The Early neo2 Registry

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ORIGINAL RESEARCH

The Early neo2 Registry: Transcatheter Aortic Valve Implantation With ACURATE *neo2* in a European Population

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BACKGROUND: ACURATE *neo2* is a transcatheter aortic valve implantation system consisting of a self-expanding bioprosthetic valve with supra-annular leaflet position and featuring innovations to facilitate placement accuracy and reduce paravalvular regurgitation.

METHODS AND RESULTS: The goal of the Early neo2 (Early neo2 Registry of the ACURATE neo2 TAVI Prosthesis) was to gather real-life data on safety and efficacy in a European transcatheter aortic valve implantation population treated with ACURATE *neo2*. Data were collected from 554 consecutive patients treated with ACURATE *neo2* at 12 European sites (mean age, 82 years; 66% women; mean European System for Cardiac Operative Risk Evaluation II, 4.5%±3.8%) between September 2020 and March 2021. The composite primary end point was the occurrence of any of the following: postoperative (in-hospital) paravalvular regurgitation grade ≥2, in-hospital acute kidney injury stage 3, postoperative pacemaker implantation, 30-day death, and 30-day stroke. The primary end point occurred in 12.6% of patients. The 30-day rates for all-cause death and all stroke were 1.3% and 2.7%, respectively, and 1.5% of patients exhibited stage 3 acute kidney injury. A total of 34 patients (6.2%) received a postoperative permanent pacemaker. Per core laboratory–adjudicated echocardiographic analysis, mean postoperative aortic valve gradient was 7.6±3.3 mm Hg, and 2.8% of patients exhibited paravalvular regurgitation grade ≥2.

CONCLUSIONS: In this report of postmarket use of the ACURATE *neo2* valve in a real-world transcatheter aortic valve implantation population, patients exhibited favorable postoperative hemodynamics and clinical outcomes and a low rate of postoperative pacemaker implantation.

Key Words: aortic regurgitation ■ aortic stenosis ■ TAVI

The safety and effectiveness of transcatheter valve implantation (TAVI) for treating aortic stenosis is well established,[1] and there are several bioprosthetic valve systems available to operators, each with features that may present a benefit in certain patients. The ACURATE *neo* valve (Boston Scientific, Marlborough, MA), a self-expanding bioprosthetic valve with supra-annular leaflet position, has demonstrated favorable clinical and echocardiographic outcomes with low death rates in early single-arm studies. A strength of ACURATE

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CLINICAL PERSPECTIVE

What Is New?

- The second-generation self-expanding ACURATE *neo2* transcatheter aortic valve implantation showed low gradients and low rates of paravalvular leak in a large European registry that included core laboratory analysis of the echocardiographic results.
- There were no coronary obstructions and a low number of new pacemakers.

What Are the Clinical Implications?

- The ACURATE *neo2* performs well in a real-world aortic stenosis population.

Nonstandard Abbreviations and Acronyms

ACURATE IDE	Safety and Effectiveness Study of ACURATE Valve for Transcatheter Aortic Valve Replacement
ACURATE Neo AS	ACURATE Neo AS Aortic Bioprosthesis for Implantation Using the ACURATE *neo* AS TF Transfemoral Delivery System in Patients With Severe Aortic Stenosis
Early neo2	Early neo2 Registry of the ACURATE neo2 TAVI Prosthesis
NEOPRO	A Multicenter Comparison of Acurate NEO Versus Evolut PRO Transcatheter Heart Valves
NEOPRO 2	A Multicenter Comparison of Acurate NEO2 Versus Evolut PRO Transcatheter Heart Valves 2
PVR	paravalvular regurgitation
SWEDEHEART	Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies
TAVI	transcatheter aortic valve implantation

neo is its hemodynamic performance. Due to its supra-annular leaflet positioning, ACURATE *neo* routinely achieves larger effective orifice areas and lower gradients than most valves with an intra-annular leaflet position.[2–4] However, in the recent Safety and Efficacy Comparison of Two TAVI Systems in a Prospective Randomized Evaluation (SCOPE 1 and SCOPE 2) studies, patients randomly assigned to treatment with ACURATE *neo* exhibited a higher incidence of moderate or greater paravalvular regurgitation (PVR) compared with those randomized to the Edwards Lifesciences Sapien 3 and Medtronic Evolut R/PRO devices, respectively.[4,5] This higher rate of PVR contributed to ACURATE *neo* missing the noninferiority primary end points in both studies.

