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Transcatheter aortic valve implantation versus surgical aortic valve replacement in patients at low to intermediate surgical risk: rationale and design of the randomised DEDICATE Trial

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KEYWORDS

- aortic stenosis
- clinical trials
- TAVI

Abstract

Transcatheter aortic valve implantation (TAVI) has become the preferred treatment option for patients with severe aortic stenosis at increased risk for surgical aortic valve replacement (SAVR) and for older patients irrespective of risk. However, in younger, low-risk patients for whom both therapeutic options, TAVI and SAVR, are applicable, the optimal treatment strategy remains controversial, as data on long-term outcomes remain limited. The DEDICATE-DZHK6 Trial is an investigator-initiated, industry-independent, prospective, multicentre, randomised controlled trial investigating the efficacy and safety of TAVI compared to SAVR in low- to intermediate-risk patients aged 65 years or older. To evaluate both treatment strategies, approximately 1,404 patients determined eligible for both TAVI and SAVR by the interdisciplinary Heart Team were randomised to TAVI or SAVR. Broad inclusion and strict exclusion criteria targeted an all-comers patient population. Procedures were performed according to local best practice with contemporary routine medical devices. The primary endpoints are a composite of mortality or stroke at 1 year and 5 years in order to incorporate midterm efficacy results and complement early safety data. Primary outcomes will be tested sequentially for non-inferiority and superiority. The DEDICATE-DZHK6 Trial has been designed to mirror clinical reality for the treatment of severe aortic stenosis and provide unique information on overall outcomes after TAVI and SAVR that can be directly applied to clinical routines. Its results will help further define optimal treatment strategies for low- to intermediate-risk patients in whom both TAVI and SAVR are currently advisable.

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Abbreviations

COVID-19	coronavirus disease
DZHK	Deutsches Zentrum für Herz-Kreislauf-Forschung (German Centre for Cardiovascular Research)
ECG	electrocardiogram
NYHA	New York Heart Association
RCT	randomised controlled trial
RMST	restricted mean survival time
SAVR	surgical aortic valve replacement
STS-PROM	Society of Thoracic Surgeons Predicted Risk of Mortality
TAVI	transcatheter aortic valve implantation
THV	transcatheter heart valve
VARC	Valve Academic Research Consortium

Introduction

Transcatheter aortic valve implantation (TAVI) has become the preferred treatment option for patients with symptomatic severe aortic stenosis at increased operative risk across all age groups and for older patients, irrespective of operative risk, if a transfemoral approach is feasible[1-3]. In younger patients for whom both therapeutic options, TAVI and surgical aortic valve replacement (SAVR), are applicable, the optimal treatment strategy remains controversial. As a response to the recently published low-risk trials[4-7], TAVI has been expanded towards this patient population. In the absence of long-term results and robust durability data for the medical devices, guidelines emphasise an individualised Heart Team approach for treatment selection[1,3,8]. The limitations of published evidence particularly relate to strict patient selection, composite primary outcomes limited to short-term follow-up and restrictions to specific transcatheter heart valve devices. We therefore designed an investigator-initiated, industry-independent, prospective, multicentre, randomised controlled trial (RCT) − the DEDICATE-DZHK6 Trial − for comparing TAVI with SAVR. In this trial, we aim to demonstrate the non-inferiority of TAVI versus SAVR at 1 and 5 years for the co-primary safety endpoints; if non-inferiority is demonstrated, we will subsequently test for superiority for the 5-year primary clinical efficacy endpoint. As the treatment strategies are being compared, SAVR or TAVI were performed according to local best practice, and all contemporary routine medical devices were allowed in both treatment strata. The trial was designed so that the patient population mirrors the clinical reality for the treatment of severe symptomatic aortic stenosis in Germany at the time of study inclusion.

Methods

RATIONALE AND TRIAL DESIGN

DEDICATE-DZHK6 (Randomized, Multi-Center, Event-Driven Trial of TAVI versus SAVR in Patients with Symptomatic Severe Aortic Valve Stenosis and Intermediate Risk of Mortality, as Assessed by STS-Score; ClinicalTrials.gov: NCT03112980; date of registration: 13 April 2017) is an RCT designed to assess the safety and efficacy of TAVI compared to SAVR in the treatment of patients with symptomatic severe aortic stenosis at low to intermediate operative risk of mortality. The lead Hamburg Ethics Committee (reference number PV5417) and the local ethics committees at the participating study sites approved the study protocol. The study flow is depicted in **Figure 1**, and the participating centres are listed in **Supplementary Table 1**. An independent data safety and monitoring board is responsible for monitoring patient safety and evaluating the efficacy and conduct of the study. All boards and committees are listed in **Supplementary Table 2**.

ELIGIBILITY AND SCREENING

Low- to intermediate-risk patients with severe symptomatic tricuspid aortic stenosis in whom both isolated SAVR or isolated TAVI were advisable, according to Heart Team consensus, were screened for enrolment into the trial. To maximise generalisability and representativeness, we applied broad inclusion criteria and strict exclusion criteria **(Table 1)**. As both medical practice and the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) calculation evolved during the recruitment phase, the initial STS-PROM cut-off value was waived, and a lower age limit of 65 years was implemented. This also took into account that current risk stratification tools performed poorly in estimating outcomes after TAVI, yielding a pragmatic Heart Team-centred screening process. Enrolment started in May 2017 and was completed in September 2022.

RANDOMISATION, TREATMENT, AND FOLLOW-UP

After informed consent was obtained, patients were randomised in a 1:1 ratio to TAVI or SAVR using a balanced stratified block randomisation with variable block lengths, stratified by STS-PROM (0-2.00%, 2.01-4.00%, 4.01-6.00%) and study site. Randomisation was performed using the validated randomisation software RITA[9] within the electronic case report forms.

The assigned treatment (TAVI or SAVR) was performed following treatment guidelines and according to local best practice[1,2]. The choice of the respective valve prosthesis, the access site, and other (peri)procedural aspects were left to the discretion of the implant team in order to mirror clinical reality and prevent a potential device-based bias. Procedures were performed in accordance with the recommendations of the "Gemeinsamer Bundesausschuss" (Federal Joint Committee, which determines the list of benefits provided by statutory health insurance) for minimally invasive heart valve procedures in Germany. Patients will be followed up for at least 5 years after randomisation, with scheduled telephone visits at 30 days, 2, 3, and 4 years and with scheduled outpatient visits at 1 and 5 years **(Figure 1)**. Clinical status, clinical events, quality-of-life questionnaires (EQ-5D), electrocardiograms (ECG), and echocardiographic and laboratory data, among other data − see protocol **(Supplementary Appendix 1)**, will be obtained. Echocardiographic and computed tomography examinations will be independently assessed by core laboratories to validate findings and increase data quality.

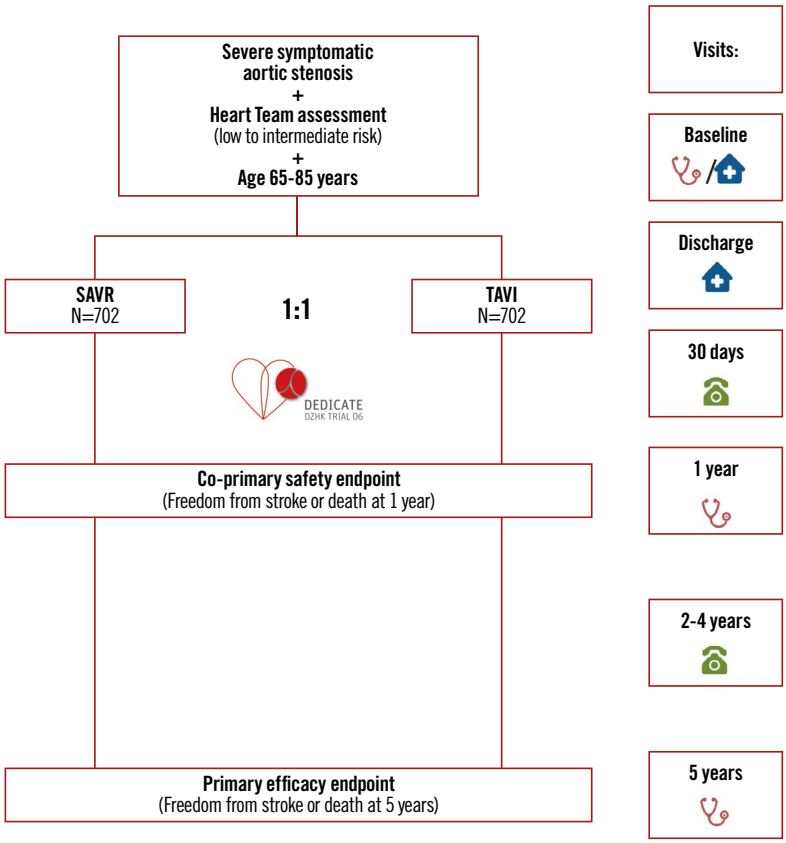

Figure 1. *Study flowchart of the DEDICATE-DZHK6 Trial. Enrolled patients are randomised in a 1:1 ratio to isolated surgical aortic valve replacement (SAVR) or isolated transcatheter aortic valve implantation (TAVI).*

STUDY ENDPOINTS

The co-primary safety endpoint, the primary efficacy endpoint and secondary endpoints are listed in **Table 2**. Outcome measures are defined in accordance with the updated Valve Academic Research Consortium (VARC)-2 consensus document[10], as this was the most current consensus document at the time of the study design and first enrolment. Endpoints are adjudicated in a blinded fashion by an independent event adjudication committee.

STATISTICAL ANALYSIS

All primary analyses will be performed in the intention-to-treat population, which includes all randomised patients by their allocated treatment. The multiple testing strategy for the 2 co-primary and the first 3 secondary endpoints is laid out in **Figure 2** using the graphical concept of hierarchical procedures[11]. In the first step, non-inferiority by the same ratio is tested for both safety at 1 year after randomisation and efficacy at 5 years after randomisation. To this end, Cox models stratified by STS-PROM score are used to estimate the cause-specific hazard ratios (HR) restricted to the respective follow-up. Patients lost to follow-up and patients with administrative censoring are treated identically, with the assumption of non-informative censoring. If non-inferiority is shown for both safety after 1 year and efficacy after 5 years, each at the 1-sided 2.5% test level using the log-rank test, superiority at 5 years after randomisation will be tested at a 2-sided level of 5% using the Cox model stratified by STS-PROM score.

To quantify survival benefits, differences in the restricted mean survival times (RMST) will be estimated. Specifically, we will test whether the RMST differs over the period from randomisation until 5-year follow-up, from randomisation until 1-year follow-up, and from 1 year to 5 years after randomisation. The RMST tests are embedded in the hierarchical testing procedure described in **Figure 2**.

Sensitivity analyses will be performed with stratification by periods of constant eligibility and lockdown for the coronavirus disease (COVID-19) pandemic. For all endpoints, 95% confidence intervals are not adjusted for multiple comparisons. Competing risk models are used to estimate cumulative incidence curves for the secondary endpoints. Predefined subgroup analyses will include age, sex, New York Heart Association (NYHA) Class, transcatheter heart valve (THV)/prosthesis type, access route, relevant baseline comorbidities, STS-PROM strata, accrual periods of constant eligibility, and lockdown for the COVID-19 pandemic, among other data **(Supplementary Appendix 2)**. The latter two were included in the statistical analysis plan after the start of the COVID-19 pandemic. Safety analyses are performed parallel with treatment.

Table 1. Eligibility criteria.

Inclusion criteria
1. Heart Team consensus that isolated TAVI and SAVR are both medically justified and advisable based on
(a) degenerative aortic valve stenosis with echocardiographically derived criteria (mean gradient >40 mmHg OR jet velocity greater than 4.0 m/s OR aortic valve area [AVA] of <1.0 cm^2 [indexed EOA <0.6 cm^2/m^2])
(b) patient symptomatic from his/her aortic valve stenosis (NYHA Functional Class ≥II OR angina pectoris OR syncope)
(c) patient classified as low to intermediate operative risk as assessed by the local Heart Team according to variables outlined in the 2017 ESC/EACTS Guidelines for Management of Valvular Heart Disease, taking into account cardiac and extracardiac patient characteristics and established risk scores (e.g., STS-PROM, EuroSCORE)
(d) transfemoral or alternative access for TAVI seems feasible; centres should follow a "transfemoral first" strategy for primary route of access; however, other routes of access are also allowed, as decided by local Heart Team consensus
2. Patient aged 65-85 years
3. Patient provided written informed consent to participate in the trial
4. Ability of patient to understand patient information and to personally sign and date informed consent to participate in study, before performing any study-related procedures
5. Patient agrees to undergo SAVR, if randomised to control treatment
6. Patient and treating physician agree that patient will return for all required postprocedural follow-up visits
7. Male gender or postmenopausal (defined as no menses for 12 months without an alternative medical cause) in case of female gender
Exclusion criteria
1. Aortic valve is congenital unicuspid or congenital bicuspid valve, or non-calcified
2. Untreated clinically significant coronary artery disease considered a contraindication to isolated aortic valve procedure (TAVI or SAVR) according to Heart Team consensus
3. Any percutaneous coronary intervention performed within 1 month prior to study procedure
4. Prior cardiac surgery
5. Untreated severe mitral or tricuspid regurgitation
6. Untreated severe mitral stenosis
7. Haemodynamic instability requiring inotropic support or mechanical circulatory support
8. Ischaemic stroke or intracranial bleeding within 1 month
9. Severe ventricular dysfunction with left ventricular ejection fraction <20% as measured by resting echocardiogram
10. Hypertrophic obstructive cardiomyopathy or severe basal septal hypertrophy with outflow gradient
11. Echocardiographic evidence of intracardiac mass, thrombus, vegetation or endocarditis
12. Any other condition considered a contraindication for an isolated aortic valve procedure
13. Symptomatic carotid or vertebral artery disease
14. Expected life expectancy <12 months due to associated non-cardiac comorbidities
15. Currently participating in another investigational drug or device trial

EACTS: European Association for Cardiac and Thoracic Surgery; EOA: effective orifice area; ESC: European Society of Cardiology; EuroSCORE: European System for Cardiac Operative Risk Evaluation; NYHA: New York Heart Association; SAVR: surgical aortic valve replacement; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; TAVI: transcatheter aortic valve implantation

Table 2. Primary and major secondary endpoints.

Primary efficacy endpoint
Freedom from stroke or death within 5 years after randomisation
Co-primary safety endpoint
Freedom from stroke or death within 1 year after randomisation
Secondary endpoints
Overall survival
Freedom from stroke or death
Freedom from cardiovascular mortality
Freedom from myocardial infarction
Freedom from stroke
Freedom from major or life-threatening/disabling bleeding
Freedom from acute kidney injury
Freedom from major vascular access site and access-related complications
Freedom from conduction disturbances and arrhythmias, need for permanent pacemaker implantation
Freedom from prosthetic valve dysfunction
Freedom from prosthetic aortic valve endocarditis
Freedom from (re)hospitalisation
Quality-of-life measures (improvement in quality-of-life assessment and functional status)
Health economic analysis comparing cost-effectiveness

Outcome measures were defined in accordance with the updated Valve Academic Research Consortium-2 consensus document[10]. Primary and major secondary endpoints are listed.

PLANNED SAMPLE SIZE

At the time that the trial was designed, data were available from only 3 RCTs which included primarily intermediate risk strata or a smaller sample size[12-14]. The expected event rates were based on these data; they were subsequently modified to include general age-related mortalities and STS-PROM scores when patients with lower operative risk were included. The initial 1-year mortality was expected to be 7.8% among patients after TAVI and 11.4% among patients after SAVR. More recent RCTs have suggested far lower event rates and hazard ratios (HR) than we had initially used for our sample size calculation[4-6,15]. Based on these contemporary data and a blinded interim analysis of the DEDICATE-DZHK6 Trial after recruitment of 881 patients, we assumed the geometric mean 1-year rate of mortality or stroke to be 6.2%. The non-inferiority margin was adjusted from HR 1.10 to HR 1.14 so that the rejectable difference of proportions at 1 year remained 1 percentage point. The enrolment of approximately 1,404 patients provides a power of 80% to reject the non-inferiority margin at 1 year for the alternative HR of 0.67 when the censoring rate was 10% per year. The same assumptions and rates of recruitment and of events, stratified by risk classes estimated at blinded interim analysis, gave a power of 94% at 5 years, which translates to a power of 76% for rejecting equal hazards in the superiority test of efficacy.

Discussion

Building on current evidence for TAVI and SAVR in patients with symptomatic severe aortic stenosis, DEDICATE-DZHK6 should provide additional data to help further define the optimal treatment strategies. Particularly for younger, low-risk patients who are amenable to both therapies, the evidence needed to inform treatment decisions with respect to longer-term outcomes is not fully established. DEDICATE-DZHK6 evaluates the impact of the treatment strategy on the primary endpoints of all-cause mortality and stroke at 1 year (co-primary safety endpoint) and 5 years (primary efficacy endpoint). The 5-year time frame for the primary endpoint ensures that early midterm results will weigh into the primary outcome of the trial and complement early 1-year safety data. A particular strength of the trial is its strict statistical analysis. The set non-inferiority margin

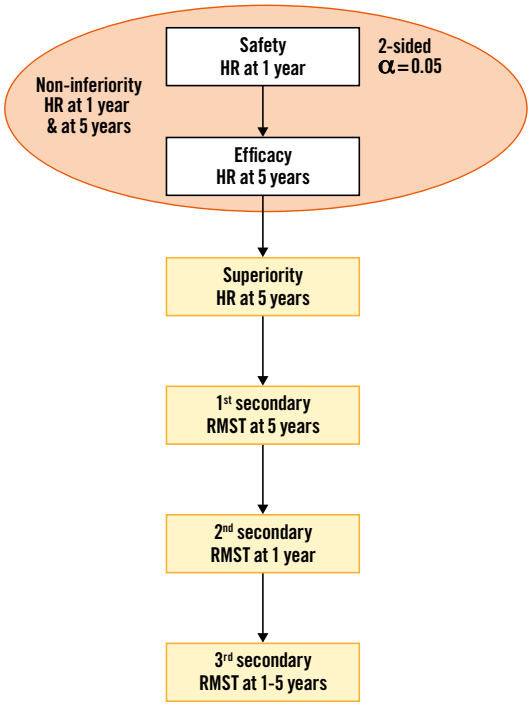

Figure 2. *Statistical testing strategy. In the first step, non-inferiority is tested for both safety at 1 year and efficacy at 5 years after randomisation using the hazard ratio (HR). Both hypotheses need to show non-inferiority at the 2-sided 0.05 test level, i.e., 0.025 1-sided, for continuation of the test procedure. If both tests show non-inferiority, the full significance level of 0.05 is transferred for superiority testing at 5 years after randomisation. All tests for the restricted mean survival time (RMST) are superiority tests at the 2-sided 0.05 test level and are only conducted when all previous tests in this hierarchical testing strategy show significance.*

corresponds to an absolute difference of event rates of approximately 1% at 1 year, while it was set as wide as 5-6% in most other trials[4-6]. A relevant risk difference of 2% would correspond to one-third of the average event rate at 1 year, which is a common value to detect clinically relevant differences and corresponds well with the alternative hypothesis of this trial. Overinterpretation of insignificant results is prevented by calculating confidence limits for several estimates. As some previous trials have indicated crossing hazards during follow-up, with lower early event rates after TAVI compared to SAVR, followed by higher event rates during the non-prespecified observation period[16,17], we decided to cover this aspect by using prespecified time frames for the primary endpoint.

Currently, robust data on the long-term durability of THVs remain scarce. The majority of systematic 5-year follow-up data stem from RCTs that enrolled older, intermediate- and high-risk patient populations[16,18-21]; few data are available up to 8 years[7]. Although current data demonstrate the durability of TAVI and SAVR to be comparable in the respective time frames, their applicability to younger, low-risk patients remains unclear, as the competing risk of mortality may mask structural valve deterioration. Furthermore, variable definitions of structural valve deterioration complicate the systematic evaluation of this important aspect. A systematic 10-year follow-up is planned for the most recent low-risk trials[17,22]; this will add important information on durability and subsequent decision-making in younger patients with a long life expectancy.

DEDICATE-DZHK6 aims to investigate treatment of isolated aortic valve disease in an all-comers patient population. The trial was designed with broad eligibility criteria, putting the local interdisciplinary Heart Team at the core of the enrolment process. If the local Heart Team agreed on the patient´s eligibility for both treatment strategies, isolated SAVR and TAVI, inclusion into the trial was recommended. The majority of RCTs in this field were planned to evaluate the performance of TAVI with one specific THV prosthesis compared to SAVR, while DEDICATE-DZHK6 was designed to compare the two treatment strategies. Periprocedural aspects, the choice of the valve prosthesis or access, antithrombotic management, and further treatment-related medical decisions were left to the discretion of the local Heart Team in order to tailor the assigned strategy to the individual patients' anatomies and comorbidities.

DEDICATE-DZHK6 is an industry-independent study, conceptualised to mirror clinical reality and provide unique information on overall outcomes that can be directly applied to clinical routine. Hence, together with the other ongoing RCTs in this field, DEDICATE-DZHK6 may help to shape treatment strategies for low-risk patients with severe symptomatic aortic stenosis in the near future.

Limitations

At the time of the trial design, there was a paucity of outcome data in low- to intermediate-risk patients to estimate event rates for DEDICATE-DZHK6. As new evidence for TAVI in these patient populations became available during the enrolment period[4-6,15] and guidelines for the treatment of valvular heart disease were updated[1], the study protocol was amended to accommodate evolving clinical practice patterns and ensure patient recruitment while retaining sufficient statistical power. While the trial had initially been conceptualised to primarily include patients at intermediate operative risk, we subsequently amended the protocol to enrol all-comer patients at low to intermediate risk. Overall, DEDICATE-DZHK6 represents a routine low- to intermediate-risk patient population. A blinded interim analysis was performed to confirm sufficient power and sample size calculations, and any changes made will be incorporated within the statistical analyses. The COVID-19 pandemic may have altered treatment strategies of elective cases over a relevant period of the recruitment period and may generally have impacted patient outcomes. Secondary analyses will be performed to address these unforeseen challenges. DEDICATE-DZHK6 targeted an all-comers tricuspid aortic stenosis population. Patients with bicuspid aortic stenoses or concomitant clinically relevant coronary or other valvular heart disease were not enrolled. As the majority of patients had already been enrolled at the time of publication of the updated VARC-3 criteria[23], we proceeded with clinical event adjudication according to the VARC-2 document[10].

Conclusions

The DEDICATE-DZHK6 Trial is an investigator-initiated, industry-independent and pragmatic German multicentre, randomised controlled study comparing TAVI and SAVR in low- to intermediate-risk patients targeting mortality or stroke at 1 and 5 years as the primary safety and efficacy outcomes. It will build on current scientific and medical evidence. Its results will support medical decisions to further define optimal treatment strategies for patients with severe aortic stenosis in whom both TAVI and SAVR are advisable.

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Conflict of interest statement

M. Seiffert received speaker or advisory fees from Abbott Vascular, Abiomed, Amgen, AstraZeneca, Boston Scientific, Bristol-Myers Squibb, Daichii Sankyo, Edwards Lifesciences, Inari Medical, Medtronic, Pfizer, Shockwave Medical, and Siemens Healthineers; and a research grant from Boston Scientific – all unrelated to the submitted work. M. Borger declares that his hospital receives speaker honoraria and/or consulting fees on his behalf from Edwards Lifesciences, Medtronic, Abbott, and Artivion. V. Falk has relevant financial activities outside the submitted work with following commercial entities: Medtronic, Biotronik, Abbott, Boston Scientific, Edwards Lifesciences, LivaNova, Berlin Heart, Novartis, JOTEC/Artivion, and Zurich Heart. C. Hamm is a member of the International Strategic Advisory Board at Medtronic. U. Landmesser reports grants to institution from Bayer, Amgen, and Novartis; and speaker or advisory fees from Abbott and Boston Scientific. H. Reichenspurner is a member of the advisory board at Medtronic; and declares that he receives speaker honoraria from Abiomed and Abbott. R. Twerenbold holds a professorship in clinical cardiology at the University Medical Center Hamburg-Eppendorf, supported by the Kühne Foundation; reports research support from the German Centre for Cardiovascular Research (DZHK) and the Swiss National Science Foundation (Grant No. P300PB_167803), speaker/consulting honoraria from Abbott, Amgen, AstraZeneca, Psyros, Roche, Siemens, Singulex, and Thermo Scientific BRAHMS, outside the submitted work. S. Blankenberg, R. Twerenbold and A. Ziegler are listed as co-inventors of an international patent on the use of a computing device to estimate the probability of myocardial infarction (International Publication Number WO2022043229A1) as well as co-founders and shareholders of ART-EMIS Hamburg GmbH. A. Ziegler is a scientific director of Cardio-CARE, which is another shareholder of ART-EMIS Hamburg GmbH. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Trial protocol (Version 9.1).

Supplementary Appendix 2. Statistical analysis plan (Version 01).

Supplementary Table 1. Trial sites.

Supplementary Table 2. Committees and boards.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-00232

Supplementary data

Supplementary Appendix 1. Trial protocol (Version 9.1). *(see end of document).*

Supplementary Appendix 2. Statistical analysis plan (Version 01). (*see end of document*).

Supplementary Table 1. Trial sites.

RWTH Aachen
Kerckhoff-Klinik Bad Nauheim
Herz- und Gefäß-Klinik Bad Neustadt/Saale
Herz- und Diabeteszentrum NRW Bad Oeynhausen
Charité Universitätsmedizin Berlin (Campus Virchow)
Charité Universitätsmedizin Berlin (Campus Benjamin-Franklin)
Charité Universitätsmedizin Berlin (Campus Mitte)
Deutsches Herzzentrum Charité Berlin
Vivantes Berlin Neukölln
Vivantes Berlin Friedrichshain
Vivantes Berlin Klinikum am Urban
Immanuel Klinikum Bernau Herzzentrum Brandenburg
BG Universitätsklinikum Bergmannsheil Bochum
Universitätsklinikum Brandenburg
Universitätsklinikum an der TU Dresden
Universitätsklinikum Düsseldorf
Universitätsklinikum Erlangen
Universitätsklinikum Frankfurt
Universitäts-Herzzentrum Freiburg-Bad Krozingen, Standort Bad Krozingen
Universitäts-Herzzentrum Freiburg-Bad Krozingen, Standort Freiburg
Universitätsklinikum Gießen und Marburg, Standort Gießen
Universitätsklinikum Göttingen
Universitätsmedizin Greifswald / Klinikum Karlsburg
Universitätsklinikum Halle/Saale
Universitäres Herz- und Gefäßzentrum Hamburg
Medizinische Hochschule Hannover
Universitätsklinikum Heidelberg
Universitätsklinikum Jena

Universitätsklinikum Schleswig-Holstein, Campus Kiel
Bundeswehrzentralkrankenhaus Koblenz
Universitätsklinikum Köln
Herzzentrum Leipzig – Universität Leipzig
Universitätsklinikum Schleswig-Holstein, Campus Lübeck
Otto-von-Guericke-Universität Magdeburg
Universitätsmedizin Mainz
Deutsches Herzzentrum München
LMU Klinikum der Universität München
Universitätsklinikum Münster
Universitätsklinikum Regensburg
Robert-Bosch-Krankenhaus Stuttgart
Universitätsklinikum Ulm

Supplementary Table 2. Committees and boards.

