IJC Heart & Vasculature 36 (2021) 100862

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.journals.elsevier.com/ijc-heart-and-vasculature

Clinical outcomes following transapical TAVR with ACURATE *neo* in the CHANGE neo TA study

Andreas Holzamer [a], Mirko Doss [b], Rene Schramm [c], Anno Diegeler [d], Lenard Conradi [e], Justus Strauch [f], David Holzhey [g], Magdalena Erlebach [h], Holger Schröfel [i], Mani Arsalan [j], Dominic J Allocco [k], Michael Hilker [a,*]

[a] *Klinikum der Universität Regensburg, Regensburg, Germany*
[b] *Kerckhoff Klinik, Bad Nauheim, Germany*
[c] *Herz-und Diabeteszentrum Nordrhein-Westfalen, Bad Oeynhausen, Germany*
[d] *Rhön-Klinikum Campus Bad Neustadt, Bad Neustadt, Germany*
[e] *Universitaetsklinik Hamburg Eppendorf, University Heart and Vascular Center Hamburg, Hamburg, Germany*
[f] *Klinik Bergmannsheil GmbH, Bochum, Germany*
[g] *Herzzentrum Universität Leipzig, Leipzig, Germany*
[h] *Deutsches Herzzentrum Muenchen, München, Germany*
[i] *University Heart Center Freiburg, Bad Krozingen, Germany*
[j] *University Hospital Frankfurt, Frankfurt, Germany*
[k] *Boston Scientific Corporation, Marlborough, MA, USA*

ARTICLE INFO

Article history:
Received 22 July 2021
Received in revised form 20 August 2021
Accepted 21 August 2021
Available online 31 August 2021

Keywords:
Aortic regurgitation
Aortic stenosis
TAVR

ABSTRACT

Background: A transapical (TA) approach to transcatheter aortic valve replacement (TAVR) may be used when a transfemoral (TF) approach is not feasible. The CHANGE neo TA study evaluated patients treated in routine clinical practice via TA-TAVR with the ACURATE *neo* bioprosthetic aortic valve.

Methods and results: This single-arm post-market study had a planned enrolment of 200 subjects; enrolment was terminated early due to declining TA-TAVR procedures at participating centers. Final enrolment was 107 patients (mean age: 79.3 years; 54.2% female; mean STS score at baseline: 6.2%). The mortality rate in the intent-to-treat population was 11.2% at 30 days (primary endpoint) and 25.6% at 12 months. The VARC-2 composite endpoint for 30-day safety occurred in 24.3% of patients. Six patients (5.6%) received a permanent pacemaker within 30 days. Site-reported echocardiographic data showed early improvements in mean aortic valve gradient (baseline: 38.8 [SD 13.1] mmHg, discharge: 6.7 [SD 3.7] mmHg) and effective orifice area (baseline: 0.7 [SD 0.2] cm^2, discharge: 1.9 [SD 0.6] cm^2), and the discharge rate of paravalvular regurgitation was low (74.7% none/trace, 24.2% mild, 1.1% severe).

Conclusions: TA-TAVR with the ACURATE *neo* valve system yields acceptable clinical outcomes, providing an alternative for patients with aortic stenosis who are not candidates for TF-TAVR.

1. Introduction

Transcatheter aortic valve replacement (TAVR) is an established percutaneous treatment option for patients with calcific aortic stenosis in whom conventional surgical valve replacement is not feasible. While TAVR is most commonly performed via transfemoral (TF) access, studies have shown that a substantial proportion of TAVR patients are not suitable candidates for TF procedures due to problems with peripheral arterial calcification [1,2]. In the early days of TAVR an antegrade transapical (TA) approach was often employed in cases where TF access seemed unachievable [3]. However, the invasive nature of the TA approach has led to a decline in its use, such that it is considered only once other alternate routes of access are precluded [4]. The first-generation ACURATE TA bioprothesis has been used to successfully treat patients via TA-TAVR, as described in detail elsewhere [5]. The CHANGE neo TA study was undertaken for the purpose of evaluating

