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Three-Year Outcomes With a Supra-Annular, Self-Expanding Bioprosthesis and a Pericardial Wrap—The FORWARD PRO Study

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ABSTRACT

Background: The self-expanding, supra-annular Evolut valve is an established platform for Transcatheter Aortic Valve Implantation (TAVI). Evolut PRO introduced an outer sealing wrap to mitigate paravalvular leakage. We evaluated the 3-year clinical outcomes and valve performance of the Evolut PRO in standard clinical practice for severe aortic stenosis (AS) patients at intermediate or higher risk for surgery.

Methods: The FORWARD PRO prospective, single-arm, multicentre, post-market clinical study enrolled 638 patients with native aortic valve stenosis or failed surgical bioprosthetic aortic valve undergoing TAVI, at intermediate or high risk, with the Evolut PRO valve. Clinical and serial echocardiographic outcomes were followed-up for 3 years.

Results: TAVI using Evolut PRO was attempted in 629 AS patients (implanted in 97%) (mean age 81.7 years; STS PROM score, 4.7%). At 3 years all-cause mortality was 25.0%, disabling stroke 6.5% (all-cause mortality or disabling stroke, 28.5%) and rate of

Abbreviations: EOA, effective orifice area; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; PPI, permanent pacemaker implantation; PVL, paravalvular leak; STS PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TAVI, transcatheter aortic valve implantation.

"X" (Twitter) media abstract: For patients with severe aortic stenosis at intermediate or high surgical risk, 3-year results from the FORWARD PRO study demonstrate favorable clinical outcomes and excellent haemodynamics with the Evolut PRO TAVI device.

Short "X" (Twitter) title: Largest 3-year outcome with Evolut PRO TAVI.

new permanent pacemaker implantation 24.7%. Excellent valve haemodynamics were maintained (mean gradient 8.8 ± 4.7 mm Hg; mean effective orifice area 2.0 ± 0.5 cm^2) at 3 years. In a paired analysis of patients with ≥ mild paravalvular leakage (PVL) at discharge, more than two-thirds demonstrated improved PVL at 3 years. Patients with ≥ mild PVL at discharge had higher median total calcium volume than those with no/trace PVL ($p < 0.001$).

Conclusions: In clinical practice TAVI with the Evolut PRO valve is associated with favorable clinical outcomes and excellent haemodynamic performance out to 3 years. The observation of improvements in PVL over time warrants further research.

1 | Introduction

Transcatheter Aortic Valve Implantation (TAVI) is an effective alternative to surgery in patients with severe aortic stenosis across the spectrum of surgical risk [1–6]. In the randomized Evolut Low Risk Trial (NCT02701283), TAVI with the self-expanding, supra-annular Evolut valve (Medtronic, Minneapolis, Minnesota) showed favorable results with regard to all-cause mortality and disabling stroke at 3 and 4 years compared to surgery [7, 8]. The mean gradient across the bioprosthesis was lower and the effective orifice area (EOA) larger with TAVI compared to a surgical aortic bioprosthesis. Conversely, more than trace aortic paravalvular leak (PVL) was more frequent after TAVI. Aortic root calcification is arguably a dominant determinant for PVL after TAVI because it may affect frame expansion and lead to eccentricity with consequent diastolic blood regurgitation [9, 10]. The Evolut PRO valve is a device iteration from the Evolut platform (Medtronic, Minneapolis, Minnesota) that was previously underused in randomized trials and has an outer pericardial wrap to increase surface area contact and mitigate PVL. A small Medtronic Evolut PRO study with 60 patients at increased operative risk (NCT02738853) reported favorable short-term clinical outcomes and excellent haemodynamic valve performance with absence of ≥ mild PVL [11]. The FORWARD PRO study (NCT03417011) was a prospective study to evaluate the clinical performance and safety of the Evolut PRO valve in contemporary clinical practice with 629 patients undergoing attempted implant. All-cause mortality was 3.2% and disabling stroke rate was 2.9% at 30-day follow-up [12]. There was excellent haemodynamic valve performance; however, there was more than trace PVL at discharge in 40.5% of patients. The aim of the current study was to extend the clinical and echocardiographic follow-up to 3 years including predictors of all-cause and cardiovascular mortality, an exploratory analysis of correlates of PVL, and the fate of PVL over time.

2 | Methods

2.1 | Patient Selection

FORWARD PRO is a prospective, single-arm, multicentre, post-market study performed in 39 TAVI centers in 14 countries. Patient eligibility was determined by local heart teams and included those with severe, symptomatic native aortic valve stenosis or a stenosed, insufficient, or combined surgical bioprosthetic valve failure necessitating valve replacement. Patients were deemed intermediate or higher risk for surgery (patients at low surgical risk were excluded). Additional inclusion and exclusion criteria have been previously reported [12]. Emergency procedures were not allowed and patients with a life expectancy of < 1 year were not enrolled.

2.2 | Study Device and Procedures

2.2.1 | Study Valve

Details of the Evolut PRO system and implantation procedure have been previously reported [11]. In brief, the Evolut PRO is a repositionable, self-expanding nitinol frame with a supra-annular valve and an outer pericardial wrap around the lower two rows of cells of the frame with the intent to mitigate PVL. In the FORWARD PRO study, Evolut PRO sizes 23-, 26- and 29-mm were available to treat aortic annuli from 18 to 26 mm in diameter. Implant procedures were performed per local standard practice.

2.2.2 | Study Procedures

All clinical sites were instructed to follow a standardized echocardiogram acquisition protocol. Echocardiograms include those performed at the study-defined visit windows at discharge, 1-year, and 3-year follow-up. Echocardiograms from unscheduled assessments were not available. Measures of the mean aortic valve gradient, EOA, total aortic regurgitation and PVL were performed at baseline, discharge, 1 and 3 years and were centrally assessed by an independent core laboratory (Mayo Clinic, Rochester, Minnesota). The severity of regurgitation was assessed using color flow, pulsed-wave and continuous-wave Doppler as previously described [13]. Echocardiography data are reported on implanted patients only, and exclude echocardiograms performed after a reintervention where the study valve is no longer functioning.