Steering Committee
Helmut Baumgartner, Münster
Stefan Blankenberg, Hamburg (Principal Investigator)
Michael A. Borger, Leipzig
Yeong-Hoon Choi, Bad Nauheim
Jochen Cremer, Kiel (Principal Investigator)
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Norbert Frey, Heidelberg
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Stefan Blankenberg, Hamburg (Principal Investigator)
Peter Clemmensen, Hamburg
Susanne Hansen, Hamburg
Anke Heiermann, Hamburg
Moritz Seiffert, Hamburg (Coordinating Investigator)
Trial Statisticians
Inke R. König, Lübeck
Reinhard Vonthein, Lübeck
Andreas Ziegler, Davos
Event Adjudication Committee
Karl Georg Häusler, Würzburg (Chair)
Ulrich Hofmann, Würzburg

Armin Gorski, Würzburg
Data Safety Monitoring Board
Tim Friede, Göttingen (Chair)
Ludwig Müller, Innsbruck
Helmut Klein, Hannover / Rochester
Advisory Board
Olaf Wendler, London
Stephan Windecker, Bern
Andreas Zeiher, Frankfurt
Echocardiography core laboratory
Andreas Hagendorff, Leipzig
Computed tomography core laboratory
Won Kim, Bad Nauheim

PROTOCOL

Randomized, Multi-Center, Event-Driven Trial of TAVI versus SAVR in Patients with Symptomatic Severe Aortic Valve Stenosis and Intermediate Risk of Mortality, as assessed by STS-Score

(DEDICATE)

Investigator-Initiated Trial

PRINCIPAL INVESTIGATORS	Stefan Blankenberg (Cardiologist), Hamburg, Germany Jochen Cremer (Cardiovascular Surgeon), Kiel, Germany
COORDINATING INVESTIGATOR	Moritz Seiffert, Hamburg, Germany
COORDINATING CENTER	Universitäres Herz- und Gefäßzentrum Hamburg, Germany
TRIAL SUPPORTING FACILITY	CTC North, Hamburg, Germany
TRIAL STATISTICIANS	R. Vonthein and Inke R. König, Lübeck; Germany; A. Ziegler, Davos, Switzerland

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1. PROTOCOL SYNOPSIS

Title:	Ran**d**omiz**ed**, Mult**i**-**C**enter, Event-Driven Trial of T**A**VI versus SAVR in Pa**t**ients with Symptomatic S**e**vere Aortic Valve Stenosis and Intermediate Risk of Mortality, as assessed by STS-Score
Acronym:	DEDICATE
Design:	Prospectively randomized (1:1), multi-center, comparator-controlled trial GROUP A: TAVI using the most appropriate CE-marked device available, with a minimum demand of experience of 30 implanted devices/type per center GROUP B: SAVR - free choice of surgical bioprosthesis and free choice of surgical access according to the surgeon's preference
Hypothesis:	TAVI is non-inferior – as measured by all-cause mortality or stroke after 1 and 5 years – compared to SAVR in the treatment of patients with symptomatic severe aortic stenosis at low to intermediate operative risk of mortality
Primary endpoint:	Freedom from stroke or death within 5 years after randomization (efficacy endpoint)
Co-primary safety endpoint:	Freedom from stroke or death within 1 year after randomization (safety endpoint)
Secondary Endpoints:	The following secondary endpoints will be assessed at every study visit (V2-V10) unless stated otherwise and compared between TAVI and SAVR groups: Overall survival Freedom from cardiovascular mortality [1] Freedom from myocardial infarction [1] Freedom from stroke [1] Freedom from major or life-threatening / disabling bleeding [1] Freedom from acute kidney injury [1] Freedom from vascular access site and access-related complications [1] Freedom from conduction disturbances and arrhythmias, need for permanent pacemaker implantation [1]

[1] Kappetein AP et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012;60(15): 1438-54.

Freedom from residual aortic regurgitation ≥ moderate [1]

Composite device success [1]

Composite early safety (at 30 days) [1]

Composite clinical efficacy (after 30 days) [1]

Freedom from prosthetic valve dysfunction [1]

Freedom from prosthetic aortic valve endocarditis

Freedom from the composite time-related valve safety [1]

Quality of life measures [1]

(Re-)Hospitalization

Health economic analysis

Key Inclusion Criteria:

1. Heart team consensus **that TAVI and SAVR are both** medically justified and **advisable** based on:

a) Degenerative aortic valve stenosis with echocardiographically derived criteria:

- Mean gradient >40 mmHg or
- Jet velocity greater than 4.0 m/s or
- Aortic valve area (AVA) of < 1.0 cm^2 (indexed EOA < 0.6 cm^2/m^2).

b) Patient is symptomatic from his/her aortic valve stenosis

- NYHA Functional Class ≥ II or
- Angina pectoris or
- Syncope.

c) Patient is classified as low to intermediate operative risk as assessed by the local heart team according to the variables outlined in the 2017 ESC/EACTS guidelines for the management of valvular heart disease [1], taking into account cardiac and extracardiac patient characteristics and established risk scores (e.g. STS-PROM, EuroSCORE).

d) A transfemoral or alternative (e.g. transapical, transaortic, tansaxillary) access for TAVI seems feasible. Centers should follow a "transfemoral first" strategy for the primary route of access; however, other routes of access are also allowed, as decided by local heart team consensus

[1] Baumgartner H et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38(36):2739-91.

2. Patients aged 65 – 85 years
3. Patient has provided written informed consent to participate in the trial.
4. Ability of the patient to understand the patient information and to personally sign and date the informed consent to participate in the study, before performing any study related procedures.
5. The patient agrees to undergo SAVR, if randomized to control treatment
6. The patient and the treating physician agree that the patient will return for all required post-procedure follow-up visits
7. Male patients or postmenopausal (defined as no menses for 12 months without an alternative medical cause) in case of female gender

Key Exclusion Criteria:

1. Aortic valve is a congenital unicuspid or congenital bicuspid valve, or is non-calcified
2. Untreated clinically significant coronary artery disease considered a contraindication to an isolated aortic valve procedure (TAVI or SAVR) according to heart team consensus
3. Any percutaneous coronary intervention performed within 1 month prior to the study procedure
4. Prior cardiac surgery
5. Untreated severe mitral or tricuspid regurgitation
6. Untreated severe mitral stenosis
7. Hemodynamic instability requiring inotropic support or mechanical circulatory support
8. Ischemic stroke or intracranial bleeding within 1 month
9. Severe ventricular dysfunction with left ventricular ejection fraction < 20% as measured by resting echocardiogram
10. Hypertrophic obstructive cardiomyopathy or severe basal septal hypertrophy with outflow gradient
11. Echocardiographic evidence of an intracardiac mass, thrombus, vegetation or endocarditis
12. Any other condition considered a contraindication for an isolated aortic valve procedure
13. Symptomatic carotid or vertebral artery disease
14. Expected life expectancy < 12 months due to associated non-cardiac comorbidities

15. Currently participating in another investigational drug or device trial

Statistical Analysis:

Efficacy: Efficacy will be analyzed for the primary outcome as freedom of stroke or death within 5 years after randomization. The log-rank test will be used in the intention-to-treat population with stratification by center and STS score using a one-sided significance level of 2.5%.

Safety: Safety will be analyzed for the co-primary outcome as freedom of stroke or death within 1 year after randomization. The log-rank test will be used in the intention-to-treat population with stratification by center and STS score using a one-sided significance level of 2.5%.

If both efficacy and safety have been demonstrated by showing that TAVI is non-inferior to SAVR, superiority of TAVI over SAVR will be tested the log-rank test with time frame 5 years stratified by center and STS score in the intention-to-treat population using a two-sided significance level of 5%.

Non-inferiority margin: The non-inferiority margin used for both efficacy and safety testing is a hazard ratio (HR) of 1.14 for TAVI over SAVR.

Effect size for power calculation: The effect size assumed for the power calculation is: ln(HR) = ln(0.67) – delta with non-inferiority margin delta = ln(1.14), i.e., HR = 0.59.

Secondary endpoints: The first secondary endpoint, is mortality or stroke within 5 years after randomization, analyzed by restricted mean survival time (RMST) with timeframe 5 years. Components mortality and stroke of the primary composite endpoint and other event times are analyzed like the primary endpoint. Mortality is considered as a competing risk, if it is not part of the endpoints.

Endpoints will additionally be analyzed by use of regression models with adjustment of the main confounding factors including stratification variables. Secondary analyses are interpreted as exploratory.

Randomization: Experimental versus control intervention in a 1:1 ratio using stratified block randomization with variable block length, stratified by STS-PROM and study centre.

Sample Size: The sample size was projected at approximately 1,404 patients overall (702 patients TAVI and 702 patients SAVR). Analysis will be performed by intention-to-treat.

Follow-Up: Discharge or 7 days (whichever comes first), 30 days, 1 year and annual follow-up to at least year 5 after randomization.

Duration: First patient in to last patient out: 118 months.

Participating Centers: The trial is planned to be conducted in approximately 45 study sites in Germany.

2. INTRODUCTION

2.1 BACKGROUND

Symptomatic aortic valve stenosis (AS) represents the most common valvular heart disease in developed countries and is associated with high morbidity and mortality. Its impact on public healthcare resources increases as the Western population ages (Nkomo VT et al. 2006). According to a meta-analysis the prevalence of AS in the elderly (≥75 years of age) is 12.4%, and severe AS is present in 3.4% of whom 75.6% are symptomatic (Osnabrugge RLJ et al. 2013). Stratification according to the Society of Thoracic Surgeons Predicted Risk of Operative Mortality (STS-PROM) demonstrates that the majority of patients belongs to a low or intermediate risk cohort: 5.2% (STS-PROM > 10%), 15.8% (STS-PROM 6-10%) and 79.1% (STS-PROM <6%).

Surgical aortic valve replacement (SAVR) was considered the standard of care in patients with severe symptomatic aortic stenosis for many years. However, the risk associated with the surgical approach increases in elderly patients and those with comorbidities. After Conformité Européenne (CE) mark approval of the first transcatheter heart valves 2007, the number of patients undergoing transcatheter aortic valve implantation (TAVI) in Europe has increased exponentially in subsequent years. In the meantime, profound evidence has been collected regarding the use of TAVI in patients deemed inoperable or at increased surgical risk (Vahanian A et al 2012, Baumgartner H et al 2017).

In the PARTNER (Placement of Aortic Transcatheter Valves) B trial, TAVI was shown to lead to substantial gains in both survival and quality of life (QOL) compared with standard medical/valvuloplasty treatment in patients with severe AS who were unsuitable for SAVR based on anatomic factors or high surgical risk (Leon MB et al. 2010, Reynolds MR et al. 2011). Five-year results confirmed the survival benefits of TAVI over conservative treatment at mid-term follow-up (Kapadia SR et al. 2015). In operable patients with severe, symptomatic AS who are at high surgical risk, the PARTNER A trial demonstrated a similar 1-, 2-, and 5-year survival for TAVI using the Edwards SAPIEN valve compared with standard surgical AVR (Smith CR et al. 2011, Kodali SK et al. 2012, Mack et al. 2015). Although rates of periprocedural complications differed between the treatment groups, the overall rates of major safety events (including stroke) at 5 years were similar. Additionally, TAVI resulted in significant early benefits in health-related QOL. However, these benefits were no longer present 6 to 12 months post-procedure and were observed only after transfemoral TAVI (Reynolds MR et al. 2012).

The CoreValve US pivotal trial documented a significantly better survival at one and two years in patients who underwent TAVI with the Medtronic CoreValve compared to SAVR for the treatment of severe aortic stenosis (Adams DH et al. 2014, Reardon MJ et al 2015). The mean STS-PROM and EuroSCORE scores in the CoreValve trial were approximately 7.5% and 18%, respectively, indicating a lower risk if compared to the PARTNER A cohort (STS-PROM of app. 10%). Furthermore, the stratification of 2-year mortality according to STS score (<5%, 5 to 14.9%, or ≥15%) revealed a significant association between the outcomes of TAVI and the STS score in the PARTNER A cohort, with the survival benefit of TAVI diminishing with higher STS scores (P = 0.01 with the use of the log-rank test, Makkar RR et al NEJM 2012). Two-year results on all-cause mortality from the CoreValve US pivotal trial confirmed this observation with a HR 0.56 in favor TAVI in patients with an STS-PROM of ∞ 7% (HR 0.91 for STS-PROM > 7%). However, longer follow-up demonstrated similar survival for both treatment options at 5 years (Gleason TG et al. 2018)

Data from the German Aortic Valve Registry (GARY) demonstrated a 1-year mortality of 9.5% (EuroSCORE 10-20%) and 9.7% (> 75 years of age) after isolated SAVR (Mohr FW et al 2014). In patients

with STS<4, 1-year mortality was 4.8% after SAVR and 10.0% after TAVI, and after propensity score weighing because of different mean age of 67.5 at SAVR and 78.9 at TAVI, 1-year mortality was about to 9% for both (Bekeredjian R et al. 2018). Brennan et al reported an all-cause mortality of 9.5% and 24.9% at one and four years, respectively, in patients older than 80 years of age with an STS-PROM <5% who underwent isolated SAVR in the US (Brennan JM et al Circulation 2012). Data on five-year mortality were available only in lower risk cohorts and were 12.9 % in patients with a mean age of 62 years after isolated SAVR (Kvidal P et al. 2000). One-year mortality in the general population is 1% at 60 years, 2% at 69 years, 4% at 76 years, 6% at 80 years and 9% at 83 years for men and about 2/3 of that for women (Statistisches Bundesamt, Sterbetafel 2015/2017) and the additional mortality in elderly patients may explain part of the difference.

As a result, five-year mortality would be approximately 45% after SAVR in patients with mean age 79 years. Extrapolation of the CoreValve data would result in five-year mortality 53% after SAVR.

A paradigm-shift in TAVI from inoperable and high-risk towards low to intermediate risk patients began several years ago (Lange R et al. 2012). Evidence from the large GARY-registry (Hamm CW et al. 2014) suggested that European centers performing TAVI were increasingly selecting patients deemed to be at lower surgical risk than specified for the original CE mark label or those enrolled in the larger randomized controlled trials. Around 60% of all German TAVI patients had a EuroSCORE below 20%, classifying these patients at low to intermediate surgical risk. However, conclusive evidence from randomized controlled trials to support routine use of TAVI in low to intermediate risk patients is still insufficient.

The Nordic NOTION trial addressed this knowledge gap and randomized 280 lower risk patients (≥ 70 years of age, mean STS-PROM 3.0) to TAVI or SAVR. Recently published 1-year results did not find significant differences with regard to the primary outcome (all-cause mortality, stroke, myocardial infarction) or all-cause mortality (4.9% [TAVI] vs. 7.5% [SAVR], p=0.38). Limitations relate to the small sample size and large rate of screening failures in this trial (Thyregod HGH et al. 2015). Based on these data, the Medtronic CoreValve Evolut R THV received CE-mark for the treatment of aortic stenosis in patients at intermediate risk as of August 2016. The PARTNER 2A trial randomly assigned TAVI and SAVR to patients deemed at intermediate risk (mean STS-PROM 5.8%). Published 2-year data demonstrated a non-inferiority with regard to the primary outcome of death or disabling stroke (TAVI: 19.5%, SAVR: 21.1%, p=0.25) (Leon MB et al. 2016). Interestingly, a crossing of hazards was observed during longer follow-up with increased event rates for TAVI compared to SAVR between 2 and 5 years (Makkar R et al. 2020).

A propensity score analysis of more recent 1-year data after TAVI with the latest balloon-expandable prosthesis compared to older SAVR data from the PARTNER IIA trial suggested a superiority with regard to the composite endpoint of death, stroke and residual aortic regurgitation ≥moderate (Thourani V. et al. 2016). These latest data remain limited due to the study design of propensity score analysis with a historical patient cohort. Nevertheless, the U.S. Food and Drug Administration approved an expanded indication for the Sapien XT and Sapien 3 transcatheter heart valves for patients with aortic stenosis at intermediate risk as of August 2016 and additional CE-mark for this indication was obtained.

Based on four randomized trials (Adams DH et al. 2014, Leon MB et al. 2016, Nielsen HH et al. 2012, Thyregod HGH et al. 2015), a meta-analysis (Siemieniuk RA et al. 2016) and rapid recommendations (Vandvik PO et al. 2016) published in the British Medical Journal issued a recommendation of transfemoral TAVI over SAVR in low to intermediate risk patients (≥ 85 years of age: strong recommendation, 75-84 years: weak recommendation). The German Cardiac Society issued similar recommendations (Kuck KH et al. 2016).

The SURTAVI trial confirmed non-inferiority of TAVI vs. SAVR in intermediate risk patients treated with the CoreValve and CoreValve Evolut R THV prostheses (Reardon MJ et al. 2017), and resulted in 1-year mortality for STS<3% of 1.5% vs. 5.7%, for STS between 3% and 5% of 5.5% vs. 5.3%, and for STS>5% of 11.1% vs 9.1% (Serruys et al. 2018). The revised European guidelines on the treatment of valvular heart disease summarize current evidence and recommend SAVR in patients at low surgical risk (STS-PROM < 4% or other risk factors) while treatment options for patients at increased surgical risk (STS-PROM ≥4% or other risk factors) should be decided upon by an interdisciplinary heart team according to individual patient characteristics (Baumgartner H et al. 2017).

With the limited data at present, further investigations have to evaluate both treatment options on a broader basis in an all-comers intermediate risk population to reflect clinical reality. If TAVI proves to be non-inferior to SAVR in intermediate risk patients, it is estimated that further 145,000 patients would become eligible for TAVI (Osnabrugge RLJ et al. 2012). In the future, TAVI may compete with SAVR in patients at low surgical risk, a group comprising 730,000 severe AS patients in the European countries and North America (Osnabrugge RLJ et al. 2012). Independent investigator-initiated trials will be able to answer this important question sufficiently. Company-sponsored formal economic evaluation demonstrated that the benefits of TAVI in inoperable patients were achieved at an acceptable incremental cost to society, at least in the context of the U.S. health system. Although TAVI is cost effective in the United States for patients at high and prohibitive risk, data from other countries show that, for intermediate-risk patients, the costs of TAVI at 1 year are considerably higher than the costs of SAVR (Osnabrugge RLJ et al. 2012). Health economic research within this trial will focus on the analysis of the incremental cost-effectiveness of TAVI compared to SAVR in patients at low to intermediate risk.

Most recently, three important manuscripts have been published. The PARTNER 3 trial demonstrated a reduced rate for the composite primary endpoint for TAVI with the balloon-expandable THV compared to SAVR in patients at low operative risk (Mack M et al 2019). Results were particularly driven by increased rates of rehospitalization and follow-up was limited. Two-year results demonstrated an approximation of the event curves for disabling stroke and death after one year with higher event rates in the TAVI arm (Leon MB et al. 2021). The Evolut Low Risk Trial reported non-inferiority for TAVI with the self-expanding THV and SAVR at two years with regard to the composite endpoint of death or stroke (Popma JJ et al. 2019).

Long-term follow-up of both trials awaited will be of major importance to evaluate whether a crossing of hazards, as observed during 5-year follow-up in the intermediate risk PARTNER 2 trial (Makkar R et al 2020), will occur. This information will be of particular importance if expanding TAVI to younger low-risk patients.

2.2 RATIONALE

A paradigm-shift towards performing TAVI in intermediate- and low-risk patients has already begun, as procedural results of TAVI have improved significantly within the past years. Nevertheless, a prospective and independent comparison of surgical and interventional valve therapy in patients considered at low to intermediate risk that covers an “all-comers” patient population has not yet been performed. With the support of the health insurance providers and the “Deutsches Zentrum für Herz-Kreislauf-Forschung e.V.” (DZHK), DEDICATE will address this aspect that will be central to the future of heart valve therapy.

2.3 RISK-BENEFIT ANALYSIS

The study will be performed in accordance with the requirements of Good Clinical Practice, the principles of DIN ISO 14155 and the Declaration of Helsinki in its latest accepted version.

Potential benefits of TAVI vs. SAVR include the less-invasive nature of the approach, lower rates of bleeding, acute kidney injury, new-onset atrial fibrillation, and shorter recovery time. The use of extracorporeal circulation with its sequelae is not required during TAVI, as is general anesthesia. Severe periprocedural complications and the need for conversion to open heart surgery have become rare with the use of current devices and techniques. However, long-term results on outcome and valve-durability are only available for SAVR at this point and the need for permanent pacemaker implantation due to conduction disturbances and residual aortic regurgitation were observed more often after TAVI compared to SAVR. Overall, procedural results and periprocedural complications are expected to be similar among patients undergoing SAVR or TAVI, as specified in 2.1. Subsequently, both treatment options are advisable in patients included in this trial. Both approaches (TAVI and SAVR) are regularly performed in the participating study centers in daily clinical routine. All devices used are CE-marked for implantation in high-risk patients and some recently received CE-mark or FDA-approval for use in intermediate- and low-risk patients . In addition, German healthcare insurance providers will reimburse for both SAVR and TAVI as part of routine clinical treatment. In summary, there is clear scientific equipoise justifying a randomized clinical trial to address the remaining knowledge gaps and the risk-benefit evaluation is judged positive.

3. STUDY POPULATION

The study population consists of patients with severe symptomatic aortic stenosis considered at low to intermediate risk for surgical aortic valve replacement. To maximize generalizability and representativeness we use broad inclusion criteria and strict exclusion criteria.

4. STUDY OBJECTIVES AND ENDPOINTS

The objective is to demonstrate that safety and effectiveness of TAVI is non-inferior – as measured by rates all-cause mortality rates and stroke at 12 and 60 months – compared to SAVR in the treatment of patients with symptomatic severe aortic stenosis at low to intermediate risk.

Primary and secondary outcomes will be assessed at regular visits as specified below. Deaths and hospitalizations will be validated through death certificates and information from the primary care physicians. Endpoint data will be collected from hospital and primary care physician records and assessed in accordance with the updated consensus document on endpoint definitions (Kappetein AP et al. 2012). Clinical events will be assessed and validated by an independent event adjudication committee in accordance with current guidelines.

4.1 PRIMARY OBJECTIVES

The primary objective of this trial is to determine the safety and effectiveness of TAVI compared to SAVR in the treatment of patients with symptomatic severe aortic stenosis at low to intermediate operative risk of mortality.

4.1.1 PRIMARY ENDPOINT

1. The primary endpoint of the study is freedom from stroke or death within 5 years after randomization.
2. The co-primary safety endpoint of the study is freedom from stroke or death within 1 year after randomization.

Freedom from stroke or death within 5 years after randomization will be used as primary efficacy endpoint. Freedom from stroke or death within 1 year after randomization will be used as one-year co-primary safety endpoint. The publication of the co-primary safety endpoint will only serve for safety reasons and should not be used in guidelines to judge efficacy of TAVI and SAVR in low to intermediate risk patients. The latter decision should only be made when five-year results are available. Freedom from stroke or death is used as primary outcome due to its strength in measuring both safety and efficacy at once.

4.2 SECONDARY OBJECTIVES

Secondary outcome measures were defined in accordance with the updated Valve Academic Research Consortium-2 consensus document (Kappetein AP et al. 2012), which have been validated in several trials and serve as standardized endpoints. Additional variables were added to allow for meaningful comparison of both treatment options.

4.2.1 SECONDARY ENDPOINTS

In detail, the following secondary endpoints were defined and will be assessed at every study visit (V2-V10) unless stated otherwise and compared between TAVI and SAVR cohorts:

- Freedom of stroke or death
- Overall survival
- Freedom from cardiovascular mortality [1]
- Freedom from the composite of all-cause mortality and stroke [1]
- Freedom from myocardial infarction [1]
- Freedom from stroke [1]
- Freedom from major or life-threatening / disabling bleeding [1]
- Freedom from acute kidney injury [1]
- Freedom from major vascular access site and access-related complications [1]
- Freedom from conduction disturbances and arrhythmias, need for permanent pacemaker implantation [1]
- Freedom from residual aortic regurgitation ≥ moderate [1]
- Composite device success [1], including
    - Freedom from procedural mortality
    - Correct positioning of a single THV in the proper position with intended performance (no prosthesis- patient mismatch and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, AND no moderate or severe prosthetic valve regurgitation)
- Composite early safety (at 30 days) [1], including [1]
    - All-cause mortality
    - Stroke (disabling and non-disabling)
    - Life-threatening bleeding
    - Acute kidney injury stages 2/3
    - Coronary artery obstruction requiring intervention
    - Major vascular complication
    - Valve-related dysfunction requiring repeat procedure

[1] Kappetein AP et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012;60(15): 1438-54.

Composite clinical efficacy (after 30 days) [1], including

- All-cause mortality
- Stroke (disabling and non-disabling)
- Rehospitalisation for worsening heart failure or valve-related symptoms
- NYHA III or IV
- Valve-related dysfunction (mean aortic valve gradient >20 mmHg, EOA <0.9-1.1 cm^2 and/or DVI <0. 35 m/s, AND/OR moderate or severe prosthetic valve regurgitation)

Freedom from prosthetic valve dysfunction [1]

- Mean aortic valve gradient >20 mmHg, EOA <0.9-1.1 cm^2 and/or DVI <0.35 m/s, AND/OR moderate or severe prosthetic valve regurgitation)

Freedom from prosthetic aortic valve endocarditis

Freedom from the composite time-related valve safety [1], including

- Structural valve deterioration, including repeat procedures
- Prosthetic valve endocarditis or thrombosis
- Thromboembolic events (e.g. stroke)
- VARC bleeding (unless clearly unrelated to valve therapy)

Quality of life measures [1], including

- Improvement in quality of life assessment
- Improvement in functional status

(Re-)Hospitalization, including

- Length of stay in-hospital
- Length of stay at intensive care unit
- Length of stay at rehabilitation facility
- Length of stay at nursing home
- Number of rehospitalisations
- Ratio of days alive out of hospital versus total days alive

Health economic analysis comparing cost-effectiveness

- Incremental cost-effectiveness of TAVI compared to surgical valve replacement, by using QALY´s, life years gained, and cost data obtained

5. STUDY DESIGN

The study is a comparator-controlled, multi-center, randomized trial to compare TAVI and SAVR in an unselected real-world population of patients at low to intermediate surgical risk. Approximately 1,404 AS patients with low to intermediate risk will be randomized (1:1 ratio) to either TAVI or SAVR, and patients will be followed up for 5 years after randomization. The choice of the valve to be implanted and the access site will be at the discretion of the implanting team, to prevent a potential device-based bias and an industry-independent design of this trial will allow insights into the performance of currently available valve types, individually chosen for the respective patient. Procedures will be performed in accordance with the recommendations of the “Gemeinsamer Bundesausschuss (G-BA)" for minimally-invasive heart valve procedures[1]. All patients with aortic stenosis and low to intermediate risk will be included in a nested registry to evaluate an all-comers patient population (see 5.7 for details).

[1] Beschluss des Gemeinsamen Bundesausschusses über eine Richtlinie zur minimalinvasiven Herzklappenintervention: Erstfassung vom 22. Januar 2015, BAnz AT 24.07.2015 B6

5.1 STUDY DURATION

Up to 45 German heart centers will participate in this trial. The planned duration from first patient in to last patient out is approximately 118 months.

5.2 STUDY POPULATION

The screening period is designed to determine patient eligibility according to the in- and exclusion criteria. All patients evaluated for the treatment of severe aortic stenosis at the participating centers are potentially eligible for this trial. The study is intended to reflect a "real-world" perspective of patients undergoing TAVI. To maximize generalizability and representativeness we use broad inclusion criteria and strict exclusion criteria aiming at patients with symptomatic AS at low to intermediate risk, as judged by the local heart team, taking into account cardiac and extracardiac patient characteristics and established risk scores (e.g. STS-PROM, EuroSCORE) according to ESC/EACTS guidelines for the management of valvular heart disease (Baumgartner H et al. 2017). A nested registry is implemented to document recruitment and patient selection (see 5.7 for details).

Another central aspect of this trial refers to the heart team approach with a designated interventional cardiologist and a designated cardiac surgeon involved in the screening process and patient selection. A heart team consensus that both treatment options (SAVR and TAVI) are feasible is required.

As combined SAVR and CABG are associated with a significantly higher perioperative morbidity and mortality than SAVR alone, a strategy for revascularization has to be defined before enrollment into the trial if significant coronary artery disease is present. Patients with untreated and clinically significant coronary artery disease considered a contraindication to an isolated aortic valve procedure (TAVI or SAVR) are excluded from the trial. The need for coronary revascularization is defined by local heart team consensus.

5.3 INFORMED CONSENT

If both SAVR and TAVI are advisable in patients according to heart team consensus, informed written consent will be obtained for the DEDICATE trial and the DZHK Basis Biomaterial Collection ("Biomaterialsammlung") by the local principal investigator or his/her designee from patients (or their legal representatives). This will be performed prior to any protocol-specific procedure. Failure to provide informed consent renders the subject ineligible for participation in the trial.

