jaa Just accepted article

EuroIntervention

Title: Real-World Experience with the Evolut PRO Self-Expanding Transcatheter Aortic Valve: The International FORWARD PRO Study.

Authors: Ganesh Manoharan, MBBCh, M.D; Eberhard Grube, M.D, PhD; Nicolas M. Van Mieghem, M.D, PhD; Stephen Brecker, M.D; Claudia Fiorina, M.D; Ran Kornowski, M.D; Haim Danenberg, M.D; Hendrik Ruge, M.D; Holger Thiele, M.D; Patrizio Lancellotti, M.D, PhD; Lars Søndergaard, M.D, PhD; Corrado Tamburino, M.D, PhD; Jae K. Oh, M.D; Yunhua Fan, MS; Stephan Windecker, M.D

DOI: 10.4244/EIJ-D-20-00279

Citation: Manoharan G, MBBCh, Grube E, Van Mieghem NM, Brecker S, Fiorina C, Kornowski R, Danenberg H, Ruge H, Thiele H, Lancellotti P, Søndergaard L, Tamburino C, Oh JK, Fan Y, Windecker S. Real-World Experience with the Evolut PRO Self-Expanding Transcatheter Aortic Valve: The International FORWARD PRO Study. *EuroIntervention* 2020; Jaa-821, 2020, doi: 10.4244/EIJ-D-20-00279

Manuscript submission date: 13 March 2020

Revisions received: 24 June, 29 July 2020

Accepted date: 30 July 2020

Online publication date: 04 August 2020

Title: Real-World Experience with the Evolut PRO Self-Expanding Transcatheter Aortic Valve: The International FORWARD PRO Study

Running Title: Real-world Use of the Evolut PRO Valve

Authors: Ganesh Manoharan[1], MBBCh, MD; Eberhard Grube[2], MD, PhD; Nicolas M. Van Mieghem[3], MD, PhD; Stephen Brecker[4], MD; Claudia Fiorina[5], MD; Ran Kornowski[6], MD; Haim Danenberg[7], MD; Hendrik Ruge[8], MD; Holger Thiele[9], MD; Patrizio Lancellotti[10], MD, PhD; Lars Søndergaard[11], MD, PhD; Corrado Tamburino, MD, PhD[12]; Jae K. Oh, MD[13]; Yunhua Fan, MS[14]; Stephan Windecker, MD[15]

Affiliations:

[1]Regional Cardiology Department, Royal Victoria Hospital, Belfast, United Kingdom;
[2]Department of Medicine, University of Bonn, Bonn, Germany;
[3]Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands;
[4]Cardiology Clinical Academic Group, Saint George's Hospital, London, United Kingdom;
[5]Cardiothoracic Department, Spedali Civili Hospital of Brescia, Brescia, Italy;
[6]Department of Cardiology, Rabin Medical Center – Beilinson Hospital, Petah Tikva, Israel;
[7]Department of Interventional Cardiology, Hadassah Medical Organization, Jerusalem, Israel;
[8]Department of Cardiovascular Surgery, German Heart Center Munich at the Technical University of Munich, Munich, Germany;
[9]Department of Cardiology, Heart Center Leipzig at University of Leipzig and Leipzig Heart Institute, Leipzig, Germany;
[10]Department of Cardiology; University of Liege Hospital, GIGA Cardiovascular Sciences, CHU Sart Tilman, Liège, Belgium;
[11]Department of Cardiology, Rigshospitalet, Copenhagen, Denmark;
[12]Department of Cardiology, Gaspare Rodolico Hospital – Catania, Catania, Italy;
[13]Department of Cardiology, Mayo Clinic, Rochester, MN, USA;
[14]Department of Statistics, Medtronic, Minneapolis, MN, USA;
[15]Department of Cardiology, University Hospital Bern, Bern, Switzerland

Funding: Medtronic (Minneapolis, MN) funded the FORWARD PRO study.

ClinicalTrials.gov Identifier: NCT03417011

Address for Correspondence:
Ganesh Manoharan MBBCh, MD, FRCP(I), FRCP(Edin)
Cardiology Department
Royal Victoria Hospital
Grosvenor Road
Belfast BT12 6BA UK
gmanoharan@msn.com

DISCLOSURES: Dr. Manoharan has served as a proctor for Medtronic and Abbott; 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; Prof. Van Mieghem has received grant support from Abbott Vascular, Boston Scientific, Edwards Lifesciences and Medtronic and advisory fees from Abbott, Boston Scientific, Pulse Cath BV and Medtronic; Dr. Brecker has received consultant fees from Medtronic, Boston Scientific and Meril Life Sciences; Dr. Fiorina has no conflicts to report; Dr. Kornowski has no conflicts to report; Dr. Danenberg is a clinical proctor for Medtronic; Dr. Ruge has no conflicts to report; Prof. Thiele has no conflicts to report; Prof. Lancellotti has no conflicts to report; Prof. Søndergaard has no conflicts to report; Dr. Tamburino reports personal fees from Medtronic during the conduct of the study and personal fees from Medtronic outside the submitted work; Dr. Oh has received research support for the echocardiographic core laboratory from Medtronic; Ms. Fan is an employee and shareholder of Medtronic, plc; Prof. Windecker has received grant support from Abbott, Amgen, Bayer, Biotronik, BMS, Boston Scientific, Cardinal Health, CSL Behring, Daiichi Sankyo, Edwards LifeSciences, Johnson&Johnson, Medtronic, Polares Medical, Querbeet, Sanofi and Terumo outside the submitted work.