An independent Clinical Events Committee adjudicated all deaths (as cardiovascular or non-cardiovascular) and safety-related events. Frailty was defined per Valve Academic Research Consortium-2 guidelines [14].

All patients underwent multi-slice computed tomography (MSCT) before the procedure, which was centrally assessed (Medtronic, Santa Ana, California). Both annular dimensions for valve sizing and left ventricular outflow tract (LVOT) dimensions were centrally assessed. However, quantitative calcium analyses were performed only for the annulus and not for the LVOT. Comprehensive quantitative calcium analyses were derived from the semi-automated calcium scoring tool in 3mensio software system (Research Version 8.1, Pie Medical,

the Netherlands). The segmentation threshold was set to the mode (or peak) of Hounsfield Units (HU) in the contrast-enhanced blood in the aortic root and LVOT plus 200 HU for each patient. Total calcium volume was the sum of the calcium from the valve basal plane to the leaflet tips and calcium from the basal plane to 10 mm into the LVOT.

The study followed the Declaration of Helsinki principles, and all patients signed an informed consent or data release form. The study was compliant to the ISO 14155:2011 international standard and to the local laws and regulations of the countries it was conducted in, including those for data protection.

2.2.3 | Endpoints

The study primary endpoint of all-cause mortality at 30 days has been reported [12]. Secondary endpoints include annual adverse events including mortality and cardiovascular mortality, composite all-cause mortality or disabling stroke, New York Heart Association (NYHA) functional class, haemodynamic valve performance and PVL as assessed by the independent echocardiography core laboratory at 1 and 3 years as well as the rate of new permanent pacemaker implantation (PPI).

2.3 | Statistical Analysis

The primary analysis cohort for this study comprises patients who underwent attempted implant of an Evolut PRO valve. A separate analysis that included only the TAVI in native valve cases was also performed. Baseline categorical variables are presented as counts and percentages, and continuous variables as mean values ± standard deviation (SD). Clinical outcomes to 3 years are reported as the number of events with Kaplan-Meier estimates as percentages. Univariable and multivariable Cox proportional hazard regression analyses were performed to examine baseline, procedural and early post-procedural variables as potential predictors of all-cause mortality and cardiovascular mortality to 3 years. The landmarked uni- and multivariable analyses of all-cause mortality and cardiovascular mortality included only implanted patients who were alive and participating in the study through 30 days. Model results are reported as hazard ratios with 95% confidence intervals. Chained equations were used to perform a single imputation of missing data. A list of clinically relevant covariates was produced (i.e., univariable predictors). Candidate variables were selected from univariable predictors with p-value ≤ 0.15, using a stepwise method with thresholds for entry and exit of $p = 0.10$. PPI within 30 days, PVL at discharge, and prosthesis-patient mismatch (PPM) at discharge were forced to be included in the multivariable models. Kaplan-Meier analyses of cardiovascular and all-cause mortality stratified by new PPI and discharge PVL are landmarked at 30 days postprocedure, with the log-rank test used for comparisons among groups. PVL changes from discharge to 1 and 3 years are reported as counts and percentages. An exploratory analysis focused on the change in PVL severity in patients who were alive at 3 years of follow up and had available echocardiography studies for core laboratory evaluation at discharge, 1 and 3 years. Computed tomographic baseline characteristics stratified by the severity of PVL at discharge are also reported and compared between groups using two-sample t-tests. Selected analyses were repeated among native aortic valve stenosis patients only (excluding TAV-in-SAV). A threshold of $p < 0.05$ was used for statistical significance. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

3 | Results

A total of 638 patients with symptomatic severe aortic stenosis or aortic bioprosthesis failure were enrolled between March 2018 and December 2018 in 39 centers across 14 countries. TAVI with the Evolut PRO valve was attempted in 629 intermediate or high-risk patients and implanted in 610 (97%) (Supporting Information S1: Figure S1) [12]. Among those who were still alive and participating in the study at the 3-year visit window, 94.1% completed the 3-year visit. Patients with an attempted Evolut PRO TAVI had a mean age of 81.7 ± 6.1 years, 62% were women, mean Society of Thoracic Surgeons Predicted Risk of Mortality (STS PROM) score was 4.7% ± 3.3% and one-third of the patients were considered frail (Table 1). Twenty-five patients (mean age 79.0 ± 6.1 years, 36.0% women, mean STS PROM score 7.7% ± 5.9%) underwent TAVI in a failing surgical bioprosthesis. Supporting Information S1: Table S1 reports the baseline characteristics of the remaining 604 patients that underwent a native TAVI and Supporting Information S1: Figure S2 displays the outcome of all-cause mortality or disabling stroke for these patients. Baseline characteristics and all-cause mortality or disabling stroke rates through 3 years in the native valve patients were alike the full cohort.

3.1 | Clinical Outcomes

Clinical outcomes at 30 days and 1, 2, and 3 years are shown in Table 2. The composite endpoint of all-cause mortality or disabling stroke at 3 years was 28.5% (Supporting Information S1: Figure S3), with all-cause mortality 25.0% and disabling stroke 6.5%.

At 3 years, the rate of new PPI was 24.7% (Supporting Information S1: Figure S4). A new PPI was required in 117 patients (20.9%) up to 30 days and in an additional 18 patients after 30 days. Clinical valve thrombosis occurred in one patient at 1-year (rate 0.2%), and was treated with oral anticoagulants, and no additional cases occurred through 3 years.

Endocarditis was identified in no patients up to 30 days, and in eight (1.4%) patients between 30 days and the first year. Five additional patients experienced valve endocarditis between 1 and 3 years.

