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1-Year Outcomes With the Evolut R Self-Expanding Transcatheter Aortic Valve

From the International FORWARD Study

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ABSTRACT

OBJECTIVES This study sought to report the 1-year safety and efficacy outcomes in the FORWARD (CoreValve Evolut R FORWARD) study following transcatheter aortic valve replacement (TAVR) with the next-generation Evolut R device (Medtronic, Minneapolis, Minnesota) in routine clinical practice.

BACKGROUND The FORWARD study reported low incidences of mortality, disabling stroke, and significant paravalvular leak following TAVR in routine clinical practice at 30 days. Longer-term results in large patient populations with the Evolut R self-expanding, repositionable transcatheter heart valve (THV) are lacking.

METHODS This was a prospective, single-arm, multinational, multicenter, observational study investigating efficacy and safety following TAVR with the next-generation self-expanding THV. Between January and December 2016, 1,040 patients underwent attempted implant of the Evolut R self-expanding repositionable valve at 53 sites worldwide. An independent Clinical Events Committee adjudicated safety endpoints based on Valve Academic Research Consortium-2 definitions. An independent echocardiographic core laboratory evaluated all echocardiograms.

RESULTS The mean age was 81.8 ± 6.2 years, 64.8% were women, and patients had a mean Society of Thoracic Surgeons Predicted Risk of Mortality score of 5.5 ± 4.5% and EuroSCORE II of 5.7 ± 5.0%. The 1-year all-cause mortality rate was 8.9%, with a cardiovascular mortality rate of 6.9%. At 1 year, the incidence of disabling stroke was 2.1%, and a pacemaker was implanted in 19.7% of patients. The incidence of more than mild paravalvular leak was 1.2%.

CONCLUSIONS The FORWARD study demonstrated good safety and efficacy profiles for the next-generation Evolut R THV up to 1-year follow-up, with very low mortality and adverse events. (CoreValve Evolut R FORWARD Study [FORWARD]; NCT02592369) (J Am Coll Cardiol Intv 2018;11:2326–34) © 2018 by the American College of Cardiology Foundation.

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Transcatheter aortic valve replacement (TAVR) is now a Class IA/B recommendation for treatment of patients with severe aortic stenosis who are at elevated surgical risk (1,2). Since the first transcatheter aortic valve implant nearly 16 years ago, the incidence of severe adverse events following TAVR has been greatly reduced due to improvements in technology, implanter experience, and the utilization of local heart teams for patient selection. The adoption of multidisciplinary heart teams for selecting patients suitable for TAVR allows centralized decision making and also provides a vehicle for tracking the latest recommendations for procedural and postoperative care (3).

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Clinical outcomes from routine practice provide insight into the use of TAVR by including experience with new transcatheter heart valves (THVs) and the evolution of patient selection in the real world. The Evolut R is a current-generation self-expanding THV (Medtronic, Minneapolis, Minnesota) that can be partially or fully repositioned for accurate valve placement. This valve was first evaluated at 8 centers in a first-in-man study of 60 patients that reported low valve gradients and no death or stroke, and only 3.4% of patients had clinically significant (more than mild) paravalvular leak (PVL) at 30 days (4). In a larger prospective, controlled study of the Evolut R THV in the United States at 23 clinical sites, the mortality rate at 30 days was 2.5%, and 5.3% of patients had clinically significant PVL (5).

Expanding the use of new valves to broader patient populations helps provide important information to implanters and patients on expected outcomes. The FORWARD (CoreValve Evolut R FORWARD) study was designed to investigate the safety and effectiveness of the Evolut R THV in routine clinical practice. Our initial paper reported good safety and effectiveness at 30 days, with a mortality rate of 1.9% and clinically significant PVL in 1.9% of patients (6). Reports of outcomes beyond 30-day follow-up and in larger patient groups are lacking. Here, we report the 1-year outcomes from the FORWARD study.

METHODS

STUDY DETAILS. The FORWARD study is a prospective, single-arm, multicenter, international, observational post-market study carried out at 53 centers on 4 continents, the details of which have been previously reported (6). The objective of this study was to document the use of the Evolut R THV in patients considered for nonurgent TAVR for severe, symptomatic aortic stenosis or a failed aortic bioprosthesis in routine practice.

Study monitoring, in a risk-based process, was performed at a minimum for all patient consent documentation and primary- and secondary-related endpoints, as well as study-defined adverse events by the sponsor (Medtronic). Although patients were followed up based on local standard of care, review of patients was recommended at hospital discharge, at 30 days, and annually for at least 3 years.

An independent Clinical Events Committee adjudicated Valve Academic Research Consortium-2 serious adverse events (7). Post-procedural transthoracic echocardiographic assessments were performed at discharge and 1 year. Investigational sites were instructed to follow a standardized protocol for acquisition of echocardiographic endpoint data, and an independent echocardiographic core laboratory (Mayo Clinic, Rochester, Minnesota) centrally assessed all echocardiogram studies. The Declaration of Helsinki principles were followed, and all patients signed an informed consent or data release form.