* Corresponding author at: Department of Cardiothoracic Surgery, University Hospital Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany.
E-mail addresses: andreas.holzamer@klinik.uni-regensburg.de (A. Holzamer), m.doss@kerckhoff-klinik.de (M. Doss), rschramm@hdz-nrw.de (R. Schramm), anno.diegeler@campus-nes.de (A. Diegeler), lconradi@uke.de (L. Conradi), justus.strauch@bergmannsheil.de (J. Strauch), david.holzhey@helios-gesundheit.de (D. Holzhey), Erlebach@dhm.mhn.de (M. Erlebach), holger.schroefel@uniklinik-freiburg.de (H. Schröfel), mani.arsalan@kgu.de (M. Arsalan), dominic.allocco@bsci.com (D.J Allocco), michael.hilker@klinik.uni-regensburg.de (M. Hilker).

https://doi.org/10.1016/j.ijcha.2021.100862
2352-9067/

patients treated in routine clinical practice via TA-TAVR with the next-generation ACURATE *neo* valve system.

2. Methods

CHANGE neo TA is a single-arm, multicenter post-market study; all subjects with severe aortic stenosis for whom TA-TAVR was the most suitable approach, as per heart-team consensus, were considered eligible for enrolment. The ACURATE *neo* valve system (Boston Scientific, Marlborough, MA, USA) is a self-expanding supra-annular bioprosthetic valve with a pericardial sealing skirt designed to reduce paravalvular leak [6]. It is available in three sizes (S/M/L) to treat native annulus diameters of 21–27 mm. The ACURATE *neo* TA Delivery System, used to deliver the valve via the antegrade TA approach, has a smaller external diameter compared with the prior generation delivery system, reducing the potential for myocardial injury related to insertion through the ventricular apex. The delivery system can be used with all sizes of ACURATE *neo*.

The primary endpoint was the 30-day rate of all-cause mortality among all enrolled subjects (ie, the intent-to-treat [ITT] population). See Supplementary Table S1 for all study endpoints. Other safety and performance data, including echocardiographic data, were collected through 12 months of follow-up per standard of care. Baseline and outcome variables were summarized using descriptive statistics for continuous and discrete variables. All statistical analyses were performed using the SAS System software, version 9.3 or later (SAS Institute Inc., Cary, NC, USA).

The protocol was approved by locally appointed institutional review boards/ethics committees and written informed consent was obtained from each patient. The study was conducted in accordance with the International Conference for Harmonization Good Clinical Practice (ICH-GCP) regulations and guidelines and the ethical principles outlined in the Declaration of Helsinki and registered with ClinicalTrials.gov (NCT03454360).

3. Results

The CHANGE neo TA study initially had a planned enrolment of approximately 200 subjects; however, due to declining TA-TAVR procedures at participating centers, enrolment was terminated early. The study enrolled 107 patients at 10 German centers between February 2018 and March 2020 (ITT population; enrolment by site is detailed in Supplementary Table S2). One patient did not receive an ACURATE *neo* valve – the site noted that proper positioning was not possible due to unusual resistance in the aorta; upon removal of the delivery system, the radiopaque tip detached (recorded as a device malfunction) and had to be surgically removed. The patient was treated with a non-study valve and followed for safety through 30-day follow-up. Of the remaining 106 patients, 1 patient missed their 30-day follow-up visit; 20 patients did not have clinical follow-up performed at 12 months due to early study termination. Study flow and patient follow-up details are shown in Supplementary Fig. S1.

The mean age of enrolled patients was 79.3 years and 54.2% were female. The mean STS score in the study population was 6.2% and 84.1% of patients had a New York Heart Association (NYHA) functional status of Class III or IV. Based on site-reported assessment, calcification of the aortic leaflets was severe in 34.0% of patients. Additional baseline demographics, risk factors, and pre-existing clinical conditions are detailed in Supplementary Table S3.

Procedural characteristics are detailed in Supplementary Table S4. The distribution of valve sizes implanted was 27.3% S, 27.3% M, and 45.3% L. The procedural mortality rate was 0%. There were 2 instances of cardiac tamponade, and one repeat procedure for valve-related dysfunction (post-implant echocardiography revealed grade 3 paravalvular regurgitation, and a TAV-in-TAV procedure was performed; the access route and the name/manufacturer of the valve were not recorded by the site).