ABSTRACT

Aims: The Evolut PRO is a new transcatheter heart valve with an outer pericardial wrap intended to reduce paravalvular leak and facilitate tissue ingrowth. We evaluated clinical performance and safety of the Evolut PRO valve in standard practice.

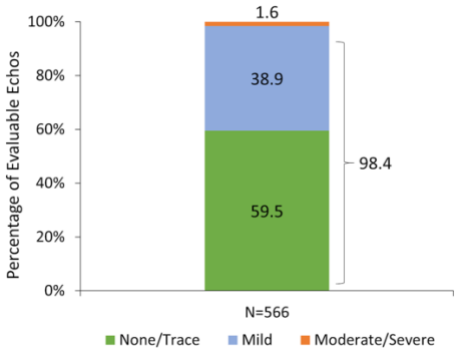
Methods and results: FORWARD PRO is a prospective, multinational, multicenter observational study. Transcatheter aortic valve implantation with the Evolut PRO valve (23-, 26-, or 29-mm) was attempted in 629 non-consecutive patients from 39 centers from February 2018 to January 2019. The primary endpoint was the rate of all-cause mortality at 30 days compared to a prespecified performance goal. An independent Clinical Events Committee adjudicated safety endpoints based on VARC-2 definitions. All echocardiograms were centrally assessed by an independent core laboratory (Mayo Clinic, Rochester, MN).

Baseline characteristics include mean age 81.7±6.1 years, 61.8% female, STS score 4.7%±3.3%, and 33.6% were frail. All-cause mortality at 30 days was 3.2% was lower than the prespecified performance goal of 5.5% (p=0.004). Greater than mild AR was present in 1.8% of patients at discharge.

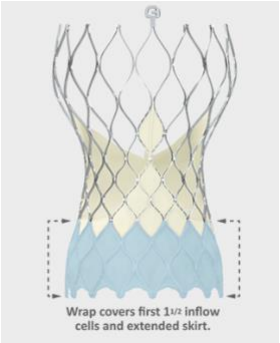
Conclusions: The FORWARD PRO study confirmed the safety and efficacy of the Evolut PRO transcatheter aortic valve system with an external pericardial wrap.

KEY WORDS

Aortic stenosis; TAVI; Transthoracic echocardiogram; Transesophageal echocardiogram



Panel A



Panel B

CONDENSED ABSTRACT

The FORWARD PRO is a prospective, multinational, independently adjudicated study investigating the supra-annular, self-expanding and repositionable Evolut PRO valve in routine clinical practice. Baseline characteristics include mean age 81.7±6.1 years, 61.8% female, mean STS score of 4.7%±3.3%, and 33.6% of patients were considered frail. Treatment with the device was attempted in 629 non-consecutive patients. Majority were treated by conscious sedation (80.1%) and by iliofemoral access (97.0%). All-cause mortality at 30 days was 3.2%. Greater than mild AR was present in 1.8% of patients at discharge, confirming the safety and efficacy of the Evolut PRO valve.

ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation
AVG = aortic valve gradient
CEC = Clinical Event Committee
EOA = effective orifice area
NYHA = New York Heart Association
PVL = paravalvular leak
STS PROM = Society of Thoracic Surgeons Predicted Risk of Mortality
TAVI = transcatheter aortic valve implantation
VARC = Valve Academic Research Consortium

INTRODUCTION

Procedure planning with computed tomography (CT), optimal valve size selection, repositionable valve technology and adherence to 'best practices' to optimize transcatheter aortic valve implantation (TAVI) have improved overall outcomes and the rates of paravalvular leak (PVL), compared with early TAVI studies[1,2]. However, while in the intermediate and low risk studies[3-6], the overall mortality outcomes were similar between TAVI and surgery, the rates of PVL were less with surgical valves.

Technological iterations are being made to further mitigate the risk of PVL. The addition of an external pericardial wrap to the Evolut R valve resulted in the next generation Evolut PRO transcatheter aortic valve system (Medtronic, Minneapolis, Minnesota). The Evolut PRO system retains all the characteristics of its predecessor (supra-annular valve function, repositionable and low-profile delivery system via the InLine sheath) and has an outer pericardial wrap at the inflow portion of the valve.

Initial use of the Evolut PRO valve in 60 patients in the US showed that 72.4% of patients had no or trace aortic regurgitation (AR) at 30 days[7], whilst maintaining the safety profile of the procedure. Use of the Evolut PRO valve in a large cohort of patients from the US STS /ACC/ TVT Registry also showed that compared to the Evolut R valve, the Evolut PRO valve had lower rates of AR at 30 days[8].

The FORWARD PRO study evaluated the clinical performance and safety of the Evolut PRO valve in a larger cohort of patients using standard clinical practice.

METHODS

Study Details

FORWARD PRO is a prospective, single-arm, multi-center, interventional post-commercialization study. Patient selection was based on the Evolut PRO system Instructions for Use. Sites were instructed to enroll consecutive patients and use a Medtronic valve. Eligible patients had symptomatic native AV stenosis or a failed surgical AV bioprosthesis (stenotic and/or insufficient) requiring replacement, and were at high or greater risk for surgery per the heart team, or were >75 years old and at intermediate risk for surgery (STS PROM≥4% or with an estimated hospital mortality ≥4% per the heart team). Additional conditions such as frailty were considered[9]. Emergency procedures and patients with a life expectancy of <1 year were not allowed.

An independent Clinical Events Committee (CEC) adjudicated deaths and safety endpoint-related events. The study sponsor (Medtronic) performed risk-based monitoring that included 100% monitoring of patient consent, primary and secondary-related endpoints and study-specific adverse events. Patients underwent clinical evaluations at baseline, hospital discharge and 30 days and will be followed for 5 years.

