%, 19%, 23%, and 28.0%, respectively (Figure 1B).

When patients with 30-day mortality were excluded, 5-year all-cause and cardiovascular mortality were 51.0% and 25.0%, respectively, as shown by the landmark analysis (Figures 2A and 2B).

The presence of moderate or severe paravalvular regurgitation after TAVI was associated with

FIGURE 1 Kaplan-Meier Analysis



Kaplan-Meier percentage of **(A)** mortality rate and **(B)** rate of cardiovascular mortality at 5-year follow-up. CI = confidence interval.

increased late mortality compared with none or mild (63% vs. 51%; p = 0.034) (Online Figure 1). The overall neurological event rate at 5 years was 7.5%, of which more than two-thirds occurred early after the procedure (**Figure 3**); antiplatelet/anticoagulant therapy taken by the patients at the moment of stroke/transient ischemic attack is reported in Online Appendix Table 1.

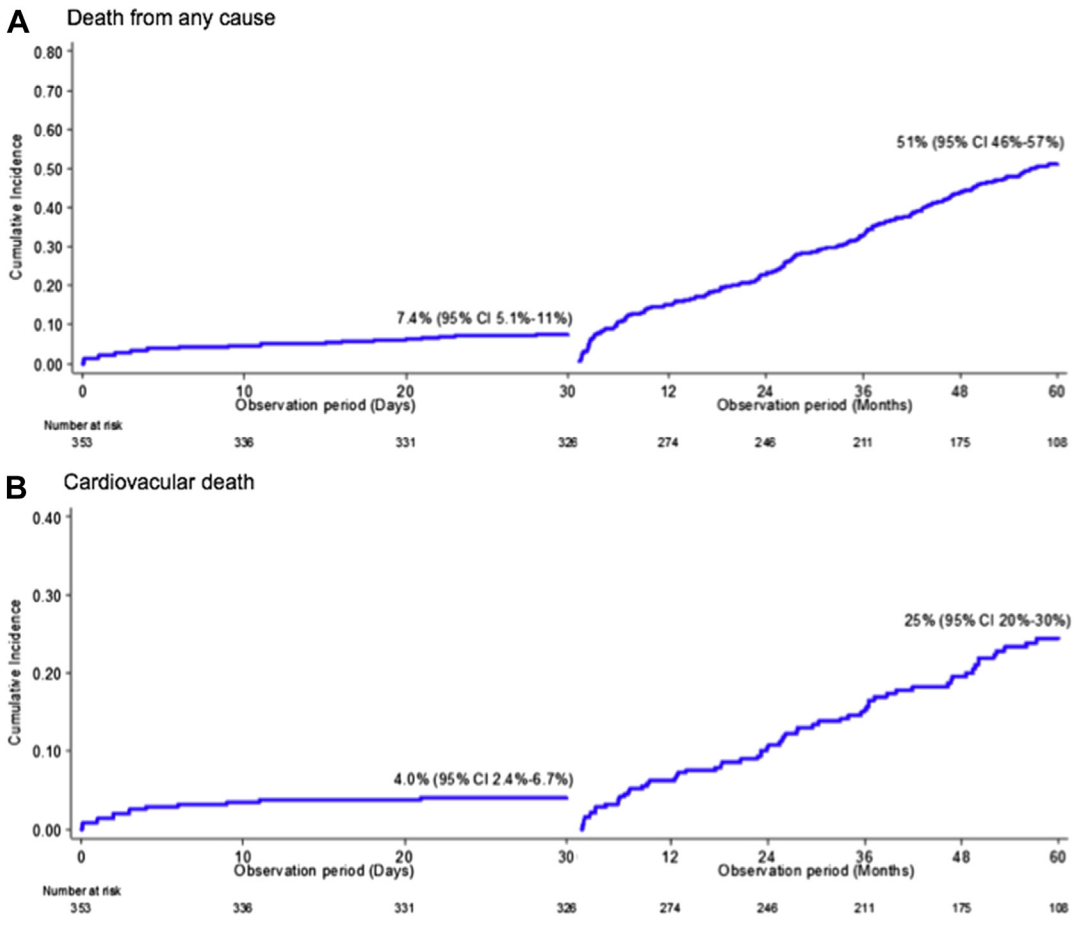
During follow-up, there were 241 rehospitalizations for cardiovascular reasons in 164 (46%) patients. Among all rehospitalizations, acute heart failure was the most frequently reason reported (42.7%), followed by requirement of permanent pacemaker implantation (17.4%) (**Table 3**).