STUDY DEVICE. The Evolut R THV is a self-expanding supra-annular porcine pericardial valve within a Nitinol frame that can be implanted using a 14-F equivalent EnVeo R InLine Sheath (Medtronic) in access vessels with a diameter ≥5.0 mm. A 23-, 26-, or 29-mm valve was available to accommodate aortic annuli of 18 to 26 mm in diameter as determined from multislice computed tomography (MSCT). Details of the implant procedure have been previously reported (4). Implanter experience was required and defined as having performed at least 50 procedures with a Medtronic self-expanding THV, of which at least 10

ABBREVIATIONS AND ACRONYMS

MSCT = multislice computed tomography

NYHA = New York Heart Association

PPI = permanent pacemaker implantation

PVL = paravalvular leak

STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality

TAVR = transcatheter aortic valve replacement

THV = transcatheter heart valve

stock options from Claret Medical; and has received grant support from Medtronic and Claret Medical. Dr. Scholtz has received honoraria and travel expense reimbursements from Medtronic. Dr. Chevalier has served as a consultant and proctor for Medtronic. Dr. Gooley has served as a proctor for Medtronic and a proctor and consultant for Boston Scientific. Ms. Zeng is an employee and shareholder of Medtronic. Dr. Oh has received research support for the echocardiographic core laboratory from and served as a consultant for Medtronic. Prof. Grube has served as a consultant for Medtronic.

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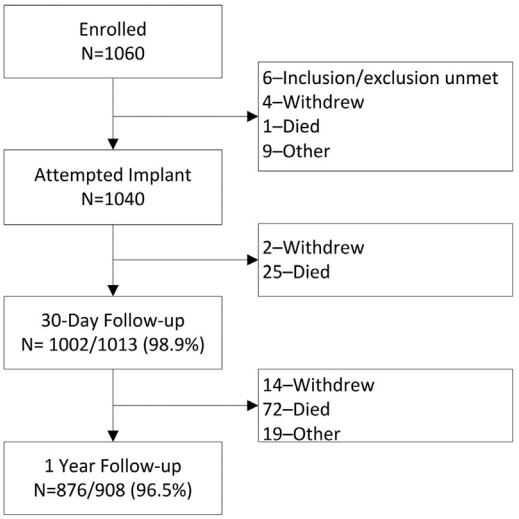
FIGURE 1 Patient Disposition Through 1 Year



Patient follow-up through 1 year; 96.5% of patients eligible completed the 1-year follow-up in this real-world study. Exits and deaths are reported for the 1-year follow-up window of 365 to 425 days post-procedure.

TABLE 1 Demographics and Baseline Clinical Characteristics for the Attempted Implant Patient Cohort (N = 1,040)*

Age, yrs	81.8 ± 6.2
Body surface area, m^2	1.8 ± 0.2
Female	674 (64.8)
Society of Thoracic Surgeons Predicted Risk of Mortality, %	5.5 ± 4.5
EuroSCORE II, %	5.7 ± 5.0
Logistic EuroSCORE, %	17.3 ± 11.6
NYHA functional class	
I	14 (1.4)
II	275 (26.6)
III	659 (63.8)
IV	85 (8.2)
Diabetes mellitus	308 (29.6)
Serum creatinine >2 mg/dl	56 (5.6)
Chronic lung disease/chronic obstructive pulmonary disease	267 (26.3)
Peripheral artery disease	236 (22.8)
Cerebrovascular disease	176 (17.0)
Previous coronary artery bypass grafting	111 (10.7)
Previous percutaneous coronary intervention	289 (27.9)
Previous myocardial infarction	157 (15.3)
Atrial fibrillation	357 (34.5)
Other comorbidities and medical history	
Porcelain aorta†	50 (4.8)
Severely atherosclerotic aorta†	116 (11.2)
Frailty‡	354 (34.2)
Pulmonary hypertension	457 (46.1)
Left ventricular ejection fraction, %	60.6 ± 12.0
Pre-existing permanent pacemaker or defibrillator	127 (12.2)
Assisted living	158 (15.3)

Values are mean ± SD or n (%) that reflect missing values. *Since our initial report in 1,038 patients, consent was lost for 1 patient and consent was validated in 3 patients; therefore, we now report on 1,040 patients. †Heavy circumferential calcification or severe atheromatous plaques of the entire ascending aorta extending to the arch such that aortic cross-clamping is not feasible. ‡Per Valve Academic Research Consortium-2 (7).

EuroSCORE = European System for Cardiac Operative Risk Evaluation; NYHA = New York Heart Association.