5.4 INCLUSION CRITERIA

To participate in this trial, the patient must meet all of the following inclusion criteria:

1. Heart team consensus **that TAVI and SAVR are both** medically justified and **advisable** based on:

a) Degenerative aortic valve stenosis with echocardiographically derived criteria:
   - Mean gradient >40 mmHg or
   - Jet velocity greater than 4.0 m/s or
   - Aortic valve area (AVA) of < 1.0 cm^2 (indexed EOA < 0.6 cm^2/m^2).

b) Patient is symptomatic from his/her aortic valve stenosis
   - NYHA Functional Class ≥ II or
   - Angina pectoris or
   - Syncope.

c) Patient is classified as low to intermediate operative risk as assessed by the local heart team according to the variables outlined in the 2017 ESC/EACTS guidelines for the management of valvular heart disease [1], taking into account cardiac and extracardiac patient characteristics and established risk scores (e.g. STS-PROM, EuroSCORE).

d) A transfemoral or alternative (e.g. transapical, transaortic, transaxillary) access for TAVI seems feasible. Centers should follow a "transfemoral first" strategy for the primary route of access; however, other routes of access are also allowed, as decided by local heart team consensus

2. Patients aged 65-85 years
3. Patient has provided written informed consent to participate in the trial.
4. Ability of the patient to understand the patient information and to personally sign and date the informed consent to participate in the study, before performing any study related procedures.
5. The patient agrees to undergo SAVR, if randomized to control treatment
6. The patient and the treating physician agree that the patient will return for all required post-procedure follow-up visits
7. Male patients or postmenopausal (defined as no menses for 12 months without an alternative medical cause) in case of female gender

5.5 EXCLUSION CRITERIA

Patients are not eligible to participate in this trial if <u>any</u> of the following exclusion criteria are met:

1. Aortic valve is a congenital unicuspid or congenital bicuspid valve, or is non-calcified
2. Untreated clinically significant coronary artery disease considered a contraindication to an isolated aortic valve procedure (TAVI or SAVR) according to heart team consensus
3. Any percutaneous coronary intervention performed within 1 month prior to the study procedure
4. Prior cardiac surgery
5. Untreated severe mitral or tricuspid regurgitation
6. Untreated severe mitral stenosis
7. Hemodynamic instability requiring inotropic support or mechanical circulatory support
8. Ischemic stroke or intracranial bleeding within 1 month
9. Severe ventricular dysfunction with left ventricular ejection fraction < 20% as measured by resting echocardiogram
10. Hypertrophic obstructive cardiomyopathy or severe basal septal hypertrophy with outflow gradient
11. Echocardiographic evidence of an intracardiac mass, thrombus, vegetation or endocarditis
12. Any other condition considered a contraindication for an isolated aortic valve procedure
13. Symptomatic carotid or vertebral artery disease

[1] Baumgartner H et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38(36):2739-91.

14. Expected life expectancy < 12 months due to associated non-cardiac comorbidities
15. Currently participating in another investigational drug or device trial

5.6 VISITS

Phase of study	Pre-study	Pre-procedural	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visits 7-9	Visit 10	Additional Visits
Date	-6 weeks to Day 0	-6 weeks to Day 0	Day 0 Procedure	Day 1	Day 3	Discharge or Day 7	Day 30 (+/-7 days)	1 year (365-390 days after procedure)	Annually years 2-4 (+/- 90 days)	5 years (1825-2005 days after procedure)	At least one year and 5 years after recruitment completed
Mode of visit	In-patient or out-patient	In-patient or out-patient	In-patient	In-patient	In-patient	In-patient	Phone call	Out-patient	Phone call	Out-patient	Phone Call
Informed consent	X										
Inclusion / exclusion criteria	X										
STS-PROM, EuroSCORE (1 & 2)		X									
Randomization SAVR or TAVI		X									
Medical history [1]		X [1]									
Co-medication [1]		X [1]				X [1]	X	X [1]	X	X [1]	
Physical examination (incl. vital signs, height, weight) [1]		X [1]				X [1]		X [1]		X [1]	
NYHA, CCS, history of syncope [1]		X [1]				X [1]	X	X [1]	X	X [1]	
Number of hospitalizations		X [1,2]					X [3]	X [1,3]	X [3]	X [1,3]	X [3]
6-Minute walk test [1]		X [1]				X [1]		X [1]		X [1]	
Frailty assessment		X [1]				X		X		X	
Quality of life survey (EQ-5D)		X				X	X	X	X	X	
Depression scale (CES-D)		X					X	X	X	X	
NIH Stroke scale		X				X		X		X	
Barthel Index		X				X [4]	X [4]	X [4]	X [4]	X [4]	X [4]
Modified Rankin Scale		X				X [4]	X [4]	X [4]	X [4]	X [4]	X [4]
Blood count [1]		X [1]		X [1]	X [1]	X [1]		X [1]		X [1]	
Metabolic panel, including creatinine, urea, GFR [1]		X [1]		X [1]	X [1]	X [1]		X [1]		X [1]	
Liver panel, LDH [1]		X [1]				X [1]		X [1]		X [1]	
NT-proBNP [1]		X [1]				X [1]		X [1]		X [1]	
CK/CK-MB + hsTNT or hsTNI [1]		X [1]		X [1]	X [1]	X [1]		X [1]		X [1]	
aPTT/INR [1]		X [1]				X [1]		X [1]		X [1]	

ECG [1]		X [1]		X [1]	X [1]	X [1]		X [1]		X [1]	
Transthoracic echocardiography [1]		X [1 *]	X [1]			X [1 *]		X [1 *]		X [1 *]	
Transesophageal echocardiography [1]		X [1]	X [1]								
Pacemaker/defibrillator interrogation						X [1,5]		X [1,5]		X [1,5]	
Coronary angiography [1]		X [1]									
MDCT [1]		X [1]									
Procedural parameters [1,6]			X [1,6]								
Postprocedural parameters [1, 7]				X [1,7]	X [1,7]	X [1,7]					
Safety events			X	X	X	X	X	X	X	X	X
DZHK Biomaterial Collection		X						X [8]		X [8]	
Survival status											X[9]

[1] Collection of data acquired during clinical routine following current guidelines; no study-specific procedures.

[2] Hospitalisation due to heart failure within past 6 months.

[3] Hospitalisation due to heart failure since past visit.

[4] Modified Rankin Scale and Barthel Index to be performed in any patient with a stroke.

[5] Interrogation only for patients with permanent pacemakers or defibrillators.

[6] Mode of anesthesia, access route, duration of surgery/intervention, volume of contrast media, dose-area-product, use of cardiopulmonary bypass / hemodynamic support, specifications of implanted valve prosthesis, echocardiography/angiography with particular emphasis on valve prosthesis function, transfusion of blood products, safety events.

[7] Duration of hospital stay and intensive care unit stay, ventilation time, transfusion of blood products.

[8] If applicable.

[9] incl. date of death, if applicable

* Echocardiographic image data at baseline, discharge, one and five years will be transferred to the core-laboratory for independent evaluation

5.6.1 PRE-STUDY PROCEDURES

If both SAVR and TAVI are advisable in a patient, informed written consent will be obtained from this patient for this study, and eligibility will be verified by checking inclusion/exclusion criteria.

5.6.2 PRE-PROCEDURAL WORKUP

After informed consent to the trial, routinely acquired data on the following items will be documented in the eCRF. Pre-procedural assessment and diagnostics will not be influenced by the study and will follow DZHK [1] and institutional standard operating procedures for the treatment of severe aortic stenosis. All diagnostic examinations deemed necessary by the heart team to ensure clinical safety and decision-making will be performed before randomization.

The following data will be documented if available as part of clinical routine for all patients eligible for the study [2]:

1. Medical history
2. Physical examination, including pulse, blood pressure, height, weight.
3. Concomitant medication
4. NYHA and CCS classification, history of syncope
5. Number of hospitalizations due to heart failure within past 6 months
6. 6-Minute walk test
7. Frailty assessment: Clinical frailty scale
8. Laboratory work
    a. Complete blood count including platelet count
    b. Metabolic panel including creatinine, urea, GFR
    c. Liver panel, LDH
    d. NT-proBNP
    e. CK/CK-MB and high-sensitive troponin T (hsTnT) or troponin I (hsTnI)
    f. aPTT / INR
9. 12-lead ECG
10. Comprehensive transthoracic echocardiogram according to recommendations[3]; transfer of echocardiographic image data to the echocardiography core-laboratory
11. Comprehensive transesophageal echocardiogram (<3 months prior to study procedure)
12. Multidetector computed tomography performed as per institutional standard (contrast-enhanced and with ECG triggering, if applicable) to assess aortic annulus geometry and size, root anatomy and assess access route options (<3 months prior to study procedure)

[1] DZHK SOP K01 V1.0 1 („Basisdatensatz“), K02 V1.0 („Anamnese/Diagnosen“), DZHK SOP K04 V1.0 („6MWT“), DZHK SOP K03 V1.0 („EKG”)
[2] Collection of data acquired during clinical routine following current guidelines; no study-specific procedures
[3] DZHK SOP K08 V1.0 („Echokardiographie“) and Hagendorff A et al. Die konventionelle Standarduntersuchung in der transthorakalen Echokardiographie bei Patienten mit degenerativer Aortenklappenstenose. Ultraschall in Med 2012;33: 520-43.

13. Coronary angiography to assess for relevant coronary artery disease performed as per institutional standard (<6 months prior to study procedure)

The following study-specific procedures will be performed as part of the trial:

1. Informed Consent
2. Check I/E criteria
3. Quality of life survey (EQ-5D)
4. Depression scale (CES-D)
5. NIH Stroke scale
6. Barthel Index
7. Modified Rankin Scale
8. Assessment of STS-PROM and logistic EuroSCORE (versions 1 and 2)
9. Basis Biomaterial Collection according to DZHK-standard [1]: Additional samples (7.5ml EDTA blood, 7.5 ml serum, 6 ml citrate blood, 10 ml urine) will be drawn during routine blood draw.
10. Randomization

5.6.3 RANDOMIZATION

Patients will be randomized in the order they qualify. Randomization will be done to obtain comparable treatment groups within the eCRF. Randomization will be executed in a 1:1 ratio to the experimental intervention or control intervention using balanced stratified block randomization with variable block length, stratified by STS-PROM (0-2%, 2.01-4% vs. 4.01-6%) and implanting site (study center). Randomization will be performed using the validated randomization software RITA.

5.6.4 VISIT 1: STUDY INTERVENTION (DAY 0)

SAVR is performed at the discretion of the cardiac surgeon to give a pragmatic reference. However, SAVR has to be performed by board-certified cardiac surgeons. Investigators are reminded of current clinical guidelines to compare with current best practice. Similarly, for TAVI the medical devices will be used which are CE-marked, most appropriate and best suited for the individual patient and which are routinely in use at the study centers (>30 procedures before DEDICATE study entry). TAVI procedures should be performed in a joint setting – preferably a hybrid OR – by interventional cardiologists and cardiac surgeons as a team approach. Centers should follow a "transfemoral first" strategy for the primary route of access; however, other routes of access are also allowed and will ultimately selected by the implanting team. Procedures will be performed according to institutional standards.

Relevant procedural data will be collected for all patients during the intervention, including [2]:

1. Mode of anesthesia
2. Access route
3. Duration of surgery / intervention
4. Volume of contrast media, dose-area-product
5. Use of cardiopulmonary bypass / hemodynamic support

[1] DZHK SOP B01 V1.21 („Biomaterialgewinnung) and B02 V1.21 („Biomaterialverarbeitung")
[2] Collection of data acquired during clinical routine following current guidelines; no study-specific procedures.

6. Specifications of implanted valve prosthesis
7. Echocardiography / angiography (if performed as part of clinical routine) with particular emphasis on valve prosthesis function [1]
8. Transfusion of blood products
9. Safety events

All patients will receive concomitant therapy according to current guidelines, as assessed by the patient's physician. Antiplatelet and anticoagulation regimen is left at the investigator's discretion.

An attempted implant was defined when the patient was brought into the procedure room and any of the following have occurred: anesthesia administered, vascular line placed, transesophageal echocardiogram placed or any monitoring line placed.

5.6.5 VISITS 2-10, ADDITIONAL: FOLLOW-UP

Post-procedural care will be carried out according to institutional standard operating procedures and according to current guidelines. Laboratory work will be adapted to clinical needs. Each patient will undergo neurological assessments at designated clinical visits, which will be performed according standardized tests. All patients with suspected neurological deficits will be evaluated by a neurologist as soon as possible and will undergo brain imaging if indicated. Particular emphasis will be put on sufficient echocardiographic follow-up. Echocardiographic imaging and data assessment will follow the DZHK standard operating procedure on standardized echocardiographic assessment and current recommendations to allow for sufficient evaluation by the core-laboratory [2]. In addition, particular evaluation of valve prosthetic function will be performed according to standardized VARC-2 criteria [1]. Follow-up procedures will be conducted, as specified below.

<u>Days 1 and 3 (Visits 2 and 3):</u>

1. Laboratory work [3]
    a. Complete blood count including platelet count
    b. Metabolic panel including creatinine, urea, GFR
    c. CK/CK-MB and high-sensitive troponin T (hsTnT) or troponin I (hsTnI)
2. 12-lead ECG [3]
3. Safety events

<u>Day 7 or discharge, whichever comes first (Visit 4):</u>

1. Physical examination, including pulse, blood pressure, height, weight [3]
2. Duration of hospital stay and intensive care unit stay [3]
3. Ventilation time [3]
4. Concomitant medication, particularly including anticoagulation and antithrombotic medication [3]

[1] Kappetein AP et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012;60(15): 1438-54.
[2] DZHK SOP K08 V1.0 („Echokardiographie") and Hagendorff A et al. Die konventionelle Standarduntersuchung in der transthorakalen Echokardiographie bei Patienten mit degenerativer Aortenklappenstenose. Ultraschall in Med 2012;33: 520-43.
[3] Collection of data acquired during clinical routine following current guidelines; no study-specific procedures.

5. Transfusion of blood products [3]
6. NYHA and CCS classification, history of syncope [3]
7. 6-Minute walk test [1]
8. Frailty assessment: Clinical frailty scale
9. Laboratory work [1]
    a. Complete blood count including platelet count
    b. Metabolic panel including creatinine, urea, GFR
    c. Liver panel, LDH
    d. NT-proBNP
    e. CK/CK-MB and high-sensitive troponin T (hsTnT) or troponin I (hsTnI)
    f. aPTT / INR
10. 12-lead ECG [1]
11. Pacemaker/defibrillator interrogation (for patients with permanent pacemakers or defibrillators only) [1]
12. Comprehensive transthoracic echocardiogram [1],[2], particular evaluation of valve prosthetic function according to VARC-2 criteria [3]; transfer of echocardiographic image data to the echocardiography core-laboratory
13. Quality of life survey (EQ-5D)
14. NIH Stroke scale
15. Modified Rankin Scale and Barthel index for any patient with a previous stroke
16. Safety events

<u>Data collection at 1-year (365-395 days after procedure) (visit 6) and 5-years (1825-2005 days after procedure (visit 10):</u>

1. Concomitant medication, particularly including anticoagulation and antithrombotic medication [1]
2. Physical examination, including pulse, blood pressure, height, weight [1]
3. NYHA and CCS classification, history of syncope [1]
4. Number of hospitalizations due to heart failure since past visit [1]
5. 6-Minute walk test [1]
6. Frailty assessment: Clinical frailty scale
7. Laboratory work [1]
    a. Complete blood count including platelet count
    b. Metabolic panel including creatinine, urea, GFR
    c. Liver panel, LDH

[1] Collection of data acquired during clinical routine following current guidelines; no study-specific procedures.
[2] DZHK SOP K08 V1.0 („Echokardiographie“) and Hagendorff A et al. Die konventionelle Standarduntersuchung in der transthorakalen Echokardiographie bei Patienten mit degenerativer Aortenklappenstenose. Ultraschall in Med 2012;33: 520-43.
[3] Kappetein AP et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012;60(15): 1438-54.

   d. NT-proBNP
   e. CK/CK-MB and high-sensitive troponin T (hsTnT) or troponin I (hsTnI)
   f. aPTT / INR
8. 12-lead ECG [1]
9. Pacemaker/defibrillator interrogation (for patients with permanent pacemakers or defibrillators only) [1]
10. Comprehensive transthoracic echocardiogram [1],[2], particular evaluation of valve prosthetic function according to VARC-2 criteria [3]; transfer of echocardiographic image data to the echocardiography core-laboratory
11. Quality of life survey (EQ-5D)
12. Depression scale (CES-D)
13. NIH Stroke scale
14. Modified Rankin Scale and Barthel index for any patient with a previous stroke
15. Safety events
16. Biobanking according to DZHK standard [4], additional samples (7.5ml EDTA blood, 7.5 ml serum, 6 ml citrate blood, 10 ml urine) will be drawn during routine blood draw.

Data collection by telephone interview at 30 ± 7 days and years 2-4 ± 90 days (visits 5, 7-9):

1. Concomitant medication, particularly including anticoagulation and antithrombotic medication
2. NYHA and CCS classification, history of syncope
3. Number of hospitalizations due to heart failure since past visit
4. Modified Rankin Scale and Barthel index for any patient with a previous stroke
5. Quality of life survey (EQ-5D)
6. Depression scale (CES-D)
7. Safety events

If a patient cannot be contacted for a follow-up visit, the investigator will document the efforts undertaken to contact the patient, referring physicians, family members, or other alternate contacts noted in the subject's records. These efforts should include 3 attempts of telephone contacts at separate dates and times, and a registered letter. If the patient cannot be reached in any way for their follow-up visits and misses the scheduled visit, new efforts will be undertaken to locate them at subsequent follow-up visits. In the event that the patient's implanted valve is explanted, the patient needs to be continued to be followed for the duration of the study. In addition, obtained data will be evaluated with health-economic measures to investigate incremental cost-effectiveness of TAVI compared to surgical valve replacement, by using QALY´s, life years gained, and cost data obtained.

[1] Collection of data acquired during clinical routine following current guidelines; no study-specific procedures.
[2] DZHK SOP K08 V1.0 („Echokardiographie") and Hagendorff A et al. Die konventionelle Standarduntersuchung in der transthorakalen Echokardiographie bei Patienten mit degenerativer Aortenklappenstenose. Ultraschall in Med 2012;33: 520-43.
[3] Kappetein AP et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012;60(15): 1438-54.
[4] DZHK SOP B01 V1.1 („Biomaterialgewinnung) and B02 V1.1 („Biomaterialverarbeitung").

All study-related procedures will be performed according to DZHK standards for data acquisition at assigned time intervals. All collected ECGs, echocardiograms (DICOM format), and MDCT (DICOM format) will be collected and sent to the core lab for independent analysis. Data will be used for adjudication of events, endpoints, and post-hoc analyses.

Data collection for primary and follow-up analysis (Additional visits):

After the last patient has reached at least 1 year and 5 years of follow-up, an additional telephone visit is requested for all patients during follow-up. that includes the following data:

1. Survival status and time, i.e. date of the visit or – in case of death – date of death.
2. Safety events
3. Number of hospitalizations due to heart failure since past visit
4. Modified Rankin Scale and Barthel index for any patient with a previous stroke

5.7 NESTED REGISTRIES

The DEDICATE trial is intended to include all-comers patients. Information on all-comers results is of utmost importance for the scientific community as present trials focus on selected patient groups only.

In order to obtain information on an all-comers population during the recruitment period, study sites will be asked to (Figure 1):

≠ Document the overall number of TAVI procedures and isolated SAVR during the time of recruitment at the respective trial site

≠ Collect anonymized basic clinical data of all patients who are eligible to participate in the DEDICATE trial according to the inclusion/exclusion criteria (meet all inclusion criteria [except IC 3-6 covering informed consent] and none of the exclusion criteria) but who are not randomized within the DEDICATE trial. These patients, who cannot be randomized, are mainly from the following two groups:

a.) Patients in whom TAVI and SAVR are both advisable according to heart team consensus but who are not willing to sign informed consent for study participation despite physician recommendation.

b.) Patients in whom TAVI and SAVR are not both advisable according to heart team consensus.

Anonymized basic clinical data from the two abovementioned groups a.) and b.) will be collected at a single timepoint (discharge of patients). The coordinating investigator at each site will be responsible for complete (100%) reporting of this all-comers population.

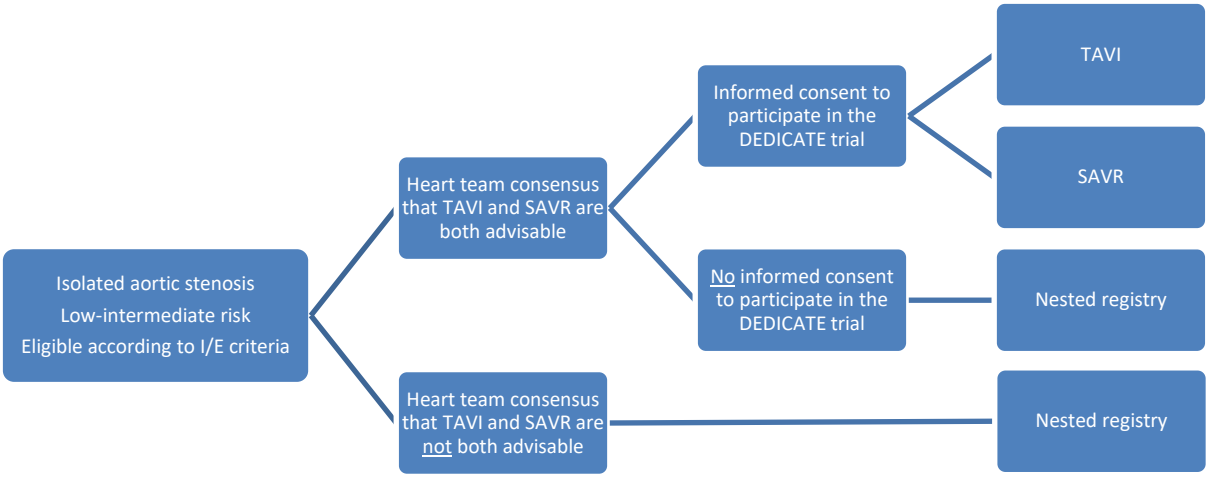

Figure 1: DEDICATE RCT and nested registries

5.8 PATIENT WITHDRAWAL

All subjects will be followed up unless they withdraw their consent. A subject may withdraw his/her consent at his/her own request without given reasons at all time during the trial. This will be without disadvantages for the subject. A study subject that has withdrawn from study participation will not be replaced. Withdrawal will be addressed to the study center and forwarded to the central data management of the DZHK by study personnel. Withdrawal from the study yields withdrawal of Biomaterial Collection (in case of participation). After patient withdrawal, all data will be anonymized and biomaterial will be destroyed (if applicable).

6. SAFETY EVALUATION

6.1 SAFETY EVALUATION AND REPORTING

According to DIN ISO 14155 the principal investigator is responsible for the continuous safety evaluation of the clinical trial. CTC North will provide the principal investigator with a list of all safety events reported via the eCRF on a quarterly basis. The principal investigator is responsible for the final risk assessment. A safety report including a line listing of all safety events and an overall safety statement will be submitted to the ethics committee on a quarterly basis during the conduct of the trial.

Safety events are defined in accordance with the standardized endpoints of the updated VARC [1] document and as specified in the appendix section of this document.

According to the "Medizinproduktegesetz" and "Medizinprodukte-Sicherheitsplanverordnung", operator and local investigators are responsible for the proper and timely submission of incident reports ("Vorkommnisse") as part of the "Vigilanzsystem" to the Federal Institute for Drugs and Medical Devices (BfArM). An incident is any malfunction, any failure or deterioration in the characteristics or performance of a medical device as well as any inaccuracy in the labeling or instructions for use which has led, or could have led, directly or indirectly, to the death or serious deterioration in the state of health of a patient or user or another person. Incidents should be reported

[1] Kappetein AP et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012;60(15): 1438-54.

without delay in accordance with the required urgency of attention but in any case within a maximum of 30 days of these becoming known.

In addition, local investigators must document these incidents on the appropriate pages of the eCRF at the time of reporting to BfArM. The trial management may contact the study centers for additional information if deemed necessary to classify and adjudicate the events.

To evaluate potential safety events, the Event Adjudication Committee (EAC) will receive blinded eCRF data (prepared by the trial management), and adjudicate on patient status changes, pre-defined safety events and endpoints. Where appropriate, the EAC may receive unblinded data (on a patient level or treatment group level).

The Data Safety and Monitoring Board (DSMB) will assess the adjudicated safety data and, if needed, critical efficacy endpoints of the trial. The DSMB will receive a blinded summary of these data (prepared by an independent statistician) and will particularly evaluate the participant risk versus benefit ratio. In addition, the DSMB will monitor external factors relevant to the trial, for example scientific and therapeutic developments that may affect participant safety or ethical status. Based on the observed benefits or adverse effects, the DSMB will make recommendations to the Steering Committee concerning continuation, termination or modifications of the trial.

6.2 INDIVIDUAL PATIENT AND COHORT TRIAL STOPPING CRITERIA

Individual criteria: The individual patient can prematurely terminate his or her study participation at any time by withdrawing consent to the trial. Principal investigator can prematurely terminate study participation if any circumstances occur in which the health of the patients would be endangered upon continued participation in the clinical trial. In case of premature termination, reasons and circumstances for termination and the patient's clinical status should be documented. Potential safety events will be collected.

Cohort criteria: After consultation with the DSMB and the Steering committee, the principal investigators may terminate the trial at any time if serious safety concerns arise for the patients. These include (a) unacceptably high rates of safety events/incidences based on the judgement of the DSMB and steering committee, (b) unexpected safety events requiring a revision of the risk-benefit evaluation, and (c) insufficient recruitment rate. In the case of study termination, participating sites will be informed of the procedures to be followed to ensure adequate consideration is given to the protection of the patient's safety. The principal investigator has to inform the ethics committee and the involved regulatory affairs about trial termination.

7. STATISTICAL CONSIDERATIONS AND ANALYSIS STRATEGY

All statistical analyses will be conducted by the Institute for Medical Biometry and Statistics at the University of Lübeck. All analyses will be described in detail in a statistical analysis plan (SAP) which will be finalized before the randomization of the last patient. The analysis strategy is the treatment policy strategy of ICH-E9(r2). The primary estimand is the hazard ratio of the composite endpoint of all-cause mortality or stroke within 5 years of follow-up in the intention-to-treat data that are censored at loss to follow-up, but not at deviations from the assigned treatment. The co-primary estimand is the hazard ratio of the composite endpoint of all-cause mortality or stroke within 1 year of follow-up in

the intention-to-treat data that are censored at loss to follow-up, but not at deviations from the assigned treatment. The third estimand of interest is the difference of restricted mean survival time (RMST) of the composite endpoint of all-cause mortality or stroke at 5 years after randomization in the intention-to-treat data that are censored at loss to follow-up, but not at deviations from the assigned treatment. The non-inferiority objective requires a sensitivity analysis in which the estimand differs by modeling intercurrent changes of treatment by a time-dependent covariate (AT for as-treated data). The whole primary analysis will be based on the full analysis set using the intention-to-treat (ITT) principle; the AT set is analyzed as secondary analyses for safety endpoints and efficacy endpoints, and both analyses should yield similar conclusions. Neither interim analyses nor design adaptations are planned.

7.1 DESCRIPTIVE STATISTICS

The type of descriptive statistics used in this trial are described in the following:

Type M (measurement): Median and range with 95% confidence Hodges-Lehmann intervals for the difference of medians.

Type N (normal): Means and standard deviations (SD) for each treatment group and 95% confidence interval for the difference of means.

Type LN (log-normal): Type N statistics are computed for logarithms and converted back to geometric means, ratio of geometric means and coefficients of variation.

Type O (ordinal): Absolute and relative frequency distributions and 95% confidence Wald interval for the odds ratio from an ordinal logistic regression on allocated treatment

Type P (proportion): Absolute and relative frequencies together with 95% confidence score intervals for the difference of proportions.

Type R (restricted time): Kaplan-Meier-curves and restricted mean survival time (RMST) with 95% confidence interval.

Type T (time to event): Cumulative incidence curves using sub-distribution hazards and cause specific hazard ratio (HR) with 95% confidence interval estimated from Cox-regression with mortality as a competing risk, where that is no part of the endpoint.

The disposition of patients will be described by a CONSORT (consolidated standards of reporting trial) flow chart.

Demographics, measures of disease severity and variables of known or presumed predictive and prognostic value are summarized by statistics of location and scatter for each treatment group by ITT. Differences of location are reported. Specifically:

1. Heart rate, blood pressure, height and weight are described by means and standard deviations (SD) and 95% confidence intervals for the difference of means. These statistics are called Type N below. For body mass index (BMI), Type N statistics are computed for logarithms and converted back to geometric mean concentrations or ratio of geometric means and coefficients of variation. These statistics are called Type LN below.
2. Concomitant medication is summarized to functional groups of drugs. The numbers and proportions of patients taking these drugs are displayed together with 95% confidence score intervals for the difference of proportions. These statistics are called Type P below.

