Received: 17 May 2021 | Revised: 21 June 2021 | Accepted: 12 July 2021

DOI: 10.1002/ccd.29889

ORIGINAL STUDIES

WILEY

EDITORIAL COMMENT: Expert Article Analysis for:
Serious adverse events related to transcatheter aortic valve replacement are infrequent: FORWARD 3-years

Final 3-year clinical outcomes following transcatheter aortic valve implantation with a supra-annular self-expanding repositionable valve in a real-world setting: Results from the multicenter FORWARD study

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Abstract

Objectives: The Evolut R FORWARD study confirmed safety and effectivenesss of the Evolut R THV in routine clinical practice out to 1 year. Herein, we report the final 3-year clinical follow up of the FORWARD study.

Background: Transcatheter aortic valve replacement (TAVR) is a proven alternative to surgery in elderly patients with symptomatic severe aortic stenosis. Long-term clinical outcome data with the Evolut R platform are scarce.

Methods: FORWARD is a prospective multicenter observational study that evaluated the Evolut R system in routine clinical practice at 53 centres. Eligible patients had symptomatic native aortic valve stenosis or failed surgical aortic bioprosthesis and elevated operative risk per Heart-Team assessment. TAVR was attempted in 1039 patients.

Results: Mean age was 81.8 ± 6.2 years, 64.9% were women, STS score was 5.5 ± 4.5% and 34.2% were frail. Rates of all-cause mortality and disabling stroke were 24.8% and 4.8% at 3 years. Early need for a new pacemaker implantation after TAVR (all-cause mortality: with new PPI; 21.0% vs. without; 22.8%, $p = 0.55$) and the presence of > trace paravalvular regurgitation (all-cause mortality: no or trace; 22.0% vs. ≥ mild; 25.5%, $p = 0.29$) did not affect survival. Between 1 and 3 years incidence rates of valve related intervention, endocarditis and clinically relevant valve thrombosis were low.

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Funding information
Medtronic funded the FORWARD study

Conclusions: The Evolut R valve maintained a favorable safety profile through 3 years in routine clinical practice. Rates of transcatheter heart valve-related adverse events were low.

KEYWORDS
safety outcomes, self-expanding, supra-annular, transcatheter aortic valve implantation, transcatheter aortic valve replacement.

1 | INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has become a proven alternative to surgical aortic valve replacement (SAVR) for elderly patients with symptomatic severe aortic stenosis.[1] Transcatheter heart valve (THV) iterations introduced sealing fabric, repositioning features and smaller profile to mitigate the risks of paravalvular regurgitation (PVR), conduction disorders and access-site complications. Safety and short-term performance of next generation THV platforms in clinical practice have been well documented, but clinical outcomes beyond 1-year are scarce. Recent randomized trials reported favorable 1- and 2-year outcomes with next generation TAVR versus SAVR in younger patients at low operative risk and with a relatively long life expectancy.[2,3] In this context preserved clinical benefit beyond the first year after the index TAVR procedure becomes crucial for its growing adoption in clinical practice. The Evolut R FORWARD study confirmed safety and effectivenesss of the Evolut R THV in routine clinical practice out to 1 year.[4,5] Herein, we report the final 3-year clinical follow up of the FORWARD study.

2 | METHODS

2.1 | Study details and patients

FORWARD is a prospective, multicenter, multinational, single-arm study that evaluated the clinical and device performance of the Evolut R system (Medtronic, Minneapolis, Minnesota) used in routine clinical practice. Eligible patients were recruited from 53 centres in 20 countries and had symptomatic severe native aortic valve stenosis or a failing (through stenosis, regurgitation or combined) surgical aortic bioprosthesis. Patient risk stratification and selection was based on local heart-team assessment. Complete study details have been previously reported.[4,5] Patients were followed at discharge, and 1-, 2-, and 3 years post-procedure. Echocardiographic assessments were collected up to 1 year.

2.2 | Study device

The Evolut R THV has a self-expanding nitinol frame with supra-annular functioning porcine leaflets and is repositionable and fully retrievable after partial deployment. It is introduced via a 14F equivalent EnVeo R InLine Sheath to accommodate arterial vessels ≥5.0 mm. In the FORWARD study, the Evolut R valve was available in 23-, 26-, and 29-mm sizes to treat aortic valve diameters of 18–26 mm. Valve selection was based on computed tomography (CT) sizing per manufacturer's instructions for use.