The FORWARD PRO steering committee (G.M., E.G., N.V.M., P.L., L.S., C.T., S.W.) designed the study in collaboration with the sponsor and had oversight of study activities. The study followed the Declaration of Helsinki principles and all patients signed an informed consent. The corresponding author decided to submit this manuscript for publication.

Study Device

The Evolut PRO is a repositionable, self-expanding supra-annular valve within a Nitinol frame and was available in 3 sizes during the study; 23-, 26- or 29-mm to treat aortic annuli diameters of 18–26 mm. An outer porcine pericardial wrap, 1.5 cells in height, was sutured to the inflow portion of the valve frame to diminish post-TAVI PVL. To assist with accurate positioning, the valve can be partially or fully recaptured until released from the delivery system. The valve could be implanted using an 16F equivalent EnVeo R InLine Sheath (Medtronic) in access vessels with a diameter ≥5.5 mm or a 20F standard sheath in diameters ≥6 mm. The decision to use the InLine or a separate introducer sheath was at the operators' discretion. Implant procedures were performed per the standard procedures of the implanting physicians.

Study Procedures

It was required that all patients undergo multislice CT prior to the procedure for proper device sizing and procedural planning. Transthoracic echocardiography was performed prior to the procedure and before hospital discharge and centrally assessed by an independent core laboratory (Mayo Clinic, Rochester, Minnesota). An integrated approach using color flow, pulsed-wave and continue-wave Doppler was used to assess the severity of AR[10]. The unifying 5-class grading scheme was used to grade AR[11]. The modified Rankin score[12] was performed at baseline, discharge, every follow-up visit and 90 days after the onset of any confirmed or suspected neurological event.

Endpoints

The primary endpoint was the rate of all-cause mortality at 30 days compared with a prespecified performance goal of 5.5%;the upper 2-sided 95% limit from the Evolut R US Study[13]. Secondary endpoints include the proportion of patients with <mild AR at discharge compared with a prespecified performance goal of 67.1%[14]. Additional secondary endpoints include the Valve Academic Research Consortium (VARC-2)[15] composite safety endpoint at 30 days and its components; death, stroke, life-threatening bleeding, major-vascular complication, stage 2 or 3 acute kidney injury, coronary artery obstruction requiring intervention, or valve-relate dysfunction requiring repeat aortic-valve procedure. Permanent pacemaker implantations (PPI), forward flow valve haemodynamics, prosthesis-patient mismatch (PPM) per VARC-2[15] and New York Heart Association (NYHA) functional class are also reported.

Statistical Analysis

The primary analysis cohort for this study comprises patients who underwent attempted implant of an Evolut PRO valve. Haemodynamic assessments are reported for implanted patients. For the primary endpoint, a sample size of 564 patients was required to attain 90% power in a one-sided test at the 0.05 level of significance, which was increased to 600 to account for attrition. The one-sided exact binomial test was performed for the primary endpoint. Additionally, the Kaplan-Meier event rate for 30-day all-cause mortality was presented.

The secondary haemodynamic endpoint of the incidence of no/trace AR at discharged was compared to a 1-sided test at the 0.025 significance level. Baseline categorical variables are presented as percentages and continuous variables as mean±standard deviations. Event rates are reported as Kaplan-Meier estimates. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Patients

There were 638 patients enrolled at 39 centers in 14 countries between February 2018 and January 2019, of which 629 underwent attempted implant (**Figure 1)**. The mean age was 81.7±6.1 years, 61.8% were women, and the mean STS PROM was 4.7%±3.3%. Most patients (64.3%) had NYHA functional class III or IV and 33.6% were frail (**Table 1)**.

Procedural Characteristics

Of the 629 patients, 610 (97.0%) were implanted with the Evolut PRO valve, 15 patients received a non-study valve, and 4 were not implanted with a TAV; 1 had a major vascular complication requiring surgical repair, 1 experienced a femoral dissection, 1 had a cardiac tamponade after pre-dilation during the procedure, and in 1 patient only a percutaneous coronary intervention was performed (**Figure 1)**. These 19 patients were followed for 30 days and then exited from the study.

Most patients were implanted via iliofemoral access (97.0%) using local anesthesia/conscious sedation (80.1%) **(Table 2)**. The repositioning function of the Evolut PRO valve was used in 182 patients (29.3%). Pre-implant balloon valvuloplasty was performed in 34.0% and post-implant dilation was performed in 31.1% of patients. There were 5 patients (0.8%) who received 2 valves during the procedure; these were due to valve embolization in 2 patients, valve migration in 1, and ectopic valve deployment in 2 patients.

30-Day Endpoints and Outcomes

The primary endpoint of all-cause mortality at 30 days was 3.2% (one-sided 95% upper CI= 4.6%), significantly lower than the performance goal of 5.5%, p=0.004 (**Table 3 and Figure 2)**. Cardiovascular death occurred in 2.7% of patients. The VARC-2 composite safety endpoint rate was 9.4% (**Table 3)**.

Disabling stroke was observed in 18 patients (2.9%), of which 7 died within 30 days. The major vascular complication rate was 3.0%. During the procedure, 1 patient experienced a coronary occlusion (0.2%). There were no cases of valve related dysfunction requiring a repeat procedure. A new permanent pacemaker was implanted in 116 patients (20.7%), of which 25 (21.7%) had right bundle branch block at baseline. The NYHA class improved in most patients (77.9%), with 55.4% of patients reporting NYHA class I at 30 days (**Figure 3)**.