Moderate or greater PVR has been linked to an increased risk of death after TAVI[6–8] and, as such, is a continuing area of concern. The ACURATE *neo2* valve, an evolution of ACURATE *neo* launched in Europe in September 2020, preserves the supra-annular valve positioning and simplified implant technique of the ACURATE platform and features radiopaque markers to aid reference in positioning, as well as augmented internal and external porcine pericardium sealing skirts to further reduce PVR (Figure). Recently, the ACURATE Neo AS (ACURATE Neo AS Aortic Bioprosthesis for Implantation Using the ACURATE *neo* AS TF Transfemoral Delivery System in Patients With Severe Aortic Stenosis) study demonstrated the safety and performance of the ACURATE *neo2* valve in patients with severe aortic valve stenosis, with a low rate of PVR and improved hemodynamics through 12 months.[9] However, there has been no large ACURATE *neo2* data set with core laboratory assessment presented after this CE-mark study. Here, we report the results of a large investigator-initiated European registry of TAVI with ACURATE *neo2*, which includes core laboratory–adjudicated echocardiographic data.

METHODS

Study Design

The Early neo2 (Early neo2 Registry of the ACURATE neo TAVI Prosthesis) was established to collect data from at least 500 consecutive patients with TAVI treated with ACURATE *neo2* at European sites where the valve was commercially available. The participating sites enrolled consecutive patients treated with ACURATE *neo2* starting from the commercial launch in September 2020. The registry protocol allowed all patients to be included, even those outside the CE-mark indication (eg, patients with bicuspid anatomy, valve-in-valve indications, pure aortic insufficiency). The study protocol included a 30-day clinical follow-up. The protocol was approved by locally appointed institutional review boards/ethics committees, with the main ethics application at the Swedish Ethical Review Authority. Patient consent was waived by the ethics committee. The study was registered at ClinicalTrials.

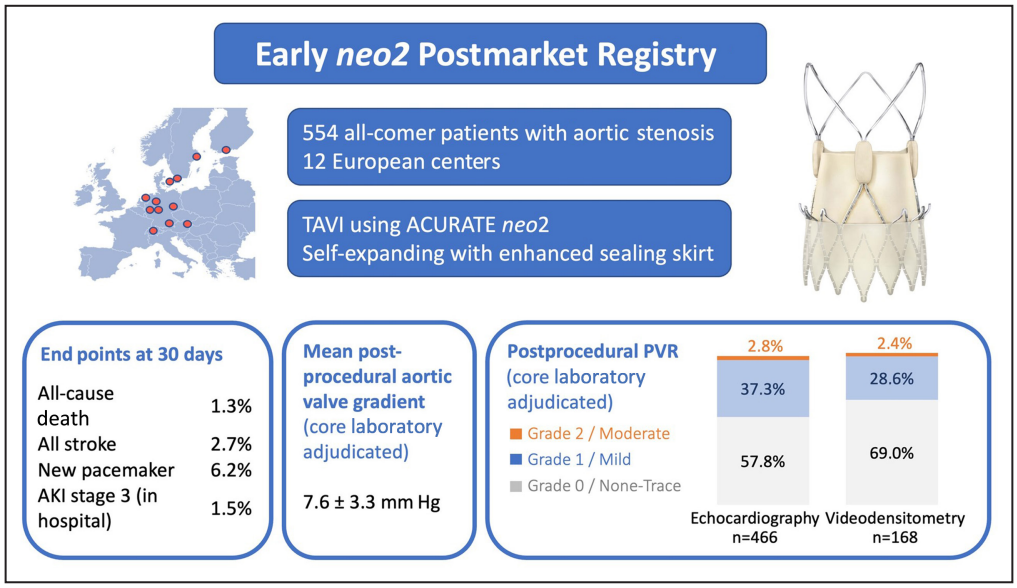

Figure. ACURATE *neo2* design and key study data.
The ACURATE *neo2* valve preserves the supra-annular leaflet positioning and simplified implant technique of the ACURATE platform and features augmented porcine pericardium sealing skirts to minimize PVR. Patients treated with ACURATE *neo2* in the Early neo2 registry exhibited favorable clinical outcomes, low postoperative aortic valve gradients, a low rate of pacemaker implantation, and reduced PVR. AKI indicates acute kidney injury; PVR, paravalvular regurgitation; and TAVI, transcatheter aortic valve implantation.

gov (NCT04810195), conducted in accordance with the International Conference for Harmonization Good Clinical Practice regulations and guidelines and the ethical principles outlined in the Declaration of Helsinki, and reported according to Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[10] The data that support the findings of this study are available from the corresponding author upon reasonable request.