2.3 | Study procedures

Medtronic personnel performed risk-based monitoring that included 100% review of all patient consent forms, study endpoints and study-specific adverse events. Adverse events were adjudicated by a clinical events committee using Valve Academic Research Consortium 2 definitions.[6] Echocardiographic assessments were performed at baseline, discharge and 1 year and centrally assessed by an echocardiographic core laboratory (Mayo Clinic, Rochester, MN). The FORWARD study followed the Declaration of Helsinki principles and signed informed consent or data release form was received from all patients.

2.4 | Endpoints

The primary endpoint of the FORWARD study was all-cause mortality at 30 days and has been previously reported.[4] Secondary endpoints include annual assessments of quality of life per the New York Heart Association (NYHA) classification and adverse events to 3 years.

2.5 | Statistical analysis

The primary analysis cohort for this report comprised patients who underwent attempted implant of an Evolut R valve. Continuous variables are reported as mean and standard deviation and categorical variables are reported as counts and frequencies. Adverse event rates are reported as Kaplan–Meier (KM) estimates. KM estimates of mortality for patients with and without a new permanent pacemaker implantation (PPI) within 30 days post procedure were compared using the log-rank test. For this comparison, patients with a prior PPI, and patients who died within 30 days were excluded. KM estimates of mortality for patients stratified by the severity of PVR at discharge, for which day zero was set to the date the PVR was assessed, were compared using the log-rank test. KM estimates of adverse events for

men and women were also compared using the log-rank test. Landmark KM analyses of death, stroke and new PPI including all patients alive, still participating in the study, and event-free at each start point (baseline, 1- and 2 years) were performed. Baseline and procedural variables were considered for selection for a multivariable Cox proportional hazards model of mortality. Frailty, moderate or severe PVR at discharge and a new PPI within 30 days were forced into the model. Univariable predictors of mortality with p values ≤0.20 and with no more than 10% missing data were selected and stepwise multivariable analyses were performed with a significance level of 0.15 for entry and exit of independent variables. A p value <0.05 was considered significant. Patients with a baseline pacemaker or who died or exited the study within 30 days were excluded from the model. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

3.1 | Patients

A total of 1039 patients underwent attempted TAVR with the Evolut R valve (Figure 1). Baseline characteristics are shown in Table 1. The mean age was 81.8 ± 6.2 years and 674 patients (64.9%) were female. The mean Society of Thoracic Surgeons (STS) score was 5.5% ± 4.5%, 743 (72%) had NYHA class III/IV symptoms and frailty was present in 354 patients (34.2%). TAVR was performed for a failing surgical aortic bioprosthesis in 50 patients (4.8%).

3.2 | Clinical outcomes

Clinical outcomes to 3 years are shown in Table 2. All-cause mortality was 24.8%, cardiovascular mortality was 16.4% and the disabling

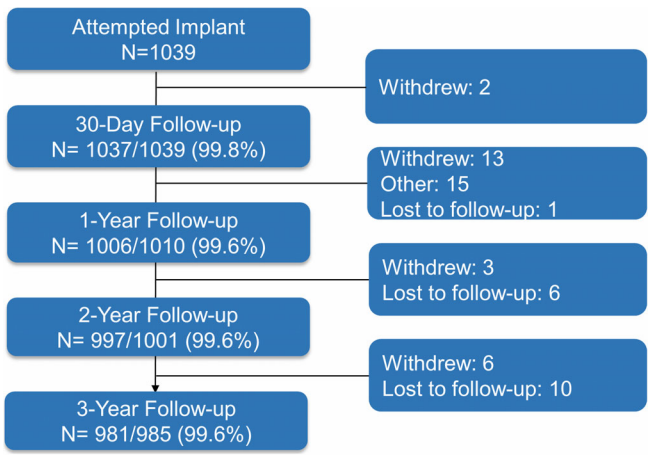

FIGURE 1 Patient dispositionNumber of patients with completed follow-up as a proportion of the number of patients with expected follow-up. Patients who died were not lost to follow-up and counted as known status for each time point [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Baseline characteristics for all patients and for patients with a failed surgical bioprosthesis