Haemodynamics

At discharge, the mean aortic valve gradient (AVG) was 7.9±4.7 mm Hg and the mean effective orifice area (EOA) was 2.1±0.6 cm^2 (**Figure 4A)**. The secondary endpoint of no or trace AR was 59.2% (one-sided 97.5% lower confidence limit of 55.1%) as compared to the performance goal of 67.1% (p >0.99) was not met. The rate of moderate or severe AR was 1.8% (**Figure 4B).** Severe prosthesis-patient mismatch was present in 17 patients (4.4%), with no differences in the distribution of the severity of PPM between men and women.

DISCUSSION

We report 30-day procedural and clinical outcomes from the FORWARD PRO study, the largest study of the Evolut PRO valve with independent echocardiographic core laboratories assessments and independent CEC-adjudicated results. Key findings include lower than expected all-cause mortality of 3.2%; a low disabling stroke rate of 2.9%; low major vascular

complication rate of 3.0% and favorable aortic valve haemodynamics, with an AVG of 7.9±4.7 mmHg and EOA of 2.1±0.6 cm^2, and moderate or severe AR of 1.8%. However, the pre-defined performance goal of no or trace AR was not met.

The 30-day mortality rate of 3.2% in our study was significantly lower than the prespecified performance goal of 5.5%, and lower than the STS PRO of 4.7±3.3%. This was comparable to reports of self-expanding and balloon-expandable valves in intermediate-risk patients [3,6,14].

The addition of an outer pericardial wrap to mitigate PVL increased the device outer diameter by 2 French sizes (currently 16F equivalent). Despite this, the major vascular complication rate remained low at 3.0%. This was lower than previous reports from real-world use of the Evolut R in the FORWARD study (6.5%)[14] or the SAPIEN 3 valve (Edwards LifeSciences, Irving, California) in the SOURCE 3 Registry (4.1%)[16]. This may in part be due to the smaller outer diameter and resultant trauma caused by advancing the delivery system 'sheathless', using the InLine delivery system in most patients (85.9%) and increased operator experience in managing vascular access. The rate of life-threatening or disabling bleeding was also low (3.3%).

It has been hypothesized that the external pericardial wrap could lessen desired friction when interacting with the surrounding tissue, resulting in reduced stability of the valve during deployment. Yet the proportion of patients in which the resheath/recapture feature was used in the FORWARD PRO Study was 29.3%, comparable to that reported from the FORWARD Study of the Evolut R valve (25.6%)[14]. Additionally, the incidence of valve embolization or migration was similar in this study of the Evolut PRO valve (0.5%) and in the FORWARD Study

of the Evolut R valve (0.9%). There were no patients who required a repeat procedure. All these observations would suggest that the stability of the Evolut PRO system is not affected by the pericardial wrap.

A disabling stroke was observed in 18 patients (2.9%) in the present study and is similar to other contemporary TAVI studies of the same valve[8,14], and was 1.4%, 3.2% and 1.2% in the FORWARD study, Placement of Aortic Transcatheter Valves (PARTNER) 2 Trial and the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) Trial, respectively[3,6,14]. There were no strokes in patients treated using an embolic protection device; however, the numbers are too small to draw meaningful conclusions. Coronary artery occlusion was reported in 1 patient. There was no incidence of annular rupture or valve thrombosis observed in the FORWARD PRO study.

Haemodynamic Assessments

All aortic-valve echocardiographic measures in the FORWARD PRO study were core-laboratory assessed. Previous generations of the self-expanding supra-annular valve have produced excellent haemodynamics post deployment, with discharge AVG and EOA in the CoreValve US Pivotal Extreme Risk Trial of 9.6±4.4 mm Hg and 1.9± 0.6 cm^2, respectively[17]. Similar findings were observed in the FORWARD Study using the Evolut R valve (8.5±5.6 mm Hg and 1.9±0.6 cm^2 respectively)[14]. It has been hypothesized that the external wrap on the Evolut PRO device could adversely impact the forward flow haemodynamics. Reassuringly, we observed low AVGs (7.9±4.7 mm Hg) and EOAs (2.1±0.6 cm^2) in our study, consistent with other reports of the Evolut PRO valve[7,8]. Moreover, most patients had mild or less pre-discharge PVL (98.4%). These findings are like that observed in the FORWARD study that

reported 98.1% of patients with mild or less AR. This study, however, did not meet its secondary endpoint of no or trace AR at discharge (59.2%) as compared to the performance goal of 67.1% (p >0.99), which was based on the results of the FORWARD study that evaluated the predicate Evolut R valve. This is similar to a single center report from Germany comparing 148 Evolut R valve patients with 74 Evolut PRO valve patients[18] but contrary to the findings of the smaller US Evolut PRO study, where initial experience in 60 patients demonstrated no/trace PVL in 72.4% of patients[7]. Possible reasons for this difference in this study may include: 1. Degree of annular calcification and distribution–the significantly larger and less selected cohort of patients would have included a more heterogeneous group of patients, with larger calcification burden, adversely impacting the PVL observed; 2) More patients in the Forrest et al cohort underwent pre-dilation as compared to this study (52% vs 34%) while the rate of post-dilation was similar (27% vs 31%) and perhaps pre-dilation improves device contact with the surrounding anatomy and resultant seal; 3) Assessment of PVL/AR was extremely sensitive in the current study and the differentiation between trace and mild AR is difficult to make. The addition of an external pericardial wrap on the Evolut PRO valve did not adversely affect the new post-TAVI pacemaker rate of 20.7%. Previous generations of this device, by adhering to 'best practice' to reduce conduction disturbances, have reported permanent pacemaker rates of 21.6% with the CoreValve device[17] and 17.5% with the Evolut R device, respectively[14]. The new PPI rate reported here could also be due to a large (30%) proportion of patients with pre-existing conduction disturbances.