The mortality rate in the ITT population was 11.2% at 30 days (primary endpoint) and 25.6% at 12 months. The VARC-2 composite endpoint for 30-day safety occurred in 24.3% of patients. A permanent pacemaker was implanted in 6 patients (5.6%) prior to 30-day follow-up. There were no cases of coronary obstruction, and no instances of prosthetic valve endocarditis or thrombosis. Additional safety outcomes are shown in Table 1. Patients exhibited functional improvement based on NYHA Classification (see Supplementary Table S5). At 30 days, 84.9% of patients showed improvement over baseline by at least 1 functional class, and 42.5% improved by at least 2 classes. This trend continued at 12 months, with 83.1% and 39.0% showing improvement from baseline by at least 1 or 2 classes, respectively.

Site-reported echocardiographic outcomes in the as-treated population were assessed by transthoracic and/or transesophageal echocardiography (TTE/TEE). As shown in Fig. 1A, mean aortic gradient improved from baseline to discharge and remained low through 12 months; mean effective orifice area (EOA) increased from baseline to discharge and remained stable through 12 months. Among patients treated with ACURATE *neo*, paravalvular regurgitation (PVR) was evaluated at discharge as none/trace in 74.7% (68/91), mild in 24.2% (22/91), and severe in 1.1% (1/91). Post-dilatation was attempted to treat the patient with severe PVR, but repeat echo revealed persistent severe PVR; further escalation of therapy was not pursued due to the patient's health status and progression of complications, and the patient died on Day 33 post-TAVR. The proportion of patients with no/trace PVR remained consistent through 12-month follow-up (69.2% at 30 days, 73.2% at 12 months); greater than mild PVR was not detected in any patients at 30 days or 12 months (Fig. 1B).

4. Discussion

Among patients with aortic stenosis who are candidates for TAVR, those with smaller arterial vessels, peripheral vascular disease, and/or heavy arterial calcification are ill-suited for TF-TAVR, but may be candidates for TAVR via a TA approach. Patients undergoing TA-TAVR are more likely to have higher baseline risk scores and more comorbidities compared with patients treated with TF-TAVR [7–10]. Registry data and meta-analyses have shown this often translates into an elevated risk for early mortality [8–14].

As reported here, the ACURATE *neo* valve system and ACURATE *neo* TA Delivery System demonstrated acceptable safety and performance when used for TA-TAVR in routine clinical practice. The rate of procedural success in the CHANGE neo TA study (96.3%) was similar to that achieved with the first-generation ACURATE TA valve in the SAVI-1 and SAVI-2 registries (97.8%) [15]. Although 30-day mortality was relatively high in the current study (11.2%), it is consistent with the 30-day rate reported in the SAVI registries (6.8%), and in TA-TAVR patients in other large registries such as FRANCE-2 (14.7%) [10] and UK TAVI (11.2%) [9]. It is difficult, however, to determine whether the higher mortality rate is a consequence of poorer health and greater risk in the patient population, or the more invasive nature of the TA-TAVR procedure. Additionally, as TA-TAVR became less routine at participating centers, the decline in experience may have led to an increased risk for mortality. Nevertheless, rates of other complications at 30 days were low: there were no instances of coronary obstruction, only one patient experienced a disabling stroke, and 2 patients (1.9%) experienced major vascular complications. Other studies have like-

Table 1
Safety Outcomes (ITT population).