Characteristic	All patients $N = 1039$	Patients with failed surgical bioprosthesis[a] $N = 50$
Age, years	81.8 ± 6.2	78.0 ± 8.3
Body surface area, m^2	1.8 ± 0.2	1.9 ± 0.2
Female	674 (64.9)	15 (30.0)
STS score, %	5.5 ± 4.5	5.1 ± 3.3
EuroSCORE II, %	5.7 ± 5.0	9.8 ± 7.0
NYHA functional class		
I	14 (1.4)	0 (0.0)
II	275 (26.6)	4 (8.0)
III	658 (63.8)	43 (86.0)
IV	85 (8.2)	3 (6.0)
STS risk factors		
Prior myocardial infarction	157 (15.3)	10 (20.0)
Prior percutaneous coronary intervention	289 (27.9)	15 (30.0)
Prior coronary artery bypass grafting	111 (10.8)	15 (30.0)
Prior aortic valve	50 (4.8)	50 (100)
History of atrial fibrillation	358 (34.6)	16 (32.0)
Diabetes mellitus	308 (29.7)	8 (16.0)
Serum creatinine >2 mg/dl	56 (5.6)	2 (4.1)
Dialysis	27 (2.6)	1 (2.0)
Chronic lung disease/ COPD	267 (26.4)	11 (23.4)
Peripheral artery disease	236 (22.8)	9 (18.0)
Cerebrovascular disease	177 (17.1)	9 (18.0)
Other comorbidities and medical history		
Porcelain aorta[b]	50 (4.8)	0 (0.0)
Moderate or severe LVOT calcification[c]	128 (17.7)	2 (6.5)
Frailty[d]	354 (34.2)	7 (14.3)
Pulmonary hypertension[e]	456 (46.0)	28 (59.6)
Left ventricular ejection fraction, %[f]	60.6 ± 11.9	60.9 ± 11.7
Prior pacemaker	127 (12.2)	9 (18.0)
Assisted living	158 (15.3)	3 (6.5)

Note: Data presented as means ± standard deviation or no. (percentage) that reflect missing values.

Abbreviations: COPD, chronic obstructive pulmonary disease; NA, not available; NYHA, New York Heart Association; STS, The Society of Thoracic Surgeons.

[a]A subset of the 1039 patients.

[b]Heavy circumferential calcification or severe atheromatous plaques of the entire ascending aorta extending to the arch such that aortic cross-clamping is not feasible.

[c]Left ventricular outflow tract (LVOT) calcification was available in 724 patients overall and in 31 patients in the prior SAV group.

[d]Primary or secondary pulmonary hypertension with pulmonary artery systolic pressures greater than two-thirds of systemic pressure.

[e]Per Valve Academic Research Consortium-2 definition[6].

[f]By visual estimation.

TABLE 2 Clinical outcomes for all patients through 3 years

	1 year	2 years	3 years
All-cause mortality	91 (8.9)	169 (16.7)	248 (24.8)
Cardiovascular mortality	70 (6.9)	115 (11.6)	158 (16.4)
Stroke	38 (3.7)	50 (5.1)	64 (6.9)
Disabling	23 (2.3)	32 (3.3)	44 (4.8)
Non-disabling	16 (1.6)	19 (1.9)	21 (2.2)
Valve-related dysfunction requiring repeat procedure	9 (0.9)	11 (1.1)	11 (1.1)
Myocardial infarction	19 (1.9)	28 (3.0)	32 (3.5)
Life threatening or disabling bleeding	49 (4.8)	62 (6.2)	66 (6.7)
Valve thrombosis	0 (0.0)	2 (0.2)	2 (0.2)
Valve endocarditis	4 (0.4)	5 (0.5)	8 (0.9)
Permanent pacemaker implanted[a]	203 (19.8)	214 (21.0)	222 (22.0)
Permanent pacemaker implanted[b]	200 (22.2)	211 (23.6)	219 (24.7)