3. NYHA and CCS classification are reported as absolute and relative frequency distributions and 95% confidence Wald interval for the odds ratio from an ordinal logistic regression on allocated treatment. These statistics are called Type O below. History of syncope is reported as Type P.
4. Number of hospitalizations due to heart failure within past 6 months: Type O.
5. Quality of life survey (EQ-5D) as recommended in the respective manual. As a fallback procedure, these are summarized by median and range with 95% confidence Hodges-Lehmann intervals for the difference of medians. These statistics are called Type M below.
6. NIH Stroke scale: Type O.
7. Barthel Index: Type O. In addition, the Barthel index will be dichotomized (BI ≥ 95 vs. BI < 95) and analyzed as Type P. Modified Rankin Scale: Type O. Dichotomized Modified Rankin Scale (MRS ≥ 3 vs. MRS < 3), Type P.
8. Modified Rankin Scale for any patient with a previous stroke: Type O.
9. STS-PROM: Type O; logistic EuroSCORE (version 1 and 2): Type N.
10. 6-Minute walk test: Type M.
11. Frailty assessment: Clinical frailty scale: Type O.
12. Laboratory work (<2 weeks prior to procedure). When concentrations are measured or ratios computed: Type LN.
    a. Complete blood count including platelet count: Type LN.
    b. Metabolic panel including creatinine, urea, GFR: Type LN.
    c. Liver panel, LDH: Type LN.
    d. NT-proBNP: Type LN.
    e. CK/CK-MB and high-sensitive troponin T (hsTnT) or troponin I (hsTnI) (<24h prior to procedure): Type LN.
    f. aPTT / INR: Type LN.
    g. Biobanking, if done: Type P.
13. 12-lead ECG (<2 weeks prior to procedure) findings (like “new left bundle branch block”): Type P; measurements (like S-T-time): Type N.
14. Comprehensive transthoracic and / or transesophageal echocardiogram (< 3 months prior to procedure): Transvalvular mean gradient in mm Hg and effective orifice area in cm^2: Type M; degree of aortic valve regurgitation: Type O.
15. Multidetector computed tomography (contrast-enhanced and with ECG triggering, if applicable): Aortic annulus size: Type LN; aortic annulus geometry, root anatomy, and assess access route options: Type P.
16. Coronary artery disease (by angiography): Type P.

7.2 PRIMARY ENDPOINTS

The primary endpoint is freedom of stroke or death within 5 years after randomization (Type T). This primary endpoint may have the interpretation of a weighted mean HR restricted to that timeframe because of crossing survival curves in recently published randomized controlled trials comparing TAVI and SAVR. As a consequence, the restricted mean survival time (RMST) analysis of the same data serves as the first secondary endpoint (Type R). This will be complemented by analyses of RMST restricted to

0 to 1 and to 1 to 5 years, so as to provide valid and easy to interpret estimands in the case of crossing hazards.

The co-primary safety endpoint is freedom of stroke or death within 1 year after randomization.

7.3 PRIMARY HYPOTHESES AND SAMPLE SIZE DETERMINATION

7.3.1 PRIMARY HYPOTHESES

Co-primary safety hypothesis: TAVI is non-inferior to SAVR in survival without stroke within 1 year of follow-up:

H_{02}: HR ≤ 1.14 or $\ln(o_{TAVI}) \geq \ln(o_{SAVR}) + \ln(1.14)$,

H_{A2}: HR > 1.14 or $\ln(o_{TAVI}) < \ln(o_{SAVR}) + \ln(1.14)$,

where HR is the hazard ratio of the hazard o_{TAVI} after TAVI divided by the hazard o_{SAVR} after SAVR.

This hypothesis will be analyzed using the one-sided log-rank test stratified by trial site and STS score (0-2%, 2.01-4%, 4.01-6%).

Primary efficacy hypothesis: TAVI is non-inferior to SAVR in survival free of stroke within 5 years of follow-up:

H_{01}: HR ≤ 1.1 or $\ln(o_{TAVI}) \geq \ln(o_{SAVR}) + \ln(1.14)$,

H_{A1}: HR > 1.1 or $\ln(o_{TAVI}) < \ln(o_{SAVR}) + \ln(1.14)$.

Here, the same notation is used as above.

This hypothesis will be analyzed using the one-sided log-rank test stratified by trial site and STS score (0-2%, 2.01-4%, 4.01-6%).

Only if non-inferiority has been shown for both primary hypotheses, the following *superiority hypotheses* will be tested: TAVI is superior to SAVR in stroke free survival time within one and five years of follow-up:

H_{03}: HR = 1.0 or $\ln(o_{TAVI}) = \ln(o_{SAVR})$,

H_{A3}: HR ≠ 1.0 or $\ln(o_{TAVI}) \neq \ln(o_{SAVR})$.

Here, the same notation is used as above.

This hypothesis will be analyzed using the two-sided log-rank test stratified by trial site and STS score (0-2%, 2.01-4%, 4.01-6%). Data from strata will be pooled in case of less than 10 events per stratum.

The global significance level is 5% two-sided, i.e., 2.5% one-sided. Non-inferiority of TAVI with respect to SAVR may be claimed as a result of this trial only when both one-sided 97.5% confidence intervals for the HR cover values less than 1.14 only. Superiority of TAVI over SAVR may be claimed if TAVI is not inferior to SAVR and additionally TAVI is superior to SAVR at the two-sided level 5% test after five years of follow-up. The testing strategy is visualized (Bretz F et al. 2009) in Figure 2.

The adjustment for two primary tests is done by hierarchical testing for the following reason: TAVI needs to be non-inferior to SAVR at both points in time. The 1-year endpoint protects against the higher mortality during and immediately after SAVR. The second time point reflects a reasonable planning horizon for patients aged about 65 to 75 years at randomization.

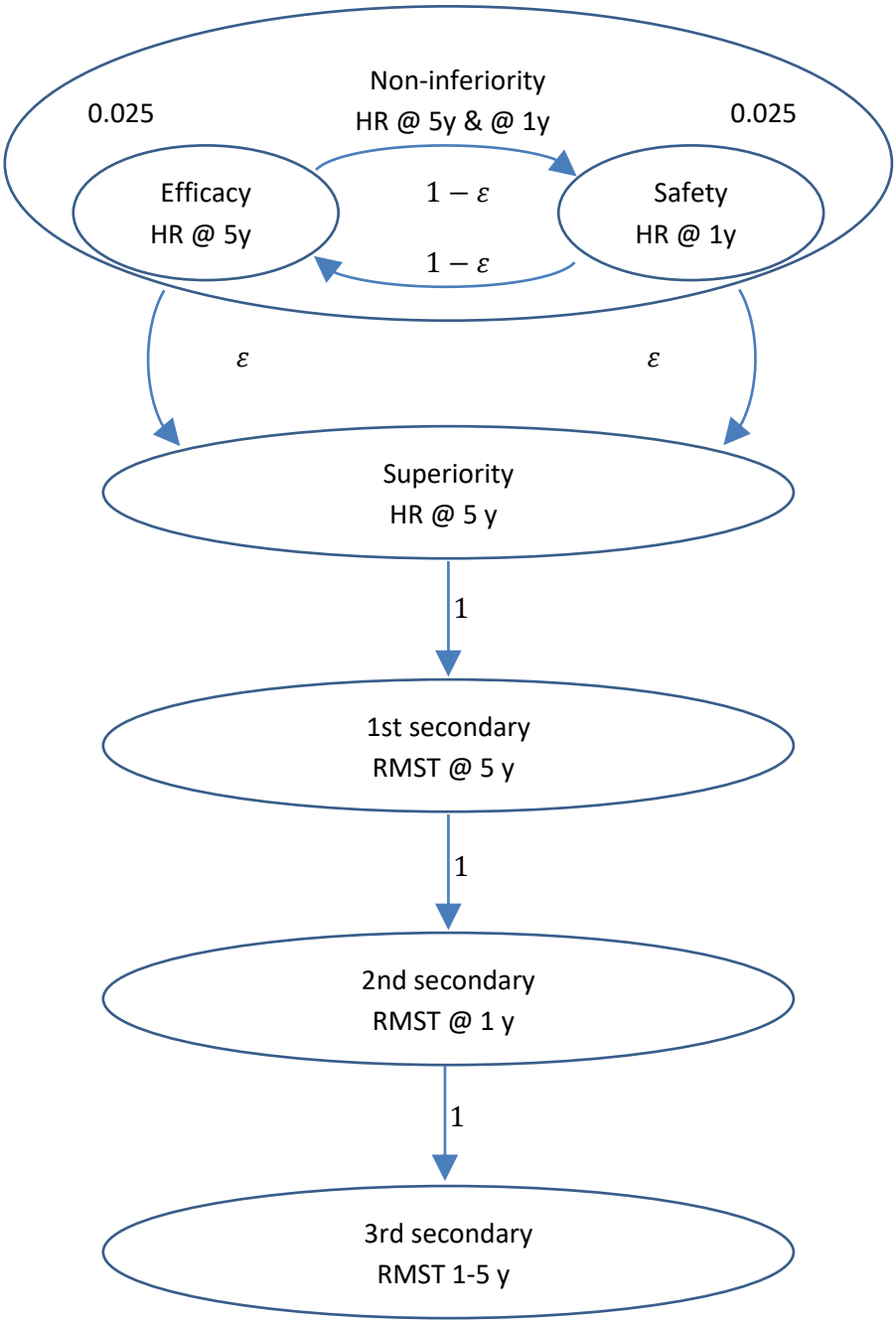

Figure 2: Testing strategy. Multiple significance level 0.05 is spread equally to two non-inferiority tests initially and is inherited by subsequent nodes representing tests according to the proportions near the arrows, with ε the smallest positive number.

7.3.2 SAMPLE SIZE DETERMINATION

Co-primary safety hypothesis

Assumptions at the commencement of the trial:

Treatment allocation ratio 1:1

Significance level one-sided 0.025

Power 0.8

Proportion dead at 12 months after SAVR: MS_1 = 7.8 %

Proportion dead at 12 months after TAVI: MT_1 = 5.8 %

Accrual time 21 months

Minimal follow-up time 12 months

Expected time to 196 events 15 months

Censoring rate 10% per year

Evaluable sample size: 1560 (780 TAVI + 780 SAVR)

Assumptions after last blinded interim analysis of recruitment, age and STS:

Treatment allocation ratio 1:1

Significance level one-sided 0.025

Power 0.8

Hazard ratio at the null-hypothesis: 1.14

Hazard ratio at the alternative: 0.67

Proportions at 3 and 12 months: see Table 2

Recruitment rate per STS-class: see Table 2

Accrual time per STS-class: see Table 2

Follow-up time: 12 months

Censoring rate 10% per year

Evaluable sample size: 1,404 (702 TAVI + 702 SAVR)

The sample size was planned so that the one-sided 97.5% confidence interval for the HR between TAVI and SAVR of overall survival will not cover 1.14 with power 80 % when patients are followed-up 1 year after randomization, as this would correspond to an absolute difference of 1% at 1 year at the anticipated hazard rates. It was assumed that event times follow constant hazard rates in the first three months, from then to 1 year, and from then until the end of follow-up. The event rates in the first two periods were set to the so far observed values 4.1% / 3 months and 6.2% / 12 months.

STS-strata specific recruitment rates before the amendment were used.

As HRs were reported only up to two digits, recruitment targets a total of approximately 1,404 patients, i.e., approximately 702 patients per treatment group.

Primary efficacy hypothesis

Assumptions at commencement of the trial:

Treatment allocation ratio 1:1

Significance level one-sided 0.025

Hazard ratio 0.74

Accrual time 4.3 years

Minimal follow-up time 5 years

Censoring rate 10% per year

Sample size 1592

Expected events: 306

Power: 0.938

Assumptions after last blinded analysis of recruitment:

Treatment allocation ratio 1:1

Significance level one-sided 0.025

Hazard ratio at the null-hypothesis: 1.14

Hazard ratio at the alternative: 0.67

Accrual time 4.7 years with rates displayed in Table 2

Minimal follow-up time 4 years

Censoring rate 10% per year

Sample size 1,176

Power: 0.94 for non-inferiority, 0.76 for superiority, 0.80 for non-inferiority at alternative 0.75.

The longer observation period for the primary hypothesis compared to the co-primary safety hypothesis will result in more observed events, but a mean HR closer to 1.

7.4 SECONDARY ENDPOINTS

All secondary outcomes will be tested by appropriate tests and models in an exploratory sense, using a two-sided significance level of 5% without adjustment for multiple testing. The first secondary endpoint, i.e., restricted mean time to mortality or stroke 5 years after randomization, will be analyzed by ΔRMST (Royston&Parmar 2011 Stat. Med., 2013 BMC Med Res Methodol). Other event times will be analyzed like the two primary endpoints.

7.5 MISSING DATA

The intervention of this trial will be made at baseline. All primary endpoints of this trial are time-to-event endpoints. Loss to follow-up can therefore be expected to be low for the primary endpoint. Furthermore, all patients will be included up to their time point of censoring using standard survival analysis techniques.

For secondary non-survival endpoints, missing values will be imputed using multiple imputation with at least 50 imputations, and regression results will be pooled by Rubin's rule. Variables other than time-to events and with more than 25% missing values will not be used.

7.6 REPORTS

All statistical analyses will be done and all statistical reports will be drafted by the Institute for Medical Biometry and Statistics of the University of Lübeck.

7.7 RELEVANT STATISTICAL ANALYSIS CONSIDERATIONS

7.7.1 RATIONALE FOR NON-INFERIORITY LIMIT

The CoreValve US pivotal trial hinted at superiority of TAVI over SAVR in patients of all strata of cardiovascular risk with little benefit for high-risk patients. DEDICATE will focus on patients with low to intermediate risk for mortality in Europe. Since younger patients with low to intermediate risk will be included, mortality rates for patients from CoreValve with STS ≤ 7 could be used for planning the intermediate risk stratum. Using the exponential model, the two-year mortality rate of MT_2 = 15.0 % after TAVI translates to a one-year-mortality rate of MT_1 = 7.8 %. If HR equals 0.74, thus is close to the value observed in all CoreValve patients, one-year mortality after SAVR is MS_1 = 11.4 %. These

assumptions for MT_1 and MS_1 are close to the one-year mortalities observed in CoreValve adjusted for age 76 years instead of 83 years.

Assuming men:women 1:1, one-year mortality in Germany [Lifetable 2015/2017, DeStatis 18 Oct 2018] was 1.77% at 70, 2.06% at 72, 2.68% at 75, 3.28% at 77, 4.16% at 79, 4.81% at 80, 5.46% at 81, 6.24% at 82, and 7.03% at 83 years. Using linear interpolation to calculate natural mortality, and subtracting the result from one-year mortality M_1 reported for trials, one could define excess mortality. And, after SAVR, this, as does one-month mortality in trials, M_{30d}, has the agreement with the STS score, (Table 1) that the score was constructed to have for SAVR, while excess 1-year mortality seems lower after TAVR as hypothesized, especially in low-risk patients.

Trial	Arm	Age	STS	n	M_1	HR	nat.Mort	exz.Mort	Mort./ Stroke
NOTION	TAVR	79.2	2.9	145	4.9%	0.644	4.49%	0.41%	
NOTION	SAVR	79.0	3.1	135	7.5%		4.37%	3.13%	
SURTAVI STS < 3	TAVR	75.1	2.3	131	1.50%	0.258	2.70%	-1.20%	
SURTAVI STS < 3	SAVR	75.4	2.3	123	5.70%		2.78%	2.92%	
SURTAVI STS 3-5	TAVR	80	4	480	6.50%	0.850	6.50%	0.00%	
SURTAVI STS 3-5	SAVR	79.9	4	405	7.60%		4.75%	2.85%	
SURTAVI	TAVR	79.9	4.4	864	8.1%	0.917	4.92%	3.18%	
SURTAVI	SAVR	79.7	4.5	796	8.8%		4.80%	4.00%	
PARTNER3	TAVR	73.3	1.9	496	1.0%	0.41	2.31%	-1.31%	1.8%
PARTNER3	SAVR	73.6	1.9	454	2.5%		2.37%	0.13%	3.3%
Evolut LR	TAVR	74.1	1.9	725	2.4%	0.798	2.47%	-0.07%	
Evolut LR	SAVR	73.6	1.9	678	3.0%		2.37%	0.63%	
UK TAVI	TAVR	81.1	2.6	458	4.6%	0.69	5.43%	-0.83%	8.5%
UK TAVI	SAVR	81.0	2.7	455	6.6%		5.36%	1.24%	9.0%

Table 1: Clinical data from similar trials.

Consequently, the expected one-year mortality after SAVR is calculated as the sum of background mortality at the expected age plus the expected STS score. Assuming DEDICATE will recruit its patients as up to blinded interim analysis, the blinded interim analysis yields the 1-year-event rates in Table 2.

Trial stratum	Age	STS	Recruitment			Events per year			
	mean	mean	obs. n/yr	yr	expct. n/y	Mortality	Mortality or Stroke		
						< 12 mo	< 3 mo	< 12 mo	> 12 mo
DEDICATE 0-2	75	1.31	179	3.2		3.30%	2.32%	4.62%	1.16%
DEDICATE 2-3	77	2.37	113	4.7		3.78%	3.10%	6.19%	2.03%
DEDICATE 3-4	78	3.37	38	4.9		4.17%	3.79%	7.56%	2.93%
DEDICATE 4-6	77	4.70	15	4.9		12.8%	7.44%	14.8%	4.75%
DEDICATE	76.3	2.18			251	4.09%		6.30%	

Table 2: Assumptions for DEDICATE. Numbers are from a blinded interim analysis of 881 cases.

The non-inferiority margin needs to be chosen so that TAVI is still superior to any treatment without aortic valve replacement. The PARTNER cohort B study compared TAVI with conservative treatment in patients not suitable for SAVR. Using the hazard ratio (HR = 0.58) for patients from the PARTNER trial gives a limit of HR = 0.78. This HR was shifted to the safe side of 0.877 to demonstrate that TAVI has more than half the effect assumed of SAVR over conservative treatment to give a HR of $0.67 \cdot 0.877 = 0.588$ between the observed hazard after TAVI and the hazard after TAVI at the non-inferiority limit.

7.7.2 DESCRIPTION OF OUTCOME VARIABLES

Outcome is described by allocated treatment.

Event rates: Type P; event times: Type T, and additionally: The primary efficacy analysis (Type T) will be a one-sided 0.975-confidence interval for HR. The co-primary analysis (Type T) will be a one-sided 0.975 Wald-type confidence interval for the HR. Both are described by ΔRMST, as well. The difference between first and following years will be explored by landmark analyses of event times after day 365. The relevant parameter for health economic analyses is the number needed to treat (NNT). Point and 95% confidence interval estimates will be obtained for the absolute risk reduction at one year based on the ideas of Com-Nougou et al. 1993 (Stat Med 12:1353-64) and Freitag et al. 2006 (Stat Med 25:1201-17) to infer the number needed to treat (NNT) and its 95% confidence interval. The following outcomes will be analyzed this way:

1. Overall Survival.
2. Freedom from cardiovascular mortality.
3. Freedom from the composite of all-cause mortality and stroke.
4. Freedom from myocardial infarction.
5. Freedom from stroke.

6. Freedom from major or life-threatening / disabling bleeding.
7. Freedom from acute kidney injury.
8. Freedom from conduction disturbances and arrhythmias, need for permanent pacemaker implantation.
9. Freedom from the composite time-related valve safety, including
    i. Structural valve deterioration, including repeat procedures,
    ii. Prosthetic valve endocarditis or thrombosis,
    iii. Thromboembolic events (e.g. stroke),
    iv. VARC bleeding (unless clearly unrelated to valve therapy).
10. (Re-)Hospitalization, including
    i. Length of stay in-hospital,
    ii. Length of stay at intensive care unit,
    iii. Length of stay at rehabilitation facility,
    iv. Length of stay at nursing home,
    v. Number of rehospitalizations,
    vi. Ratio of days alive out of hospital versus total days alive.

Type P only:

11. Freedom from major vascular access site and access-related complications.
12. Freedom from residual aortic regurgitation ≥ moderate.
13. Composite device success, including
    i. Freedom from procedural mortality,
    ii. Correct positioning of a single THV in the proper position with intended performance (no prosthesis- patient mismatch and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, AND no moderate or severe prosthetic valve regurgitation).
14. Composite early safety (at 30 days), including
    i. All-cause mortality,
    ii. Stroke (disabling and non-disabling),
    iii. Life-threatening bleeding,
    iv. Acute kidney injury stages 2/3,
    v. Coronary artery obstruction requiring intervention,
    vi. Major vascular complication,
    vii. Valve-related dysfunction requiring repeat procedure.
15. Composite clinical efficacy (after 30 days), including
    i. All-cause mortality,
    ii. Stroke (disabling and non-disabling),
    iii. Rehospitalisation for worsening heart failure or valve-related symptoms,
    iv. NYHA III or IV,
    v. Valve-related dysfunction (mean aortic valve gradient >20 mmHg, EOA <0.9-1.1 cm^2 and/or DVI <0. 35 m/s, AND/OR moderate or severe prosthetic valve regurgitation).
16. Freedom from prosthetic valve dysfunction

   i. Mean aortic valve gradient >20 mmHg, EOA <0.9-1.1 cm^2 and/or DVI <0. 35 m/s, AND/OR moderate or severe prosthetic valve regurgitation).

17. Quality of life measures, including
   i. Improvement in quality of life assessment,
   ii. Improvement in functional status.

Mixed Types:

18. Incremental cost-effectiveness of TAVI compared to surgical valve replacement, by using QALY´s: life years gained: Type N; cost data obtained directly from health insurances: Type LN.
19. Laboratory work: Type LN, Biobanking: Type P.
20. 12-lead ECG findings (like “new left bundle branch block”): Type P; measurements (like S-T-time): Type N.
21. NIH Stroke scale: Type O.
22. Duration of hospital stay and intensive care unit stay: Type T.
23. Ventilation time: Type T.
24. Concomitant medication, particularly including anticoagulation and antithrombotic medication: Type P.
25. Transfusion of blood products: Type P.
26. Barthel Index: Type O.
27. Modified Rankin Scale for any patient with a previous stroke: Type O.
28. 6-Minute walk test: Type M.
29. Comprehensive transthoracic or transesophageal echocardiogram, particular evaluation of valve prosthetic function according to VARC-2 criteria: Transvalvular mean gradient in mmHg and effective orifice area in cm^2: Type M; degree of aortic valve regurgitation: Type O.
30. NYHA and CCS classification: Type O; history of syncope: Type P.
31. Number of hospitalizations due to heart failure since past visit: Type O.
32. Quality of life survey (EQ-5D): Type M.
33. Pacemaker/defibrillator interrogation (for patients with permanent pacemakers or defibrillators only): Type P.

7.7.3 DESCRIPTION OF SAFETY VARIABLES

Safety is described by actual treatment. Occurrences, causality (dichotomized), and resolution: Type P; intensities: Type O; durations: Type M.

7.7.4 EXPLORATION OF PREDICTIVE VARIABLES

The primary analysis is not adjusted for other predictive variables, as inclusion criteria are narrow so that there should be no interaction between treatment and baseline. This assumption will be verified exploratorily by fitting logistic regression models and Cox regression models, checking the proportionality assumptions and estimation of interactions effects, for which 95% confidence intervals will be calculated. Prespecified are the following analyses for overall survival and for survival free from stroke:

1. Overall survival and survival free from stroke by treatment as a time-dependent covariate, stratified by STS and centre,

2. Overall survival and survival free from stroke by treatment, STS and treatment-STS interaction,
3. Overall survival and survival free from stroke by treatment, age and the treatment-age interaction,
4. Overall survival and survival free from stroke by treatment, STS, age and the STS-age interaction,
5. Overall survival and survival free from stroke by treatment, sex and the treatment-sex interaction,
6. Overall survival and survival free from stroke by treatment, baseline NYHA and treatment-NYHA interaction,
7. Overall survival and survival free from stroke by treatment, left-ventricular ejection fraction (LVEF) and treatment-LVEF interaction,
8. Overall survival and survival free from stroke by treatment, chronic renal failure (CRF) and treatment-CRF interaction,
9. Overall survival and survival free from stroke by treatment, coronary artery disease (CAD) and treatment-CAD interaction,
10. Overall survival and survival free from stroke by treatment, Diabetes and treatment-diabetes interaction,
11. Overall survival and survival free from stroke by treatment, prior stroke and treatment-stroke interaction,

7.7.5 SUBGROUP ANALYSES

Subgroup analyses will be pre-specified for the following variables: age, sex, NYHA class, THV/prosthesis type, access route and secondary endpoints, e.g., residual aortic regurgitation and QoL.

8. ETHICAL ASPECTS

8.1 ETHICAL GUIDELINES

The principal investigator has the overall responsibility for the conduct of the study. The trial will be conducted following the principles of DIN ISO 14155 and according to the Declaration of Helsinki in its latest accepted version. Study protocol, patient information and consent form, and substantial amendments will be approved by the responsible ethics committees before start of the trial. All study procedures, including development of the protocol, case report form and investigator site file, content of patient information and consent, application for ethics approval, data processing, central and on-site monitoring and evaluation will follow the Standard Operating Procedures (SOP) of the trial-supporting facility, the biostatistics group, the DZHK and the central data management. The central data management provided by the Institute of Medical Informatics in Göttingen and an independent trusted third party at University Medicine Greifswald complies with federal and European regulations (DIN ISO 14155). The data transfer facility provided by the central data management ensures a fully traceable data lifecycle from patient inclusion until data publication including long term archiving. The quality management system of the trial-supporting facility has been repeatedly audited by funding bodies as well as by local authorities.

All documents and data will be handled with strict confidentiality. Names and person-related data will be handled in accordance with the conditions of the German Data Protection Act. In the

documentation and data analysis phase, the patient-related data will be recorded pseudonymously and will be identifiable only by randomization number.

8.2 INFORMED CONSENT

Informed consent is mandatory and must be obtained from all study patients prior to their participation in this trial. The patient has been informed of the nature of the trial, agrees to its provision, and has provided written informed consent as approved by the IRB of the respective clinical site Informed consent consists of two parts: Patient's information form and Patient's consent which include the study procedures and DZHK Biomaterial collection. First, patients will be informed in written and oral form regarding the key facts of the study, the procedures that have to be followed, and the reasonably foreseeable risks or discomforts and potential benefits. As a second step, the research team will give each participant an informed consent document with details about the study including its purpose, duration, procedures, and key contacts, as well as risks and potential benefits. The patients then will decide whether to give written and oral consent. At any time, patients may withdraw their consent for any reason without any negative consequences regarding their treatment.

The documents will be in a language understandable to the subject and will specify who informed the subject. A copy of the signed informed consent document will be given to the subject. The original signed consent document will be retained by the investigator and a scanned version will be sent to the trusted third party in Greifswald by an encrypted e-mail attachment[1]. The investigator will not undertake any measures specifically required only for the clinical trial until valid consent has been obtained. If the subject has a primary physician the investigator should inform the subject's primary physician about the subject's participation in the trial and if the subject agrees to the primary physician being informed. After reading the informed consent document, the subject must give consent in writing. The subject's consent must be confirmed by the personally dated signature of the subject and by the personally dated signature of the person conducting the informed consent discussions.

8.3 ETHICS COMMITTEE

Prior to participation in this study, on behalf of each investigator CTC North will submit the protocol and informed consent for review to their responsible ethics committee. Further, any substantial amendments to the protocol, as well as associated changes to the informed consent form, will be submitted to the ethics committee, and written approval must be obtained from the ethics committee prior to implementation.

9. REGULATORY CONSIDERATIONS

9.1 RESPONSIBILITIES

All study procedures, including development of the protocol, case report form and investigator site file, content of patient information and consent, application for ethics approval, data processing, central and on-site monitoring, and evaluation will follow the Standard Operating Procedures (SOP) of the trial-supporting facility, the biostatistics group and the DZHK (including those of the central data management).

Query Management is conducted by CTC North GmbH & Co. KG. Query management will be performed for the primary endpoint as defined in the Data Management Plan (DMP). In case of discrepancies, the data management team is authorized to directly contact the responsible person at the trial site. All

[1] DZHK SOP THS-01 V1.5 („Erfassung von personenidentifizierenden Daten und des Informed Consent")

queries will be implemented into the DZHK secuTrial database. This will allow the trial sites to conduct data corrections more easily and it will also guarantee that the queries are filed to the corresponding variables in the database. The investigator has to agree the contact per e-mail or phone.

A detailed methodology for the data management in this trial will be documented in the DMP that will be dated and maintained by CTC North GmbH & Co. KG. This plan has to be signed by the principal investigator, the data manager responsible for eCRF development, the responsible data manager and the trial statistician. The document may modify the plans outlined in this protocol; however, any major modifications of the data handling will also be reflected in a protocol amendment.