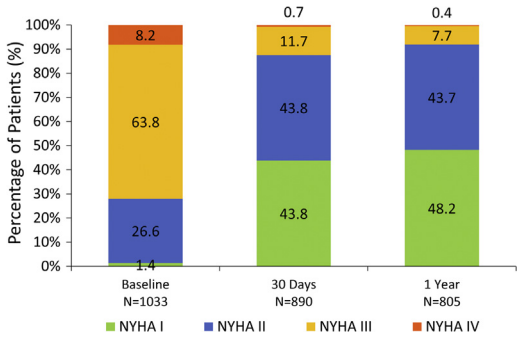
included the Evolut R valve. Because this study was designed to document the use of TAVR in routine practice, anatomical feasibility and valve selection were based on the manufacturer's Instructions for Use.

PATIENTS. The study cohort comprised patients with symptomatic native aortic valve stenosis or a failed surgical bioprosthetic valve requiring replacement at high or greater surgical risk who were considered for elective TAVR. Patient selection details have been previously reported (6). Local heart teams comprising interventional cardiologists and cardiac surgeons determined patient eligibility. All patients underwent gated MSCT for screening and valve size selection.

STUDY ENDPOINTS. The primary endpoint was 30-day all-cause mortality and has been previously reported (6). Secondary endpoints included hemodynamic assessment of the aortic valve at 1 year, as well as 1-year rates of death, stroke, bleeding, major vascular complications, coronary artery obstruction, and valve-related dysfunction requiring repeat procedure.

STATISTICAL ANALYSIS. The primary analysis group for this report comprised all patients who underwent attempted implant of the Evolut R THV. Follow-up duration is reported as median (interquartile range). Continuous variables are presented as mean ± SD and categorical variables are presented as frequency and percentage. Hemodynamic assessments were analyzed for implanted patients. Paired PVL data are reported for patients with echocardiographic assessment at both discharge and at 1 year and compared using the chi-square test. Event rates are reported as Kaplan-Meier estimates. Baseline and procedural characteristics were used to perform a univariable and multivariable Cox proportional hazards model to determine predictors of 1-year mortality. Univariable predictors with a $p < 0.20$ were entered into the model and stepwise multivariable analyses performed. Kaplan-Meier estimates were used for the

FIGURE 2 NYHA Functional Class



New York Heart Association (NYHA) functional class at baseline, 30 days, and 1 year.

TABLE 2 Serial Echocardiographic Findings

	Baseline (n = 962)*	Discharge (n = 972)*	1 Year (n = 662)*
Mean AV gradient, mm Hg	41.8 ± 16.1 (915)	8.5 ± 5.6 (868)	8.1 ± 4.2 (635)
Max AV velocity, m/s	4.0 ± 0.8 (914)	1.9 ± 0.5 (869)	1.9 ± 0.4 (635)
Aortic valve area, cm^2	0.8 ± 0.3 (631)	1.9 ± 0.6 (541)	1.9 ± 0.6 (454)
LV ejection fraction, %	60.6 ± 12.0 (872)	62.4 ± 10.9 (892)	62.1 ± 9.9 (626)
Total aortic regurgitation	822	826	593
None	141 (17.2)	159 (19.4)	222 (37.4)
Trace	359 (43.7)	394 (47.7)	239 (40.3)
Mild	285 (34.7)	256 (31.0)	125 (21.1)
Moderate	29 (3.5)	15 (1.8)	7 (1.2)
Severe	8 (1.0)	1 (0.1)	0 (0.0)
Paravalvular regurgitation		813	587
None	NA	170 (20.9)	232 (39.5)
Trace	NA	375 (46.2)	224 (38.2)
Mild	NA	251 (30.9)	124 (21.1)
Moderate	NA	15 (1.9)	7 (1.2)
Severe	NA	1 (0.1)	0 (0.0)

Values are mean ± SD (patients with specific measurements) or patients (percent of evaluable echocardiograms).
*Number of echocardiograms.
LV = left ventricular; NA = not applicable; V = aortic valve.

time to event analyses and were compared using the log-rank test. For patients without an event, the date of censoring was the latest date of all follow-up visits, assessments, and events. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