A total of five patients required a repeat valve-related intervention in the period of 30-days up to 3 years (1095 days). One patient required surgery for prosthetic valve endocarditis. Surgical explant of the Evolut valve was followed by the uneventful implantation of a new surgical aortic valve. The other four patients underwent a transcatheter procedure (Supporting Information S1: Table S2).

NYHA symptom assessment at both baseline and 3 years was available for 352 patients. Of these, 240 (68.2%) had

TABLE 1 | Demographics and baseline clinical characteristics—attempted implant.

Characteristic	$N = 629$
Age, years	81.7 ± 6.1
Body surface area, m^2	1.8 ± 0.2
Female	389 (61.8)
STS PROM score, %	4.7 ± 3.3
STS PROM score < 4.0%	326 (51.8)
New York Heart Association (NYHA) Class	
I	29 (4.7)
II	190 (31.0)
III	371 (60.5)
IV	23 (3.8)
Prior myocardial infarction	85 (13.6)
Prior percutaneous coronary intervention	174 (28.2)
Prior coronary artery bypass grafting	65 (10.5)
Prior aortic valve	25 (4.0)
Atrial fibrillation	210 (33.6)
Diabetes mellitus	215 (34.3)
Serum creatinine > 2 mg/dL	31 (4.9)
Chronic lung disease/chronic obstruction pulmonary disease	159 (26.2)
Peripheral artery disease	95 (15.3)
Cerebrovascular disease	118 (18.9)
Prior cerebrovascular accident	78 (12.5)
Other comorbidities and medical history	
Porcelain aorta[a]	27 (4.4)
Frailty	207 (33.6)
Pulmonary hypertension[b]	205 (33.5)
Left ventricular ejection fraction[c], %	60.0 ± 11.0
Pre-existing permanent pacemaker or defibrillator	66 (10.5)
Assisted living	93 (14.8)

Note: Data presented as mean ± standard deviation or number (percentage).
Abbreviation: STS PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.
[a]Site-reported heavy circumferential calcification or severe atheromatous plaques of the entire ascending aorta extending to the arch such that aortic cross-clamping is not feasible.
[b]Moderate (systolic pulmonary artery pressure 31–55 mm Hg) or severe (systolic pulmonary artery pressure > 55 mm Hg).
[c]Core Lab reported.

improvement in their NYHA class, 92 (26.1%) remained the same, and 20 (5.7%) had worsening of their NYHA symptoms.

3.2 | Predictors of All-Cause and Cardiovascular Mortality

In the Kaplan-Meier analysis, all-cause mortality was higher for both baseline PPI/ICD and new PPI within 30 days compared to no new PPI within 30 days ($p = 0.095$ and $p = 0.043$ respectively, Figure 1A). Cardiovascular mortality was higher for baseline PPI/ICD compared to both new PPI within 30 days and no new PPI within 30 days ($p = 0.071$ and $p < 0.001$ respectively, Figure 1B) and there was no significant difference between new and no new PPI within 30 days ($p = 0.251$). Discharge PVL of none/trace versus mild versus moderate/severe was not significantly associated with all-cause mortality ($p = 0.950$) or cardiovascular mortality ($p = 0.307$) to 3 years (Figure 1C, D); only few patients had > mild PVL.

In the multivariable model (Supporting Information S1: Table S3), the following variables were identified as correlates of all-cause mortality: cardiac tamponade within 30 days, acute kidney injury stage 2 or 3 within 30 days, prior atrial fibrillation, immunocompromise, moderate or greater calcification of LVOT, increased STS-PROM score, and frailty. Compared with no new PPI within 30 days, baseline PPI and new PPI within 30 days were not significantly associated with all-cause mortality (HR 1.36, 95% CI 0.77–2.40, $p = 0.293$ and HR 1.47, 95% CI 0.95–2.27, $p = 0.084$, respectively). Discharge PVL of ≥ mild and discharge PPM of ≥ moderate were not associated with all-cause mortality. The multivariable model for cardiovascular mortality (Supporting Information S1: Table S4) identified several significant predictors, including cardiac tamponade within 30 days, acute kidney injury stage 2 or 3 within 30 days, moderate or greater LVOT calcification, prior atrial fibrillation, and lower body surface area. Compared with no new PPI within 30 days, baseline PPI was associated with cardiovascular mortality (HR 2.35, 95% CI 1.17–4.70, $p = 0.016$) while new PPI within 30 days was not (HR 1.30, 95% CI 0.65–2.61, $p = 0.459$). Discharge PVL of ≥ mild and discharge PPM of ≥ moderate were not associated with cardiovascular mortality.

3.3 | Bioprosthetic Valve Performance

Overall, transthoracic echocardiography exams were available for 255 of 427 patients (59.7%) alive and participating in the study at 3 years. EOA was 2.0 ± 0.5 cm^2 and mean aortic valve gradient was 8.8 ± 4.7 mm Hg at 3 years (data for all available patients in Figure 2). EOA and mean aortic valve gradient post TAVI remained consistent through 3 years of follow-up. PVL was graded as none/trace at 3 years in 80.3% of all available patients (Figure 3A) and 80.9% in the paired analysis (Figure 3B). Table 3 displays the change in PVL over time for patients with echocardiography at both discharge and 1 year follow-up or both discharge and 3 years follow-up, respectively. PVL improved from discharge to 3 years in most cases (67.9% of patients with mild PVL at discharge; 100% of patients with moderate PVL at discharge). Moderate and severe PVL rates were similar across the different patient subgroups when patients were stratified according to the type of balloon aortic valvuloplasty implemented.

3.4 | Multi-Slice Computed Tomography (MSCT)

The baseline MSCT measurements for patients with no or trace PVL and those with mild or greater PVL at discharge are shown in Table 4. Aortic root dimensions and total aortic valve calcium were significantly greater for patients with mild or greater PVL

TABLE 2 | Clinical outcomes up to 3 years—attempted implant.