Trial-relevant personal data will be analyzed only after pseudonymization. Data are secured against unauthorized access. Access may be given according to legal regulations to the sponsor, monitor, the regulating authorities (BfArM, European Union authorities) and the ethics committees of the trial sites.

The Data and Safety Monitoring Board (DSMB) will be responsible for making recommendations regarding any potential problems during the conduct of the study. It is also responsible for reviewing the final results of the clinical study regarding the analysis of safety events. The adjudicated events will be reported to the DSMB. All final decisions regarding study termination or modification rest with the principal investigator after consultation of the Steering Committee and the DSMB.

A study report will be written and submitted to the relevant ethics committees in accordance with local requirements.

9.2 DATA COLLECTION

This trial will be performed using an electronic case report form (eCRF). All protocol-required information collected during the trial must be documented in the eCRF by the investigator, or a designated representative. All data entry, modification or deletion will be recorded automatically in an electronic audit trail indicating the individual subject, the original value, the new value, the reason for change, who made the change and time and date of the change. All data changes will be clearly indicated. Former values can be viewed in the audit trail. All electronic data will be entered by the site (including an electronic audit trail) in compliance with applicable record retention regulations.

The system will be secured to prevent unauthorized access to the data or the system. Only people provided with a user ID and a password will be able to enter or change data. The investigator will maintain a list of individuals who are authorized to enter or correct data.

Computer hardware and software (for accessing the data) will be maintained at or made available for the site in compliance with applicable regulations. All technical preconditions for each trial site are recorded in the data management plan (DMP).

The system is capable of making exact copies of data in legible paper form for inspections and audits. The investigator or a designated subinvestigator, following review of the data in the eCRF, will confirm the validity of each subject's data by electronic signature or by signing a paper printout of a listing of all patients enrolled in the trial.

The architecture of the computer system will be described in the DMP.

9.3 DATA HANDLING

During data entry integrity checks help to minimize entry failures. These data entry checks are based on the data validation plan, signed by the principal investigators and the trial statistician. The data entry system allows the trial monitors to control the entry process with the help of the built-in review functions. Comments and requests can be promptly processed by the trial site.

After completion of data entry, the database access rights will be taken away and the database will be exported into the data transformation system.

Final checks for plausibility, consistency and completeness of the data will be performed. Based on these checks, queries will be produced. Any missing data or inconsistencies will be reported back to the respective site and clarified by the responsible investigator. If no further corrections are to be made in the database, it will be declared closed and will be transferred to the trial statistician for statistical analysis.

All data management activities concerning the set-up of the eCRF and the edit checks will be done according to the current Standard Operating Procedures (SOPs) of Universitätsmedizin Göttingen, Institut für Medizinische Informatik and the trusted third party at Institute for Community Medicine, Greifswald.

9.4 CONSENT MANAGEMENT AND PSEUDONYMISATION

The original signed consent document will be retained by the investigator and a scanned version will be uploaded on an independent website within the SecuTrial surface secured by TLS 1.2 and client certificates to the trusted third party in Greifswald [1]. The trusted third party at University Medicine Greifswald will provide electronic management of person identifying data, study and context associated pseudonyms, as well as consent management and a quality control system. In addition to study personnel, identifying data will only be available to few specially trained employees at the trusted third party who are subject to the obligation of professional secrecy.

A personal ID is generated for every patient recruited and held on trust by the trusted third party. Secondary pseudonyms are generated automatically, consist of a randomly generated nine-digit number series and do not comprise any indication of identifying data of the patient. Pseudonyms directly sent to study centers will be generated as “pheno” – phenotype pseudonyms – to record medical data in the central data management system and “lims” – biomaterial pseudonyms – to store biomaterial at the local study sites. Within this system further pseudonyms can be generated for images or data use.

Identification of personal data from pseudonyms will only be possible by the study center and the trusted third party. All other persons involved in the study, including the data management at University Medicine in Göttingen, will only have access to pseudomised data.

9.5 STORAGE AND ARCHIVING OF DATA

According to DIN ISO 14155, the investigator of each site will archive all trial data (subject identification list, source data) and relevant correspondence in the Investigator Site File (ISF). The ISF, all source data and all documents itemized in section X of DIN ISO 14155 will be archived after finalization of the trial at trial site. The trial master file (TMF) will be archived at the University of Hamburg according to DIN ISO 14155.).

The principal investigators are responsible for storage and archiving of the trial data (source data and CRFs). Storage and archiving of the electronic data during the trial will be assured by the DZHK.

[1] DZHK SOP THS-01 V1.65 („Erfassung von personenidentifizierenden Daten und des Informed Consent“)

9.6 STORAGE AND ARCHIVING OF BIOMATERIAL

Biomaterial will be stored at local study sites within locally given conditions or sent to Universitäres Herz- und Gefäßzentrum, Hamburg. Biomaterial data will be stored under LIMS-pseudonyms within a laboratory information system provided by the DZHK.

9.7 MONITORING AND AUDIT

Monitoring responsibilities are delegated to CTC North GmbH & Co. KG.

Monitors will be selected according to their experience and qualification and will receive a study specific protocol and monitoring plan training. The monitoring plan will be developed by CTC North and approved by the Sponsor.

Monitoring will be performed by telephone selection and initiation visits and by on site regular monitoring and close out visits. For the definition of extent and nature of the monitoring, a risk assessment will be performed to define key study data, which will be the focus for the monitoring activities. Each site will be visited after recruitment of the first subjects to verify adherence to the protocol, and data quality. The following monitoring visits will be adapted to each site's performance quality and recruitment rate. Details will be specified in the monitoring plan for this trial.

The Investigator (or his/her deputy) agrees to co-operate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved. In compliance with regulations regarding the monitoring of clinical studies it is required that investigators permit monitors and members of Event Adjudication Committee (EAC) to review the portion of patient's medical record that is directly related to the study. This shall include, but is not limited to, relevant study documentation: medical histories to verify eligibility, laboratory test results to verify transcription accuracy, diagnostic and treatment reports, admission/discharge summaries for hospital admission occurring while the patient is on the study and autopsy reports – if an autopsy was performed – for deaths occurring during or in temporal proximity to the study.

9.8 FINANCING AND INSURANCE

The trial will be financed through a grant provided by the Deutsches Zentrum für Herz-Kreislauf-Forschung e.V. and with financial support from the Deutsche Herzstiftung e.V.. Study centers will be reimbursed according to randomized treatment by the health insurance companies, similar to standard clinical care.

For the general risk of the disease itself and the performed treatment, the individual patients are covered by the hospital liability insurance. As described above, the study is performed according to current standard clinical treatment. The study-specific procedures solely include non-invasive examinations (e.g. questionnaires) and do not expose the patients to any significant additional risks. In addition, this study is <u>not</u> considered a clinical trial according to the definition of the "Medizinproduktegesetz". Hence, no additional study-specific insurance is required.

9.9 QUALIFICATION OF INVESTIGATORS AND STUDY CENTERS

All study centers follow the recommendations of the G-BA for minimally-invasive heart valve interventions [1] and were found to be appropriate study centers with regard to their qualification for the study treatments and clinical trial participation by the principal investigators. Prerequisites include

[1] Beschluss des Gemeinsamen Bundesausschusses über eine Richtlinie zur minimalinvasiven Herzklappenintervention: Erstfassung vom 22. Januar 2015, BAnz AT 24.07.2015 B6

on-site cardiology and cardiac surgery departments at the study site and close interdisciplinary cooperations according to current European guidelines (ESC/ EACTS) on the management of valvular heart disease. Furthermore, at least two different CE-marked transcatheter heart valve types are requested to be available at the study site with sufficient local expertise for these devices (minimum of 30 implanted devices/type per center). Procedures will be performed by experienced and board-certified interventional cardiologists and cardiac surgeons with the appropriate skills.

10. QUALITY ASSURANCE AND QUALITY CONTROL

All data in this project are captured in electronic case report forms (eCRFs) and stored into an electronic clinical database. Quality control and data validation procedures such as programmed automatic edit and consistency checks will ensure data validity and accuracy immediately at the point of entry into this database. The database application which is used to capture electronic clinical trial data is fully CFR part 11 compliant. It thus is access restricted, contains rights and roles functionalities, demands electronic signatures, maintains an electronic audit trail and provides appropriate backup functionalities. The interface between data management and the responsible trial statistician will be checked immediately within 6 months after first patient in.

After data entry, quality assurance will be performed by on site monitoring (10% source data verification) and data management activities. Details will be described in a study specific monitoring plan and a data management plan.

The database will only be locked after all queries and discrepancies that may occur during data entry have been resolved. After database lock, data management will export the data in electronic format and transfer it to the trial statistician for analysis.

The eCRF including programming of automatic edit and consistency checks will be developed by Universitätsmedizin Göttingen, Institut für Medizinische Informatik. The monitoring and query management activities in this project will be conducted by CTC North GmbH & Co. KG.

Quality check of scanned paper-based consent forms will be performed on a regular basis by the trusted third party and reported to study management on a monthly basis.

11. STUDY ADMINISTRATIVE STRUCTURE

11.1 TRIAL MANAGEMENT

The trial management is responsible for appropriate execution of the trial in compliance with standards, regulations and legislation.

Trial Sponsor			
University of Hamburg			
Trial Management			
#	**Name**	**Affiliation**	**Responsibility/Role**
1	S. Blankenberg	Universitäres Herz- und Gefäßzentrum Hamburg, Klinik für Kardiologie	Principal Investigator

2	M. Seiffert	Universitäres Herz- und Gefäßzentrum Hamburg, Klinik für Kardiologie	Coordinating Investigator
3	P. Clemmensen	Universitäres Herz- und Gefäßzentrum Hamburg, Klinik für Kardiologie	Head Clinical Study Center, University Heart and Vascular Center Hamburg
Trial statistician			
#	**Name**	**Affiliation**	
1	A. Ziegler	Medizincampus Davos, Cardio-CARE, Davos	
2	I.R. König	Universität zu Lübeck, Institut für Medizinische Biometrie und Statistik	
3	R. Vonthein	Universität zu Lübeck, Institut für Medizinische Biometrie und Statistik, Deputy	
Trial Supporting facilities			
#	**Name**	**Affiliation**	**Responsibility/Role**
1	S. Borregaard and Team of CTC North	Clinical Trial Center (CTC) North GmbH & Co. KG	Project management, regulatory affairs, clinical monitoring and data quality management
2	S. Hanß	Universitätsmedizin Göttingen, Institut für Medizinische Informatik	Data management
3	D. Stahl	Universitätsmedizin Greifswald, Institut für Community Medicine	Trusted third party
4	M. Kraus	Research Unit Molecular Epidemiology, Institute of Epidemiology II, Helmholtz-Zentrum München	Ethics coordination DZHK

11.2 STEERING COMMITTEE

The steering committee is responsible for overseeing the good execution and administrative progress of the trial; will meet regularly to monitor patient accrual, to determine policy regarding individual publications arising from data generated from the performance of the study.

Steering Committee			
#	**Name**	**Affiliation**	**Responsibility/Role**
1	S. Blankenberg	Universitäres Herz- und Gefäßzentrum Hamburg, Klinik für Kardiologie	Principal Investigator

2	J. Cremer	Universitätsklinikum Schleswig-Holstein (Campus Kiel), Klinik für Herz- und Gefäßchirurgie; DGTHG	Principal Investigator Representative DGTHG
3	M. Seiffert	Universitäres Herz- und Gefäßzentrum Hamburg, Klinik für Kardiologie	Coordinating Investigator
4	H. Reichenspurner	Universitäres Herz- und Gefäßzentrum Hamburg, Klinik für Herz- und Gefäßchirurgie	Member
5	N. Frey	Universitätsklinikum Heidelberg, Klinik für Kardiologie, Angiologie, Pneumologie	Member
6	C. Hamm	Kerckhoff-Klinik Bad Nauheim, Abteilung Kardiologie; Uniklinikum Gießen; DGK	Member Representative DGK
7	Y. – H. Choi	Kerckhoff-Klinik Bad Nauheim, Abteilung Herzchirurgie	Member
8	T. Walther	J.W. Goethe Universität Frankfurt, Klinik für Thorax-, Herz- und Thorakale Gefäßchirurgie	Member
9	U. Landmesser	Charité Universitätsmedizin Berlin (CBF), Medizinische Klinik für Kardiologie	Member
10	V. Falk	Deutsches Herzzentrum Berlin, Klinik für Herz-, Thorax-, und Gefäßchirurgie	Member
11	S. Massberg	Universitätsklinikum der LMU München, Medizinische Klinik und Poliklinik I	Member
12	C. Hagl	Universitätsklinikum der LMU München, Herzchirurgische Klinik und Poliklinik	Member
13	H. Thiele	Herzzentrum Leipzig, Klinik für Kardiologie	Member
14	M.A. Borger	Herzzentrum Leipzig, Klinik für Herzchirurgie	Member
15	H. Baumgartner	Universitätsklinikum Münster, Klinik für Kardiologie III	Member

16	R. Vonthein, I.R. König or A.Ziegler	Universität zu Lübeck, Institut für Medizinische Biometrie und Statistik	Trial statistician

11.3 EVENT ADJUDICATION COMMITTEE (EAC)

An independent EAC will classify clinical events as defined in this protocol and according to severity and causality and adjudicate safety and efficacy endpoints. The EAC will receive blinded CRF data (prepared by the trial management), and adjudicate on patient status changes, pre-defined safety events and endpoints. Where appropriate, the EAC may receive unblinded data (on a patient level or treatment group level) that should be reviewed in a closed session. A charter defines the working procedures of the EAC.

Event Adjudication Committee		
#	**Name**	**Affiliation**
1	K. G. Häusler	Neurologische Klinik und Poliklinik, Universitätsklinikum Würzburg
2	U. Hofmann	Medizinische Klinik I, Universitätsklinikum Würzburg
3	A. Gorski	Klinik und Poliklinik für Thorax-, Herz- und Thorakale Gefäßchirurgie, Universitätsklinikum Würzburg

11.4 DATA AND SAFETY MONITORING BOARD (DSMB)

An independent DSMB will be established to protect the safety of study participants. The DSMB will assess the overall progress, safety data and, if needed, critical efficacy endpoints of the trial. The DSMB will receive a blinded summary of these data (prepared by an independent statistician) and will evaluate the progress of the trial; assess data quality and timeliness, participant recruitment, accrual and retention, and participant risk versus benefit. In addition, the DSMB will monitor external factors relevant to the trial, for example scientific and therapeutic developments that may affect participant safety or ethical status. Based on the observed benefits or adverse effects, the DSMB will make recommendations to the sponsor and steering committee concerning continuation, termination or modifications of the trial. A charter defines the working procedures of the DSMB.

Data Safety and Monitoring Board (DSMB)		
#	**Name**	**Affiliation**
1	T. Friede	Institut für Medizinische Statistik, Universitätsmedizin Göttingen
2	L. Müller	Universitätsklinik für Herzchirurgie, Medizinische Universität Innsbruck, Österreich
3	H. Klein	Division of Cardiology, University of Rochester Medical Center, Rochester, NY, USA

Additional experts may participate in DSMB meetings, if deemed appropriate by the Steering Committee.

11.5 ADVISORY BOARD

The advisory board will provide guidance on central aspects of the trial and appropriate execution of the study.

Advisory Board		
#	**Name**	**Affiliation**
1	A. Zeiher	Universitätsklinikum Frankfurt, Medizinische Klinik III
2	S. Windecker	Inselspital Bern, Universitätsklinik für Kardiologie, Switzerland
3	O. Wendler	King's College London, Cardiothoracic Surgery, United Kingdom

12. IMAGING CORE LABORATORIES

Echocardiographic examinations of all patients performed during study follow-up will be digitally recorded (DICOM format) and sent to the echocardiography core laboratory for independent assessment. Experienced echocardiographers who are blinded to the treatment will assess relevant parameters (e.g. annulus diameter, hemodynamic measurements) to increase data quality. All measurements will be performed according to standardized criteria of the echocardiography core laboratory and following current guidelines and recommendations.

In addition, DICOM data from routinely performed MDCT scans performed at baseline during the study (if applicable) will be collected and sent to a core laboratory for assessment.

13. PUBLICATION POLICY

The results of the DEDICATE trial will have a large impact on therapeutic strategies for AS. DEDICATE will contribute to improve evidence-based therapy of these patients, and if successful, the results of DEDICATE will likely influence future guideline recommendations. As such, the results will be published in a premier international peer-reviewed journal. Publications will satisfy CONSORT, the recommended reporting guidelines for randomised controlled trials (Schulz KF et al., 2010).

Results of the one-year co-primary safety endpoint will be published immediately. Irrespective of the outcome for co-primary safety endpoint, the trial will continue until data are complete for the five-year follow-up of last patient in. The primary outcome comprising data from the five-year follow-up will be published separately. In the publication for the one-year co-primary safety endpoint, the interpretation will be stated that these data only serve for safety reasons but not for efficacy. It will be supplemented by a statement that these safety data should not be used in guidelines to judge efficacy of TAVI and SAVR in low to intermediate risk patients. It will be stated that the decision on efficacy should only be made when five-year mortality results (primary endpoint) are available.

The sole acquisition of data does not qualify for authorship. All authors must meet each of the following 4 criteria:

1. Substantial contribution to conception and design of study protocol and/or analysis and interpretation of data.
2. Drafted the article or revised it critically for important intellectual content.
3. Approved the final version for publication.
4. Agreed to be accountable for all aspects of the work regarding data accuracy and integrity.

Final decisions on main publications, sub-publications and authorships will be made by the principal investigators and the steering committee.

14. LIST OF ABBREVIATIONS

AKI	Acute Kidney Injury
AS	Aortic Stenosis
AT	As Treated analysis
AVA	Aortic Valve Area
BARC	Bleeding Academic Research Consortium
BMI	Body Mass Index
BSA	Body Surface Area
CABG	Coronary artery bypass grafting
CCS	Canadian Cardiovascular Society classification of angina pectoris
CE	Conformité Européene
CI	Confidence Interval
CRO	Clinical Research Organisation
DICOM	Digital Imaging and Communications in Medicine
(e)CRF	(Electronic) Case Report Form
EOA	Effective Orifice Area
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
DVI	Doppler velocity index
DZHK	Deutsches Zentrum für Herz-Kreislauf-Forschung e.V.
EAC	Event Adjudication Committee
EC/ IRB	Ethics Committee/ Institutional Review Board
ECG	Electrocardiogram
EuroSCORE	European System for Cardiac Operative Risk Evaluation
FU	Follow-up
GCP	Good Clinical Practice
HR	Hazard Ratio
ICH	International Conference on Harmonisation
ITT	Intention To Treat analysis
LAD	Left anterior descending coronary artery
MDCT	Multidetector Computed Tomography
MI	Myocardial Infarction
mRS	Modified Ranking Scale
NNT	Number Needed to Treat

NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PI	Principal Investigator
QALY	Quality Adjusted Life Year
QoL	Quality of Life Questionnaire
RR	Relative Risk
SE	Safety Events
SSE	Serious Safety Event
SAVR	Surgical Aortic Valve Replacement
SOPs	Standard Operating Procedures
STS-PROM	Society of Thoracic Surgeons Predicted Risk of Operative Mortality
TAVI	Transcatheter Aortic Valve Implantation
TEE	Transesophageal echocardiography
THV	Transcatheter Heart Valve
TTE	Transthoracic echocardiography
VARC	Valve Academic Research Consortium

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APPENDIX 1: DEFINITIONS

ACUTE KIDNEY INJURY (AKI) [1]:

The observation period for the diagnosis of AKI is 7 days after the study procedure.

Stage 1

- ≠ Increase in serum creatinine to 150–199% (1.5–1.99x increase compared with baseline) OR increase of ≥0.3 mg/dl (≥26.4 mmol/l) OR
- ≠ Urine output <0.5 ml/kg/h for >6 but <12 h

Stage 2

- ≠ Increase in serum creatinine to 200–299% (2.0–2.99x increase compared with baseline) OR
- ≠ Urine output <0.5 ml/kg/h for >12 but <24 h

Stage 3

- ≠ Increase in serum creatinine to ≥300% (>3x increase compared with baseline) OR serum creatinine of ≥4.0 mg/dl (≥354 mmol/l) with an acute increase of at least 0.5 mg/dl (44 mmol/l) OR
- ≠ Urine output <0.3 ml/kg/h for >24 h OR
- ≠ Anuria for ≥12 h

AORTIC REGURGITATION (PROSTHETIC AORTIC VALVE REGURGITATION [1]:

See definition "Prosthetic valve dysfunction: Prosthetic aortic valve regurgitation", following [1].

ARRHYTHMIAS AND CONDUCTION DISTURBANCES [1]:

>Up to 72 h, continuous rhythm monitoring is recommended in order to maximize the detection of arrhythmias

Data elements to be collected should include

- ≠ Baseline conduction abnormalities, paroxysmal or permanent atrial fibrillation (or flutter), and the presence of permanent pacemaker
- ≠ Implant-related new or worsened cardiac conduction disturbance (new or worsened first-degree atrioventricular block, second-degree atrioventricular block (Mobitz I or Mobitz II), third-degree atrioventricular block, incomplete right bundle branch block, right bundle branch block, intraventricular conduction delay, left bundle branch block, left anterior fascicular block, or left posterior fascicular block, including block requiring a permanent pacemaker implant
- ≠ Persistent or transient high-degree AV block. High-grade AV block is persistent if it is present every time the underlying rhythm is checked
- ≠ New permanent pacemaker implantation, with precision of the indication and the number of days post-implant of the placement of new permanent pacemaker
- ≠ New-onset atrial fibrillation (or flutter)

[1] Kappetein AP et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012;60(15): 1438-54.

≠ Any new arrhythmia resulting in hemodynamic instability or requiring therapy (e.g. cardioversion, antiarrhythmic therapy)

BLEEDING COMPLICATIONS [1]:

Life-threatening or disabling bleeding

≠ Fatal bleeding (Bleeding Academic Research Consortium[2] [BARC] type 5) OR Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC [2] type 3b and 3c) OR

≠ Bleeding causing hypovolaemic shock or severe hypotension requiring vasopressors or surgery (BARC [2] type 3b) OR

≠ Overt source of bleeding with drop in haemoglobin ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units (BARC [2] type 3b)

Major bleeding (BARC [2] type 3a)

≠ Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dl or requiring transfusion of two or three units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND

≠ Does not meet criteria of life-threatening or disabling bleeding

Minor bleeding (BARC [2] type 2 or 3a, depending on the severity)

≠ Any bleeding worthy of clinical mention (e.g. access site hematoma) that does not qualify as life-threatening, disabling, or major

CANADIAN CARDIOVASCULAR SOCIETY (CCS) CLASSIFICATION OF ANGINA PECTORIS:

Class I: Ordinary physical activity (such as walking and climbing stairs) does not cause angina. Angina with strenuous or rapid or prolonged exertion at work or recreation.

Class II: Slight limitation of ordinary activity. Angina upon walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in the cold, in wind or under emotional stress, or only during the few hours after awakening. Angina if walking more than two blocks on a level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.

Class III: Marked limitation of ordinary physical activity. Walking one to two blocks on a level and climbing one flight of stairs in normal conditions and at a normal pace.

Class IV: Inability to carry on any physical activity without discomfort. Anginal syndrome may be present at rest.

CLINICAL EFFICACY AFTER 30 DAYS (COMPOSITE ENDPOINT) [1]:

≠ All-cause mortality

≠ Stroke (disabling and non-disabling)

≠ Rehospitalisation for worsening heart failure or valve-related symptoms

≠ NYHA III or IV

[1] Kappetein AP et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012;60(15): 1438-54.
[2] Mehran R et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123(23):2736-47.

≠ Valve-related dysfunction (mean aortic valve gradient >20 mmHg, EOA <0.9-1.1 cm^2 and/or DVI <0. 35 m/s, AND/OR moderate or severe prosthetic valve regurgitation)

DEVICE SUCCESS (COMPOSITE ENDPOINT) [1]:

Freedom from procedural mortality and correct positioning of a single THV in the proper position with intended performance (no prosthesis- patient mismatch and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, AND no moderate or severe prosthetic valve regurgitation).

EARLY SAFETY AT 30 DAYS (COMPOSITE ENDPOINT) [1]:

≠ All-cause mortality
≠ Stroke (disabling and non-disabling)
≠ Life-threatening bleeding
≠ Acute kidney injury stages 2/3
≠ Coronary artery obstruction requiring intervention
≠ Major vascular complication
≠ Valve-related dysfunction requiring repeat procedure

ENDOCARDITIS [1]:

≠ Fulfillment of the Duke endocarditis criteria OR
≠ Abscess, paravalvular leak, pus, or vegetation secondary to infection by histological or bacteriological studies during a re-operation OR
≠ Findings of abscess, pus, or vegetation involving a repaired or replaced valve during an autopsy

MORTALITY [1]:

Etiology:

≠ All-cause mortality
≠ Cardiovascular mortality
  - Death due to proximate cardiac cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure)
  - Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease
  - All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure
  - All valve-related deaths including structural or non-structural valve dysfunction or other valve-related safety events
  - Sudden or unwitnessed death
  - Death of unknown cause
≠ Non-cardiovascular mortality
  - Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide)

[1] Kappetein AP et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012;60(15): 1438-54.

Chronology:

- ≠ Immediate procedural mortality (all-cause mortality within 72 hours after the study intervention)
- ≠ Procedural mortality (all-cause mortality within 30 days after the study intervention or during index procedure hospitalization)
- ≠ Mortality after 30 days (all-cause, cardiovascular, and non-cardiovascular) will be reported during five-year follow-up. In determining the cause of death, the adjudication committee should consider the clinical context at the time of the index procedure and during the time interval leading up to death. All efforts (including the use of death registries) should be made to identify, precisely characterize, and appropriately classify any death.

MYOCARDIAL INFARCTION (MI)[1]:

- ≠ Peri-procedural MI (within 72 h after the study intervention)
  - New ischemic symptoms (e.g. chest pain or shortness of breath), or new ischemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q- waves in at least two contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality) AND
  - Elevated cardiac biomarkers (preferable CK-MB) within 72 h after the index procedure, consisting of at least one sample post-procedure with a peak value exceeding 15x as the upper reference limit for troponin or 5x for CK-MB. If cardiac biomarkers are increased at baseline (>99th percentile), a further increase in at least 50% post-procedure is required AND the peak value must exceed the previously stated limit
- ≠ Spontaneous MI (later than 72 h after the index procedure) in accordance with the universal definition of MI (Thygesen K et al 2012):
  - Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with the evidence of myocardial ischemia with at least one of the following:
    - Symptoms of ischemia
    - ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]
    - New pathological Q-waves in at least two contiguous leads
    - Imaging evidence of a new loss of viable myocardium or new wall motion abnormality
  - Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/ or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
  - Pathological findings of an acute myocardial infarction

[1] Kappetein AP et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012;60(15): 1438-54.

NYHA CLASSIFICATION OF HEART FAILURE

Class I No limitation of activities; patients suffer no symptoms from ordinary activities.

Class II Mild limitation of activity; patients are comfortable with rest or mild exertion.

Class III Marked limitation of activity; patients are comfortable only at rest.

Class IV Patients who should be at complete rest, confined to bed or chair; any physical activity brings on

PROSTHETIC VALVE DYSFUNCTION [1]:

	Prosthetic aortic valve stenosis		
	Normal	***Mild stenosis***	***Moderate/severe stenosis***
Peak velocity (m/s)	<3	3-4	>4
Mean gradient (mmHg)	<20	20-40	>40
Doppler velocity index	>0.35	0.35-0.25	<0.25
Effective orifice area (cm^2)	>1.1 (>0.9 if BSA<1.6m^2)	1.1-0.8 (0.9-0.6 if BSA<1.6m^2)	<0.8 (>0.6 if BSA<1.6m^2)
	Prosthesis patient mismatch		
	Mild	***Moderate***	***Severe***
Indexed effective orifice area (cm^2/m^2)	>0.85 (>0.7 if BMI ≥30 kg/m^2)	0.85-0.65 (0.9-0.6 if BMI ≥30 kg/m^2)	<0.65 (<0.6 if BMI ≥30 kg/m^2)
	Prosthetic aortic valve regurgitation		
	Mild	***Moderate***	***Severe***
Diastolic flow reversal (PW-descending aorta)	Absent / brief diastolic	Intermediate	Prominent, holodiastolic
Circumferential extent of prosthetic valve paravalvular regurgitation (%)	<10	10-29	≥30
Regurgitant volume (ml/beat)	<30	30-59	≥60
Regurgitant fraction (%)	<30	30-49	≥50
EROA (cm^2)	0.1	0.1-0.29	≥0.3

[1] Kappetein AP et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012;60(15): 1438-54.