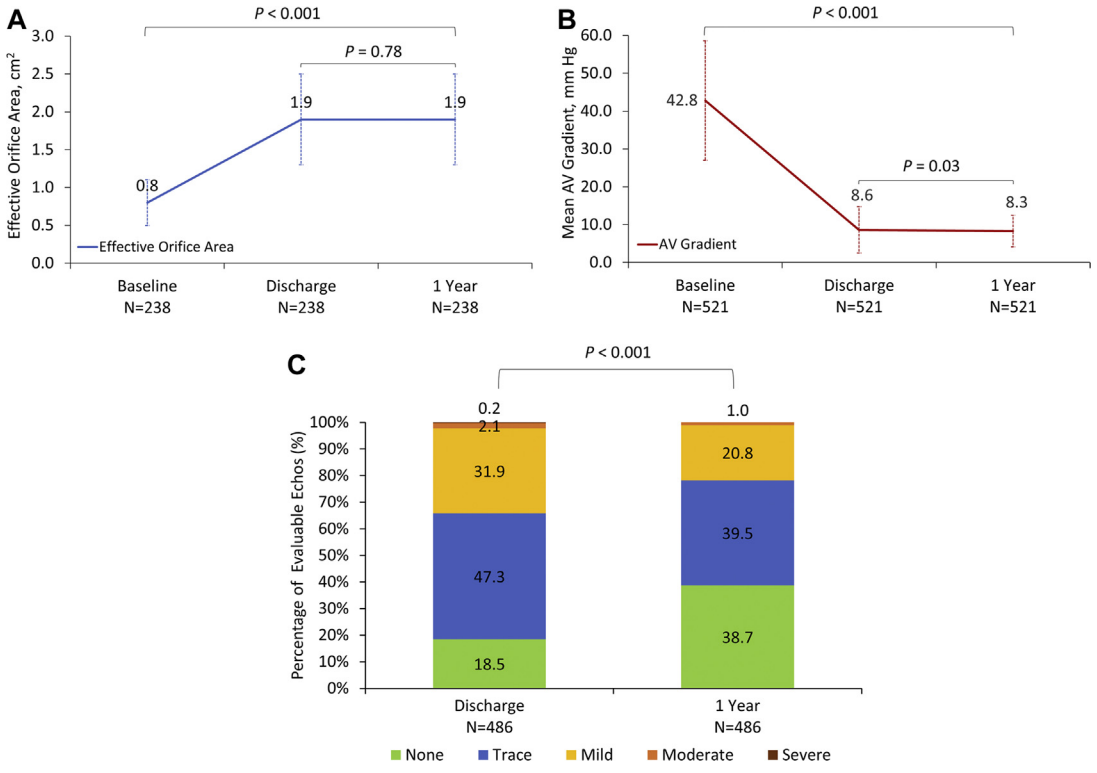
PATIENTS. Between January 2016 and December 2016, 1,040 patients underwent attempted implant of the Evolut R THV at 53 centers in 20 countries (Figure 1). All follow-up visits and adverse events occurring through February 7, 2018, are included in this report. Median follow-up was 12.5 months (interquartile range: 12.0 to 13.5 months). Baseline characteristics and medical history are found in Table 1. The mean age was 81.8 ± 6.2 years, 64.8% were women. They had multiple comorbidities with a mean Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score of 5.5 ± 4.5% (median 4.1%) and a EuroSCORE II score of 5.7 ± 5.0% (median 4.1%). The majority of patients (72.0%) had New York Heart Association (NYHA) functional class III or IV symptoms at baseline (Figure 2), and frailty was noted in 34.2% of patients.

PROCEDURAL CHARACTERISTICS. Nearly all patients (98.0%) were treated via a transfemoral approach, and 65.1% were implanted using local anesthesia and conscious sedation. Other access routes included the subclavian artery (1.6%), direct aortic (0.3%), surgical femoral artery cutdown (n = 1), and carotid artery (n = 1). A total of 1,026 patients received the Evolut R THV, of which 1,016 (99.0%) were successfully implanted in the correct anatomical position. The 23-mm valve was implanted in 62 (6.0%) patients, the 26 mm in 375 (36.5%) patients and the 29 mm in 589 (57.4%) patients. Pre-TAVR balloon valvuloplasty was performed in 476 (45.8%) patients, and a post-TAVR balloon valvuloplasty was performed in 344 (33.4%) patients.

Repositioning to optimize implant characteristics, a feature of the resheathable Evolut R THV, was used in 25.8% of patients and was completed successfully in 99.2% of patients. Of the 1,040 patients who underwent attempted implant, 50 (4.8%) were treated for a failed bioprosthetic valve, and an embolic protection device was used in 43 (4.1%) patients.

VALVE HEMODYNAMICS. A 1-year echocardiogram for core laboratory assessments of aortic valve hemodynamics was available in 676 of 908 available patients (74.4%). Aortic valve hemodynamics improved immediately post-procedure and were sustained through 1 year (Table 2). The mean gradient at 1 year was 8.1 ± 4.2 mm Hg and the mean effective orifice area was 1.9 ± 0.6 cm^2. Mild or less PVL was present in 98.8% of patients, and no patients had severe PVL. Assessment of PVL at 1 year was available for 11 of the 16 patients who had significant PVL (more than mild) at discharge, of which 9 had improved. Figure 3 shows a significant improvement in mean aortic valve gradient ($p = 0.03$) and PVL ($p < 0.001$) from discharge to 1 year in patients with data available at both time points.