Device Details

Like its predecessor, the ACURATE *neo2* transcatheter bioprosthetic aortic valve comprises a self-expanding nitinol frame with axial, self-aligning stabilization arches and supra-annular porcine pericardium leaflets (Figure). The upper crown is designed to capture the native leaflets, providing coronary clearance; the lower crown anchors the valve with minimal protrusion into the left ventricular outflow tract, to reduce the potential for conduction system interference.[11] To reduce PVR, the integrated internal and external porcine pericardium sealing skirts were augmented to provide active sealing and better conform to irregular calcified anatomy (Figure, Video S1). ACURATE *neo2* is available in 3 sizes (small/medium/large) to treat native aortic annuli 21 to 27 mm in diameter. Valve sizing was assessed at each site by computed tomography; final size selection was at the discretion of individual operators.

Statistical Analysis

Clinical outcomes data were collected according to Valve Academic Research Consortium-2 guidelines.[12] The composite primary end point includes occurrence of any of the following: postoperative (in-hospital) aortic insufficiency/PVR moderate or higher, postoperative (in-hospital) new permanent pacemaker implantation, in-hospital acute kidney injury (grade 3), 30-day death, and 30-day stroke. Predischarge echocardiograms (within 7 days of procedure) were analyzed by an independent core laboratory (CORRIB, Galway, Ireland) to evaluate aortic valve gradient, PVR, and other standard echocardiographic measures (eg, ejection fraction and dimensions). To further assess aortic insufficiency, the core laboratory also evaluated postoperative aortography from a subset of sites using quantitative videodensitometric angiography, an objective method that has been clinically validated in prior studies.[13,14] All baseline and outcome variables were summarized using descriptive statistics, and statistical analyses were performed with jamovi version 1.6 software.

RESULTS

Study Cohort

The registry collected data from 554 patients treated with ACURATE *neo2* between September 2020 and March 2021 at 12 European centers. Clinical follow-up

Table 1. Patient Demographics and Baseline Clinical Characteristics

Variable	Value (n/N)
Age, y	81.6±5.9 (554)
Sex, % female	66.0 (364/552)
STS score, % ±SD	4.0±3.2 (299)
EuroSCORE II, % ±SD	4.5±3.8 (548)
NYHA class III or IV	63.2 (350/554)
Diabetes, medically treated	32.1 (178/554)
COPD, moderate or severe	14.6 (81/554)
Previous stroke or TIA	13.0 (72/554)
Previous PCI	30.1 (141/468)
Previous cardiac surgery	9.2 (51/554)
Prior implanted pacemaker	9.9 (55/554)
History of atrial fibrillation	38.3 (212/554)
Indication valve-in-valve	2.2 (12/554)
Echocardiographic measurements (site reported)	
Mean aortic valve gradient, mm Hg ±SD	43.3±14.8 (549)
Aortic valve area (effective orifice area), cm^2 ±SD	0.72±0.17 (531)
Left ventricular ejection fraction, % ±SD	56.2±10.1 (547)
Aortic regurgitation grade >2	1.8 (10/546)
Bicuspid anatomy	2.2 (12/554)

Values reported are mean±SD (N) or % (n/N), unless otherwise specified. Baseline echocardiography was obtained before the procedure up to 3 months before the procedure. COPD indicates chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; NYHA class, New York Heart Association Functional Classification; and STS score, Society of Thoracic Surgeons short-term risk score.