Study Limitations

FORWARD PRO is a real-world, contemporary standard practice study. Patient selection bias could have been introduced into the study as selection was based on local heart team evaluation. The utilization of an independent echocardiographic core laboratory and an independent CEC adjudication, however, ensured the unbiased verification of the echocardiographic data and clinical events.

CONCLUSIONS

The 30-day results of the FORWARD PRO study, evaluating the Evolut PRO valve, supports its safety and clinical effectiveness in treating symptomatic patients with severe aortic stenosis at intermediate, high or greater risk for surgical aortic valve replacement. Longer term follow-up will be required to further evaluate these findings.

Acknowledgements: 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.

IMPACT ON DAILY PRACTICE

Our analysis from the FORWARD PRO study reported a low rate of the primary endpoint of all-cause mortality (3.2%) with real-world use of the Evolut PRO valve, which can be resheathed and/or recaptured to aid in accurate valve positioning. This valve also has an outer pericardial wrap with the intent to reduce PVL. In our study, only 1.6% of patients had moderate or severe PVL at discharge. It is also recognized that the PVL rates observed with this genre of valve may

improve with time. Longer-term follow-up data will help further evaluation of the safety, efficacy and PVL rates profile of this novel device.

REFERENCES

1. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J, Jr., Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK, Investigators USCC. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014;370:1790-1798.

2. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364:2187-2198.

3. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG, Investigators P. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016;374:1609-1620.

4. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, Leipsic J, Hahn RT, Blanke P, Williams MR, McCabe JM, Brown DL, Babaliaros V, Goldman S, Szeto WY, Genereux P, Pershad A, Pocock SJ, Alu MC, Webb JG, Smith CR, Investigators P. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 2019.

5. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, Bajwa T, Heiser JC, Merhi W, Kleiman NS, Askew J, Sorajja P, Rovin J, Chetcuti SJ, Adams DH, Teirstein PS, Zorn GL, 3rd, Forrest JK, Tchetche D, Resar J, Walton A, Piazza N, Ramlawi B, Robinson N, Petrossian G, Gleason TG, Oh JK, Boulware MJ, Qiao H, Mugglin AS, Reardon MJ, Evolut Low Risk Trial I. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med* 2019;380:1706-1715.

6. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Sondergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, Chetcuti S, Gleason T, Heiser J, Lange R, Merhi W, Oh JK, Olsen PS, Piazza N, Williams M, Windecker S, Yakubov SJ, Grube E, Makkar R, Lee JS, Conte J, Vang E, Nguyen H, Chang Y, Mugglin AS, Serruys PW, Kappetein AP, Investigators S. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2017;376:1321-1331.

7. Forrest JK, Mangi AA, Popma JJ, Khabbaz K, Reardon MJ, Kleiman NS, Yakubov SJ, Watson D, Kodali S, George I, Tadros P, Zorn GL, 3rd, Brown J, Kipperman R, Saul S, Qiao H, Oh JK, Williams MR. Early outcomes with the Evolut PRO repositionable self-expanding transcatheter aortic valve with pericardial wrap. *J Am Coll Cardiol Intv* 2018;11:160-168.

8. Forrest JK, Kaple RK, Tang GHL, Yakubov SJ, Nazif TM, Williams MR, Zhang A, Popma JJ, Reardon MJ. Three generations of self-expanding transcatheter aortic valves: A report from the STS/ACC TVT Registry. *J Am Coll Cardiol Intv* 2020;13:170-179.

9. Afilalo J, Mottillo S, Eisenberg MJ, Alexander KP, Noiseux N, Perrault LP, Morin JF, Langlois Y, Ohayon SM, Monette J, Boivin JF, Shahian DM, Bergman H. Addition of frailty and disability to cardiac surgery risk scores identifies elderly patients at high risk of mortality or major morbidity. *Circ Cardiovasc Qual Outcomes* 2012;5:222-228.

10. Little SH, Oh JK, Gillam L, Sengupta PP, Orsinelli DA, Cavalcante JL, Chang JD, Adams DH, Zorn GL, 3rd, Pollak AW, Abdelmoneim SS, Reardon MJ, Qiao H, Popma JJ. Self-expanding transcatheter aortic valve replacement versus surgical valve replacement in patients at high risk for surgery: a study of echocardiographic change and risk prediction. *Circ Cardiovasc Interv* 2016;9:DOI: 10.1161/CIRCINTERVENTIONS.1115.003426.

11. Pibarot P, Hahn RT, Weissman NJ, Monaghan MJ. Assessment of paravalvular regurgitation following TAVR: a proposal of unifying grading scheme. *JACC Cardiovasc Imaging* 2015;8:340-360.

12. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19:604-607.

13. Popma JJ RM, Khabbaz K, Harrison JK, Hughes GC, Kodali S, George I, Deeb Gm, Chetcuti S, Kipperman R, Brown J, Qiao H, Slater J, Williams MR. Early clinical outcomes after transcather aortic valve replacement using a novel self-expanding bioprosthesis in patients with severe aortic stenosis suboptimal for surgery: Results of the Evolut R US Study. *J Am Coll Cardiol Intv* 2017;10:268-275.

14. Grube E, Van Mieghem NM, Bleiziffer S, Modine T, Bosmans J, Manoharan G, Linke A, Scholtz W, Tchetche D, Finkelstein A, Trillo R, Fiorina C, Walton A, Malkin CJ, Oh JK, Qiao H, Windecker S, Investigators FS. Clinical outcomes with a repositionable self-expanding transcatheter aortic valve prosthesis The International FORWARD Study. *J Am Coll Cardiol* 2017;70:845-853.

15. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodes-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB.

Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *Eur Heart J* 2012;33:2403-2418.

16. Wendler O, Schymik G, Treede H, Baumgartner H, Dumonteil N, Ihlberg L, Neumann FJ, Tarantini G, Zamorano JL, Vahanian A. SOURCE 3 Registry: Design and 30-Day results of the European post approval registry of the latest generation of the SAPIEN 3 transcatheter heart valve. *Circulation* 2017;135:1123-1132.

17. Popma JJ, Adams DH, Reardon MJ, Yakubov SJ, Kleiman NS, Heimansohn D, Hermiller J, Hughes GC, Harrison JK, Coselli J, Diez J, Kafi A, Schreiber T, Gleason TG, Conte J, Buchbinder M, Deeb GM, Carabello B, Serruys PW, Chenoweth S, Oh JK, Investigators CUSC. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol* 2014;63:1972-1981.

18. Hellhammer K, Piayda K, Afzal S, Kleinebrecht L, Makosch M, Hennig I, Quast C, Jung C, Polzin A, Westenfeld R, Kelm M, Zeus T, Veulemans V. TheLatest evolution of the Medtronic Corevalve system in the era of transcatheter aortic valve replacement: Matched comparison of the Evolut PRO and Evolut R. *J Am Coll Cardiol Interv* 2018;11:2314-2322.

FIGURE LEGENDS

Figure 1. Title. Patients.

Figure 1. Caption. The primary analysis cohort for outcomes was the attempted implant cohort and for echocardiographic outcomes it was the implanted cohort. *See text for details.

Figure 2. Title. Primary endpoint of all-cause mortality at 30 days.

Figure 2. Caption. Kaplan Meier estimate of all-cause mortality. CL = confidence limit.

Figure 3. Title. New York Heart Association Functional Class to 30 Days

Figure 3. Caption. NYHA functional class at baseline and 30 days.

Figure 4. Title. Aortic Valve Haemodynamics

Figure 4. Caption. A) Aortic valve EOA and AVG at baseline and discharge; B) severity of AR per independent core laboratory assessment. Values reported as mean ± standard deviation. 98.2% of patients had less than mild AR.

TABLES

Table 1. Demographics and Baseline Clinical Characteristics.

Characteristic	N = 629
Age, years	81.7 ± 6.1
Body surface area, m^2	1.8 ± 0.2
Female	389 (61.8)
STS PROM, %	4.7 ± 3.3
< 4%	326 (51.8)
4% to 8%	238 (37.8)
≥ 8%	65 (10.3)
NYHA functional class	
I	29 (4.7)
II	190 (31.0)
III	371 (60.5)
IV	23 (3.8)
STS Risk Factors	
Unstable angina	6 (1.0)
Stable angina	79 (12.9)
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)
History of atrial fibrillation	210 (33.6)
Diabetes mellitus	213 (34.0)
Serum creatinine > 2 mg/dL	31 (4.9)
Dialysis	13 (2.1)
Chronic lung disease/COPD	158 (26.0)
Peripheral artery disease	95 (15.3)
Cerebrovascular disease	118 (18.9)
Other Comorbidities and Medical History	
Porcelain aorta*	27 (4.4)
Frailty	207 (33.6)

Characteristic	N = 629
Pulmonary hypertension†	205 (33.5)
Left ventricular ejection fraction, %	60.0 ± 11.0
Pre-existing permanent pacemaker or defibrillator	66 (10.5)
Assisted living	93 (14.8)
Baseline ECG	
Atrial fibrillation or flutter	124 (19.8)
Right bundle branch block	65 (10.4)
Left bundle branch block	54 (8.6)
1st Degree atrioventricular block	90 (14.4)
2nd or 3rd Degree atrioventricular block	6 (1.0)

Data presented as means ± standard deviation or no. (percentage) that reflect missing values. *Heavy circumferential calcification or severe atheromatous plaques of the entire ascending aorta extending to the arch such that aortic cross-clamping is not feasible. †Primary or secondary pulmonary hypertension with pulmonary artery systolic pressures greater than two-thirds of systemic pressure. COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association; STS PROM = The Society of Thoracic Surgery Predicted Risk of Mortality.

Table 2. Procedural Characteristics.

	N=629
Local anaesthesia	504 (80.1)
Iliofemoral access	610 (97.0)
Inline Sheath used alone	540 (85.9)
Concomitant PCI	23 (3.7)
Embolic protection	58 (9.2)
Resheath/recapture performed	182 (29.3)
Implanted valve size*	
23 mm	24 (3.9)
26 mm	192 (31.5)
29 mm	394 (64.6)
Pre-implant balloon valvuloplasty	214 (34.0)
Post-implant balloon dilation	195 (31.1)
NCS implant depth, mm†	4.8 ± 2.7 (455)
LCS implant depth, mm†	5.5 ± 2.7 (450)
More than 1 valve implanted	5 (0.8)

Data presented as no. (percentage) or mean ± standard deviation (no.).*610 patients implanted.
†By aortography.

Table 3. Clinical outcomes at 30 days.

	N = 629
All-cause mortality or disabling stroke	30 (4.8)
Cardiovascular mortality	17 (2.7)
Disabling stroke	18 (2.9)
VARC-2 Composite safety endpoint*	59 (9.4)
All-cause mortality	20 (3.2)
All stroke	24 (3.8)
Life-threatening or disabling bleeding	21 (3.3)
Major vascular complication	19 (3.0)
Acute kidney injury stage 2 or 3	7 (1.1)
Coronary artery obstruction	1 (0.2)
Valve-related dysfunction requiring repeat procedure	0 (0.0)
Myocardial infarction	2 (0.3)
Valve thrombus	0 (0.0)
Valve embolization or migration*	3 (0.5)
Ectopic valve deployment*	2 (0.3)
Permanent pacemaker implanted†	118 (18.9)
Permanent pacemaker implanted‡	116 (20.7)

Data presented as no. of patients with an event (Kaplan-Meier estimate). *Per VARC-2[15]. †Includes patients with permanent pacemaker or implantable cardioverter defibrillator at baseline. ‡Excludes patients with permanent pacemaker at baseline.