FIGURE 3 Paired Hemodynamic Assessments to 1 Year



Core laboratory assessment of aortic valve (AV) hemodynamic measurements for patients with data at baseline (except for paravalvular leak), discharge, and 1 year: **(A)** effective orifice area, **(B)** mean gradient, and **(C)** paravalvular leak. The p value is based on chi-square test for paravalvular leak and based on the paired *t* test for mean gradient and effective orifice area. Error bars in **A** and **B** represent SD.

1-YEAR OUTCOMES. Clinical outcomes at 30 days and 1 year are shown in Table 3. Since our previous report of 30-day outcomes (6), 69 patients died, for a 1-year all-cause mortality rate of 8.9% and a cardiovascular mortality rate of 6.9%. Cardiac decompensation was the most common cause of cardiovascular mortality, and cancer was the most common cause of noncardiovascular mortality. Figure 4 shows Kaplan-Meier estimates of 1-year mortality stratified by the median EuroSCORE II (Figure 4A) and STS-PROM (Figure 4B). An additional 6 patients experienced a stroke, resulting in a 1-year stroke rate of 3.4%, and 3 patients had a disabling stroke to 1 year (2.1%). Of the 3 patients who had a disabling stroke since the 1-month follow-up, 1 patient died. A pacemaker was implanted in 19.7% of patients by 1 year. Post-procedural (within 30 days) new permanent pacemaker implantation (PPI) had no impact on 1-year mortality (6.9% with new PPI vs. 9.4% without new PPI; p = 0.27). There were no incidences of valve thrombosis or annular rupture reported.

Between 30 days and 1 year, 2 patients had a major vascular complication. In 1 patient, it was due to femoral artery stenosis and the other was due to arterial bleeding; both events were treated surgically. One further patient presented with clinical evidence of coronary ischemia, requiring coronary artery bypass surgery.

Valve-related dysfunction requiring repeat procedure was reported in 2 patients since the 1-month report (Table 3). One patient was hospitalized for worsening heart failure 6 months post-procedure during which a balloon dilation of the Evolut R valve was performed for aortic regurgitation, the other patient had intermittent systolic anterior motion of the mitral valve and underwent explant of the THV and surgical implantation of aortic and mitral bioprostheses.

PREDICTORS OF MORTALITY. Univariable and multivariable predictors of 1-year mortality are reported in Table 4. Baseline and procedural variables were included in the model. The strongest multivariant predictors of 1-year mortality were the

TABLE 3 Outcomes Through 1 Year

	30 Days	1 Year
All-cause mortality or disabling stroke		
All-cause mortality	20 (1.9)	89 (8.9)
Cardiovascular	19 (1.8)	69 (6.9)
Myocardial infarction	8 (0.8)	18 (1.8)
All stroke	29 (2.8)	35 (3.4)
Disabling stroke	18 (1.7)	21 (2.1)
Nondisabling	11 (1.1)	14 (1.4)
TIA	4 (0.4)	11 (1.1)
Valve embolization or migration	10 (1.0)	10 (1.0)
Valve-related dysfunction requiring repeat procedure	7 (0.7)	9 (0.9)
Valve thrombus	0 (0.0)	0 (0.0)
Coronary artery obstruction	0 (0.0)	1 (0.1)
Endocarditis	1 (0.1)	5 (0.5)
Major vascular complication	72 (6.9)	74 (7.1)
Life-threatening or disabling bleeding	38 (3.7)	43 (4.2)
Major bleeding	64 (6.2)	67 (6.5)
Permanent pacemaker implanted*	184 (17.8)	202 (19.7)
Permanent pacemaker implanted†	183 (20.2)	199 (22.1)

Values are n (Kaplan-Meier rate to 365 days). *Including patients implanted pacemakers or implantable cardioverter-defibrillators at baseline. †Excluding patients with implanted pacemakers or implantable cardioverter-defibrillators at baseline.

TIA = transient ischemic attack.

presence of renal disease, decreased body mass index, and diabetes at baseline, followed by length of hospital stay and major vascular complication within 30 days post-procedure. Significant PVL was not tested in our predictor model as all of the patients with moderate (n = 15) or severe (n = 1) PVL at discharge were still living at 1 year.

FUNCTIONAL STATUS. NYHA functional class at each follow-up is shown in **Figure 2**. At 30 days, 76.7% of patients reported an improvement in NYHA functional class, 22.0% reported no change, and 1.2% reported worsening. At the 1-year follow-up, 80.5% of patients reported improvement in NYHA functional class compared with baseline, 18.5% reported no change, and 8 (1.0%) patients reported worsening of symptoms. None of the patients with worsening symptoms had more than mild PVL, 1 patient had chronic lung disease, 4 had a new pacemaker implanted following TAVR, and 1 patient had a pre-existing pacemaker.