Outcome	30 Days	1 Year	2 Years	3 Years
All-cause mortality or disabling stroke	30 (4.8)	73 (12.0)	116 (19.4)	167 (28.5)
All-cause mortality	20 (3.2)	59 (9.7)	99 (16.6)	146 (25.0)
Cardiovascular mortality	17 (2.7)	41 (6.8)	58 (9.8)	76 (13.4)
All stroke	24 (3.8)	36 (5.9)	41 (6.9)	48 (8.5)
Disabling	18 (2.9)	28 (4.6)	32 (5.4)	37 (6.5)
Non-disabling	6 (1.0)	8 (1.3)	9 (1.5)	11 (2.0)
Valve-related dysfunction requiring repeat procedure	0 (0.0)	2 (0.4)	5 (0.9)	5 (0.9)
Life-threatening or disabling bleeding	21 (3.3)	27 (4.4)	31 (5.2)	34 (5.8)
Myocardial infarction	3 (0.5)	4 (0.7)	6 (1.0)	8 (1.5)
Coronary obstruction	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Prosthetic valve thrombosis (clinical)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)
Valve endocarditis	0 (0.0)	8 (1.4)	12 (2.2)	13 (2.4)
Valve embolization or migration	4 (0.6)	4 (0.6)	4 (0.6)	4 (0.6)
Permanent pacemaker implant (PPI)[a]	119 (19.0)	128 (20.6)	135 (22.0)	138 (22.7)
Permanent pacemaker implant (PPI)[b]	117 (20.9)	126 (22.7)	132 (24.0)	135 (24.7)

Note: Data presented as number of events (Kaplan-Meier estimates as percentage).
[a]Includes patients with a permanent pacemaker at baseline.
[b]Excludes patients with a permanent pacemaker at baseline.

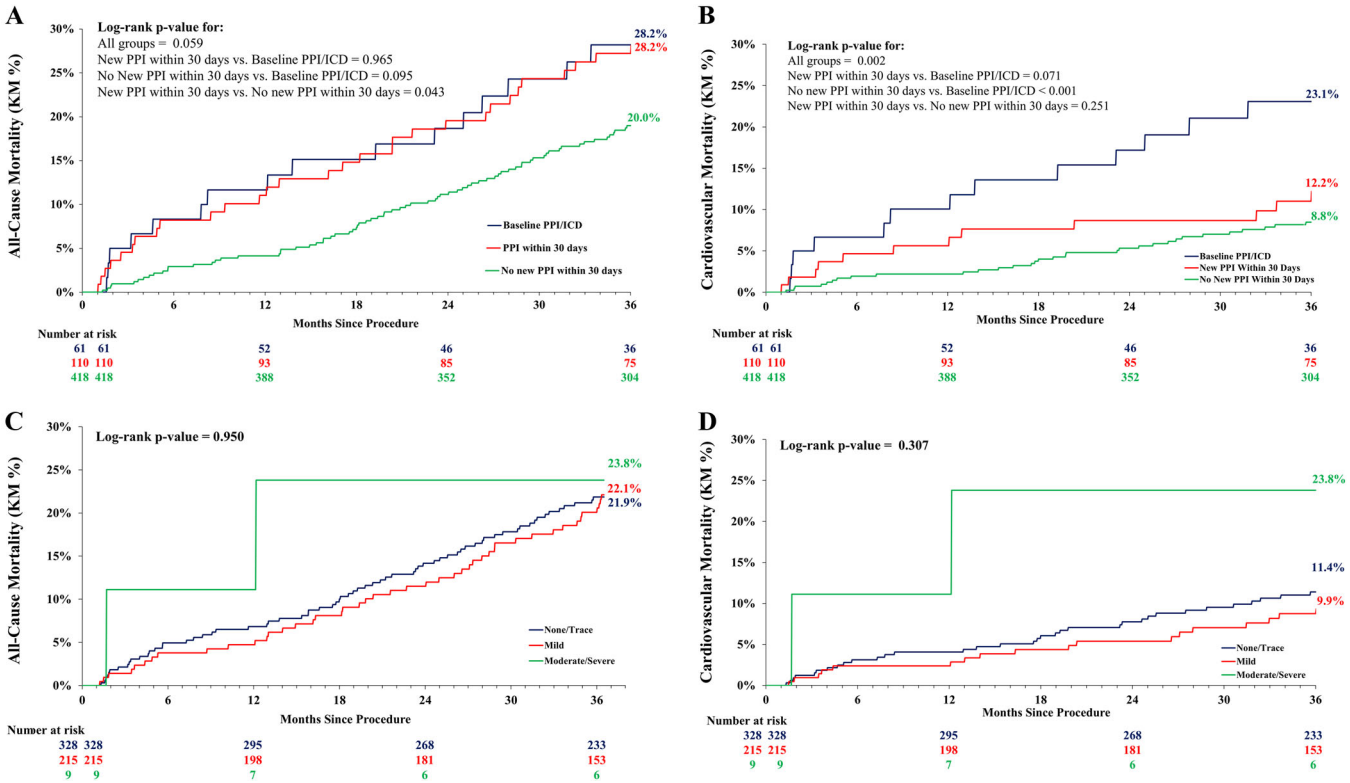
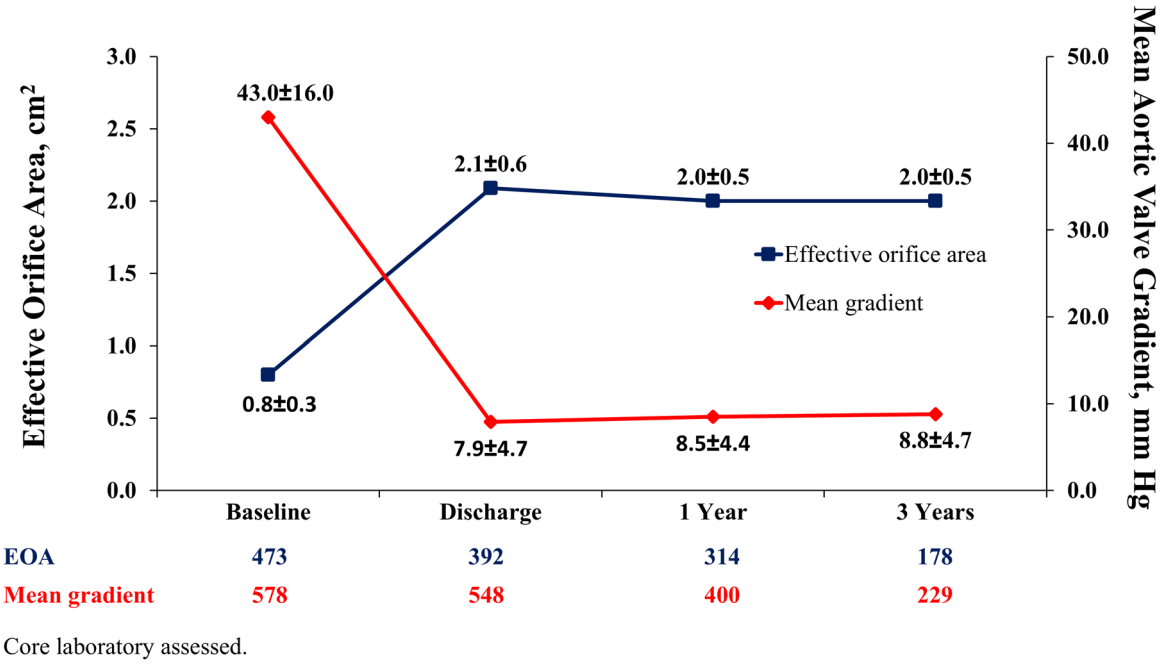