Events	30 Days (N = 107) Rate % (n)	30 Days (N = 107) 95% CI	12 Months (N = 87) Rate % (n)	12 Months (N = 87) 95% CI
VARC-2 Composite Early Safety	24.3 (26)	[16.5, 33.5]	–	–
All-cause mortality*	11.2 (12)	[5.9, 18.8]	25.6 (22)	[16.8, 36.1]
Cardiovascular death	8.4 (9)	[3.9, 15.4]	17.4 (15)	[10.1, 27.1]
Stroke*	1.9 (2)	[0.2, 6.6]	3.5 (3)	[0.7, 9.9]
Disabling Stroke	0.9 (1)	[0.0, 5.1]	1.2 (1)	[0.0, 6.3]
Major Vascular complications*	1.9 (2)	[0.2, 6.6]	4.7 (4)	[1.3, 11.5]
Life-threatening or disabling bleeding*	6.5 (7)	[2.7, 13.0]	9.3 (8)	[4.1, 17.5]
Myocardial Infarction	1.9 (2)	[0.2, 6.6]	3.5 (3)	[0.7, 9.9]
Acute Kidney Injury (Stage 2/3)*	8.4 (9)	[3.9, 15.4]	9.3 (8)	[4.1, 17.5]
Hospitalization for valve-related symptoms or worsening congestive heart failure	2.8 (3)	[0.6, 8.0]	9.3 (8)	[4.1, 17.5]
New permanent pacemaker implantation (PPI)	5.6 (6)	[2.1, 11.8]	5.8 (5)	[1.9, 13.0]
New PPI without prior pacemaker†	6.3 (6/95)	[2.4, 13.2]	6.4 (5/78)	[2.1, 14.3]
New onset of atrial fibrillation/flutter	9.3 (10)	[4.6, 16.5]	9.3 (8)	[4.1, 17.5]
TAVR-related complications				
Valve malpositioning‡	0.0 (0)	[0.0, 3.4]	0.0 (0)	[0.0, 4.2]
Coronary obstruction requiring intervention*	0.0 (0)	[0.0, 3.4]	0.0 (0)	[0.0, 4.2]
Ventricular septal perforation	0.0 (0)	[0.0, 3.4]	0.0 (0)	[0.0, 4.2]
Cardiac tamponade	1.9 (2)	[0.2, 6.6]	2.3 (2)	[0.3, 8.1]
TAV-in-TAV deployment§	0.9 (1)	[0.0, 5.1]	1.2 (1)	[0.0, 6.3]
Repeat procedure for valve-related dysfunction*‖	0.9 (1)	[0.0, 5.1]	1.2 (1)	[0.0, 6.3]
Prosthetic valve endocarditis	0.0 (0)	[0.0, 3.4]	0.0 (0)	[0.0, 4.2]
Prosthetic valve thrombosis	0.0 (0)	[0.0, 3.4]	0.0 (0)	[0.0, 4.2]

Note: Twenty patients were not part of the ITT population at 12-month follow-up due to early termination of study.
Mortality and stroke information are captured from CEC Data. All other events information is captured from site reported data.
* Component of VARC-2 composite safety endpoint.
† Includes subjects with prior defibrillator implantation.
‡ Includes valve migration, valve embolization, and ectopic valve deployment.
§ Performed to resolve post-implant paravalvular regurgitation, grade 3.
‖ Patient was treated with TAV-in-TAV procedure (see note above).

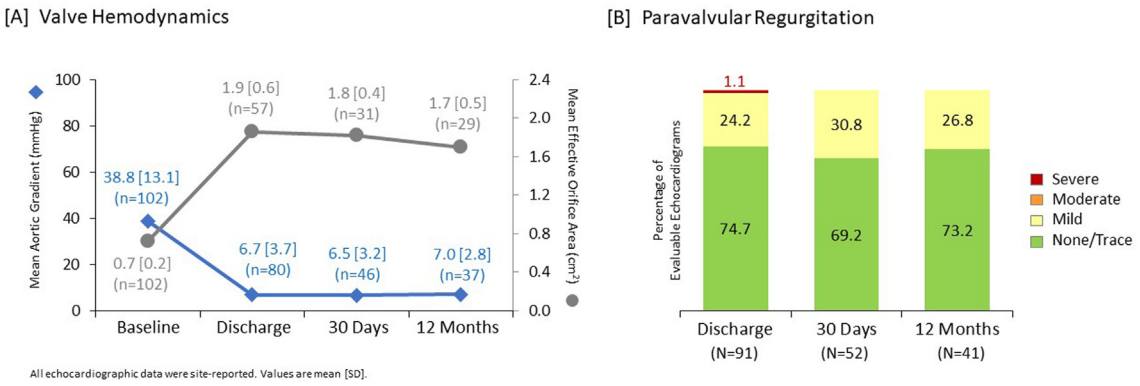

Fig. 1. Site-reported echocardiographic outcomes.

wise shown that TA-TAVR may be associated with a lower risk of major vascular complications than TF-TAVR [13,16,17]. CHANGE neo TA patients also had a lower rate of pacemaker implantation at 30 days than observed with the prior generation ACURATE TA (5.6% versus 10.2% in the SAVI registries) [15]. This rate aligns with findings from patients treated with TF-TAVR in the SAVI-TF registry, in which a low pacemaker rate was shown to be a strength of the ACURATE *neo* platform [18].