PROCEDURAL COMPLICATIONS [1]:

- ≠ Conversion to open surgery secondary to any procedure-related complications (TAVI only)
- ≠ Unplanned use of cardiopulmonary bypass during the procedure (TAVI only)
- ≠ Coronary obstruction
- ≠ Ventricular septal perforation
- ≠ Mitral valve apparatus damage or dysfunction
- ≠ Cardiac tamponade
- ≠ Valve malpositioning
- ≠ Valve migration
- ≠ Valve embolization
- ≠ Ectopic valve deployment
- ≠ TAV-in-TAV deployment

STROKE [1]:

Diagnostic criteria:

- ≠ Acute episode of a focal or global neurological deficit with at least one of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke
- ≠ Stroke: duration of a focal or global neurological deficit ≥24 h; OR <24 h if brain imaging documents an acute or new hemorrhage or acute ischemic lesion; OR the neurological deficit results in death
- ≠ TIA: duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct
- ≠ No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumour, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with the designated neurologist
- ≠ Confirmation of the diagnosis by at least one of the following:
    - Neurologist or neurosurgical specialist
    - Brain imaging (CT scan or MRI), but stroke may be diagnosed on clinical grounds alone

Stroke classification:

- ≠ Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by ischemia.
- ≠ Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage
- ≠ Undetermined: insufficient information to allow categorization as ischemic or haemorrhagic

Stroke definitions:

[1] Kappetein AP et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012;60(15): 1438-54.

- ≠ Disabling stroke: a modified Ranking Scale (mRS) score of 2 or more at 90 days and an increase in at least one mRS category from an individual's pre-stroke baseline
- ≠ Non-disabling stroke: an mRS score of <2 at 90 days or one that does not result in an increase in at least one mRS category from an individual's pre-stroke baseline

Each patient will undergo neurological assessments at designated clinical visits. All patients with suspected neurological deficits will be evaluated by a neurologist as soon as possible.

TIME-RELATED VALVE SAFETY (COMPOSITE ENDPOINT) [1]:

- ≠ Structural valve deterioration, including repeat procedures
- ≠ Prosthetic valve endocarditis or thrombosis
- ≠ Thromboembolic events (e.g. stroke)
- ≠ VARC bleeding (unless clearly unrelated to valve therapy)

VALVE THROMBOSIS [1]:

Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment.

VASCULAR ACCESS SITE AND ACCESS-RELATED COMPLICATIONS [1]:

Major vascular complications

- ≠ Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm OR
- ≠ Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) leading to death, life-threatening or major bleeding*, visceral ischemia, or neurological impairment OR
- ≠ Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR
- ≠ The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia or neurological impairment OR
- ≠ Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR
- ≠ Surgery for access site-related nerve injury OR
- ≠ Permanent access site-related nerve injury

Minor vascular complications

- ≠ Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneuysms, hematomas, percutaneous closure device failure) not leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment OR
- ≠ Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR

[1] Kappetein AP et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012;60(15): 1438-54.

- ≠ Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR
- ≠ Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)

Percutaneous closure device failure

- ≠ Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning

All vascular complications should be reported as access (e.g. iliac rupture) or non-access site-related (e.g. dissection of ascending aorta if not caused by cannulation in the case of transaortic access)

16. SIGNATURES

Principal Investigator: Prof. Dr. Stefan Blankenberg _____
Date/ signature

Principal Investigator: Prof. Dr. Jochen Cremer _____
Date/ signature

Trial Statistician: Prof. Dr. Inke R. König
Dr. Reinhard Vonthein
Prof. Dr. A. Ziegler
_____
Date/ signature

Coordinating Investigator: Dr. Moritz Seiffert _____
Date/ signature

Head Clinical Study Center: Prof. Dr. Peter Clemmensen _____
Date/ signature

Statistical Analysis Plan (SAP)

Ran**d**omiz**ed**, Mult**i**-**C**enter, Event-Driven Trial of T**A**VI versus SAVR in Pa**t**ients with Symptomatic S**e**vere Aortic Valve Stenosis and Intermediate Risk of Mortality, as assessed by STS-Score

DEDICATE

Version V01

11.05.2023

SAP Changes

Nr	Description	Date	Version	Version Protocol
01	First version	11.05.2023	01	9.1

Signatures

The signing persons have read and revised the present Statistical Analysis Plan for the study DEDICATE and agree to its content.

Lübeck, den _____
PD Dr. Reinhard Vonthein, Independent Biostatistican

Lübeck, den _____
Prof. Dr. Inke König, Independent Biostatistican

Davos, den _____
Prof. Dr. Andreas Ziegler, Independent Biostatistician

Hamburg, den _____
PD Dr. med. Moritz Seiffert, Coordinating Investigator

Hamburg, den _____
Prof. Dr. med. Stefan Blankenberg, Principal Investigator

Kiel, den _____
Prof. Dr. med. Jochen Cremer, Principal Investigator

Hamburg, den _____
Prof. Dr. med. Stefan Blankenberg, for the Sponsor UKE

Abbreviations

Abbreviation	Description
AT	As Treated
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
bpm	beats per minute
CI	Confidence Interval
cm	centimeter
CONSORT	Consolidated Standards of Reporting Trials
DVP	Data Validation Plan
eCRF	electronic Case Report Form
e.g.	for example
EUDAMED	European Union Database on Medical Devices
FU	Follow-Up
GCP	Good Clinical Practice
H_0	Null hypothesis
H_1	Alternative hypothesis
HR	Hazard Ratio
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification
IMBS	Institut für Medizinische Biometrie und Statistik
ITT	Intention-To-Treat
kg	kilogram
m	meter
max	maximum
mm	millimeter
mmHg	millimeter of mercury
No	Number
OP	Operation
OS	Overall Survival
PH	Proportional Hazard
PID	Personal Identification
PP	Per Protocol
QoL	Quality of Life
SA	Safety Analysis
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System, software
SAVR	Surgical Aortic Valve Replacement
SDM	Study Data Management
SFS	Stroke free survival

Abbreviation	Description
SOP	Standard Operating Procedure
TAVI	Transcatheter Aortic Valve Intervention
TIA	Transient Ischemic Attack

Table of Content

1. Aim

Central assumptions, methods and procedures for the statistical analysis are described in the study protocol. The statistical analysis plan (SAP) specifies in detail the statistical and biostatistical approaches and procedures to be used.

2. Responsibilities

The study data management (SDM) of the CTC-North (until 2022) and the IMBS (since 2023), carry out the data management according to standard operating procedures (SOP). The processes themselves are based on the requirements of the good clinical practice (GCP). Queries will be forwarded to the centers for processing via the electronic case report form (eCRF).
Statistical analyses will be performed independently by the IMBS. The SDM provides the data for the analysis after query management according to the data validation plan (DVP) is completed. Discrepancies, which emerge retrospectively or are overlooked, complicate or distort the statistical analysis. To achieve high data quality, SDM and biostatisticians cooperate closely. Discrepancies, which may be discovered after database closure during statistical analysis, will be documented in the program code.

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3. Study design und amendments

3.1 Study

Study design:	Prospective, randomized, parallel, multicenter, national, open label
Study type:	Intervention study (non-inferiority)
Clinical development stage:	Post-marketing
Randomization:	1:1
Number of participating sites:	Approximately 40
Planned sample size:	Approximately 1404
Registration of first patient:	10.05.2017
Planned study end:	15.09.2027
Aim:	The primary objective of the study is to demonstrate the non-inferiority of Transcatheter aortic valve implantation (TAVI) compared to Surgical aortic valve replacement (SAVR) for the purpose of validating the consensus treatment guideline with evidence. The primary aim of the study is to show that the stroke-free survival time in the TAVI group is non-inferior compared to the stroke-free survival time in the SAVR group.
Registration of the study:	Clinicaltrials.gov: NCT03112980
EUDAMED-No.:	None

3.2 Study Amendments

3.2.1 Ethics committee

Only points concerning the statistical part of the study are described below in short:

No	Application date	Description	Approval date
1	01.09.2017	Change of - eligibility: age <85y, STS-PROM > 2 instead of 3 - sample size 1600 rationale	15.09.2017
2	18.02.2019	Change of - eligibility: Age >70 instead of STS-PROM - sample size 1600 calculation	06.03.2019
3	25.06.2020	Change of - Age >65 rather than 70 - primary outcome measure time to stroke or death instead of survival time, landmark HR as effect measure - sample size 1760 no longer event driven	10.06.2020
4	08.06.2021	Change of - primary outcome: no longer landmark HR - sample size 1404 rationale: non-inferiority HR 1.14 instead of 1.1	21.06.2021

3.2.2 BfArM

Not submitted to regulatory agencies.

4. Background

During the study, the ESC guideline of 2014 was updated in 2017 and in 2021 prompting amendments to the trial protocol.

4.1 Trial objective

The primary objective of the study is to demonstrate the non-inferiority of TAVI effectiveness compared to SAVR for the purpose of validating the consensus treatment guideline with evidence.
The primary aim of the study is to show that the stroke-free survival time in the patients assigned to TAVI is non-inferior compared to the stroke-free survival time in the patients assigned to SAVR (hazard ratio (HR) < 1.14 at 1 year, <1 at 5 years).

4.2 Outcome measures

Primary and secondary endpoints are described below. The questionnaires and their scores used to assess secondary endpoints of the study are described in subsection 4.5.

4.2.1 Primary outcome measure

The primary endpoint is stroke-free survival. Individual time is defined as time from randomization date to the date of the occurrence of the earliest of the following events:

- stroke: hemorrhagic, ischemic, disabling or not, but not TIA, as assessed by the Endpoint Adjudication Committee
- Death of any cause

For patients having none of these events, this time is censored at the last time that one of these events could have been detected, usually the last follow-up (FU) visit before the end of the study.

4.2.2 Secondary outcome measures

4.2.2.1 Overall survival

Overall survival (OS) is defined as time from date of randomization until date of death of any cause. Patients without having an event will be censored at the last time the patient was examined according to the documentation.

4.2.2.2 Stroke

Stroke is defined as comprising all, ischemic and hemorrhagic stroke whether disabling or not, but not TIA. Time to stroke will be analyzed as time from date of randomization until date of first stroke. Patients without having a stroke will be censored at the last time the patient was examined according to the documentation.

4.2.2.3 Event times

Further events and composite endpoints will be evaluated according to VARC-2 definitions as described in the trial protocol. Time to event will be analyzed as time from date of randomization until date of first event of that kind. Patients without having such an event contribute times that are censored at the last time the patient was examined according to the documentation. This applies, in addition to the primary endpoint and its components, to

- Cardiovascular death
- Stroke, disabling
- Stroke or TIA
- Myocardial infarction (periprocedural or spontaneous)
- New permanent pacemaker implantation
- New-onset atrial fibrillation
- New-onset left bundle branch block
- Prosthetic valve dysfunction
- Prosthetic aortic valve endocarditis
- Prosthetic valve thrombosis
- Aortic valve reintervention
- Rehospitalization
    - due to heart failure
    - cardiovascular
    - overall

For analysis see subsection 9.4.1.

4.2.2.4 Events

All events will be evaluated according to VARC-2 definitions as described in the trial protocol. Numbers of cases, in which they occurred, are reported.

- Mortality
  - Periprocedural
  - Cardiovascular
  - All-cause
- Myocardial infarction
  - All
  - Periprocedural
  - Spontaneous
- Stroke
  - Disabling and non-disabling
  - Disabling
  - non-disabling
  - TIA
- Bleeding
  - Life-threatening / disabling and major
  - Life- threatening / disabling
  - Major
- Acute kidney injury (within 7 days)
  - Stages 1, 2, 3
  - Stages 2, 3
  - Stage 3
- Vascular access complications (access site related)
  - Major and minor
  - Major
  - Minor
  - Percutaneous closure device failure
- Vascular access complications (not access site related)
  - Major and minor
  - Major
  - Minor
- Arrythmia
  - Atrial fibrillation
  - Pacemaker implantation
- Prosthetic valve dysfunction
- Prosthetic aortic valve endocarditis
- Prosthetic valve thrombosis

Four composite endpoints according to VARC-2 will not be reported (see 10.).

4.2.2.5 Recurrent events

- Events that can occur repeatedly will be counted per case. The sums are reported. The times between randomization and last observation on a patient are summed up to patient-years. Yearly incidence rates are calculated as ratios of the two sums. The distributions of individual event numbers are compared by descriptive P values of Jonkheere-Terpstra tests. This applies to Myocardial infarction
    - Myocardial infarction (periprocedural or spontaneous)
    - Spontaneous myocardial infarction
- Stroke
    - Disabling and non-disabling
    - Disabling
    - non-disabling
    - TIA
- Bleeding
    - Life-threatening / disabling and major
    - Life- threatening / disabling
    - Major
- Rehospitalization
    - due to heart failure
    - cardiovascular
    - overall
- Prosthetic valve dysfunction
- Prosthetic aortic valve endocarditis
- Prosthetic valve thrombosis

4.2.2.6 Prosthetic aortic valve endocarditis Repeated echocardiography, laboratory analysis, and quality of life assessment

Reporting of repeated measurements by echocardiography and laboratory analysis and quality of life assessments describes participants at baseline, intervention, and follow-up. They may be reported at the respective places, but are planned to be reported in separate tables. All data produced are summarized. Reports may focus on the most relevant variables. Most variables are metric.

4.2.3 Safety/tolerability

Reporting of adverse events, as it is required by GCP standards in clinical trials of single medical devices is not conducted in this pragmatic trial of a complex intervention strategy, so that tables and listings like those required for periodic safety update reports on single medical devices cannot be produced. There are, however, mostly safety endpoints among the primary and secondary endpoints.

4.2.4 Health economics

This trial aims to provide the basis for health economic evaluations by reports on health care utilization and quality of life rather than costs incurred. Health care utilization is measured as

- Length of stay in-hospital
- Length of stay at intensive care unit
- Length of stay at rehabilitation facility
- Length of stay at nursing home
- Ratio of days alive out of hospital versus total days alive

Due to the intercurrent pandemic, all length of stay variables are doubled up by the same without the times in which COVID-19 was the reason for admission. For analysis see .

4.3 Interventions

The description of interventions TAVI and SAVR serves the purpose of making the trial results reproducible. As interventions differ in many respects and are somewhat comparable only in a few respects, the As Treated description of interventions applies to just one treatment arm for many variables. In the ITT data, however, a few cross-overs will fill most voids. Case numbers will be very low then.
Some aspects are covered by echocardiography and laboratory analysis, which may be reported separately.

4.4 Population

The participants of the trial are described, so as to define the population for generalization. This description encompasses current and prior cardiovascular problems, variables that are prognostic for outcomes, e.g. the STSPROM and age. Baseline medication, measurements of quality of life, echocardiography and laboratory analysis, may be displayed separately together with the respective data after treatment.

4.5 Measurement methods

4.5.1 Laboratory assessment units

Many laboratory measurements may be reported in a choice of units, mostly mol/l or g/l in different powers of 10. These will be converted by program code to the units given in Table 25 using the established constants.

Table 1: Conversion of units that can be chosen in the eCRF

Analyte	**Formula**
Hemoglobin g/dL	= **1.6114 *** Hemoglobin **mmol/l**
Erythrocytes 10^12/l	= Erythrocytes **Tpt/l** = Erythrocytes **/pl** = Erythrocytes **M/µl** = Erythrocytes **Mio/µl** = **1000 *** Erythrocytes **10^6/nl** = Erythrocytes **Mrd/ml**

	= Erythrocytes **T/l**
WBC 10^9/l	= **1000 *** WBC **Tpt/l** = WBC **/nl** = WBC **K/µl** = WBC **Ts/µl** = **1000 *** WBC **10^3/nl** = **1000 *** WBC **Mrd/ml** = WBC **G/l**
Thrombocytes 10^9/l	= **1000 *** Thrombocytes **Tpt/l** = Thrombocytes **/nl** = Thrombocytes **K/µl** = Thrombocytes **Ts/µl** = **1000 *** Thrombocytes **10^3/nl** = **1000 *** Thrombocytes **Mrd/ml** = Thrombocytes **G/l**
Serum-Creatinine µmol/l	= **88.4 *** Serum Creatinin **mg/dl**
GFR (CKD-EPI) ml/min/1.73m2	= GFR (CKD-EPI) **ml/min**
Urea mg/dl	= **6.006 *** Urea **mmol/l**
Albumin g/L	= **10 *** Albumin **g/dl** = **66 *** Albumin **mmol/L**
Bilirubin µmol/l	= **17.1 *** Bilirubin **mg/dl**
ASAT/GOT U/l	= **60 *** ASAT/GOT **µkatal/l**
ALAT/GPT U/l	= **60 *** ALAT/GPT **µkatal/l**
LDH U/l	= **60 *** LDH **µkatal/l**
NT-proBNP ng/L	= **1000 *** NT-proBNP **µg/l** = NT-proBNP pg/ml
Troponin T ng/L	= **1000 *** Troponin T **ng/ml** = Troponin T **pg/ml**
Troponin I ng/L	= **1000 ***Troponin I **µg/l** = **10 ***Troponin I **ng/dl** = **1000 ***Troponin I **ng/ml** = **1000000 *** Troponin I **g/l**
CK total U/l	= **60 *** CK total **µkatal/L**
CK-MB U/l	= **60 *** CK-MB **µkatal/L**
Cholesterol total mmol/l	= **0.026 *** Cholesterol total **mg/dl**

The following questionnaires will be used to assess the secondary endpoints of the study. All endpoints will be analyzed according to the manuals, if applicable.

4.5.2 NIH SS

The NIH SS was answered by investigators solely for the purpose of enabling the EAC to check on their classification of stroke/TIA. So, its items are not analyzed in any other way than those stroke variables.

4.5.3 CES-D

The CES-D was reported in all single items and will be summarized as recommended (https://nida.nih.gov/sites/default/files/Mental_HealthV.pdf accessed 2023.04.05) by coding responses with numbers 0 to 4 and reporting the sum of these. Reverse order applies to items 4, 8, 12, 16.

4.5.4 EQ5D-5L index

The EQ5D index is calculated from the five items using the table published for Germany, version 1.2, published 2022.01.31. (https://euroqol.org/wp-content/uploads/2020/12/Germany_crosswalk_SAS.txt and https://euroqol.org/wp-content/uploads/2020/12/Germany_valueset_SAS.txt, accessed 2023.03.29)

5. Database

Database for statistical analyses are the data sets, which will be prepared and provided by the SDM group. These data sets have already completed the plausibility checks and query management according to the DVP. Data sets are corrected accordingly. Every attribute, which is collected in the eCRF, is declared as a variable. Data have to be extended, e.g. calculations, recodings or development of new variables, which are necessary for the analyses.

5.1 Incomplete observation

Reasons for incomplete observations are documented in the eCRF as

- Lost to follow-up
- Withdrawal of consent
- Death
- Other reasons

and in the monitoring reports (patient withdrawal, study discontinuation).
Although all efforts are undertaken to follow up all patients, it might not be possible to get complete observations from these patients. Project management, SDM and study statistician will list patients included in the study, who met at least one exclusion criterion at randomization, prior to final analyses. In each publication, it will be clearly stated

- the number of patients not included in the primary analysis of data,
- the circumstances under which patients were enrolled, but excluded from the analysis.

For this purpose, lists will be provided by the SDM and study statistician (see Listing 1, Listing 2 and Listing 3).
Reporting and visualization complies with the CONSORT guidelines.

5.2 Protocol deviations and protocol violations

Protocol deviations will be recorded in the eCRF and in the attachments of the monitoring reports and will be reviewed prior to database lock.
Deviations will be categorized as follows

- Randomization

- Inclusion/exclusion criteria
- Informed consent form
- Missed study procedure or visit
- Out of window procedure or visit
- Other treatment than assigned
- Unreported safety event
- Others

Further protocol deviation categories may be identified during the study. Protocol deviations will be recorded and referenced to determine subjects to be excluded from the populations described in Chapter 7. The final decision regarding inclusion and exclusion of subjects from the analysis populations will be based on a listing of protocol deviations. This will be determined during a data review meeting before database lock with input from Clinical and Biostatistics team members and approval from the sponsor (see Listing 1).
Protocol deviations will be summarized by type, major or minor, by center and by category for all enrolled subjects (see Table 3 and Table 4).

Time windows for data acquisition at each study visit are shown in Table 2. Time windows are negligible for time to event endpoints, since time of an event or of the last FU date will be used irrespective of the time window below. For other measurements like QoL, a minor protocol deviation may be documented, and for analysis, a visit will be assigned to the next scheduled visit, if not more than half a unit of time (day, week, month, year) away, e.g. 3-year visit after 3.7 years is missing at 3 years and may be counted as 4 years visit, if that was conducted more than 0.3 years off-target. The better fit will be used. The time windows for analysis are listed in Table 2.

Table 2: Time windows for data acquisition at each study visit referring to days after V01

Visit	**Time window per protocol**	**Time window with minor deviation**
Screening	Maximum 6 weeks before V01	Maximum 6 weeks before V01
V01	0 to 0.5 days	0 to 0.5 days
V02 (day)	0.5 to 1.5 days	0.5 to 2 days
V03	2.5 to 3.5 days	2 to 5 days
V04 (week)	6.5 to 7.5 days	5 to 18 days (if not at discharge)
V05 (month)	23 to 37 days	18 to 45 days
V06 (year)	365 to 390 days	184 to 557 days
V07 to V09	730, 1096, 1461± 90 days	730, 1096, 1461± 182 days
V10	1825-2005 days	>1643 days

6. Analysis timing

A formal interim analysis of the primary endpoint at a predetermined point in time with the aim of ending the study early is not planned. Publications are planned about

- the co-primary safety endpoint with at least one year of follow-up for all participants,
- the co primary efficacy endpoint with at least five years of follow-up for all participants.

With regard to safety events, the incoming data will be evaluated at regular intervals by the Endpoint Adjudication Committee and the results will be reported to the study management. The Data and Safety Monitoring Board (DSMB) will be scheduled once a year for the review of the safety data. Safety data includes detailed information on safety events inducing deaths.

7. Sets of Patients

Inclusion and exclusion criteria are described in detail in the study plan.
Patients with invalid written informed consent or who withdrew their informed consent to not just further visits, but also for usage of data that had already been reported, will be excluded from all data sets.
The trial protocol stipulates that the primary analysis follows the intention to treat principle for efficacy endpoints. Accordingly, such analyses are reported in the main text of publications of the clinical trial report, while sensitivity analyses using other sets are published as supplementary material.
This SAP contains examples of tables, listing, and figures, that may be produced more than once each. They may be produced for the different analysis sets and with 1 year data and with 5 years data. Some such replicates are included, some are indicated using the notation: "at [1 | 5] years in [ITT | AT] data", if all four combinations are meant. The legend of one table or figure would contain just one of the options within a pair of square brackets and separated by a vertical line.

7.1 Intention-To-Treat set

Implementation: no ○ ● yes
The Intention-to-Treat (ITT) analysis set comprises all randomized patients including all patients with minor and major protocol deviations (see section 5.2), discontinuation of therapy or change of therapy and all patients with missing values.

7.2 Full Analysis set

Implementation: no ● ○ yes
The full analysis (FA) set will be a subset of the ITT where patients will be excluded from the analysis, if at least one of the following criteria is met:

- Violation of at least one inclusion or exclusion criterion at randomization
- No aortic valve replacement was attempted.

7.3 Per Protocol set

Implementation: no ● ○ yes

The per protocol (PP) data set includes all patients who were treated as described in the protocol. This includes all patients without major protocol violations.
Patients

- with violation of at least one inclusion or exclusion criterion at baseline
- without aortic valve replacement by the assigned strategy

will be excluded from this data set for the respective analysis.

A listing of patients receiving more than one aortic valve replacement will be created and discussed with the Clinical and Biostatistics team members (see Listing 1).

7.4 Safety set

Implementation: no ● ○ yes
The safety analysis (SA) set is used for the analysis of AE and every variable presenting safety and tolerability of the examined intervention. The monitoring of safety and tolerability, i.e., recording of AE/SAE, begins at the time point a patient is admitted to the study defined by the date on which the informed consent form is signed and end at the study end visit. Therefore, events occurring after signing the informed consent form and before start of therapy will already be referred as AE/SAE. Patients will be analyzed as treated. Patients may experience an AE or SAE prior to the first treatment. These patients will be classified and reported as untreated.
Patients who were not randomized and without any baseline assessments will be dropped from the SA set.

7.5 As treated set

Implementation: no ○ ● yes
This set was termed "as treated (AT)" in the protocol. It comprises of all randomized participants that received TAVI or SAVR regardless of assignment. It may be analyzed with treatment as a time-varying covariate to account for switches of treatment at revisions. This would be explicitly stated. In the other cases, treatment is just the actual initial treatment.
Patients, who were not randomized and without any baseline assessments, will be dropped from the AT set as would be patients that were treated with neither TAVI nor SAVR during the index hospitalization.

8. Handling of missing values, missing data and outliers

8.1 Missing values and missing data

In general, missing values are assumed to be missing at random and missing values are neglected. Missing values will not be replaced, and the corresponding value is set to "missing". If variables for calculation of endpoints or covariates contain >25% missing values, these variables and all subsequently calculated variables are used in univariate description only (without imputation).

Handling of missing values on single items in the questionnaires will be accounted for in summary scores according to the respective manuals (see subsection 4.5).

Missing values in the data from the Endpoint Adjudication Committee will be imputed by the value observed by the trial site, while core-lab data will not. If echocardiography data at discharge (V04) is missing and there are echocardiography data measured at day 3 (V03), then the former is imputed by the latter.

If, after query management, there will be still patients, in whom aortic valve replacement was attempted, with missing values in the treatment actually received (item treatment regimen in the final documentation), then the missing treatment information will be inferred from the procedure documentation or, as a last resort, from documentation of randomization.

If one measure of aortic valve area is missing, it is imputed by the others, if any are recorded.

As we expect some missingness due to safety events like death in repeatedly measured variables, the longitudinal analyses of these rely on multiply imputed data, so as to avoid a bias.
This applies to

- echocardiography data
- biomarker data
- quality of life
- function.

Imputations will rely on numerous variables. The following covariables will be used for multiple imputation, if there are not too many missing values in these:

- Baseline variables
    - Age at randomization (years)
    - Sex
    - Body weight (kg)
    - Body height (cm)
    - STS-PROM
    - Coronary artery disease
    - Previous myocardial infarction
    - Previous stroke
    - Cerebrovascular disease
    - Peripheral vascular disease
    - COPD
    - Diabetes mellitus
    - Atrial fibrillation
    - Permanent pacemaker
    - Pulmonary hypertension
    - mRS
    - Barthel index

- Repeatedly measured variables
  - COVID lockdown date of missed observation
  - Left ventricular ejection fraction and other echo measurements
  - GFR and other laboratory measurements
  - CES-D items
  - NYHA class
  - EQ-5D variables

Besides the prognostic variables reported for the baseline, predictors should be similar variables at other points in time or should be available at or near the times of the missing observation, i.e. have few missing values themselves.
Predictors that are too closely correlated with variables to be imputed or are identical to dependent or independent variables in adjusted analyses relying on the imputed value need to be excluded from the specific slice of the imputation model. The correlation should not exceed 0.9.
Multiple imputation will be done using the full conditional approach. Multiple imputation uses Markov chain algorithms. Variables will be imputed m ≥ 50 times with predictive mean matching using and k ≥ 50 iterations. The latter permits investigating imputation performance. Random numbers will be generated using Xoshiro256+, if available, and the seed will be set to 42.
The 50 results are then summarized following Rubin's rule. SAS code will be more complicated than

```
PROC MI data = itt_dataset seed = 1234 out=itt_dataset_mi;
   FCS regpmm(Distance0--Distance5/Distance0--Distance5    visit
visit*Distance0--Distance5) / NBITER=50;
   MNAR modelobs(Distance0--Distance5/Distance0--  Distance5 visit
visit*Distance0--Distance5);
TRANSFORM log (Distance0--Distance5);
RUN;
```

for metric variables, and for categorical variables than

```
PROC MI data = itt_dataset seed = 1234 out=itt_dataset_mi;
   FCS discrim(nyha0--nyha5 = nyha0--nyha5    visit
visit*LogDistance0--LogDistance5);
   MNAR modelobs(nyha0--nyha5/nyha0--nyha5    LogDistance0--
LogDistance5 visit visit*LogDistance0--LogDistance5);
RUN;
```

The assumption, that missingness is not at random, leads to treatment, assigned and actual, being excluded from the variables used to predict the missing values. As that may lead to bias in the opposite direction, imputation stratified by assigned treatment should serve as a sensitivity analysis.