FIGURE 1 | Clinical outcomes to 3 years. Kaplan-Meier curves of: (A) PPI impact on all-cause mortality; (B) PPI impact on cardiovascular mortality, (C) Discharge PVL impact on all-cause mortality, (D) Discharge PVL impact on cardiovascular mortality. ICD, implantable cardioverter-defibrillator; KM, Kaplan-Meier; PPI, permanent pacemaker implantation; PVL, paravalvular leak. [Color figure can be viewed at wileyonlinelibrary.com]

at discharge. The median (first quartile, third quartile) total calcium volume was 507.1 (308.3, 801.7) mm^3 in patients with no or trace PVL and 767.0 (468.6, 1219.2) mm^3 in those with mild or greater PVL at discharge ($p < 0.001$). Oversizing by $\geq 15\%$ (compared to 5%–15% and $< 5\%$) was more common in patients with no or trace PVL (75.9%) than with mild or greater PVL at discharge (58.4%), $p < 0.001$ across the three oversizing categories.



Core laboratory assessed.

FIGURE 2 | Valve haemodynamics to 3 years. Mean aortic valve gradients and EOA assessed out to 3 years by echo core lab. Values presented as mean values ± standard deviation. EOA, effective orifice area. [Color figure can be viewed at wileyonlinelibrary.com]

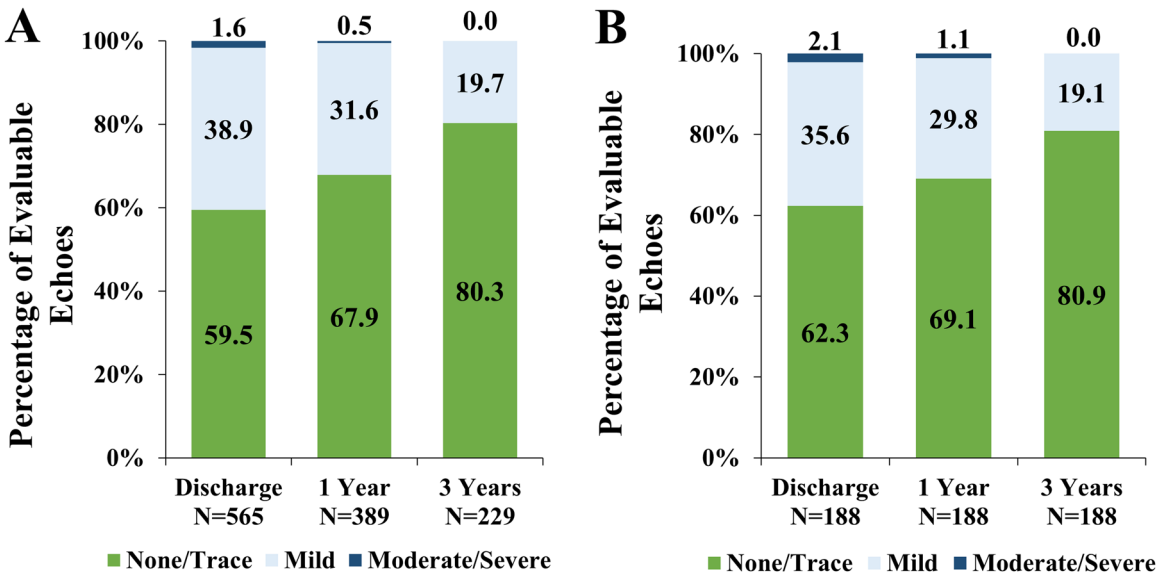


FIGURE 3 | Paravalvular leak (PVL) to 3 years. Percent of patients with echocardiography assessment of PVL performed within study-defined visit windows at discharge, 1 year and 3 years (no unscheduled assessments): (A) All available patient data; (B) Patients with echo data at discharge, 1 and 3 years (paired data). Values presented as percentages. PVL, paravalvular leak. [Color figure can be viewed at wileyonlinelibrary.com]

4 | Discussion

FORWARD PRO is the largest prospective study evaluating clinical and valve performance of the Evolut PRO platform in patients with severe aortic stenosis or a failing surgical aortic bioprosthesis at higher surgical risk. A quarter of patients had died at 3 years of follow-up. STS score and frailty were among the predictors of 3-year mortality. Larger dimensions and more calcification of the aortic root and less oversizing were associated with more than trace PVL. Balloon dilatations before or after the Evolut implantation had no effect on moderate/severe PVL rates. In an exploratory paired analysis, more than trace PVL at discharge improved at 3 years in more than two-thirds of patients. Haemodynamic valve performance was excellent and remained stable out to 3 years. Bioprosthetic valve degeneration and failure were rare out to 3 years (0% frame fractures, 0.9% repeat valve-related interventions, no new incidences of thrombosis after 1 year).