Only one patient in the study exhibited greater than mild PVR, based on site-reported echocardiography. In a study of this size, it is difficult to determine which factors contributed to this low rate. It is possible that the step-by-step training procedures employed in the trial, coupled with the radiopaque markers present on the ACURATE *neo* TA Delivery System, aided operators in refining the rotational orientation of the device for optimal commissural alignment, lowering the risk for PVR.

It should be noted that use of the TA pathway has declined in recent years [4]. This trend is likely to continue, particularly with the advent of flexible, low-profile transfemoral delivery systems designed to more easily navigate tortuous peripheral vasculature and reduce the risk for vascular damage with TF-TAVR. More and more, patients selected for TA-TAVR will embody a severely diseased patient population, particularly with regard to peripheral artery disease.

5. Study limitations

As patients undergoing TA-TAVR represent a very high-risk patient population, the results of this study are not generalizable to other patient populations. The sample size is also relatively small, and follow-up was performed per standard of care. Addi-

tionally, 1 year follow-up data were unavailable for some patients due to early termination of the study in response to declining TA-TAVR procedures. Nonetheless, we believe there is an obligation to report the CHANGE neo TA clinical outcomes and echocardiographic data, which may be of interest to treating physicians.

6. Conclusions

Results of the CHANGE neo TA study suggest that use of the ACURATE *neo* valve system and ACURATE neo TA Delivery System for TA-TAVR yields acceptable clinical outcomes and provides an alternative means of access in patients with aortic stenosis who would benefit from TAVR but for whom TF access is not feasible.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: 'AH and MH report proctoring for Boston Scientific and consulting on the CRC board for the ongoing ACURATE IDE study; MD and DH report proctoring for Boston Scientific; LC reports being an advisory board member for Boston Scientific; DJA is an employee and shareholder of Boston Scientific; all other authors report no conflicts of interest.'.

Acknowledgments

The authors thank Songtao Jiang, MS (Boston Scientific Corporation) for statistical analysis, and MaryEllen Carlile Klusacek, PhD (Boston Scientific Corporation) for assistance in manuscript preparation.

Funding

The CHANGE neo TA study was sponsored and funded by Symetis S.A., a subsidiary of Boston Scientific Corporation. The data and study protocol for this clinical trial may be made available to other researchers in accordance with the Data Sharing Policy outlined on the Boston Scientific website.

Author contributions and Declaration of Competing Interest

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. All authors have made substantial contributions to the conception and design of the study, or acquisition of data, or analysis and interpretation of data. All authors reviewed the article and were given the opportunity to revise it critically for important intellectual content, and all authors provided final approval of the version to be submitted.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2021.100862.