Note: Data presented as no. of patients with an event (Kaplan–Meier estimate).
[a]Includes patients with permanent pacemaker or implantable cardioverter defibrillator at baseline.
[b]Excludes patients with permanent pacemaker at baseline.

stroke rate was 4.8%. Clinical outcomes by sex are shown in Table S1. All-cause mortality was higher for men than women at 3 years (28.6% vs. 22.7%, $p = 0.049$), with no difference in cardiovascular mortality (16.7% vs. 16.2%, $p = 0.866$). Mortality at 3 years was similar for patients who received a new PPI within 30 days post-TAVR as compared to patients that did not (21.0% vs. 22.8%, $p = 0.550$) (Figure 2 (A)). The presence of more than trace PVR was also not associated with mortality (25.5% vs. 22.0%, $p = 0.288$) (Figure 2(B)).

Multivariable predictors of mortality at 3 years are displayed in Table 3. Univariable predictors are show in Table S2. Serum creatinine >2 mg/dl, severely atherosclerotic aorta, pulmonary hypertension, cirrhosis of the liver and not bathing independently (as a particular item of the Katz activites of daily living score) were associated with higher risk of mortality. Pre-TAVR balloon dilation was protective.

Figure 3 illustrates landmark analyses of mortality, stroke and need for new pacemaker. The mortality rate was 8.9% at 1 year, 8.6% from 1 to 2 years and 9.7% from 2 to 3 years. The stroke rates were 3.7%, 1.4%, and 1.8% for the same time intervals, respectively. The need for a new PPI was 22.2%, 1.8%, and 1.5%.

New York Heart Association class was available for 592 patients at both baseline and 3-year follow-up (Figure 4). Improvement in NYHA class occurred in 477 patients (80.6%), no change in 107 (18.1%) and 8 (1.4%) patients had worsening of their symptoms.

A THV-related reintervention was required in 2 patients after 1 year. One patient with an Evolut 26-mm valve had symptomatic severe prosthesis-patient mismatch (effective orifice area [EOA], 0.7 cm^2 mean gradient, 32 mm Hg, stroke volume index, 15 ml/m^2) and received a 23-mm SAPIEN valve (Edwards LifeSciences, Irving, CA) 23 months after the index procedure. A second patient developed mitral valve endocarditis and septic shock 18 months after the index procedure. The patient expired 1 day after complex surgery that included root enlargement and aortic and mitral valve replacement.

There were 4 patients who experienced aortic bioprosthesis endocarditis within the first year after the index procedure and 4 patients between 1 and 3 years, who were all treated medically.

Clinical THV thrombosis occurred in 2 patients, both after TAVR in a failed surgical bioprosthesis. One patient became dyspneic 17 months post-index procedure. Echocardiography revealed a mean AV gradient of 35.1 mm Hg and EOA of 0.59 cm^2. Computed tomography confirmed hypoattenuation and reduced leaflet motion of the 3 valve leaflets. The patient was started on oral anticoagulants and the thrombus resolved as documented by follow-up CT. A second patient developed THV thrombosis 16 months after a complicated index TAVR in which a 26-mm Evolut valve was implanted in a failed surgical valve but dislodged during the index procedure and was treated with a 23-mm balloon-expandable THV. The THV thrombosis was confirmed by CT and the patient was placed on anticoagulation therapy.

Baseline characteristics for the 50 patients who underwent TAVR for a failing surgical aortic bioprosthesis are shown in Table 1. The majority of surgical bioprosthesis sizes were ≤ 23 mm and most received a 23-mm Evolut R valve (Table S3 and S4). All-cause mortality rates were 6.0% at 1 year, 12.0% at 2 years, and 24.3% at 3 years (Table S5). The stroke rate was 8.1% at 1 year without any subsequent events through 3 years. The new PPI rate was 7.4% at 1 year, without any subsequent implants through 3 years. At 3 years NYHA class remained improved in 87.1% of survivors as compared to baseline.