Figure 1

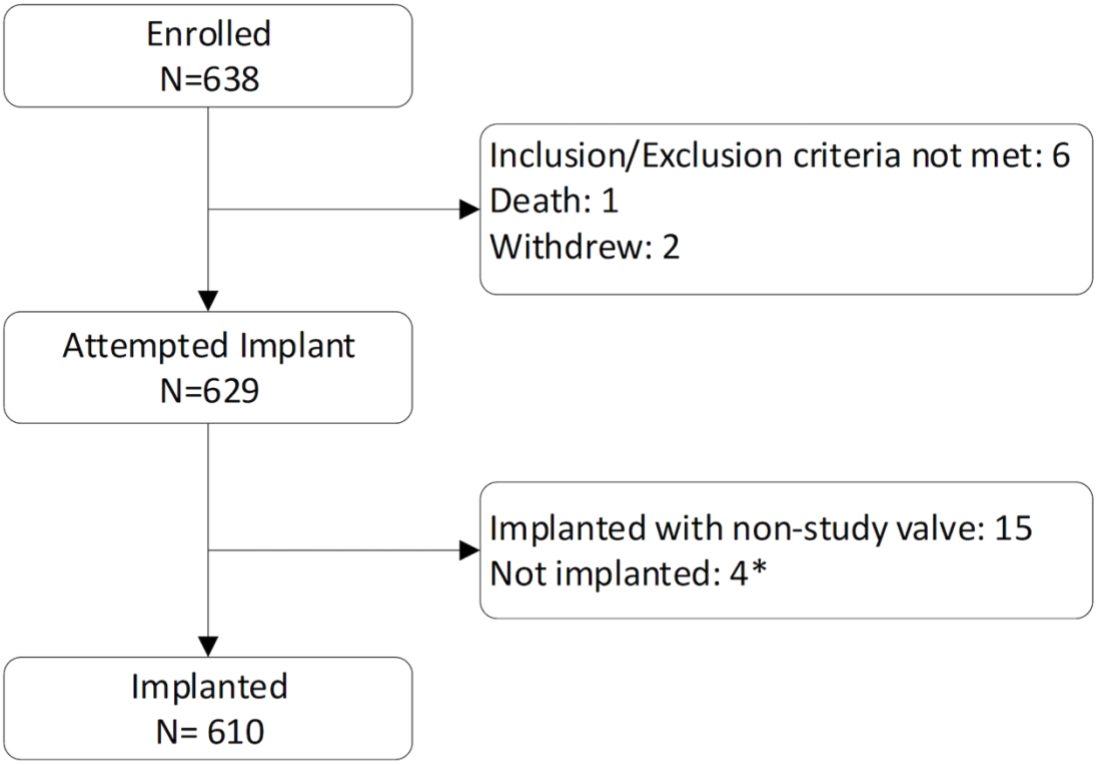


Figure 2

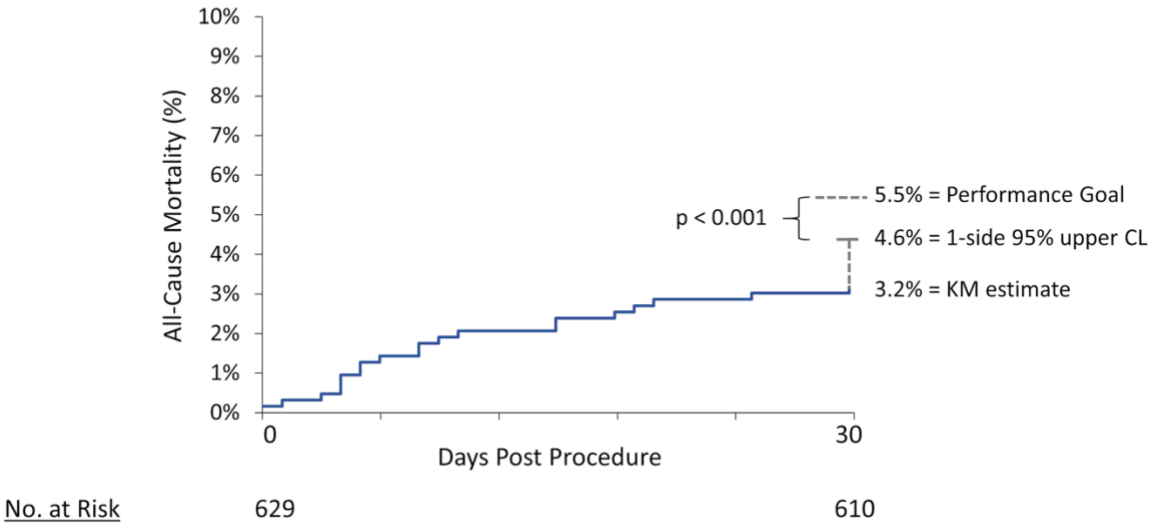


Figure 3