After adjustment for confounders by multivariable analysis, moderate/severe mitral regurgitation (MR) (adjusted HR: 1.49; 95% CI: 1.02 to 2.17; p = 0.038), baseline NYHA functional class III or IV (adjusted HR: 1.62; 95% CI: 1.04 to 2.52; p = 0.033), and STS score (adjusted HR: 1.02; 95% CI: 1.01 to 1.04; p = 0.003) were found to be independently associated with all-cause mortality. Independent predictors of cardiovascular mortality were chronic obstructive pulmonary disease (COPD) (adjusted HR: 2.13; 95% CI: 1.07 to 4.23; p = 0.031) and moderate/severe MR (adjusted HR: 2.87; 95% CI: 1.47 to 5.61; p = 0.002) (**Table 4**).

At the Poisson regression; moderate/severe MR (IRR: 2.06; 95% CI: 1.12 to 3.78; p = 0.020), chronic renal insufficiency (IRR: 2.77; 95% CI: 1.05 to 7.34; p = 0.040), diabetes mellitus (IRR: 1.86; 95% CI: 1.01 to 3.44; p = 0.047), and COPD (IRR: 2.67; 95% CI: 1.42 to 5.02; p = 0.002) were found to be independently associated with an increased risk of repeated hospitalization due to heart failure (**Table 5**).

PROSTHESIS PERFORMANCE. The graph depicting prosthesis performances at follow-up is reported in **Figure 4**. On transthoracic echocardiography, mean pressure gradients decreased from 55.6 ± 16.8 mm Hg (pre-TAVI) to 10.3 ± 6.5 mm Hg (in-hospital post-TAVI) (p < 0.001). Transaortic gradient remained steady over the subsequent 4 years and slightly increased at 5 years (12.8 ± 10.9 mm Hg). The degree of PVR over time is depicted in Online Figure 2. One patient underwent early redo TAVI with a SAPIEN XT valve at day 6 due to severe paravalvular regurgitation. Late prosthesis failure occurred in 5 cases (1.4%); among these, redo TAVI (valve-in-valve), was successfully carried out in 2 patients (0.6%) presenting with symptomatic prosthesis restenosis at days 1,693 and 1,465, respectively. The other 3 cases of prosthesis failure did not undergo further invasive interventions: 1 case of endocarditis with severe aortic regurgitation (day 1,681) who died due to noncardiovascular reasons, 1 case of asymptomatic valve degeneration with severe insufficiency (day 1,674), and 1 case of worsening of paravalvular regurgitation from moderate to severe (day 355) who is alive at 2-year follow-up. Ten other patients (2.8%) showed late mild stenosis with a mean transaortic gradient ranging from 20 to 40 mm Hg. No other cases of structural or nonstructural valvular deterioration were observed. Valve thrombosis or late valve embolization were not reported.

FIGURE 2 Landmark Analysis



Landmark analysis for **(A)** mortality rate and **(B)** rate of cardiovascular mortality. Two time points were considered as landmarks: 30 days and 5 years. CI = confidence interval.

DISCUSSION

TAVI has been validated by 2 randomized clinical trials as "at least" noninferior to surgery in patients with aortic stenosis who are at high risk for conventional aortic valve replacement (1-3). The most recent guidelines have consolidated the role of TAVI as an important alternative in the treatment of this important valve heart disease (13). However, although many studies have shown positive short and mid-term effectiveness of TAVI (1-5), there is still a paucity of data on the long-term durability of current TAVI prostheses (6-8).

The present multicenter analysis describes the outcomes of a cohort of TAVI patients with the longest follow-up using the currently adopted self-expanding CoreValve ReValving System device. We demonstrated favorable long-term outcomes, with a 5-year survival rate of 45% and freedom from re-hospitalization for cardiac reasons of 54%. Valve performance was excellent up to 5 years after implantation, with signs of prosthetic failure observed in only 15 patients (4.2%); notably, in only 5 cases did we report severe prosthesis dysfunction, and 2 of these were treated with a successful redo TAVI.

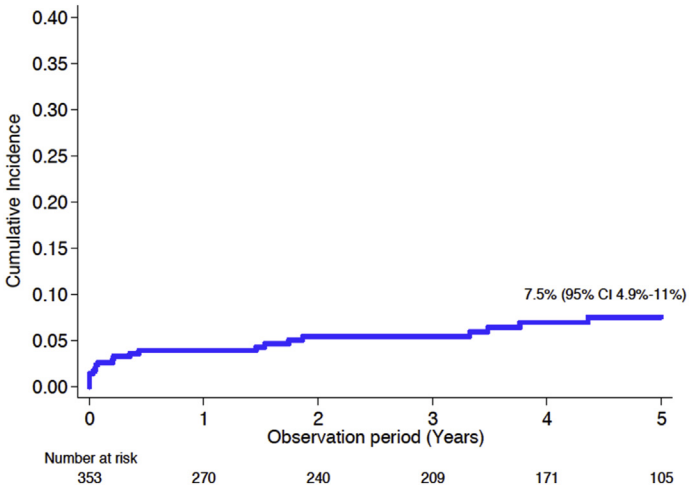
Contemporary evidence on survival rates after TAVI at long-term follow-up are restricted to a few studies exploring durability of previous-generation balloon-expandable devices. In our series of 353 consecutive patients, we found 5-year all-cause and cardiovascular mortality rates of 55% and 28%, respectively. To better assess the long-term durability of TAVI, we performed a landmark analysis excluding