4 | DISCUSSION

This 3-year analysis of the clinical follow up after TAVR with Evolut R in the FORWARD study highlights: (1) longer-term clinical safety and efficacy with Evolut R in elderly patients at intermediate to high operative risk; (2) lack of impact on mortality at 3 years related to the

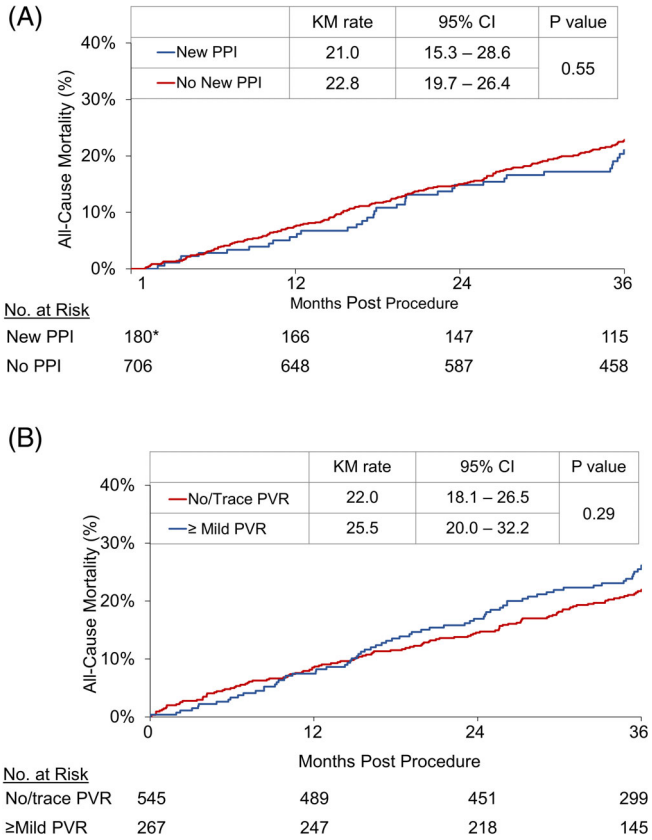

FIGURE 2 All-cause mortality through 3 years for patients with and without a new permanent pacemaker implantation and based on the severity of core-laboratory assessed paravalvular regurgitation measured at discharge.Landmark analysis of all-cause mortality at 3 years for patients with compared to patients without a new permanent pacemaker implantation (PPI) within 30 days post-TAVR (A). *Number of patients at risk at day 31. Patients with a baseline PPI and those who died within 30 days post-procedure were excluded. *p*-value based on log-rank test. Kaplan–Meier estimates of all-cause mortality for patients with no or trace compared with those with mild or more paravalvular regurgitation (PVR) at discharge (B). Day 0 was the date the echocardiogram was performed. *p*-value based on the log-rank test [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Multivariable predictors of mortality from 31 days to 3 years

	HR (95% CI)	*p*-value from Cox proportional hazards model
Frailty at baseline	1.126 (0.788–1.610)	0.530
New PPI within 30 days	0.780 (0.497–1.226)	0.282
≥Mild PVR at discharge	1.131 (0.783–1.634)	0.513
Age, years	1.034 (1.000–1.070)	0.050
STS Score, %	1.027 (0.992–1.063)	0.130
Serum creatinine >2 mg/dl	2.847 (1.642–4.938)	<0.001
Atrial fibrillation	1.376 (0.965–1.962)	0.078
Severely atherosclerotic aorta	1.923 (1.207–3.061)	0.006
Pulmonary hypertension	1.551 (1.086–2.216)	0.016
Cirrhosis of the liver	3.788 (1.515–9.473)	0.004
Does not bath independently	1.745 (1.071–2.845)	0.026
Pre-TAVR balloon dilation	0.695 (0.485–0.995)	0.047

Note: Data presented as hazard ratio (HR) and 95% confident intervals (CI). Excluding patients with baseline pacemaker or death/study exit within 30 days.

Abbreviations: PPI, permanent pacemaker implantation; PVR, paravalvular regurgitation; STS, society of thoracic surgeons; TAVR, transcatheter aortic valve implantation.

presence of more than trace PVR or need of a new pacemaker within 30 days post TAVR; (3) Low incidence of clinically significant THV related problems such as endocarditis and thrombosis including low need for valve related interventions; (4) Evolut R feasibility to treat failing surgical aortic bioprostheses.