Patients in the FORWARD PRO study may be considered at intermediate operative risk based on mean age of 81.7 years, STS PROM of 4.7% and frailty in one-third. Compared to the randomized trials evaluating TAVI versus surgery in patients at

TABLE 3 | Changes in paravalvular leak (PVL) from discharge to 1 and 3 years.

	PVL at Discharge				
	None ($N = 152$)	**Trace ($N = 184$)**	**Mild ($N = 220$)**	**Moderate ($N = 8$)**	**Severe ($N = 1$)**
PVL at 1 Year					
None	**82.0% (82/100)**	**50.4% (58/115)**	**14.0% (21/150)**	0.0% (0/5)	0
Trace	**13.0% (13/100)**	**27.0% (31/115)**	**29.3% (44/150)**	**20.0% (1/5)**	0
Mild	**5.0% (5/100)**	**22.6% (26/115)**	**56.0% (84/150)**	**60.0% (3/5)**	0
Moderate	0.0% (0/100)	0.0% (0/115)	**0.7% (1/150)**	**20.0% (1/5)**	0
Severe	0.0% (0/100)	0.0% (0/115)	0.0% (0/150)	0.0% (0/5)	**0**
PVL at 3 Years					
None	**81.7% (49/60)**	**65.0% (52/80)**	**26.9% (21/78)**	**0.0% (0/4)**	0
Trace	**16.7% (10/60)**	**18.8% (15/80)**	**41.0% (32/78)**	**25.0% (1/4)**	0
Mild	**1.7% (1/60)**	**16.3% (13/80)**	**32.1% (25/78)**	**75.0% (3/4)**	0
Moderate	0.0% (0/60)	0.0% (0/80)	0.0% (0/78)	**0.0% (0/4)**	0
Severe	0.0% (0/60)	0.0% (0/80)	0.0% (0/78)	0.0% (0/4)	**0**
Improved PVL grade from Discharge		**No change in PVL grade from Discharge**		**Worsened PVL grade from Discharge**	

Note: Values represent percentage of patients (n/N). Paired data for patients with echocardiography assessment of PVL performed within study-defined visit windows at both discharge and 1 year or both discharge and 3 years. Unscheduled echocardiograms are not available.
Abbreviation: PVL, paravalvular leak. [Color figure can be viewed at wileyonlinelibrary.com]