Table 2. Procedural Characteristics and Periprocedural Outcomes

Measure	Value (n/N)
General anesthesia used	0.2 (1/554)
Contrast usage, mL ±SD	75±49 (541)
Access site, femoral	99.5 (551/554)
Valve size implanted	
Small (23 mm)	21 (115/554)
Medium (25 mm)	42 (231/554)
Large (27 mm)	37 (208/554)
>1 valve implanted*	0.9 (5/554)
Balloon predilatation	87 (482/554)
Postdilatation	36 (197/554)
Intraprocedural death†	0.2 (1/554)
Major vascular complications	3.4 (19/551)

Values reported are mean±SD (N) or % (n/N), unless otherwise specified. Values reported are procedural event rates, unless otherwise specified. TAVI indicates transcatheter aortic valve implantation.

*Second valve required during index procedure (ACURATE, n=1; non-study valve: n=4).

†In 1 patient, balloon aortic valvuloplasty led to annular rupture, shock, and subsequent cardiopulmonary resuscitation; TAVI was attempted, but efforts to salvage the patient were unsuccessful.

data at 30 days were available for 96% of patients (530/554), and echocardiographic data were available for 84% (466/554). The study population was generally representative of patients with aortic stenosis in contemporary European practice (Table 1), with mean European System for Cardiac Operative Risk Evaluation II of 4.5%±3.8% and mean Society of Thoracic Surgeons short-term risk score of 4.0%±3.2%. At baseline, 10% of patients had a prior pacemaker, and 38% had a history of atrial fibrillation. Per site-reported echocardiography at baseline, the mean aortic valve gradient was 43±15 mm Hg. Bicuspid valves were observed in 12 patients (2.2%). Baseline computed tomography showed an average perimeter-derived annular diameter of 23.7±1.7 mm. In 36 patients (4.7%), the annular diameter was below the lowest range of the official sizing recommendation (21 mm); 1 patient (0.2%) had an annular diameter above the upper range of the official sizing recommendation (27 mm).

Clinical and Echocardiographic Outcomes

Procedural details are reported in Table 2. Nearly all procedures (99.6%) were performed via the femoral approach, with 21% of patients implanted with an S (nominal 23 mm) valve, 41% implanted with an M (nominal 25 mm) valve, and 37% implanted with an L (nominal 27 mm) valve. The average oversizing was 1.6±0.8 mm, and the average cover index (100×[nominal prosthesis diameter–annulus diameter]/nominal prosthesis diameter) was 6.4±3.4%. Twelve patients (2.2%) had a cover index <1%. Balloon predilatation was performed in 87% of patients; postdilatation was performed in 36%. Five patients (0.9%) required implantation of >1 valve. There was 1 periprocedural death, for a rate of 0.2% (in this patient, balloon aortic valvuloplasty led to annular rupture, shock, and subsequent cardiopulmonary resuscitation; TAVI was attempted, but efforts to salvage the patient were unsuccessful). The in-hospital rate of all stroke was 2.2%. There were no instances of coronary obstruction. Table 3 presents postprocedural clinical and echocardiographic outcomes. The composite primary end point was met in 12.6% of patients. A total of 34 patients (6.2%) overall received a postprocedural permanent pacemaker. At 30 days, the rate of all-cause death was 1.3%, and the rate of all stroke was 2.7%.

Patients treated with ACURATE *neo2* demonstrated favorable hemodynamic performance. The mean aortic valve gradient improved from 43±15 mm Hg at baseline (site reported) to 7.6±3.3 mm Hg postoperatively (core laboratory adjudicated). No patient had a postoperative mean gradient >20 mm Hg. Per core laboratory–adjudicated echocardiography, 2.8% of the registry population exhibited greater than mild PVR in the postprocedural period (57.8% grade 0, 37.3% grade 1, 2.8% grade 2; PVR grade could not be analyzed in 2.1%). No patients were evaluated as having

Table 3. Safety and Echocardiographic Outcomes at 30 Days

Clinical event	Value (N)
All-cause death*	1.3 (554)
Stroke (disabling and nondisabling)*	2.7 (554)
Postoperative pacemaker implantation*	6.2 (554)
Acute kidney injury (stage 3, in-hospital)*	1.5 (554)
Acute kidney injury (stage 2, in-hospital)	0.6 (554)
Valve-related dysfunction requiring repeat procedure‡	0.4 (554)
Cardiac rehospitalization	3.0 (554)
Coronary obstruction requiring intervention	0 (554)
Postoperative echocardiographic measurements (in-hospital, core laboratory adjudicated)	
Mean aortic valve area (effective orifice area), cm^2 ±SD	2.24±0.64 (466)
Mean aortic valve gradient, mm Hg ±SD	7.6±3.3 (466)
Left ventricular ejection fraction, % ±SD	57.8±9.7 (466)
Paravalvular regurgitation grade ≥2*,†	2.8 (466)