The 24.8% all-cause mortality and < 10% annual mortality rate are reassuring for the elderly patient population in the FORWARD study that could be considered at intermediate to high operative risk with an STS score of 5.5% and frailty in one-third of the cohort. The CoreValve US Pivotal High Risk trial reported 32.9% mortality at 3 years and 55.3% at 5 years in 391 patients with mean age of 83 years and STS of 7.4%.[7,8] Mortality at 5 years was 47.9% in the TAVR arm of the PARTNER 2 trial that included intermediate-risk patients with mean age of 81.5 years and an STS score of 5.8% who were treated with a second-generation balloon expandable THV.[9] Kaplan–Meier survival curves of both trials illustrated 3-year mortality rates of approximately 30%. In FORWARD, mortality at 3 years appeared higher for men than women, which is consistent with prior studies that suggested better long-term survival for women.[10,11] Age and severe comorbidities were associated with mortality at 3 years.

Previous reports from FORWARD discussed 30-day and 1-year incidences of disabling stroke (1.8% and 2.1%), more than mild PVR (1.8% and 1.2%) and need for new pacemakers (17.5% and 19.7%).[4,5] More than trace PVR and need for a new pacemaker within 30 days after TAVR were not associated with mortality at 3 years. We report now low annual rates of disabling stroke and need for new pacemakers after 1 year. FORWARD did not include echocardiography follow up beyond 1 year but clinical outcomes were reassuring given the low rate of valve related interventions, endocarditis and THV thrombosis out to 3 years that seem in line with the 2.1% reintervention and 6.2% THV endocarditis rate at 5 years of follow up in the NOTION trial.[12] Furthermore, NOTION demonstrated a higher incidence of structural valve degeneration (SVD) at 6 years with surgical aortic valve replacement (SAVR) as compared to TAVR with the self-expanding CoreValve THV (24% vs. 4.8%, $p < 0.001$) and similar rates of bioprosthetic valve failure (6.7% vs. 7.5%, $p = 0.89$).[13] Conversely, PARTNER 2 reported more SVD 5 years after TAVR with a second-generation balloon expandable THV and similar SVD with a third generation balloon expandable THV as compared to SAVR, with a valve-related reintervention in 2.7% and 1.9% of patients with a second or third generation balloon expandable THV, respectively.[14] The overall