DISCUSSION

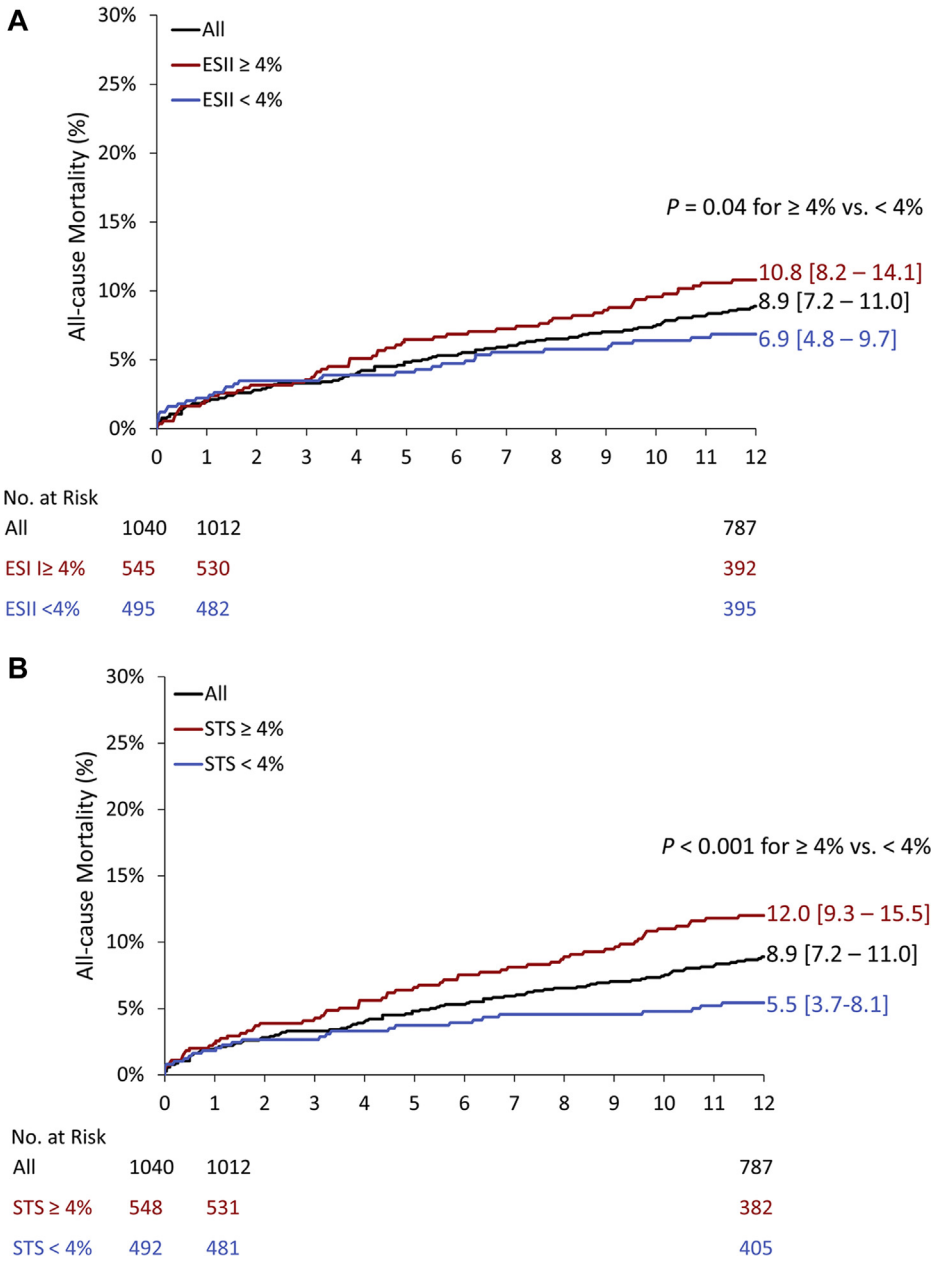
We report 1-year follow-up from the largest prospective registry evaluating the Evolut R THV in routine practice. The key findings include low 1-year mortality of 8.9% (mostly due to cardiovascular causes) in patients considered at elevated risk; low 1-year rate of disabling stroke of 2.1%, with only 3 additional events after 30 days post-procedure; and excellent aortic valve hemodynamics, with low mean gradients of 8.1 ± 4.2 mm Hg maintained to 1-year follow-up. These results are based on independent Clinical Events Committee-adjudicated adverse advents and echocardiographic core laboratory assessments.