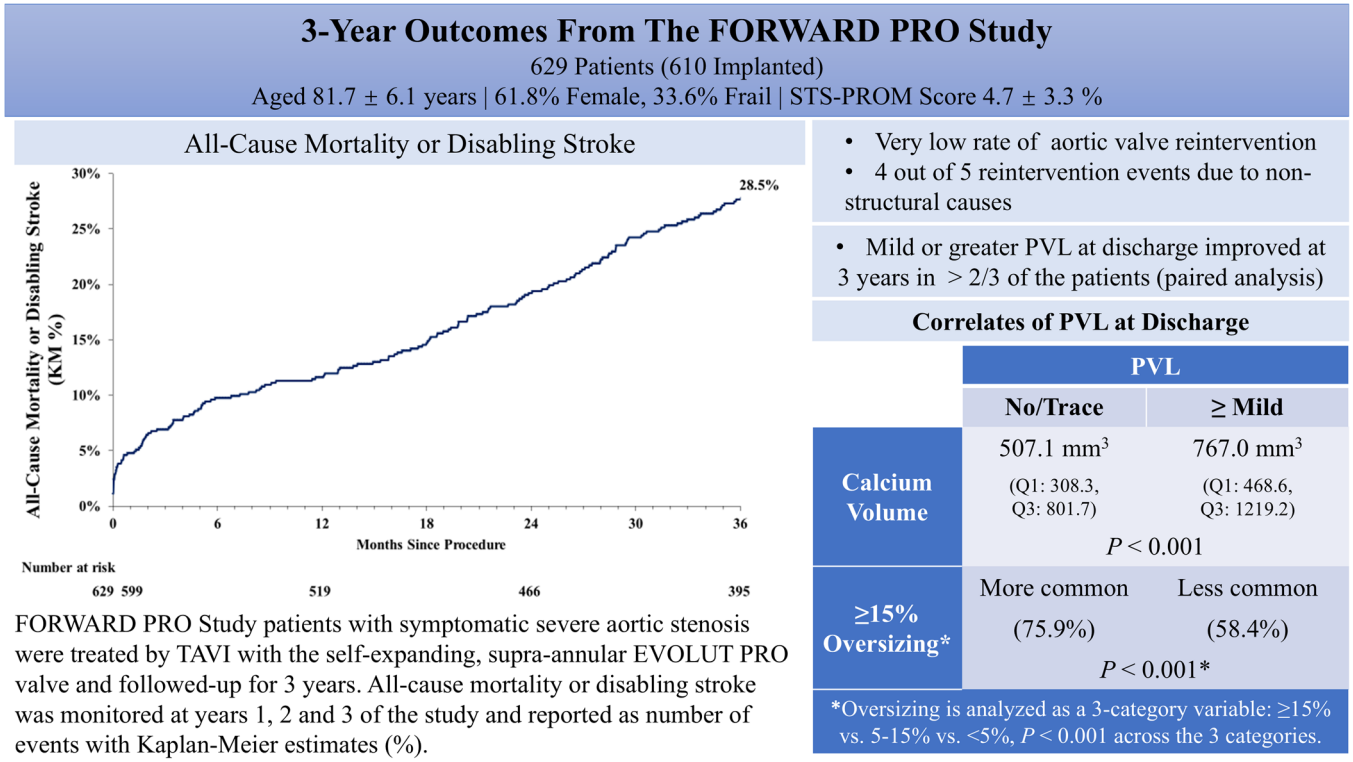
intermediate operative risk, the 25% mortality at 3 years in the FORWARD PRO study was comparable to what would be anticipated for the corresponding time period in the PARTNER 2 trial [2, 16] (mean age 81.5 years, STS PROM 5.8%, mortality 16.7% at 2 years and 46.0% at 5 years) but higher than in the SURTAVI trial [5, 17] (mean age 79.9 years, STS PROM 4.4%, mortality 11.5% at 2 years and 30.0% at 5 years). Patients in FORWARD PRO and PARTNER-2 were older than those of the SURTAVI trial. Age is a known driver for frailty, and STS PROM was among the significant predictors for mortality at 3 years in FORWARD PRO. New PPI ($p = 0.084$) and more than trace PVL after TAVI ($p = 0.804$) were not significantly associated with all-cause mortality at 3 years, which is in keeping with the 5-year outcome data in SURTAVI [17]. Notably, baseline PPI was associated with cardiovascular (HR 2.35, 95% CI 1.17–4.70, $p = 0.016$) but not all-cause mortality. This may attest to the phenotype of these patients who have arguably more ischemic and valvular heart disease and more atrial fibrillation. The 21% PPI rate in FORWARD PRO was higher than reported in more recent reports with the same self-expanding platform. An optimized TAVR care pathway and the cusp overlap implantation technique may lead to lower PPI rates [18]. Excellent bioprosthetic valve performance was exhibited by the large valve area and low residual transvalvular gradient and characterizes consecutive iterations of self-expanding supra-annular valves [19]. The Evolut PRO valve introduced an outer pericardial tissue wrap to mitigate PVL. A report from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy registry [19] confirmed a lower incidence of more than mild PVL with Evolut PRO as compared to previous device versions with no sealing wrap. More than trace PVL was present in 40.5% of patients at discharge in the FORWARD PRO study, which is higher than in the Evolut Low Risk trial [7] (28.9%). At 3 years, 20% of patients had mild PVL with no cases of more than mild PVL. Interestingly, in an exploratory paired analysis, more than trace PVL at discharge improved at 3 years in more than two-thirds of patients. A similar degree of PVL regression was noted in the multi-center CoreValve U.S. Pivotal trial in which the outer-to-outer edge dimension of the CoreValve prosthesis slightly increased with improvement of PVL in 83% at 1 year. This may be related to ongoing expansion of the nitinol frame [20]. A previous evaluation of follow up CT's after CoreValve TAVI already suggested continued expansion and increased circularity of the nitinol frame with improved apposition and enhanced sealing properties over time [21]. The data from the recently published SMART Trial appear to support the overall trends we identified regarding the lower rates of significant PVL and favorable haemodynamics with the Evolut PRO generation of valves [22]. Aortic root remodeling around the stent frame may further decrease PVL over time. These intriguing observations of improving PVL with self-expanding supra-annular valves over time seem unique for self-expanding nitinol valve frames and require further research. Aortic root phenotype and sizing algorithms were associated with PVL in FORWARD PRO. More extensive aortic root calcification has been consistently linked to PVL [9, 23]. Furthermore, device oversizing relative to the annular dimensions resulted in a lower incidence of PVL. An analysis of the CoreValve US Extreme Risk and High Risk pivotal trials previously demonstrated that gradually more oversizing was associated with lower rates of significant PVL with the first generation CoreValve platform [24]. Consistently, in FORWARD PRO, at least 15% oversizing was achieved in most patients.

Valve reinterventions were rare and primarily driven by non-structural valve degeneration. Endocarditis occurred in 13 patients (2.4%) and could be treated with antibiotics in all but one patient who required surgery.

TABLE 4 | Baseline multi-slice CT findings by severity of paravalvular leak (PVL).