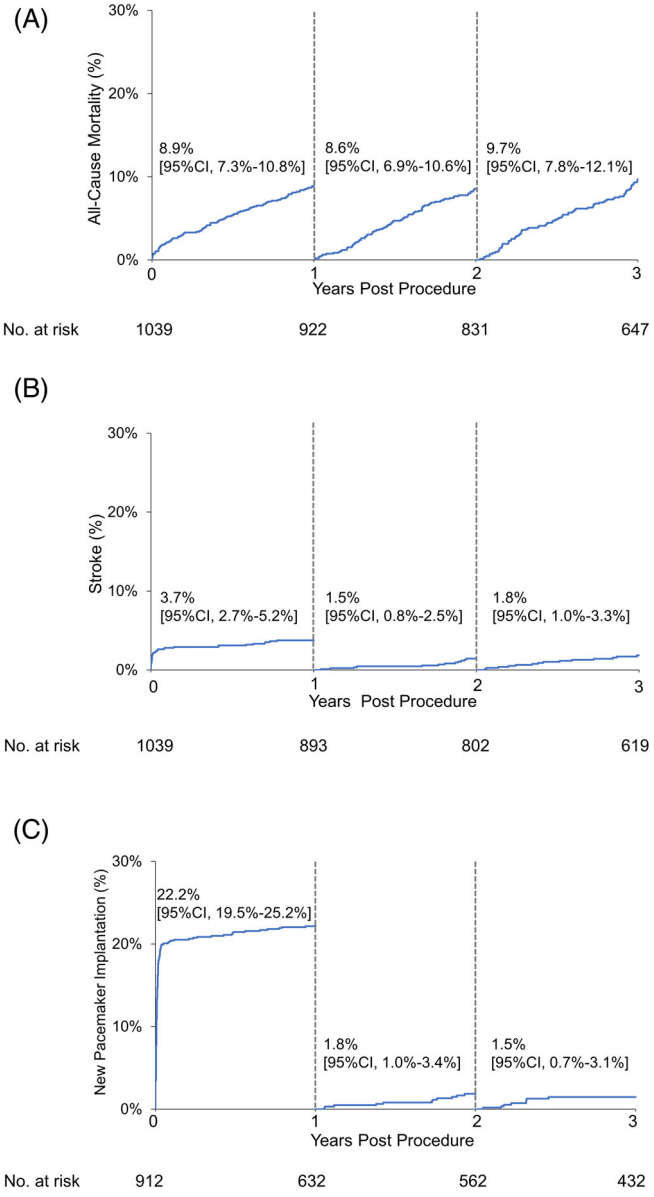

FIGURE 3 Landmark analysis of new serious adverse events. Landmark analysis of all-cause mortality (A), stroke (B), and new permanent pacemaker (C) at 1 and 2 years [Color figure can be viewed at wileyonlinelibrary.com]

rate of aortic valve endocarditis in FORWARD at 3 years was low (<1%) and all cases were medically treated. Endocarditis after TAVR is reported in up to 6.2% at 5 years and comes with a high mortality.[15] A simplified TAVR procedure avoiding general anesthesia and excessive instrumentation may limit the risk of procedure related infections and endocarditis. Notably, two-thirds of TAVR procedures in FORWARD were under local anesthesia/conscious sedation. Clinically-significant valve thrombosis was rare, was restricted to the context of TAVR in a failing surgical bioprosthesis and responded to oral anticoagulant drug therapy. FORWARD did not include systematic CT follow up after TAVR. Therefore the incidence of hypoattenuation and leaflet thickening and/or reduced leaflet motion is underreported.

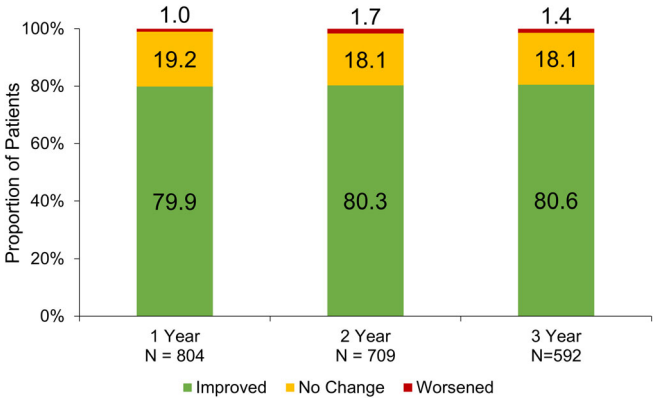

FIGURE 4 Change in New York Heart Association Class from BaselineChange in New York Heart Association classification from baseline to each annual follow-up. Change was defined as moving from 1 NYHA classification to another [Color figure can be viewed at wileyonlinelibrary.com]

FORWARD included a cohort of 50 patients who underwent TAVR in a failing surgical aortic bioprosthesis. These patients were younger and less frail and the operative risk was arguably determined by the need for resternotomy. All-cause mortality was similar to patients with TAVR for degenerated native AS (6% vs. 8.9% at 1 year and 24.3% vs. 24.8% at 3 years). The disabling stroke rate was higher and need for new pacemakers lower with TAVR in a failing surgical bioprosthesis at 1 year versus TAVR in native AS (8.1% vs. 2.3% and 7.4% vs. 22.2%). Hypothetically, more debris could be dislodged from a degenerated bioprosthesis during a TAVR procedure and its metal framework may prevent trauma to the native conduction system. A pilot study reported that filter based embolic protection devices captured debris in all patients who underwent TAVR in a failing surgical bioprostheses.[16] Whether more consistent use of cerebral embolic protection devices may also affect this clinically significant early stroke risk requires further study. Reassuringly, beyond 1 year no additional strokes or conduction disorders were reported in the cohort of patients with TAVR in a failing bioprosthesis and the stroke rate at 3 years was similar for TAVR in native AS and failing bioprosthesis. Of note, the 2 cases of THV thrombosis were restricted to the cohort of patients with TAVR in failing bioprosthesis. The antithrombotic regimen after TAVR is an ongoing subject of randomized trials and could be conceivably different in the context of TAVR in a failing bioprosthesis versus in native AS.