patients with procedural mortality (death during the first 30 days). Compared with the series published by Toggweiler et al. (6), we found better survival (49% vs. 35%); this discrepancy may be explained by the lower risk profile of patients included in the present analysis. Notably, most deaths were more likely linked to patients' comorbidities and advancing age, as demonstrated by the low rate of cardiovascular mortality at 5 years. Consistent with previous studies reporting shorter-term follow-up, predictors of both 5-year all-cause and cardiovascular mortality were generally related to baseline clinical comorbidities (STS score, NYHA functional class III or IV, and moderate/severe baseline MR or COPD) (4,14,15).

Among the main complications, we observed that bleeding and stroke occurred mainly in the earliest period after TAVI. Rehospitalization due to cardiovascular reasons after the procedure was an important issue raised by this study: it was required in 46% of patients, and among all 241 rehospitalizations, almost one-half were due to acute heart failure. Interestingly, several noncardiac comorbidities, such as COPD, chronic renal failure, and diabetes mellitus, were associated with an increased risk of repeat hospitalization for heart failure. COPD is a well-known comorbidity in patients hospitalized with acute heart failure and is also associated with a worse long-term prognosis (16,17). Similarly, diabetes mellitus and chronic renal insufficiency are commonly associated with an increased risk of adverse outcomes, including recurrent hospitalization due to heart failure (18,19). Finally, concomitant moderate or severe MR was also associated with a 2-fold increased risk of rehospitalization for decompensated acute heart failure. MR is a common finding in patients with aortic stenosis. At the time of aortic valve replacement, up to two-thirds of patients with aortic stenosis have varying degrees of MR (20). Few studies, and with discordant results, have examined the clinical effect of pre-operative MR on outcome after TAVI (20). However, the association between MR and the risk of rehospitalization due to heart failure has not been investigated yet. The results of this analysis tend to suggest that TAVI patients with significant pre-operative MR may potentially benefit from a staged invasive treatment of the mitral valvulopathy (i.e., transcatheter edge-to-edge technique), provided that they are anatomically suitable for that (21). However, the real clinical- and cost-effectiveness of this strategy has to be carefully evaluated in future studies.

TRANSCATHETER HEART VALVE PERFORMANCE. As the duration of implanted transcatheter heart valves increases, valve durability and dysfunction become more crucial issues. Durability of the transcatheter valves has been a special concern and requires systematic echocardiography follow-up at late time points. Gurvitch et al. (22) reported on clinical outcomes, valvular structural integrity, and hemodynamic changes in 70 patients evaluated a median of 3.7 years after TAVI with a balloon-expandable valve, confirming a good medium- to long-term durability and preserved hemodynamic function with no evidence of structural failure. More recently, Toggweiler et al. (6) extended the follow-up to 5 years. In 88 patients (29 patients alive at 5-year follow-up), they

FIGURE 3 Stroke



Kaplan-Meier percentage of stroke rate. CI = confidence interval.

TABLE 3 Rehospitalization

	Patients (n = 353)	Rehospitalization (n = 241)
Heart failure only	69 (19.6)	103 (42.7)
PPM implant only	42 (17.4)*	42 (17.4)
Heart failure and PPM implant	4 (1.1)	4 (1.7)
Heart failure and hemorrhagic stroke	1 (0.3)	1 (0.4)
PPM implant and cardiac ischemia	1 (0.3)†	1 (0.4)
Hemorrhagic stroke only	5 (1.4)	5 (2.1)
Ischemic stroke	15 (4.2)	16 (6.7)
Transient ischemic attack only	1 (0.3)	1 (0.4)
Cardiac ischemia only	12 (3.4)†	14 (5.8)
Vascular complications only	13 (3.7)	15 (6.2)
Other cardiovascular reasons	33 (9.3)	39 (16.2)

Values are n (%). *Denominator is 241, which represents the number of patients without PPM at discharge. †Cardiac ischemia includes any acute coronary syndromes, percutaneous or surgical revascularization, and angina attributable to coronary artery disease.

PPM = permanent pacemaker.