SAFETY. The low 1-year mortality rate of 8.9% observed in this all-comer, real-world, international trial was consistent with the 1-year rate of 8.6% in 241 high-risk patients (STS mean of 7.4%) from the Evolut R U.S. study (8). Mortality at 1 year was significantly higher in patients at increased risk (STS-PROM or EuroSCORE II ≥4%) as defined by the recent European Society of Cardiology guidelines (2). The 1-year mortality rates reported with the next-generation Evolut R device are lower than that reported from its predecessor, the CoreValve bioprosthesis, of 24.3% in an extreme-risk group (n = 489) (9), 17.9% in the CoreValve ADVANCE study (n = 1,015) (10), and 14.2% in a high-risk group (n = 390) (11). The large SOURCE (Observational Study to Evaluate Safety and Performance of SAPIEN 3 THV System in Real Life Practice) 3 registry (n = 1,949) (12), investigating the next-generation SAPIEN 3 device (Edwards Lifesciences, Irvine, California), the REPRISE II (REpositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus™ Valve System) study (n = 120) (13) investigating the Lotus device (Boston Scientific, Marlborough, Massachusetts), and the Portico TAVI (Portico TAVI Implant With Transfemoral Delivery System) study (n = 209) (14) (Abbott Vascular, Santa Clara, California) reported mortality at 1 year of 12.6%, 10.9%, and 13.8%, respectively.

The incidence of disabling stroke at 1 year of 2.1% in our study was lower than the 5.1% reported in the Evolut R U.S. study (8), and both studies utilized Valve Academic Research Consortium-2 definitions (7). The U.S. trial enrolled patients in 2014 to 2015, and the much larger FORWARD study was performed in experienced centers during 2016. The incidences of disabling stroke at 1 year in the SOURCE 3 registry, the REPRISE II study, and the Portico TAVI study were 1.4%, 3.4%, and 5.8%, respectively (12–14). There were no incidences of valve thrombosis or annular rupture observed in the FORWARD study.

Baseline renal disease and index hospitalization duration predicted 1-year mortality in FORWARD similar to that reported from the SOURCE 3 registry using the latest-generation balloon expandable heart valve (13). Larger body mass index had a weak, but significant protective effect. Standardized risk scores

FIGURE 4 All-Cause Mortality to 1 Year Stratified by Risk Score



Kaplan-Meier estimates of all-cause mortality to 1 year for all patients and stratified by **(A)** EuroSCORE II (ESII) and **(B)** Society of Thoracic Surgeons (STS) Predicted Risk of Mortality scores. 95% confidence intervals shown in **brackets**. Log-rank p values are reported.

(STS-PROM or EuroSCORE II), NYHA functional class at baseline, and acute kidney injury post-TAVR were not associated with 1-year mortality. Contrary to previous reports, grade 2 or higher PVL post-TAVR was not associated with 1-year mortality (15); in fact, in the FORWARD study, all 16 patients with more than mild PVL at discharge (moderate = 15, severe = 1), were alive at the 1-year follow-up. Echocardiographic assessment of PVL was available at 1 year in 11 of these patients at 1 year, of which 9 showed improvement.

The overall low events observed in this study are most likely due to technical improvements of the Evolut R device, supported by mandated use of the heart team for patient selection, routine use of MSCT

for procedural planning and improved TAVR experience of the centers.

HEMODYNAMICS. All echocardiographic measures of valve function in the FORWARD study were based on core laboratory assessments. The supra-annular functioning leaflets of the Evolut R device in our study may have contributed to the low mean aortic valve gradient of 8.1 mm Hg at 1 year, which is consistent with previous reports of the same valve (8,16). This compares favorably with 1-year mean valve gradients of other repositionable valves: 12.6 mm Hg reported with the Lotus valve (13) and 8.4 mm Hg with the Portico valve (14). The mean gradient at 1 year with the SAPIEN 3 balloon-expandable valve in the SOURCE 3 registry was 12.3 mm Hg (12). The mean effective orifice area in our study was 1.9 cm^2 and larger than previously reported with other repositionable and balloon-expandable valves (12–14).

In the FORWARD study, 98.8% of patients had mild or less PVL at 1 year, with no patients having severe PVL. Additionally, paired analysis showed a significant decrease in the severity of PVL from discharge to 1 year (**Figure 3C**), consistent with that reported with the earlier-generation CoreValve self-expanding valve (17). This change was attributed to gradual remodeling and continued expansion of the valve. Our study reported an incidence of no or trace PVL of 78.2% at 1 year, consistent with other reports of the Evolut R valve (76.6%) (8) and comparable to a site-reported rate of 71.6% in the transfemoral cohort from the SOURCE 3 registry (12). The proportion of patients with no or trace PVL at 1 year in the REPRISE II study was higher at 88.7% with the Lotus valve (13) and lower in the Portico TAVI study (48.3%) (14) than in our study.