5 | LIMITATIONS

The FORWARD study was a post-market study with inherent limitations. Patient selection was determined by local heart teams, which may have introduced selection bias. The protocol stipulated clinical follow-up out to 3 years and echocardiography studies were not collected beyond 1 year. Our data attested to the clinical efficacy but could not comment on the hemodynamic THV performance at 3 years. 50 patients were treated for a failing surgical bioprosthesis, which underscores its

exploratory nature in this context. Still, the FORWARD study reports the longest clinical follow-up of Evolut R TAVR in real-world practice with independent clinical event adjudication.

6 | CONCLUSIONS

The Evolut R valve maintained a favorable safety profile through 3 years in routine clinical practice. Rates of THV related issues were low.

ACKNOWLEDGMENTS

Jane Moore, MS, ELS drafted the methods and results, created all tables and figures, and formatted the paper for journal style. Maarten Hollander, MSc, and Linda Schepers, MSc from Medtronic Bakken Research Center (Maastricht, The Netherlands) were responsible for overall study management. All are employees of Medtronic, plc (Dublin, Ireland).

CONFLICT OF INTEREST

Prof. Van Mieghem has received institutional research grants from Abbott Vascular, Boston Scientific, Medtronic, Edwards Lifesciences, PulseCath BV, Abiomed and Daiichi Sankyo; Prof. Windecker reports research and educational grants to the institution from Abbott, Amgen, BMS, Bayer, Boston Scientific, Biotronik, Cardinal Health, CardioValve, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Johnson&Johnson, Medtronic, Querbet, Polares, Sanofi, Terumo, Sinomed. Prof. Windecker serves as unpaid advisory board member and/or unpaid member of the steering/executive group of trials funded by Abbott, Abiomed, Amgen, Astra Zeneca, BMS, Boston Scientific, Biotronik, Cardiovalve, Edwards Lifesciences, MedAlliance, Medtronic, Novartis, Polares, Sinomed, V-Wave and Xeltis, but has not received personal payments by pharmaceutical companies or device manufacturers. He is also member of the steering/excecutive committee group of several investigated-initiated trials that receive funding by industry without impact on his personal remuneration. Stephan Windecker is an unpaid member of the Pfizer Research Award selection committee in Switzerland; Dr. Manoharan has served as a proctor for Boston Scientific, Medtronic and St. Jude Medical; Prof. Bosmans serves as a proctor for Medtronic; Prof. Bleiziffer has served as a consultant and proctor for Medtronic, a proctor for JenaValve, a proctor for Boston Scientific, and has received travel expenses from Medtronic; Dr. Modine serves as a proctor for Medtronic; Prof. Linke has received speaker honoraria or served as a consultant for the following companies: Medtronic, St. Jude Medical, Claret Medical Inc., Boston Scientific, Edwards Lifesciences, Symetis, and Bard, and holds stock options from Claret Medical Inc. In addition, he received grant support from Medtronic and Claret Medical Inc.; Dr. Scholtz has received honoraria and travel expense reimbursements from Medtronic; Dr. Tchétché has received honoraria or consultation fees from Abbott, Boston Scientific, Edwards Lifesciences and Medtronic; Dr. Finkelstein serves as a proctor and consultant for Edwards Lifesciences and Medtronic; Dr. Ito has nothing to disclose; Ms. Eisenberg is an employee and shareholder of Medtronic, plc; Prof. Grube serves on an advisory board for Medtronic, Boston Scientific and High Life, and has an equity interest in CardioValve, Valve Medical, Shockwave, Millipede, Pie-Cardia, Pipeline, Ancora and Laminar.

DATA AVAILABILITY STATEMENT

The raw data and statistical codes are owned by the sponsor of the FORWARD study and will not be shared for purposes of reproducing the results or replicating the procedure.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Van Mieghem NM, Windecker S, Manoharan G, Bosmans J, Bleiziffer S, Modine T, et al. Final 3-year clinical outcomes following transcatheter aortic valve implantation with a supra-annular self-expanding repositionable valve in a real-world setting: Results from the multicenter FORWARD study. Catheter Cardiovasc Interv. 2022;99:171–8. https://doi.org/10.1002/ccd.29889