8.2 Outliers

Outliers in metric variables, especially those influencing the primary and secondary endpoints, will be avoided using warnings if values out of range are entered in the eCRF. Additionally, query management is performed by the SDM group. Outliers are not expected for the primary and secondary endpoints. For questionnaires, laboratory

and echo data, however, values that are not compatible with life are set to missing. Limits are specified in a separate document.

9. Statistical analyses/methods

9.1 Subject disposition

There will be a clear accounting of all patients who entered the study using tables and figures. The numbers of patients, who were randomized, and who entered and completed each phase of the study, will be provided as well as the reasons for all post-randomization discontinuations, grouped by treatment and by major reason (e.g. lost-to-follow-up, safety event, poor compliance, withdrawals).
A flow chart according to the CONSORT statement will be prepared (see **Fehler! Verweisquelle konnte nicht gefunden werden.**). Whether patients were followed-up for the duration of the study even after discontinuation should be made clear.
A listing of all patients discontinued from the study after randomization, broken down by center and treatment group, giving a patient identifier, the specific reason for discontinuation, as well as last visit will be given (see Listing 2).

9.2 Analysis of intervention group comparability

The following information will be summarized by intervention groups and in total on the ITT and the AT population.

9.2.1 Demographics and baseline characteristics

Description uses mean (SD) for symmetric continuous, median (quartiles) for metric and n/N(%) for categorical variables. these are reported by assigned treatment and for all participants.

- Prognostic factors for outcomes assessed at screening (see Table 5 to Table 8)
    - Age - years
    - Female sex
    - Body mass index – kg/m2
    - STS PROM – %
    - EuroSCORE I – %
    - EuroSCORE II – %
    - NYHA class III or IV
    - Coronary artery disease
    - Previous myocardial infarction
    - Previous PCI
    - Previous CABG
    - Previous stroke
    - Cerebrovascular disease
    - Peripheral vascular disease
    - Chronic lung disease
    - Pulmonary hypertension
    - Diabetes mellitus

  - Dyslipidemia
  - Hypertension
  - Atrial fibrillation
  - Left bundle branch block
  - Right bundle branch block
  - Permanent pacemaker
- Echocardiography (see Table 6, Table 23, Table 24)
  - Aortic valve area – cm2
  - Mean aortic valve gradient - mmHg
  - Aortic regurgitation – >=moderate
  - Mitral regurgitation – >=moderate
  - Tricuspid regurgitation – >=moderate
  - Left ventricular ejection fraction – %
  - MDCT
  - Annulus perimeter – mm
  - Annulus area – cm2
- Laboratory analysis (see Table 6 and Table 25)
  - Renal failure – grade 4/5
  - Chronic hemodialysis
  - GFR (CKD-EPI) – ml/min/1.73m2
  - Hemoglobin g/dl
  - NTproBNP – ng/L

Mosaic plots show relative frequencies by treatment of ordinal categories of

- STS PROM classes (<1, 1-2, 2-3, >3) at baseline,
- age classes (<70, 70-65, 75-80, >80) at baseline as in Figure 2.

Quantitative variables STS PROM and age are classed as in the inclusion criteria at different points in time for these plots.

9.2.2 Procedural characteristics

The following information on the aortic valve replacement will be provided (see Table 10 to Table 13) by assigned treatment (ITT) and by actual treatment (AT):

- Treatment strategy
  - according to randomization
  - cross-overs
  - others
- Access
  - Interventional: Transfemoral, transaxillary, transapical, transaortic, or other
  - Surgical: Sternotomy, partial sternotomy, or other
- Procedure
  - Procedure time – min
  - Extracorporeal circulation time – min
  - Aortic cross clamp time – min

  - Valve prosthesis (different types)
  - Valve prosthesis size – mm
  - Number of predilatations: 0, 1, 2, or 3 or more
  - Number of postdilatations: 0, 1, 2, or 3 or more
  - Access closure (different options)
  - Contrast amount – ml
  - Dose-area-product
  - Cerebral embolic protection (different devices)
- Concomitant procedures
  - PCI
  - Pacemaker implantation
  - Other
  - CABG
  - MAZE procedure
  - LAA ligation
  - Aortic root enlargement
  - Ascending aorta replacement
  - Septal myectomy
  - Mitral valve surgery
  - Tricuspid valve surgery
  - Other
- Complications
  - Unplanned extracorporeal circulation
  - Conversion to open-heart surgery
  - Coronary obstruction
  - Malpositioning of the valve
  - Prosthetic valve dysfunction
  - Mitral valve injury
  - Pericardial tamponade
  - Ventricular septum perforation
  - Patients requiring red blood cell transfusion of ≥1 unit (in-hospital)
  - Patients requiring red blood cell transfusion of ≥4 units (in-hospital)
- Hospital stay
  - Length of stay index hospitalization – days
  - ICU length of stay index hospitalization - days
  - Discharge location
  - Home
  - Rehab facility
  - Another hospital
  - Deceased
  - Other

Mosaic plots show relative frequencies by treatment of ordinal categories of implant size in mm-classes in the AT data.

9.2.3 Co-medication

Co-medication is reported at baseline and at times after the procedures. This evidence for baseline comparability and description of treatments is collected in Table 9 as absolute and relative frequencies.

9.3 Primary analyses

Analysis of the primary endpoint will be conducted on the ITT population and presented by allocated treatment, unless otherwise stated.
The primary objective of the study is to demonstrate the non-inferiority of TAVI over SAVR. The hypotheses are

$$H_0: HR \geq \text{margin} \text{ vs. } H_1: HR < \text{margin},$$

where HR is the hazard ratio of the hazards λ_e (TAVI) and λ_c (SAVR) and margin defines the non-inferiority boundary of 1.14. Significance level is set to 2.5% one-sided, so that the testing strategy may be conducted by equal tailed 95%-confidence intervals.

9.3.1 Testing strategy

This hypothesis will be analyzed using the two-sided log-rank test stratified by trial site and STS PROM class (0-2%, 2.01-4%, 4.01-6%). Data from strata will be pooled in case of less than 10 events per stratum starting with sites.
The global significance level is 5% two-sided, i.e., 2.5% one-sided. Non-inferiority of TAVI with respect to SAVR may be claimed as a result of this trial only when both one-sided 97.5% confidence intervals for the HR cover values less than 1.14 only. Superiority of TAVI over SAVR may be claimed if TAVI is not inferior to SAVR and additionally TAVI is superior to SAVR at the two-sided level 5% test after five years of follow-up. The hierarchical testing procedure would then proceed to the first secondary test, the test of superior RMST at 5 years. If that is significant, RMST at 1 year will be tested. If that is significant, RMST is tested with time restricted by 1 year from below and 5 years from above. No other claims may be confirmed.

9.3.2 Estimand

Individual time will be defined as time from randomization date to the date of the occurrence of the first event as listed in subsection 4.2.1. For patients having none of these events, this time will be censored at the last time that one of these events could have been detected, usually the last FU visit before the end of the study.

Objective	Non-inferiority of safety and efficacy
Estimand	Cause specific relative hazard of death or stoke following decision for TAVI among patients with aortic stenosis at intermediate or low risk and no clear recommendation, but traditionally treated with SAVR, who receive standard of care in Germany, while disregarding change of treatment

Treatment	Assignment to TAVI for aortic valve replacement versus SAVR while maintaining the standard of care in Germany

ESTIMAND	**ANALYSIS**
Target population Patients with aortic stenosis and no clear heart team recommendation for TAVI or SAVR	**Analysis set** ITT: All participants, who are randomized, by assigned treatment
Variable Survival without stroke	**Outcome measure** Time to stroke or death censored at end of trial, withdrawal of consent, or loss to follow-up
Handling of intercurrent events a) Absorbing event death is part of the composite endpoint (composite variable strategy) b) Treatment changes at index procedure or at revisions: Full follow-up is considered irrespective of actual treatment (treatment policy strategy) c) Reasons for loss to follow-up: Assumed to happen at random, no intercurrent event.	**Handling of missing data** a) No competing risks are considered. b) No other treatments than those assigned at randomization are considered. c) Loss to follow-up and withdrawal of consent censor event time. <u>Sensitivity analysis</u>: Only cases, in which actual treatment matches one of the assigned treatments, are considered by actual treatment (AT). Revision of aortic valve replacement censors time, if not of the assigned type, and may start time again, if the other trial treatment is attempted.
Population level summary measure Cause specific hazard ratio Proportion with event at 1 and 5 years	**Analysis approach** Cause specific hazard ratio from Cox-regression with logrank test stratified by pooled strata used in randomization. <u>Sensitivity analysis</u>: Cause specific hazard ratio from Cox-regression with random site effects and STS PROM as continuous variable and P value of Wald test . Kaplan-Meyer estimate with 95%-confidence interval

A stratified Cox proportional hazards (PH) will be used to compare outcomes between the two groups with the result expressed as a HR with corresponding 95% profile likelihood confidence interval (CI). If the upper boundary of the CI < margin = 1.14, then TAVI is non-inferior to SAVR. The Cox PH model will be implemented using SAS `PHREG` procedure with option `TIES=BRESLOW`. This approximates the EXACT method

which assumes that there is a true but unknown ordering for the tied event times as contrasted to option `TIES=DISCRETE` which assumes that the events in fact occurred at exactly the same time.

The code like following SAS code will be used to check the PH assumption and to obtain the HR and corresponding 95% CI:

```
ods graphics on;
PROC phreg data=itt_dataset;
CLASS treatment_alloc;
MODEL survtime_stroke*censor_stroke(1)= treatment_alloc /firth
risklimits=pl;/TIES=BRESLOW;
STRATA sts_class;
HAZARDRATIO CL=BOTH;
ASSESS var=( treatment_alloc) PH/ CRPANEL resample seed=1234;
RUN;
ods graphics off
* survtime_stroke represents variable containing event/censor times;
* censor_stroke represents censoring variable (1=censored, 0=event);
* treatment_alloc represents treatment group variable;
* sts_class represents the categorical stratification variable;
```

Further options to control the output may be added.

The frailty model of the sensitivity estimand is declared with the `RANDOM` statement, without the `CLASS` and `STRATA` statements and with STS PROM as covariable like

```
MODEL survtime_stroke*censor_stroke(1)= treatment_alloc stsprom /firth
risklimits=pl;/TIES=BRESLOW;
RANDOM trialsite;
* trialsite represents the categorical variable trial sites
* stsprom represents the covariable STS PROM at baseline
```

Variable `stsprom` is centered at 2 to enhance robustness against nonlinearity and ensure interpretability.

Time-varying exposure to different implants is denoted by code like

```
MODEL survtime_stroke *censor_stroke(1)= treatment time_switch /firth;
   if (switch_time = . or Time < switch_time) then do;
      censor_stroke =1.;
      time_switch=0.;
      treatment= treatment_alloc;
   end;
   else do;
      censor_stroke = 0.0;
      time_switch= fu_switch;
      treatment = 1 - treatment_alloc;
   end;
* switch_time represents time of aortic valve revision;
* time_switch represents time since aortic valve revision;
```

If convergence of profile-likelihood CI fails, Wald CI will be reported.

The P value of the stratified log-rank test will be calculated stratified by STS PROM classes used to stratify randomization. Here, the SAS `PROC LIFETEST` will be used:

```
PROC LIFETEST data=itt_dataset METHOD=KM CONFTYPE=LOGLOG;
TIME survtime_stroke*censor_stroke(1);
STRATA sts_class / group=treatment_alloc;
RUN;
* survtime_stroke represents variable containing event/censor times;
* censor_stroke represents censoring variable (1=censored, 0=event);
* treatment_alloc represents treatment group variable;
* sts_class represents the categorical stratification variable
```

Further options to control the output may be added.

Stroke free survival (SFS) for each treatment group will be estimated using Kaplan-Meier product-moment method estimates. SFS will be summarized by treatment groups and will display the following information (see Table 14):

- Number of patients in the population (n)
- Number of patients with event
- Number of patients censored
- Minimum and maximum
- Event rates at certain time points (1, 2, and 5 years) with 95% CIs

Kaplan-Meier estimates will be calculated with the `PROC LIFETEST` procedure. The CIs of the event rates will be calculated vial log-log transformation method (default option `CONFTYPE=LOGLOG`) based on standard errors computed using Greenwood's formula.
The P value from the stratified log-rank test will be displayed together with the estimated HR and two-sided 95% CI from the stratified Cox model (see Table 15).
A Kaplan-Meier plot of SFS by treatment group with number of patients at risk will be generated (see Figure 4).

9.3.3 Analysis assumptions and alternative analyses

If the PH assumption is not met, the interpretation of results needs to consider inference on RMST and descriptive results as in Table 14 as well as a Kaplan-Meier plot (see Figure 4).

9.3.4 Imputation

Imputation will not be necessary for SFS. Patients without an event will be censored the last time that a progression or death could have been detected, usually the last FU visit before the end of the study.

9.3.5 Sensitivity analyses

As sensitivity analyses, the analysis of SFS as described above will be performed using the AT data set. Repeated aortic valve replacement with a switch between TAVI and SAVR or vice versa shall be entered into the model as a time-varying covariate. These

two changes result in the first three sensitivity estimands. The next two sensitivity estimands reflect the different treatment of stratification variables in ITT and AT data.

A) Cause specific relative hazard of death or stoke following assignment to TAVI or SAVR among patients with aortic stenosis at intermediate or low risk and no clear recommendation, but traditionally treated with SAVR, while considering switches of treatment
B) Cause specific relative hazard of death or stoke following actual TAVI or SAVR among patients with aortic stenosis at intermediate or low risk and no clear recommendation, but traditionally treated with SAVR, while disregarding change of treatment
C) Cause specific relative hazard of death or stoke following actual TAVI among patients with aortic stenosis at intermediate or low risk and no clear recommendation, but traditionally treated with SAVR, considering switches of treatment
D) Cause specific relative hazard of death or stoke following assignment to TAVI or SAVR among patients with aortic stenosis at intermediate or low risk and no clear recommendation, but traditionally treated with SAVR, while disregarding switches of treatment and adjusting for STS PROM
E) Cause specific relative hazard of death or stoke following actual TAVI among patients with aortic stenosis at intermediate or low risk and no clear recommendation, but traditionally treated with SAVR, considering switches of treatment and adjusting for STS PROM.

9.4 Secondary analyses

Changes in the secondary outcomes are of interest as they will relate to the safety and efficacy as measured by the primary outcome variable. All analyses are descriptive and are intended to document the changes in these important outcomes. Multiplicity adjustments for testing of secondary endpoints is restricted to the confirmatory testing strategy. P values reported outside of the testing strategy are clearly labeled as meant to be descriptive.

Analysis of secondary efficacy endpoints will be conducted on ITT and AT populations and presented by treatment group, unless otherwise stated. Analysis of safety/tolerability endpoints will be conducted on the AT data set and presented by treatment group, unless otherwise stated.

Additional secondary analyses are related to patient-reported outcomes. Specifically, quality of life (QoL) has been measured during the trial using the EQ-5D-5L. Both QoL analyses and quality-adjusted life years (QALY) will be investigated between both treatment groups.

9.4.1 Time to event endpoints

9.4.1.1 Restricted mean time to event

For the composite primary endpoint as part of the testing strategy and for overall survival as a descriptive statistic, the mean survival by treatment is calculated and the difference estimated together with a 95%-confidence interval. Such results shall be

displayed as in Table 19. No competing risks need to be considered, as death is at least a component of the endpoints. The estimands follow the pattern:
Difference in expected [stroke-free] survival time during the first [five] year[s] after assignment to TAVI or SAVR in patients at intermediate or low risk with nor clear recommendation, but traditionally treated with SAVR, while disregarding changes of treatment and maintaining standard of care in Germany.
Program code may look like

```
PROC RMSTREG data=itt_dataset tau=5;
CLASS treatment_alloc;
MODEL survtime_stroke*censor_stroke(1) = treatment_alloc / link=linear;
   lsmeans treatment_alloc;
STRATA sts_class;
RUN;
```

Further options to control the output may be added.

9.4.1.2 Time to event

Analysis of this endpoint will be conducted on the ITT and AT population and presented by allocated treatment, unless otherwise stated. The hypotheses are

$$H_0: HR = 1 \text{ vs. } H_1: HR \neq 1,$$

where HR is the hazard ratio of the hazards λ_e (TAVI) and λ_c (SAVR). Significance level will be set to 5% two-sided by reporting equal tails 95%-confidence intervals for HR.

Individual time will be defined as time from date of randomization until date of the event. This time will not end when other events occur. Time will be censored at the time of the last FU visit before the end of the study or on the day of death, if death is not part of a composite endpoint. Events are analyzed as reported by the Endpoint Adjudication Committee, if not stated otherwise. In case these values are missing, they are imputed by the values reported by the trial site.

Objective	Non-inferiority of safety and efficacy
Estimand	Cause specific relative hazard of the event following decision for TAVI among patients with aortic stenosis at intermediate or low risk and no clear recommendation, but traditionally treated with SAVR, while disregarding change of treatment
Treatment	TAVI for aortic valve replacement or SAVR
ESTIMAND	**ANALYSIS**
Target population Patients with aortic stenosis and no clear heart team recommendation for TAVI or SAVR	**Analysis set** ITT: All participants, who are randomized, by assigned treatment
Variable Time without event	**Outcome measure**

	Time to event censored at end of trial, death, withdrawal of consent or loss to follow-up
Handling of intercurrent events a) Absorbing event death, which is not part of the composite endpoint, prevents observation of the event. It censors event time (composite variable strategy) b) Treatment changes at index procedure or revisions: Full follow-up is considered irrespective of actual treatment (treatment policy strategy) c) Reasons for loss to follow-up and withdrawal of consent: Assumed to happen at random, no intercurrent event.	**Handling of missing data** a) Event time is censored at time of death when cause-specific hazards are computed. b) No other treatments than those assigned at randomization are considered. c) Loss to follow-up and withdrawal of consent censor event time. Sensitivity analyses: i) Only cases, in which actual treatment matches one of the assigned treatments, are considered by actual treatment (AT). ii) In case one of the assigned treatments is later followed by the other, treatment is modeled as a time-varying covariate.
Population level summary measure Cause specific hazard ratio	**Analysis approach** Cause specific hazard ratio from Cox-regression with logrank test stratified by pooled strata used in randomization.

Objective	Description for further analysis
Estimand	Proportion of patients having actually experienced their first such event within a fixed time after decision between TAVI and SAVR among patients with aortic stenosis at intermediate or low risk and no clear recommendation, while disregarding change of treatment
Treatment	TAVI for aortic valve replacement

ESTIMAND	**ANALYSIS**
Target population Patients with aortic stenosis and no clear heart team recommendation for TAVI or SAVR	**Analysis set** ITT: All participants, who are randomized, by assigned treatment
Variable Time without event	**Outcome measure** Time to event censored at end of trial, withdrawal of consent, or loss to follow-up
Handling of intercurrent events a) Absorbing event death is not part of the composite endpoint, so	**Handling of missing data** a) Competing risk death is considered when estimating the

that the proportions should add up to 1 (composite variable strategy) b) Treatment changes at index procedure or revisions: Full follow-up is considered irrespective of actual treatment (treatment policy strategy) c) Reasons for loss to follow-up and withdrawal of consent: Assumed to happen at random, no intercurrent event.	sub-distribution hazards to construct the cumulative incidence function. b) No other treatments than those assigned at randomization are considered. c) Loss to follow-up and withdrawal of consent censor event time. .
Population level summary measure Proportion with event at 30 days,1, 2, and 5 years	**Analysis approach** Cumulative incidence function at 30 days, 1, 2, and 5 years estimated by sub-distribution hazards

A Cox PH model (specified below) will be used to compare outcomes between the two groups with the result expressed as a HR with corresponding 95% profile likelihood confidence interval (CI):

```
ods graphics on;
PROC phreg data=itt_dataset;
MODEL survtime_event*censor_event(1)= treatment_alloc /firth
risklimits=pl;/TIES=BRESLOW;
HAZARDRATIO CL=BOTH;
STRATA sts_class;
ASSESS var=( treatment_alloc) PH/ CRPANEL resample seed=1234;
RUN;
ods graphics off
* survtime_event represents variable containing event/censor times;
* censor_event represents censoring variable (1=censored, 0=event);
* treatment_alloc represents treatment group variable coded as 0 and
1;
* sts_class represents the categorical stratification variable
```

Further options to control the output may be added.
If convergence fails, Wald CIs will be reported.

The null hypothesis will be tested using the stratified two-sided log-rank test at 5% significance level:

```
PROC LIFETEST data=itt_dataset METHOD=KM CONFTYPE=LOGLOG;
TIME survtime_event*censor_event(1);
STRATA sts_class / group=treatment_alloc;
RUN;
* survtime_event represents variable containing event/censor;
```

```
* censor_event represents censoring variable (1=censored, 0=event);
* treatment_alloc represents treatment group variable;
* sts_class represents the categorical stratification variable
```

Further options to control the output may be added.

Cumulative incidence of the event for each treatment group will be estimated using Kaplan-Meier product-moment method estimates. It will be summarized by treatment groups and will display the following information (see Table 18):

- Number of patients in the population (n)
- Number of patients with event
- Number of patients censored
- Minimum and maximum
- Event rates at certain time points (1, 2, and 5 years) with 95% CIs

Kaplan-Meier estimates will be calculated with the `PROC LIFETEST` procedure. The CIs of the event rates will be calculated vial log-log transformation method (default option `CONFTYPE=LOGLOG`) based on standard errors computed using the Greenwood's formula.
The p-value from the stratified log-rank test will be displayed together with the estimated HR and two-sided 95% CI from the stratified Cox model (see Table 18).
Kaplan-Meier plot of cumulative incidence by treatment arm will be generated (see Figure 4).

9.4.1.2.1 Analysis assumptions and alternative analyses

If the PH assumption is not met, descriptive results as in Table 18 will be reported as well as a Kaplan-Meier plot (see Figure 4) and the p-value from the stratified log-rank test.

9.4.1.2.2 Imputation

Not necessary for survival endpoint.

9.4.1.2.3 Sensitivity analyses

As sensitivity analyses, the analysis of event time as described above will be performed using the AT data set. Repeated aortic valve replacement with a switch between TAVI and SAVR or vice versa shall be entered into the model as a time-varying covariate. These two changes applied at once result in the sensitivity estimands:

Cause specific relative hazard of the event following actual TAVI or SAVR among patients with aortic stenosis at intermediate or low risk and no clear recommendation, but traditionally treated with SAVR, considering switches of treatment.

9.4.1.3 Overall survival

Analysis of OS will be conducted on the ITT and AT population and presented by allocated treatment , unless otherwise stated. The hypotheses are

$$H_0: HR = 1 \text{ vs. } H_1: HR \neq 1,$$

where HR is the hazard ratio of the hazards λ_e (TAVI) and λ_c (SAVR). Significance level is set to 5%.
OS will be defined as time from date of randomization to date of death of any cause. Patients without having an event will be censored at the last time the patient was examined according to the documentation.

A stratified Cox PH model (specified below) will be used to compare outcomes between the two groups with the results expressed as a HR with a 95% profile likelihood CI. The following SAS code will be used to check the PH assumption and to obtain the HR and corresponding 95% CI:

```
ods graphics on;
PROC phreg data=itt_dataset;
Model survtime_os*censor_os(1)= treatment_alloc /firth risklimits=pl;
/TIES=BRESLOW;
STRATA sts_class;
HAZARDRATIO CL=BOTH;
ASSESS var=( treatment_alloc) PH/ CRPANEL resample seed=1234;
run;
ods graphics off
* survtime_os represents variable containing event/censor times;
* censor_os represents censoring variable (1=censored, 0=event);
* treatment_alloc represents treatment group variable;
* sts_class represents the categorical stratification variable
```

Further options to control the output may be added. Time-varying exposure to different implants is denoted by code like

```
MODEL survtime_os*censor_os(1)= treatment time_switch /firth;
   if (switch_time = . or Time < switch_time) then do;
      censor_os =1.;
      time_switch=0.;
      treatment= treatment_alloc;
   end;
   else do;
      censor_os = 0.0;
      time_switch= fu_switch;
      treatment = 1 - treatment_alloc;
   end;
* switch_time represents time of aortic valve revision;
* time_switch represents time since aortic valve revision;
```

Further options to control the output may be added.
If convergence fails, Wald CIs will be reported.

In addition, the null hypothesis will be tested using a stratified two-sided log rank test with 5% signifance level:

```
PROC LIFETEST data=itt_dataset METHOD=KM CONFTYPE=LOGLOG;
```

```
TIME survtime_os*censor_os(1);
STRATA sts_class / group=treatment_alloc;
RUN;
* survtime_os represents variable containing event/censor;
* censor_os represents censoring variable (1=censored, 0=event);
* treatment_alloc represents treatment group variable;
* sts_class represents the categorical stratification variable
```

Further options to control the output may be added.

OS for each treatment group will be estimated using Kaplan-Meier product-moment estimates. It will be summarized by treatment groups and will display the following information (see Table 16):

- Number of patients in the population (n)
- Number of patients with event
- Number of patients censored
- Minimum and maximum
- Event rates at certain time points (1, 2, and 5 years) with 95% CIs

Kaplan-Meier estimates will be calculated with the `PROC LIFETEST` procedure in SAS. The CIs of the event rates will be calculated via log-log transformation method (default option `CONFTYPE=LOGLOG` in SAS) based on standard errors computed using the Greenwood's formula. The p-value from the stratified log-rank test will be displayed together with the estimated HR and two-sided 95% CI from the Cox model (see Table 17)
A Kaplan-Meier plot of OS by treatment arm will be generated (see Figure 4).

9.4.1.3.1 Analysis assumptions and alternative analyses

If the PH assumption is not met, descriptive results like in Table 17 will be reported as well as a Kaplan-Meier plot (see Figure 4) and the p-value from the log-rank test.

9.4.1.3.2 Imputation

Imputation not necessary for time to event endpoints.

9.4.1.3.3 Sensitivity analyses

As sensitivity analyses, the analysis of OS as described above will be performed using the AT data set. Repeated aortic valve replacement with a switch between TAVI and SAVR or vice versa shall be entered into the model as a time-varying covariate. These two changes results in the following three sensitivity estimands:

A) Cause specific relative mortality following assignment to TAVI or SAVR among patients with aortic stenosis at intermediate or low risk and no clear recommendation, but traditionally treated with SAVR, considering switches of treatment
B) Cause specific relative mortality following actual TAVI or SAVR among patients with aortic stenosis at intermediate or low risk and no clear recommendation, but traditionally treated with SAVR, while disregarding change of treatment

C) Cause specific relative mortality following actual TAVI or SAVR among patients with aortic stenosis at intermediate or low risk and no clear recommendation, but traditionally treated with SAVR, considering switches of treatment.

9.4.2 Events

Absolute and relative frequencies of cases with events such as bleeding and rehospitalization will be reported for each treatment (see *Table* 19 *Restricted mean time survival time* [*ITT | AT*]

Variable	Restricted to years	Difference mean (95%CI) P value	TAVI (n = XX) mean (95%CI)	SAVR (n = XX) mean (95%CI)
Time to stroke or death	0 to 1	XXX (XXX to XXX) X.XXX	XXX (XXX to XXX)	XXX (XXX to XXX)
Overall survival time	0 to 1	XXX (XXX to XXX) X.XXX	XXX (XXX to XXX)	XXX (XXX to XXX)
Time to stroke or death	0 to 5	XXX (XXX to XXX) X.XXX	XXX (XXX to XXX)	XXX (XXX to XXX)
Overall survival time	0 to 5	XXX (XXX to XXX) X.XXX	XXX (XXX to XXX)	XXX (XXX to XXX)
Time to stroke or death	1 to 5	XXX (XXX to XXX) X.XXX	XXX (XXX to XXX)	XXX (XXX to XXX)
Overall survival time	1 to 5	XXX (XXX to XXX) X.XXX	XXX (XXX to XXX)	XXX (XXX to XXX)

Table 20, Table 21). Frequencies per participant will be exploratively compared between treatment groups using the asymptotic Jonckheere Terpstra test (see Table 21). Results will be visualized by paired bar plots (see Figure 7**Fehler! Verweisquelle konnte nicht gefunden werden.**).
E.g. bleeding:

```
PROC FREQ data=itt_dataset;
TABLES bleeding * treatment_alloc / jt;
RUN;
* bleeding represents grade of bleeding;
* treatment_alloc represents treatment group;
```

Further options to control the output may be added.