PACEMAKERS. By 1 year, a permanent pacemaker was implanted in 19.7% of patients, of which 18 patients received a pacemaker since the 30-day report. This is lower than reported with the Lotus self-expanding valve (13,18) and higher than reported from the SAPIEN 3 registry (12). Our results improved on the 1-year pacemaker rates in high-risk patients of 22.3% to 29.2% in randomized and real-world trials with the predicate CoreValve THV (10,11). The reduced rate may be due to the ability to reposition the Evolut R THV for optimal placement.

STUDY LIMITATIONS. The primary limitations in the FORWARD study are that this report is based on local clinical practices and the local heart team evaluated all patients for TAVR eligibility, potentially introducing selection bias. As patient follow-up was based on typical clinical treatment, the quality of some echocardiograms was suboptimal, resulting in a low yield in some echocardiographic parameters. However, an echocardiogram at 1-year follow-up for core laboratory assessment was available in 74.4% of available patients, greater than reported in other real-world trials. The small number of patients treated for a failed surgical bioprosthesis limits the ability to draw any firm clinical conclusions. The results of the FORWARD study, however, with the utilization of an independent Clinical Events Committee and echocardiography core laboratory, provides unbiased verification of the results and reflects current TAVR practices.

TABLE 4 Univariable and Multivariable Predictors of 1-Year Mortality

	Univariable		Multivariable	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Baseline characteristics				
Female	1.01 (0.66–1.57)	0.95		
Body mass index (per 1.0 kg/m^2)	0.95 (0.91–1.00)	0.04	0.90 (0.84–0.95)	<0.001
NYHA functional class III	1.38 (0.87–2.17)	0.17		
NYHA functional class IV	1.14 (0.55–2.36)	0.72		
Logistic EuroSCORE (per 1.0%)	1.02 (1.00–1.03)	0.02		
Logistic EuroSCORE ≥20%	1.31 (0.85–2.02)	0.21		
STS-PROM >5%	2.04 (1.34–3.10)	<0.001		
Previous MI	1.23 (0.71–2.12)	0.46		
Chronic lung disease (COPD)	1.77 (1.15–2.71)	0.009		
Diabetes mellitus	1.94 (1.27–2.95)	0.002	2.47 (1.46–4.17)	<0.001
Atrial fibrillation at baseline	1.61 (1.06–2.44)	0.03		
Serum creatinine >2 mg/dl	2.23 (1.15–4.31)	0.02	2.92 (1.46–5.82)	0.002
Implanted cardiac device	1.07 (0.57–2.02)	0.83		
LVEF by visual estimate (per 1.0%)	1.00 (0.98–1.02)	0.96		
LVEF ≤35%	1.09 (0.47–2.51)	0.85		
Mean aortic gradient (per 1 mm Hg)	0.99 (0.97–1.00)	0.06		
Procedural characteristics				
Anesthesia local vs. general	1.25 (0.79–1.96)	0.34		
Iliofemoral access	0.96 (0.24–3.89)	0.95		
Resheathing/recapture feature used	0.84 (0.51–1.38)	0.48		
Post-procedural characteristics				
Acute kidney injury within 7 days	5.71 (2.49–13.11)	<0.001		
Days from implant to discharge (per day)	1.05 (1.04–1.07)	<0.001	1.05 (1.03–1.06)	<0.001
Major vascular complications within 30 days	3.76 (2.21–6.37)	<0.001	2.26 (1.11–4.59)	0.03
New PPI within 30 days	0.73 (0.39–1.34)	0.31		

Univariable data with a $p < 0.20$ were entered into the multivariable stepwise Cox proportional hazards model.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PPI = permanent pacemaker implantation; PVL = paravalvular leak; STS-PROM = Society of Thoracic Surgery Predicted Risk of Mortality.

CONCLUSIONS

The 1-year results of the FORWARD multinational, multicenter study supports the safety and

effectiveness of the next-generation Evolut R THV device in treating elderly, high-risk patients with severe aortic stenosis and elevated operative risk in routine clinical practice. Longer-term follow-up is required to support routine use in lower-risk and other subsets of aortic valve disease patients.

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PERSPECTIVES

WHAT IS KNOWN? The novel resheathable, repositionable, supra-annular Evolut R valve investigated in the FORWARD study demonstrated good safety and efficacy profile up to 30-day follow-up, with all-cause mortality of 1.9% and mean aortic valve gradient of 8.5 ± 5.6 mm Hg. Longer-term safety and efficacy follow-up and the impact of resheathability is not known.

WHAT IS NEW? At 1 year, the all-cause mortality rate was low at 8.9%, with the incidence of disabling stroke of 2.1%, and the incidence of more than mild PVL was 1.2%. These longer-term results support the safety and efficacy of the Evolut R valve.

WHAT IS NEXT? TAVR is increasingly being used to treat lower-risk patients—longer-term follow-up (5 years and over) will be required to ensure safety.

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KEY WORDS FORWARD, self-expanding valve, transcatheter aortic valve implantation, transcatheter aortic valve replacement, transfemoral