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 effectiveness 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.
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 effectiveness 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 \( \leq 0.20 \) 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).

### 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 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

| TABLE 1 | Baseline characteristics for all patients and for patients with a failed surgical bioprosthesis |
|----------|---------------------------------------------------------------------------------------------|
| **Characteristic** | **All patients** | **Patients with failed surgical bioprosthesis** |
| N = 1039 | N = 50 |
| Age, years | 81.8 ± 6.2 | 78.0 ± 8.3 |
| Body surface area, m² | 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 | 50 (4.8) | 0 (0.0) |
| Moderate or severe LVOT calcification | 128 (12.7) | 2 (6.5) |
| Frailty | 354 (34.2) | 7 (14.3) |
| Pulmonary hypertension | 456 (46.0) | 28 (59.6) |
| Left ventricular ejection fraction, % | 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.

f By visual estimation.
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 shown 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 activities 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 cm² mean gradient, 32 mm Hg, stroke volume index, 15 ml/m²²) and received a 23-mm SAPIEN valve (Edwards LifeSciences, Irving, CA) 23 months after the index procedure. The 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 cm². 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.

### Table 2 Clinical outcomes for all patients through 3 years

| Event                                      | 1 year (no. of patients) | 2 years (no. of patients) | 3 years (no. of patients) |
|--------------------------------------------|--------------------------|---------------------------|--------------------------|
| 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             | 203 (19.8)               | 214 (21.0)                | 222 (22.0)               |
| Permanent pacemaker implanted⁵             | 200 (22.2)               | 211 (23.6)                | 219 (24.7)               |

Note: Data presented as no. of patients with an event (Kaplan–Meier estimate).

⁴Includes patients with permanent pacemaker or implantable cardioverter defibrillator at baseline.

⁵Excludes patients with permanent pacemaker at 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...
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%. 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.

### Table 3: Multivariable predictors of mortality from 31 days to 3 years

| Predictor                        | 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.

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. 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%). 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. 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). 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. The overall
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.

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 a 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.

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CONFLICT OF INTEREST

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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.

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