References

[1] S.H. Ewe, V. Delgado, A.C.T. Ng, et al., Outcomes after transcatheter aortic valve implantation: transfemoral versus transapical approach, Ann. Thoracic Surg. 92 (4) (2011) 1244–1251, https://doi.org/10.1016/j.athoracsur.2011.01.059.
[2] J. Rodés-Cabau, J.G. Webb, A. Cheung, et al., Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience, J. Am. Coll. Cardiol. 55 (11) (2010) 1080–1090, https://doi.org/10.1016/j.jacc.2009.12.014.
[3] A.S. Petronio, P. Capranzano, E. Barbato, et al., Current status of transcatheter valve therapy in Europe: results from an EAPCI survey, EuroIntervention 12 (7) (2016) 890–895, https://doi.org/10.4244/EIJY16M06_01.
[4] P. Overtchouk, C.H. Regional, U. de Lille, F. Lille, T. Modine, C.H. Regional, U. de Lille, F. Lille, Alternate access for TAVI: Stay clear of the chest, Intervent. Cardiol. Rev. 13 (2018) 145, https://doi.org/10.15420/icr.2018.22.1.
[5] U. Schäfer, L. Conradi, P. Diemert, et al., Symetis ACURATE TAVI: review of the technology, developments and current data with this self-expanding transcatheter heart valve, Minerva Cardioangiol. 63 (2015) 359–369.
[6] H. Möllmann, P. Diemert, E. Grube, et al., Symetis ACURATE TF™ aortic bioprosthesis, EuroIntervention 9 (2013) S107–S110, https://doi.org/10.4244/eijv9ssa22.
[7] M. Thomas, G. Schymik, T. Walther, et al., One-year outcomes of Cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: The European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve, Circulation 124 (4) (2011) 425–433, https://doi.org/10.1161/CIRCULATIONAHA.110.001545.
[8] V.H. Thourani, H.A. Jensen, V. Babaliaros, et al., Outcomes in Nonagenarians Undergoing Transcatheter Aortic Valve Replacement in the PARTNER-I Trial, Ann. Thoracic Surg. 100 (3) (2015) 785–793, https://doi.org/10.1016/j.athoracsur.2015.05.021.
[9] D.J. Blackman, P.D. Baxter, C.P. Gale, et al., Do outcomes from transcatheter aortic valve implantation vary according to access route and valve type? The UK TAVI Registry, J. Interv. Cardiol. 27 (1) (2014) 86–95, https://doi.org/10.1111/joic.12084.
[10] M. Gilard, H. Eltchaninoff, P. Donzeau-Gouge, et al., Late outcomes of transcatheter aortic valve replacement in high-risk patients: The FRANCE-2 registry, J. Am. Coll. Cardiol. 68 (15) (2016) 1637–1647, https://doi.org/10.1016/j.jacc.2016.07.747.
[11] F. Biancari, P. D'Errigo, S. Rosato, et al., Transcatheter aortic valve replacement in nonagenarians: early and intermediate outcome from the OBSERVANT study and meta-analysis of the literature, Heart Vessels 32 (2) (2017) 157–165, https://doi.org/10.1007/s00380-016-0857-3.
[12] F. Conrotto, F. D'Ascenzo, G. Francesca, et al., Impact of access on TAVI procedural and midterm follow-up: a meta-analysis of 13 studies and 10,468 patients, J. Interv. Cardiol. 27 (5) (2014) 500–508, https://doi.org/10.1111/joic.12141.
[13] D.C. Garcia, A. Benjo, R.N. Cardoso, et al., Device stratified comparison among transfemoral, transapical and transubclavian access for Transcatheter Aortic Valve Replacement (TAVR): a meta-analysis, Int. J. Cardiol. 172 (2) (2014) e318–e321, https://doi.org/10.1016/j.ijcard.2013.12.162.
[14] R. Doshi, E. Shlofmitz, P. Meraj, Comparison of outcomes and complications of transcatheter aortic valve implantation in women versus men (from the national inpatient sample), Am. J. Cardiol. 121 (1) (2018) 73–77, https://doi.org/10.1016/j.amjcard.2017.09.015.
[15] J. Börgermann, D.M. Holzhey, M. Thielmann, et al., Transcatheter aortic valve implantation using the ACURATE TA™ system: 1-year outcomes and comparison of 500 patients from the SAVI registries, Eur. J. Cardiothorac. Surg. 51 (2017) 936–942, https://doi.org/10.1093/ejcts/ezw423.
[16] F. Biancari, S. Rosato, P. D'Errigo, et al., Immediate and intermediate outcome after transapical versus transfemoral transcatheter aortic valve replacement, Am. J. Cardiol. 117 (2) (2016) 245–251, https://doi.org/10.1016/j.amjcard.2015.10.036.
[17] S. Kodali, V.H. Thourani, J. White, et al., Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis, Eur. Heart J. 37 (28) (2016) 2252–2262, https://doi.org/10.1093/eurheartj/ehw112.
[18] H. Möllmann, C. Hengstenberg, M. Hilker, et al., Real-world experience using the ACURATE neo™ prosthesis: 30-day outcomes of 1000 patients enrolled in the SAVI-TF registry, EuroIntervention 13 (2018) e1764–e1770, https://doi.org/10.4244/EIJ-D-17-00628.