Characteristic	All Patients $N = 610$	No/Trace PVL at Discharge $N = 336$	≥ Mild PVL at Discharge $N = 229$[a]	*P*-Value[b]
Annulus dimensions				
Minimum diameter, mm	20.7 ± 1.8 (566)	20.4 ± 1.8 (307)	21.1 ± 1.8 (214)	< 0.001
Maximum diameter, mm	26.4 ± 2.1 (566)	26.1 ± 2.0 (307)	26.9 ± 2.1 (214)	< 0.001
Average diameter, mm	23.5 ± 1.8 (561)	23.2 ± 1.7 (302)	24.0 ± 1.8 (214)	< 0.001
Area, mm^2	427.6 ± 63.8 (566)	416.9 ± 60.4 (307)	445.3 ± 65.4 (214)	< 0.001
Perimeter, mm	74.3 ± 5.5 (566)	73.3 ± 5.3 (307)	75.7 ± 5.6 (214)	< 0.001
Area-derived diameter, mm	23.3 ± 1.8 (566)	23.0 ± 1.7 (307)	23.7 ± 1.8 (214)	< 0.001
Perimeter-derived diameter, mm	23.6 ± 1.8 (566)	23.3 ± 1.7 (307)	24.1 ± 1.8 (214)	< 0.001
LVOT dimensions				
Minimum diameter, mm	19.3 ± 2.4 (562)	19.0 ± 2.4 (307)	19.7 ± 2.5 (211)	< 0.001
Maximum diameter, mm	27.2 ± 2.6 (563)	27.0 ± 2.5 (307)	27.5 ± 2.7 (211)	0.020
Average diameter, mm	23.2 ± 2.2 (558)	23.0 ± 2.2 (302)	23.6 ± 2.3 (211)	0.001
Area, mm^2	411.6 ± 80.0 (563)	401.9 ± 75.0 (307)	428.2 ± 85.2 (211)	< 0.001
Perimeter, mm	74.0 ± 7.0 (563)	73.2 ± 6.6 (307)	75.3 ± 7.4 (211)	< 0.001
Area-derived diameter, mm	22.8 ± 2.2 (563)	22.5 ± 2.1 (307)	23.2 ± 2.4 (211)	< 0.001
Perimeter-derived diameter, mm	23.5 ± 2.2 (563)	23.3 ± 2.1 (307)	24.0 ± 2.4 (211)	< 0.001
Aortic Valve Calcification (MDT method [15]) Calcium volumes	(566)	(307)	(214)	
NCC, mm^3	256.1 (139.3, 411.4)	227.5 (124.1, 361.4)	333.7 (155.0, 485.8)	< 0.001
RCC, mm^3	144.8 (72.9, 256.8)	119.6 (55.9, 207.0)	189.3 (92.8, 359.0)	< 0.001
LCC, mm^3	158.8 (86.8, 302.9)	137.8 (73.6, 240.1)	231.2 (119.7, 399.6)	< 0.001
Total calcium volume, mm^3	587.5 (366.7, 950.2)	507.1 (308.3, 801.7)	767.0 (468.6, 1219.2)	< 0.001
Aortic Valve Calcification (Hansson method) Calcium volumes	(565)	(306)	(214)	
NCC, mm^3	289.5 (153.4, 480.1)	266.4 (134.1, 438.6)	358.4 (189.5, 574.6)	< 0.001
RCC, mm^3	176.0 (82.8, 307.2)	142.1 (73.7, 248.7)	226.7 (100.5, 413.0)	< 0.001
LCC, mm^3	197.5 (100.4, 356.9)	153.3 (86.7, 298.9)	255.0 (143.6, 462.9)	< 0.001
Total calcium volume, mm^3	687.4 (409.0, 1147.9)	592.5 (337.0, 966.6)	910.2 (550.7, 1324.0)	< 0.001
≥ Mild Calcification of LVOT[c]	275/564 (48.8%)	135/309 (43.7%)	120/214 (56.1%)	0.005
Oversizing				< 0.001
< 5%	10/566 (1.8%)	3/307 (1.0%)	7/214 (3.3%)	
≥ 5 to < 15%	165/566 (29.2%)	71/307 (23.1%)	82/214 (38.3%)	
≥ 15%	391/566 (69.1%)	233/307 (75.9%)	125/214 (58.4%)	

Note: Data presented as mean ± standard deviation.
Abbreviations: LCC, left coronary cusp; LVOT, left ventricular outflow tract; NCC, non-coronary cusp; RCC, right coronary cusp.
[a]The number of patients with paravalvular leak (PVL) measures does not add up to the total number of patients with analyzable calcium values.
[b]P value from two-sample *t*-test comparing two PVL groups.
[c]Site-reported based on the MSCT and is defined as defined as: none = no aortic annular or LVOT calcium, any calcification is limited to the aortic valve leaflets; mild = small and non-protruding calcium confined to the aortic valve annulus; moderate = aortic annular or LVOT calcium protruding > 1 mm into the lumen; severe = extensive LVOT calcium protruding > 1 mm into the lumen.



CENTRAL ILLUSTRATION 1 | Three-year outcomes from the FORWARD PRO Study. FORWARD PRO Study patients with symptomatic severe aortic stenosis were treated by TAVI with the self-expanding, supra-annular Evolut PRO valve and followed for 3 years. All-cause mortality or disabling stroke was monitored at years 1, 2, and 3 of the study and reported as number of events with Kaplan-Meier estimates (%). KM, Kaplan-Meier; PVL, paravalvular leak; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TAVI, transcatheter aortic valve implantation. [Color figure can be viewed at wileyonlinelibrary.com]

4.1 | Study Limitations

FORWARD PRO was a post-market study with inherent limitations. Participating sites were experienced TAVI centers that used multiple transcatheter valve platforms. Local multidisciplinary heart teams determined patient eligibility for TAVI and device selection. Even though an independent clinical events committee and echocardiography core laboratory adds value to the reported data, the overall loss to clinical follow-up (13%) and the availability of echocardiography imaging at 3 years in 60% of patients reflects the challenges in contemporary clinical practice, that were even amplified by the ongoing COVID-19 pandemic that imposed lockdown measures that precluded hospital visits for echocardiography. Also notable is that the average age of the patients at 3 years of follow-up was approximately 85 years, which affected patient mobility and compliance to planned follow up visits. To mitigate the variability of actual clinical practice across different participating sites, the study set very specific requirements for the collection of echocardiographic data within study-defined visit windows. As a result, data from any unscheduled echocardiograms that may have been performed were not collected.

5 | Conclusions

In clinical practice TAVI with the Evolut PRO valve is associated with favorable clinical outcomes and excellent haemodynamic performance out to 3 years. Calcium burden and less oversizing are associated with PVL. The improvement in PVL over time is intriguing and requires further research. Central Illustration 1.

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Ethics Statement

As stated in the "Methods" section: "*The study followed the Declaration of Helsinki principles, and all patients signed an informed consent or data release form. The study was compliant to the ISO 14155:2011 international standard and to the local laws and regulations of the countries it was conducted in, including those for data protection.*"

Conflicts of Interest

Prof. Van Mieghem has received institutional grant support from Abbott Vascular, Edwards Lifesciences, Boston Scientific, Daiichi Sankyo, Astra Zeneca, PulseCath BV and Medtronic and advisory fees from Abbott Vascular, Boston Scientific, Daiichi Sankyo, Abiomed, Amgen, Anteris, JenaValve, PulseCath BV and Medtronic. Stephan Windecker reports research, travel or educational grants to the institution without

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Data Availability Statement

The data, analytical methods, and study materials are owned by the study sponsor and therefore will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.