Values reported are event rate (%) at 30 days, unless otherwise specified. PVR indicates paravalvular regurgitation.
*Component of composite primary end point.
†PVR grade could not be analyzed in 10 patients.
‡Postdilatation at nonindex procedure within 30 days in 2 cases.

severe PVR. The core laboratory also performed quantitative aortographic assessment of aortic regurgitation in a subset of patients (n=168). By this method, 69.0% of patients had no/trace PVR, 28.6% had mild PVR, and 2.4% had moderate or greater PVR, indicating good correlation between the echocardiographic data and the quantitative aortographic analysis.

DISCUSSION

The data reported here from the Early neo2 registry represent a large cohort of patients with TAVI treated with the second-generation ACURATE *neo2* valve for whom core laboratory echocardiographic data were collected. The previous-generation ACURATE *neo* valve has been demonstrated to be safe and effective but with less convincing data on PVR.[2,3,15–17]

Given the continued concern over complications related to moderate or greater PVR, design modifications intended to improve sealing capabilities and reduce the incidence of PVR were incorporated into the next-generation ACURATE *neo2* device. Indeed, the rate of greater than mild PVR at 30 days is lower in both the Neo AS study (3.0%)[9] and in the real-world registry data presented here (2.8%) than previously observed with ACURATE *neo* in the SCOPE 1 and SCOPE 2 studies (9.4% and 9.6%, respectively), and is closer to the rates observed with Sapien 3 (3.6% by Mauri et al; 2.8% in SCOPE 1) and Evolut R/PRO (3.0% in SCOPE 2).[4,5,15]

The lower rate of PVR observed in Early neo2 is consistent with recent reports from several large TAVI registries. The retrospective propensity-matched ITAL-neo registry demonstrated a lower rate of moderate or greater PVR in patients treated with ACURATE *neo2* compared with ACURATE *neo* (3.5% versus 11.2%; *P*<0.001).[18] Likewise, in a combined analysis of the NEOPRO (A Multicenter Comparison of Acurate NEO Versus Evolut PRO Transcatheter Heart Valves) and NEOPRO-2 (A Multicenter Comparison of Acurate NEO2 Versus Evolut PRO Transcatheter Heart Valves 2) registries, which reflects data from >2000 patients with TAVI, moderate or severe PVR was less frequent with ACURATE *neo2* compared with ACURATE *neo* (5% versus 2%; *P*<0.001), even among patients with highly calcified anatomy.[19] Recent data from SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies), the Swedish percutaneous valve registry, also confirm the rate of moderate PVR achieved with ACURATE *neo2* is comparable to that seen with competitor bioprosthetic valves.[20]

Of note, the low rate of more than mild PVR in the present study was achieved even though a small number of patients with more challenging bicuspid anatomy were included, in contrast with earlier studies. The reduction in PVR achieved with the improved design was highlighted in a recent core laboratory analysis comparing post-TAVI aortograms from patients treated with ACURATE *neo* (n=108) and ACURATE *neo2* (n=120).[21] The study found that mean aortic regurgitation fraction was significantly lower for *neo2* compared with *neo* (4.4%±4.8% versus 9.9%±8.2%; *P*<0.001), as was the proportion of patients with postoperative moderate or greater PVR (1.7% versus 13.9%; *P*<0.001).[21]