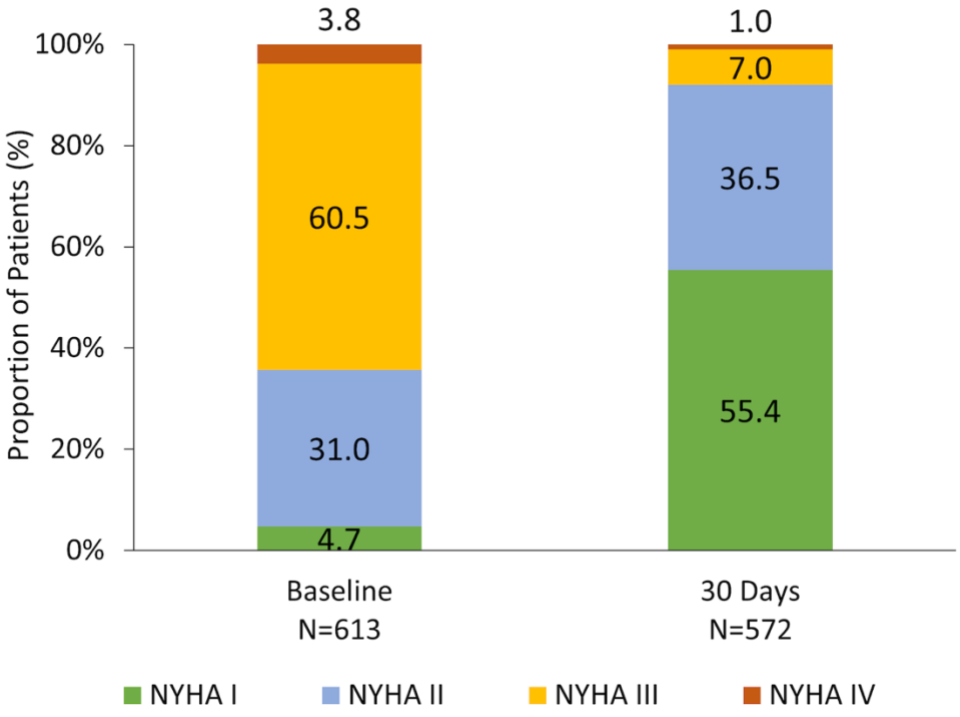
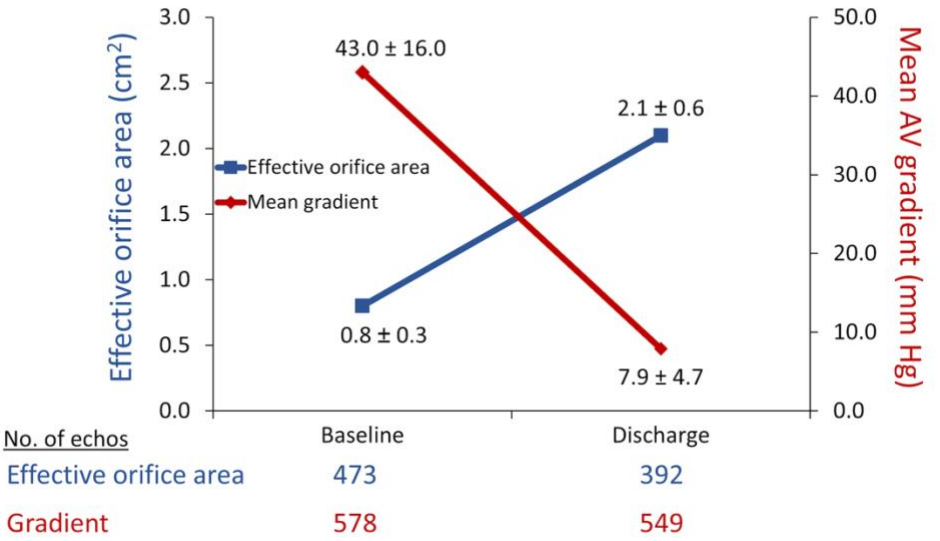


Figure 4A



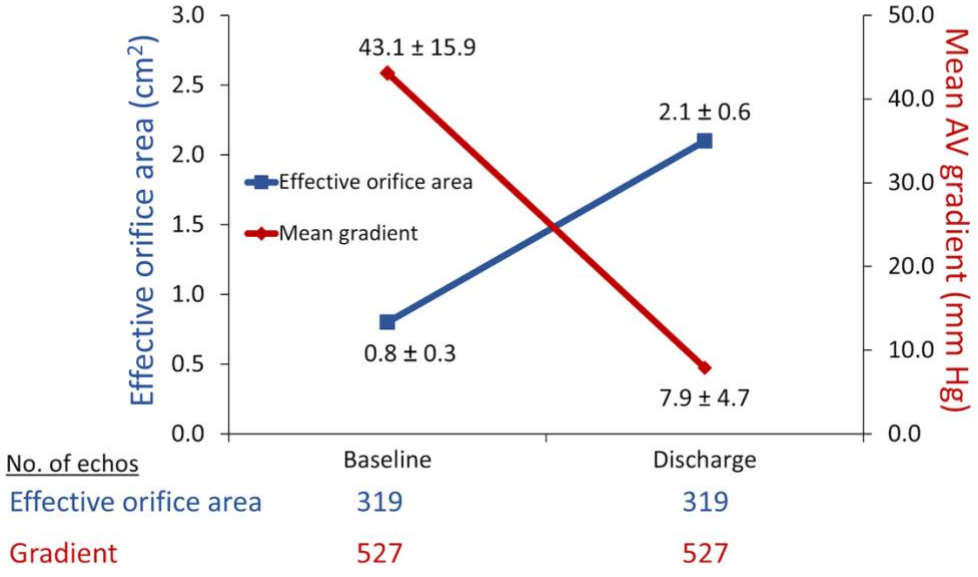


Figure 4B