TABLE 4 Multivariable Analysis: Death From Any Cause and Cardiovascular Death

	HR (95% CI)	p Value
	Death From Any Cause	
Moderate or severe MR	1.49 (1.02–2.17)	0.036
NYHA functional class III–IV	1.62 (1.04–2.52)	0.033
STS score	1.602 (1.010–1.040)	0.003
	Cardiovascular Death	
COPD	2.13 (1.07–4.23)	0.031
Moderate or severe MR	2.87 (1.47–5.61)	0.002

CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; MR = mitral regurgitation; NYHA = New York Heart Association; STS = Society of Thoracic Surgery.

TABLE 5 Poisson Regression: Repeat Hospitalization for Acute Heart Failure

	Multivariate Analysis	
	IRR (95% CI)	p Value
Moderate or severe MR	2.06 (1.12–3.78)	0.020
Chronic renal failure	2.77 (1.05–7.34)	0.040
Diabetes mellitus	1.86 (1.01–3.44)	0.047
COPD	2.67 (1.42–5.02)	0.002

IRR = incidence rate ratio; other abbreviations as in Table 4.

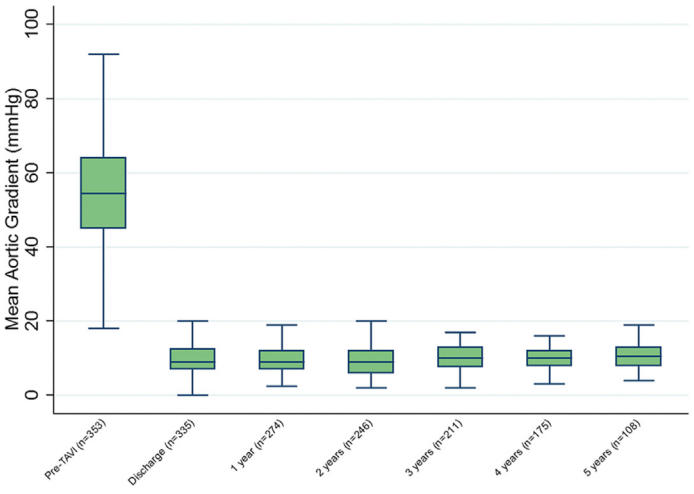
demonstrated favorable outcomes after TAVI, with signs of moderate prosthetic valve failure in 3.4% of patients and no cases of severe prosthetic regurgitation or stenosis. Similarly, in the Italian CoreValve registry (7), the durability of clinical, hemodynamic, and echocardiographic outcomes were tested at 3-year follow-up, reporting stable results over the follow-up period. There were no cases of progression of mild PVR to moderate or severe regurgitation. No cases of structural valve deterioration were observed as well.

In the present analysis, we report satisfactory long-term valve performance in terms of transprosthetic gradient, which remained steady over time, with only a slight increase reported at the 5-year time point. Signs of late significant prosthetic valve failure at 5 years after implantation were observed in 1.4% of population, whereas asymptomatic degeneration with only mild stenosis was reported in 2.8% of patients.

Surgical aortic bioprostheses have shown 10-year freedom from valvular failure in the range of 60% to 90%. Reported rates of structural valve deterioration requiring reoperation range widely from 6% to 47% by 12 to 20 years after surgical implantation (23–25). At 5 years, freedom from structural failure is generally >95%, and although early failure requiring reoperation or leading to mortality has been reported, freedom from reoperation at 5 years is also generally more than 95% (26,27).

Although larger studies are needed to determine the rate of structural deterioration of transcatheter valve at longer follow-up, the findings of this analysis tend to suggest that at 5 years, transcatheter valves performance compare favorably with the surgical bioprostheses.

FIGURE 4 Prosthesis Performance



Time trends in transaortic mean gradient. TAVI = transcatheter aortic valve implantation.

STUDY LIMITATIONS. The present analysis has 2 main limitations. First, echocardiographic parameters were not evaluated by a central core laboratory. Finally, echocardiographic data and rates of late prosthetic failure were performed in a "survival cohort," with death possibly exerting a competing risk that may have biased our results. Caution must therefore be applied when interpreting these data.

CONCLUSIONS

Our analysis showed that TAVI with the currently adopted CoreValve generation was associated with sustained clinical outcomes up to 5-year follow-up, with a low rate (1.4%) of significant prosthetic valve failure. The procedure appears to be an adequate and lasting resolution of aortic stenosis in selected high-risk patients.

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PERSPECTIVES

WHAT IS KNOWN? Data on long-term clinical outcomes of TAVI, including valve durability and structural integrity, remain scarce.

WHAT IS NEW? In this study, the TAVI procedure with the CoreValve device appears to be an adequate and lasting (up to 5 years) resolution of aortic stenosis in selected high-risk patients.

WHAT IS NEXT? The demonstration of long-term durability of TAVI may encourage physicians to adopt this new technology in more patient populations.

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APPENDIX For a supplemental table and figures, please see the online version of this article.