Several factors may have contributed to the lower PVR rates observed with ACURATE *neo2*. Prior experience with ACURATE *neo* has demonstrated the importance of patient selection, sizing, and implant technique in achieving a low PVR rate,[22] and a recent analysis of SCOPE 1 data suggests that the higher rate of PVR observed with ACURATE *neo* could be attributed to the presence of excessive annular calcium and a lower perimeter-derived cover index (ie, undersizing).[23] However, the degree of prosthesis oversizing appears to be similar in the present study and in the SCOPE 1 study. The average annulus diameter was 23.7 mm in Early neo2 versus 24.1 mm SCOPE 1, and the distribution of valve sizes used in Early neo2 (small, 21%/medium, 41%/large, 38%) is very similar to that in SCOPE 1 (small, 20%/medium, 43%/large, 34%). Therefore, it is unlikely the improvement in PVR is caused by a difference in valve sizing. Another explanation could be the use of more aggressive pre- and postdilatation strategies to reduce leak. Although it is not possible to

directly compare the specifics of balloon size/inflation between the studies, it is notable that predilatation was performed in a similar proportion of patients in Early neo2 (87%), SCOPE 1 (88%), and SCOPE 2 (79%), and postdilatation was actually less frequent in Early neo2 (36%) than it was in SCOPE 1 (52%) and SCOPE 2 (46%).[4,5]

The primary factor in the lowering of the PVR rate is likely the augmentation of the integrated pericardial sealing skirt, which is 60% taller on the second-generation *neo2* valve compared with the previous *neo* valve. Studies of other prosthetic valves that compare across generational designs have also shown a reduction in PVR. The design progression from Sapien XT to Sapien 3 included the addition of a sealing skirt, which significantly reduced the rate of mild or greater PVR,[24] and the lengthening of the skirt in the newer Sapien Ultra valve led to a 50% absolute reduction in PVR compared with Sapien 3.[25]

Data from Early neo2 confirm that in addition to the reduction in PVR, ACURATE *neo2* maintains good clinical outcomes and low mean gradients, as previously observed with ACURATE *neo*. The low gradients achieved can be attributed to the valve's supra-annular leaflet positioning. The self-expanding valve design and addition of a radiopaque marker simplifies deployment and provides improved guidance, which reduces the potential for procedural complications. For example, fewer patients in Early neo2 required an additional valve compared with those treated with ACURATE *neo* in the SCOPE 1 study (0.9% versus 3%, respectively). In general, early safety outcomes with ACURATE *neo2* are comparable to those observed with contemporary valves. The pacemaker rate of 6% seen in this study is lower than previously observed for *neo*, which ranges from 8.3% to 12%,[2,3,15,17] or *neo2* (15.0% in the Neo AS study),[9] and is in line with Swedish registry data showing patients treated with ACURATE had the lowest need for a post-TAVI pacemaker among any of the devices in the registry.[20]

Study Limitations

As a nonrandomized patient registry, the data collected in Early neo2 cannot be directly compared with those of other contemporary valves. For example, it is possible that more challenging anatomies were not selected for this study. The currently enrolling ACURATE IDE study (Safety and Effectiveness Study of ACURATE Valve for Transcatheter Aortic Valve Replacement; NCT03735667) will allow for such head-to-head comparison (1:1 randomization) between ACURATE *neo2* and either Sapien 3 or CoreValve/Evolut R/Evolut PRO.

Data interpretation in the current study is somewhat limited by the fact that clinical event rates were site reported and, as such, were not reviewed by an independent committee. Additionally, data on some variables of interest (eg, annulus calcification, valve implant depth) were not consistently collected by all sites and cannot be fully evaluated here. Echocardiographic data were analyzed by a core laboratory; however, follow-up rates were lower than desired, as is often the case with patient registries. Videodensitometry results were available only for a subset of patients; future analyses will evaluate aortographic data in a larger group.

CONCLUSIONS

This report of postmarket use of the ACURATE *neo2* valve in a real-world TAVI population is consistent with recent studies showing a lower rate of PVR compared with the prior-generation valve design. These finding are strengthened by the fact that a large proportion of patients had core laboratory–adjudicated echocardiographic data available. Patients treated with ACURATE *neo2* exhibited favorable postoperative hemodynamics and clinical outcomes and a low rate of postoperative pacemaker implantation. A future area of study will be to better understand the patient- and procedure-related factors that contribute to the development of PVR.

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Supplemental Material

Video S1

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SUPPLEMENTAL MATERIAL

Supplemental Video Legend:

Video S1. ACURATE *neo2* active sealing technology. The integrated porcine pericardial skirt of ACURATE *neo2* valve is designed to prevent paravalvular regurgitation (PVR) by conforming to the native aortic annulus (inset, arrows). The video illustrates the sealing action of the skirt in an *in vitro* model. Best viewed with Windows Media Player.