9.4.3 Repeatedly measured outcomes

Descriptive statistics will use the non-missing data from the ITT set. Frequencies will be reported separately for each level and category separately for all observational time points and separately by treatment groups. Similarly, medians and quartiles for metric variables are reported. Reporting will look like Table 20 to Table 27*Table 25*. Expected values and time specific treatment effects and the respective 95%-confidence limits are computed after multiple imputation using the existing observations, but not the assigned treatment.

Aortic regurgitation, paravalvular regurgitation, and NYHA class are explored in two-way ordinal logistic regressions with randomized treatment and time point as fixed factors as OR with 95% CI. Proportions are reported in the ITT and AT set (like Table 20). Expected values and time specific treatment effects and the respective 95%-confidence limits are computed after multiple imputation using the existing observations, but not the assigned treatment.

SAS code may look like

```
PROC MI data = itt_dataset seed = 1234 out=itt_dataset_mi;
   FCS discrim(nyha0--nyha5 = nyha0--nyha5    visit
visit*LogDistance0--LogDistance5);
   MNAR modelobs(nyha0--nyha5/nyha0--nyha5    LogDistance0--
LogDistance5 visit visit*LogDistance0--LogDistance5);
RUN;
PROC LOGISTIC data=itt_dataset_mi;
   CLASS treatment_alloc
   MODEL nyha = treatment_alloc visit;
   ODDSRATIO treatent_alloc visit;
   BY _Imputation_;
   ODS OUTPUT = ParameterEstimates = lgsparms CovB = lgscovb
RUN;
PROC MIANALYZE parms=lgsparms covb(effectvar=stacking)=lgscovb;
   MODELEFFECTS Intercept treatment_alloc visit;
RUN;
* nyha represents the ordinal variable NYHA class;
* visit represents the ordinal variable visit;
* treatment_alloc represents the binary variable assigned treatment;
```

Further options to control the output may be added.

Mean transvalvular gradient, EOA, and 6-minute walk test are explored by generalized linear model assuming lognormal distribution, using the log-link and randomized treatment and time point as fixed factors. Expected values and time specific treatment effects and the respective 95%-confidence limits are computed after multiple imputation using the existing observations, but not the assigned treatment, in the ITT and AT set (see Table 23). SAS code may look like

```
PROC MI data = itt_dataset seed = 1234 out=itt_dataset_mi;
   FCS regpmm(Distance0--Distance5/Distance0--Distance5    visit
visit*Distance0--Distance5) / NBITER=50;
   MNAR modelobs(Distance0--Distance5/Distance0--  Distance5 visit
visit*Distance0--Distance5);
TRANSFORM log (Distance0--Distance5);
RUN;
PROC GLM data = itt_dataset_mi;
   CLASS treatment_alloc;
   MODEL LogDistance0--LogDistance5 = treatment_alloc / nouni;
   REPEATED visit 4 contrast(1) / summary printe;
   LSMEANS treatment_alloc visit / cl pdiff;
   BY _Imputation_;
   ODS OUTPUT ParameterEstimates = glmparms InvXPX = glmxpxi;
QUIT;
* RUN;
```

```
PROC MIANALYZE parms = glmparms xpxi = glmxpxi edf=28;
* data=miout;
   MODELEFFECTS Intercept treatment_alloc visit;
RUN;
* Distance0 represents the 6 minutes walking distance at baseline;
* visit represents the ordinal variable visit;
* treatment_alloc represents the binary variable assigned treatment;
```

Further options to control the output may be added.

Mosaic plots show relative frequencies by treatment of ordinal categories of

- aortic regurgitation (trans- and paravalvular) at discharge, 1 and eventually 5 years,
- paravalvular aortic regurgitation at discharge, 1 and eventually 5 years, and
- NYHA class at baseline, discharge, 1 and eventually 5 years fo follow-up as in Figure 7.

9.4.4 Safety/tolerability

Safety events will be reported for the ITT and AT data sets as described above.

9.4.5 Quality of life and quality-adjusted life years

QoL was measured at baseline, discharge, 30 days and 1 year after randomization using the EuroQoL EQ-5D-5L in its German paper-based version. The EQ-5D-5L is a validated, generic patient-reported outcome measure covering 5 health domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a visual analogue self-rating scale (VAS). Patients were asked to rate severity of their current problems (level 1 = no problems, level 2 = slight problems, level 3 = moderate problems, level 4 = severe problems, 5 = extreme problems). Patients are thus classified into 5^5 = 3125 health states plus two further states, i.e., unconscious, and dead. EQ-5D-5L health states are converted into a single index value using the Crosswalk Index Value Calculator based on data from the German population, ranging from 1 (best health) to -0.205. Patients who died during the observation period are set to 0. The proportion of negative index values will be noted. Negative index values will be set to 0. As sensitivity analysis, analyses will be conducted with negative index values.
For the VAS, patients were asked to rate their own health relative to full health (score=100) and worst imaginable health state (score=0).
EQ-5D-5L Index and VAS will be reported as mean, SD, median and quartiles by treatment group and time point, differences of means and medians at each time point and 95%-confidence intervals for these differences using the formulae of Satterthwaite, and Hodges-Lehman, respectively. SAS code will look like

```
proc ttest;
      by visit;
      class treatmentalloc;
      var VAS;
   run;
proc npar1way hl alpha=.05;
      by visit;
      class treatmentalloc;
```

```
      var VAS;
      exact hl;
      ods select HodgesLehmann;
   run;
* visit is the variable indicating point in time;
* treatmentalloc is the variable indicating allocated treatment;
* VAS is the variable with VAS scores;
```

Further options to control the output may be added.

The QALY will be estimated for each individual as the area under the curve (AUC) through linear interpolation from EQ5D index values for the periods between measurements. So, there will be just one value per case for all measurements up to the tim e of reporting, which will be 1 year for the report on the co-primary safety endpint and 5 years for the report on the co-primary efficacy endpoint. these are summarized like the other metric variables.
VAS adjusted life years (VAS-AL) will be calculated analogously after transformation to the 0 to 1 scale to ensure comparability with utility-based QALY.
Reporting would look like Table 26.

9.4.5.1 Description

Descriptive statistics will use the complete cases from the ITT set.
Frequencies will be reported separately for each level and category separately for all observational time points and separately by treatment groups.
“Problems” (levels 2-5) vs. “no problems” (level 1) will be considered for each category, each time point and both treatment groups.
Needle plots of the EQ-5D index and its VAS will be generated for each treatment group and time point.
Histograms for the QALY and VAS-AL will be generated for each treatment group and time point.

9.4.5.2 Adjusted effects

Index values, QALY, and VAS-AL will be estimated from the imputed data sets.
To estimate the treatment effect, linear regression will be performed for the EQ-5D index at 1 year follow-up, the VAS at 1 year follow-up, the QALY and the VAS-AL with adjustment for age, sex, and the STS score.
As sensitivity analysis, it is intended to use center as random effect so that a linear mixed model is run after multiple imputation.

9.5 Planned subgroup analyses

Subgroup analyses will use the primary endpoint SFS and overall survival OS and the prognostic factors in the ITT set:

- Age at randomization >= 75, 70-75, <70
- Sex
- BMI <25, 25-30, >= 30
- STS-PROM >= 2
- NYHA class <=2 versus >2

- Coronary artery disease
- Previous myocardial infarction
- Previous Stroke
- Cerebrovascular disease
- Peripheral vascular disease
- COPD
- Diabetes mellitus
- Atrial fibrillation
- Permanent pacemaker
- Pulmonary hypertension
- Left ventricular ejection fraction (50%)
- GFR (>=60 ml/min/1.72m2)
- Concomitant procedures
- Amendment (with varying inclusion criteria <2, 3)
- COVID lockdown at admittance

Results for subgroups will be reported by Table 28 and visualized by forest plots of HR with two-sided 95% CIs for each subgroup and the p-value of the interaction effect (see Figure 9). Analyses described in Chapter 9.3 will be performed for each subgroup by adding an interaction term into the analyses,
For this purpose, categories with few events are pooled until >= 10 events will be on record per category, e.g. amendment "0+1". Same analyses will be performed for both data sets.

9.6 Stratified analyses

The primary endpoint SFS should also be analyzed with a stratified Cox model with treatment group as covariate (binary) in the ITT set, i.e., the model specified in Chapter 9.3.3 will be extended by `STRATA center`. The model will be stratified by center. Analysis will be conducted in the ITT set. HR and corresponding two-sided 95% CIs will be reported.
If necessary, centers will be pooled. Therefore, a list of centers with an overview of patients in each treatment regimen will be considered by the clinical and biostatistical staff members. E.g. small subgroups could be summarized by size until >= 10 events will be in each stratum. Decision on pooling can only be made when data will be available. Each stratum will define a separate baseline hazard function. The current plan with about 100 events in about 40 trial sites leads one to expect, that no stratification by sites will be done. As a surrogate, a frailty model of Cox regression with random site effects shall be estimated.
In addition, the hypothesis will be tested using a two-sided log rank test stratified by center (see Chapter 9.3.3) with added `STRATA` statement. Reporting will be according to Table 15.

9.7 Interim analyses

A formal interim analysis of the primary endpoint at a pre-determined point in time for the purpose of early termination is not planned. The co-primary safety analysis,

however, will be conducted after one year of follow-up, the co-primary efficacy endpoint after another four years. The crossing cumulative incidence curves reported in other trials, e.g. UK-TAVI, prevent the early results from changing expectations in the further follow-up, much of which will have been done already for many patients.

9.8 Exploratory analyses

SFS and OS shall be explored with respect to the prognostic variables: treatment, treatment as a time-varying covariate, STS PROM, age, and the STS PROM-age interaction. Results will be presented as in Table 29.

10. Deviation from the protocol

Lognormal assumptions are hard to defend, as other statistics than geometric means prevail in the literature, median and quartiles are reported instead of geometric means and coefficients of variation. Composite endpoints that were not reported: "Clinical efficacy", early safety, device success, and time-related valve safety. Their components are reported nevertheless. The reason is, that these VARC-2 definitions are outdated, were not reported in comparable trials, and are superseeded by their components, which are reported in finer detail.
All other deviations from the protocol are necessitated by the kind of data observed.
At blinded interim analyses, events were so rare that time to event analyses stratified by site would rely on curves with too few steps. The pre-specified pooling leads to no stratification by trials site. As a remedy, the frailty model with random effects of sites and Wald confidence limits is added as a sensitivity estimand.
Echocardiographic core lab data needs to be available at the point of analysis for these to be reported. This precludes 1 year echo data for the article on the co-primary safety endpoint.
Health economic analyses would be handled by a specialized researcher, who is not an author of this SAP. The data that the trial should contribute there seem, however, less than complete at the time of drafting this SAP.

11. Interpretation of results

Confirmatory decisions will be made on the co-primary endpoints following the testing strategy. All other P values will be only descriptive and labeled as such. Analyses of secondary endpoints will support the analysis of the primary endpoint.
If both co-primary tests are statistically significant, the conclusion is that assignment to TAVI is non-inferior to SAVR while maintaining the standard of care in Germany in patients at intermediate or low risk with no clear heart team recommendation with respect to SFS followed-up for 1 and for 5 years or to withdrawal or loss to follow-up irrespective of treatment changes.
If just the first co-primary test is statistically significant, the conclusion is that assignment to TAVI is non-inferior to SAVR while maintaining the standard of care in Germany in patients at intermediate or low risk with no clear heart team recommendation with respect to SFS followed-up for 1 year or to withdrawal or loss to follow-up irrespective of treatment changes, but that such a statement cannot be

upheld with follow-up extending to 5 years. Descriptive statistics will point to promising hypotheses for further research like superiority of SAVR in the long run.
If not even the first co-primary test is statistically significant, the conclusion is that no hypothesis about assignment to TAVI versus SAVR while maintaining the standard of care in Germany in patients at intermediate or low risk with no clear heart team recommendation with respect to SFS followed-up for 1 year or to withdrawal or loss to follow-up irrespective of treatment changes can be confirmed. Descriptive statistics will point to promising hypotheses for further research like superiority of SAVR in the short run.

12. Further analyses

Further analyses on the data of DEDICATE are not subject to this SAP and P values are explicitly labeled as descriptive.

13. Software

Analyses will be prepared using SAS® System 9.4 (SAS Inc., Cary/NC, USA) or higher. Additionally, StatXact Procs 11.1 or higher and LogXact 11.1 or higher will be used.
Figures should be realized with these or the following programs

- R 4.0.3 or higher,
- CorelDraw 12 or higher,
- InDesign CS5 or higher

14. Appendices

14.1 Planned tables

14.1.1 Protocol deviations

Table 3 Protocol deviations by center and category

Center	Treatment	Category	Number of minor protocol deviations	Number of major protocol deviations
Center A	TAVI	Randomization		
	SAVR	Inclusion/Exclusion		
		Other		
…				

Table 4 Cross table: treatment and protocol deviations

Treatment	Number of minor protocol deviations	Number of major protocol deviations
TAVI	XXXX	XXXX
SAVR	XXXX	XXXX

14.1.2 Analysis of intervention comparability

14.1.2.1 Demographics and baseline characteristics

Shown are the variables for Table 1 of all articles, each of which may report just the relevant parts.

Table 5 Demographic and baseline characteristic – symmetric continuous variables

	Total		TAVI		SAVR	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Age in years	XX	XX (XX.X)	XX	XX (XX.X)	XX	XX (XX.X)
EuroScore I (%)	XX	XX (XX.X)	XX	XX (XX.X)	XX	XX (XX.X)
EuroScore II (%)	XX	XX (XX.X)	XX	XX (XX.X)	XX	XX (XX.X)
Aortic valve area	XX	XX (XX.X)	XX	XX (XX.X)	XX	XX (XX.X)
Mean aortic valve gradient	XX	XX (XX.X)	XX	XX (XX.X)	XX	XX (XX.X)
Left ventricular ejection fraction	XX	XX (XX.X)	XX	XX (XX.X)	XX	XX (XX.X)
Blood pressure syst.	XX	XX (XX.X)	XX	XX (XX.X)	XX	XX (XX.X)
Blood pressure diast.	XX	XX (XX.X)	XX	XX (XX.X)	XX	XX (XX.X)
Heart rate	XX	XX (XX.X)	XX	XX (XX.X)	XX	XX (XX.X)

Table 6 Demographic and baseline characteristic – skew continuous variables

	Total		TAVI		SAVR	
	n	Median (quartiles)	n	Median (quartiles)	n	Median (quartiles)
Body mass index (kg/m^2)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
STS PROM (%)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
Annulus perimeter	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
Annulus area	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
GFR	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
Hemoglobin	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
GFR	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
NTproBNP	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
Frailty	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
NIH SS	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
CES-D	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)

6MWT	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
CT aortic perimeter	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
CT Aortic area	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
CT aortic diameter min	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
CT aortic diameter max	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
CT aorta ascendens area	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
CT Sinus Valsalva diameter min	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
CT Sinus Valsalva diameter max	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
CT Sinus Valsalva area	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
CT Sinus Valsalva perimeter	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
CT Sinus Valsalva height	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
CT Sinutubular transition area	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
CT LVOT diameter min	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
CT LVOT diameter max	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
CT LVOT area	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
CT LVOT perimeter	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
CT Distance to LCA	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
CT Distance to RCA	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
CT Aortic valve calcification	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
CT Femoral artery left diameter min	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)
CT Femoral artery right diameter min	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)	XX	XX (XX.X;XX.X)

Table 7 Baseline characteristics – dichotomous variables

	Total	**TAVI**	**SAVR**
	n/N (%)	n/N (%)	n/N (%)
Sex female	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Coronary artery disease	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Previous myocardial infarction	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Previous PCI	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)

Previous stroke	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Cerebrovascular disease	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Peripheral vascular disease	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Chronic lung disease	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Pulmonary hypertension	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Diabetes mellitus	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Dyslipidemia	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Hypertension	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Atrial fibrillation	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Left bundle branch block	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Right bundle branch block	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Permanent pacemaker	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Aortic regurgitation >= moderate	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Mitral regurgitation >= moderate	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Tricuspid regurgitation >= moderate	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Renal failure grade >= 4	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Chronic hemodialysis	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)

Table 8 Baseline characteristics – categorical variables (not for article 1 Table 1)

		Total	**TAVI**	**SAVR**
		n/N (%)	n/N (%)	n/N (%)
NYHA class	I	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
	II	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
	III	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
	IV	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Modified Rankin Scale	0	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
	1	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
	2	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
	3	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
	4	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
	5	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
	6	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Barthel index	>=95	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
	>=90	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
	>=85	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
	<85	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Rhythm	Sinus	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
	Atrial fibrillation	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
	Atrial flutter	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
	Other	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)

AV block	none	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
	I	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
	II	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
	III	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Hemiblock	left anterior	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
	left posterior	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
	unknown	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)

14.1.2.1 Medication

Table 9: Medication (ITT) as n/N (%)

Medication	Baseline		Discharge		30 Days		1 Year	
	TAVI	*SAVR*	*TAVI*	*SAVR*	*TAVI*	*SAVR*	*TAVI*	*SAVR*
Anticoagulation	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
- Vitamin K antagonist	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
- DOAC	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Platelet inhibition	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
- ASA	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
- Clopidogrel	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
- Ticagrelor	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
- Prasugrel	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
ACE-inhibitor	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
AT1-receptor antagonist	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Aldosterone antagonist	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Betablocker	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Sacubitril/Valsartan	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Calcium antagonist	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Statin	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
Antidiabetic	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
- Insulin	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)
- Oral antidiabetic	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)	XX/XXX (XX.X)

14.1.2.1 Procedural characteristics

Table 10 Procedural characteristics (ITT) as n/N (%)

Characteristic	**TAVI; n/N (%)**	**SAVR; n/N (%)**
Treatment		
- according to randomization	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- crossovers		
- OMT only	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)

Anesthesia type		
- General	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Conscious sedation/local anesthesia	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Other	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Access		
Interventional	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Transfemoral	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Transaxillary	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Transapical	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Transaortic	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Other	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Surgical	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Sternotomy	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Partial sternotomy	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Other	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Valve prosthesis (different types)		
	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Number of predilatations		
- 0	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- 1	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- 2	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- 3 or more	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Number of postdilatations		
- 0	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- 1	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- 2	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- 3 or more	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Access closure (different options)		
	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Dose-area-product	XXX/XXX (XXX; XXX)	XXX/XXX (XX.X%)
Cerebral embolic protection (different devices)		
	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Concomitant procedures		
- PCI	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Pacemaker implantation	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Other	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- CABG	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- MAZE procedure	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- LAA ligation	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Aortic root enlargement	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Ascending aorta replacement	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Septal myectomy	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)

- Mitral valve surgery	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Tricuspid valve surgery	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Other	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Unplanned extracorporeal circulation	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Conversion to open-heart surgery	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Coronary obstruction	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Malpositioning of the valve	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Prosthetic valve dysfunction	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Mitral valve injury	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Pericardial tamponade	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Ventricular septum perforation	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Periprocedural myocardial infarction	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Discharge location		
- Home	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Rehab facility	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Another hospital	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Deceased	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Other	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Patients requiring red blood cell transfusion of ≥1 unit (in-hospital)	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Patients requiring red blood cell transfusion of ≥4 units (in-hospital)	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)

Table 11: Procedural characteristics (AT) as n/N (%)

Characteristic	**TAVI; n/N (%)**	**SAVR; n/N (%)**
Treatment		
- according to randomization	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- crossovers		
- OMT only	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Anesthesia type		
- General	XXX/XXX (XX.X%)	
- Conscious sedation/local anesthesia	XXX/XXX (XX.X%)	
- Other		
	XXX/XXX (XX.X%)	
Access		
Interventional		
- Transfemoral	XXX/XXX (XX.X%)	
- Transaxillary	XXX/XXX (XX.X%)	
- Transapical	XXX/XXX (XX.X%)	
- Transaortic	XXX/XXX (XX.X%)	
- Other	XXX/XXX (XX.X%)	
Surgical		
- Sternotomy		XXX/XXX (XX.X%)
- Partial sternotomy		XXX/XXX (XX.X%)
- Other		XXX/XXX (XX.X%)
Valve prosthesis (different types)		
	XXX/XXX (XX.X%)	
	XXX/XXX (XX.X%)	
	XXX/XXX (XX.X%)	

Number of predilatations		
- 0	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- 1	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- 2	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- 3 or more	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Number of postdilatations		
- 0	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- 1	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- 2	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- 3 or more	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Access closure (different options)		
	XXX/XXX (XX.X%)	
	XXX/XXX (XX.X%)	
	XXX/XXX (XX.X%)	
Contrast amount – ml	XXX/XXX (XXX; XXX)	
Dose-area-product	XXX/XXX (XXX; XXX)	
Cerebral embolic protection (different devices)		
	XXX/XXX (XX.X%)	
	XXX/XXX (XX.X%)	
	XXX/XXX (XX.X%)	
	XXX/XXX (XX.X%)	
Concomitant procedures		
- PCI	XXX/XXX (XX.X%)	
- Pacemaker implantation	XXX/XXX (XX.X%)	
- Other	XXX/XXX (XX.X%)	
- CABG		XXX/XXX (XX.X%)
- MAZE procedure		XXX/XXX (XX.X%)
- LAA ligation		XXX/XXX (XX.X%)
- Aortic root enlargement		XXX/XXX (XX.X%)
- Ascending aorta replacement		XXX/XXX (XX.X%)
- Septal myectomy		XXX/XXX (XX.X%)
- Mitral valve surgery		XXX/XXX (XX.X%)
- Tricuspid valve surgery		XXX/XXX (XX.X%)
- Other		XXX/XXX (XX.X%)
		XXX/XXX (XX.X%)
Unplanned extracorporeal circulation	XXX/XXX (XX.X%)	
Conversion to open-heart surgery	XXX/XXX (XX.X%)	
Coronary obstruction	XXX/XXX (XX.X%)	
Malpositioning of the valve	XXX/XXX (XX.X%)	
Prosthetic valve dysfunction	XXX/XXX (XX.X%)	
Mitral valve injury	XXX/XXX (XX.X%)	
Pericardial tamponade	XXX/XXX (XX.X%)	
Ventricular septum perforation	XXX/XXX (XX.X%)	
Periprocedural myocardial infarction	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Discharge location		
- Home	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Rehab facility	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Another hospital	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
- Deceased	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)

- Other	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Patients requiring red blood cell transfusion of ≥1 unit (in-hospital)	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)
Patients requiring red blood cell transfusion of ≥4 units (in-hospital)	XXX/XXX (XX.X%)	XXX/XXX (XX.X%)

Table 12: Procedural characteristics (ITT) as median (quartiles)

Characteristic	**TAVI (n = XX)**	**SAVR (n = XX)**
Procedure time – min	XXX (XXX; XXX)	XXX (XXX; XXX)
Extracorporeal circulation time – min	XXX (XXX; XXX)	XXX (XXX; XXX)
Aortic cross clamp time – min	XXX (XXX; XXX)	XXX (XXX; XXX)
Valve prosthesis size – mm	XXX (XXX; XXX)	XXX (XXX; XXX)
Contrast amount – ml	XXX (XXX; XXX)	XXX (XXX; XXX)
Dose-area-product	XXX (XXX; XXX)	XXX (XXX; XXX)
Length of stay index hospitalisation – days	XXX (XXX; XXX)	XXX (XXX; XXX)
ICU length of stay index hospitalisation - days	XXX (XXX; XXX)	XXX (XXX; XXX)

Table 13: Procedural characteristics (AT) as median (quartiles)

Characteristic	**TAVI (n = XX)**	**SAVR (n = XX)**
Procedure time – min	XXX (XXX; XXX)	XXX (XXX; XXX)
Extracorporeal circulation time – min	XXX (XXX; XXX)	XXX (XXX; XXX)
Aortic cross clamp time – min	XXX (XXX; XXX)	XXX (XXX; XXX)
Valve prosthesis size – mm	XXX (XXX; XXX)	XXX (XXX; XXX)
Contrast amount – ml	XXX (XXX; XXX)	
Dose-area-product	XXX (XXX; XXX)	
Length of stay index hospitalisation – days	XXX (XXX; XXX)	XXX (XXX; XXX)
ICU length of stay index hospitalisation - days	XXX (XXX; XXX)	XXX (XXX; XXX)

14.1.3 Primary endpoint

The lines of sub-table with survival times will be reported only, if one median is not missing, one minimum is >0, or one maximum is <[1 | 5] years.

Table 14: Stroke free survival – results of Cox regression stratified by STS PROM class.

	Total (n=XXX)	**TAVI** (n=XXX)	**SAVR** (n=XXX)
Patients deceased without stroke	XXX	XX	XX
Patients with stroke	XXX	XXX	XXX
Patients censored	XXX	XXX	XXX
Survival times			
Median (years)	X.X	X.X	X.X
Minimum (years)	X.X	X.X	X.X
Maximum (years)	X.X	X.X	X.X
Event rates*			
30 days	XX.XX [XX.XX-XX.XX]	XX.XX [XX.XX-XX.XX]	XX.XX [XX.XX-XX.XX]
1 year	XX.XX [XX.XX-XX.XX]	XX.XX [XX.XX-XX.XX]	XX.XX [XX.XX-XX.XX]
2 years	XX.XX [XX.XX-XX.XX]	XX.XX [XX.XX-XX.XX]	XX.XX [XX.XX-XX.XX]
5 years	XX.XX [XX.XX-XX.XX]	XX.XX [XX.XX-XX.XX]	XX.XX [XX.XX-XX.XX]

*Kaplan-Meier estimates with corresponding 95% confidence intervals (log-log).

Table 15 Stroke free survival – results of Cox regression model stratified by STS PROM class

Endpoint	HR [95% CI]	P-value*
Stroke free survival	X.XX [X.XX to X.XX]	X.XXXX

HR = Hazard ratio, CI = confidence interval (Profile-Likelihood), *p-value from [log rank test stratified by STS PROM class.

14.1.3.1 Overall survival

The lines of sub-table with survival times will be reported only, if one median is not missing, one minimum is >0, or one maximum is <[1 | 5] years.

Table 16 Overall survival in [ITT | AT] data.

	Total (n=XXX)	TAVI (n=XXX)	SAVR (n=XXX)
Deceased patients	XXX	XXX	XXX
Patients censored	XXX	XXX	XXX
Survival times			
Median (in years)	X.X	X.X	X.X
Minimum (years)	X.X	X.X	X.X
Maximum (years)	X.X	X.X	X.X
Event rates*			
…30 days	XX.XX [XX.XX-XX.XX]	XX.XX [XX.XX-XX.XX]	XX.XX [XX.XX-XX.XX]
…1 year	XX.XX [XX.XX-XX.XX]	XX.XX [XX.XX-XX.XX]	XX.XX [XX.XX-XX.XX]
2 years	XX.XX [XX.XX-XX.XX]	XX.XX [XX.XX-XX.XX]	XX.XX [XX.XX-XX.XX]
5 years	XX.XX [XX.XX-XX.XX]	XX.XX [XX.XX-XX.XX]	XX.XX [XX.XX-XX.XX]

*Kaplan-Meier estimates with corresponding 95% confidence intervals (log-log).

Table 17 Overall survival – results of Cox regression model stratified by STS PROM class in [ITT | AT] data.

Endpoint	HR [95% CI]	P value	
Overall survival	X.XX [X.XX to X.XX]	X.XXX	

HR = Hazard ratio, CI = confidence interval (Profile-Likelihood), *p-value from log rank test stratified by STS PROM class.

14.1.4 Secondary endpoints

Table 18 Key secondary endpoints at 30 days and 1 year (ITT) with event rates estimated considering death, if not part of the endpoint, as a competing risk and with hazard ratios (HR) from cause specific hazards.
[similarly for 5 years in the second article]

End Point	*30 Days*			*12 Months*		
	TAVI n/N (%)	**SAVR n/N (%)**	**HR (95% CI)**	**TAVI n/N (%)**	**SAVR n/N (%)**	**HR (95% CI**

Death from any cause or stroke	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)
Death from any cause	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)
Stroke	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)
Stroke or TIA	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)
Stroke, disabling	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)
Cardiovascular death	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)
Myocardial infarction, periprocedural and spontaneous	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)
New-onset atrial fibrillation	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)
New-onset left bundle branch block	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)
New permanent pacemaker implantation	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)
Prosthetic valve dysfunction	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)
Prosthetic valve endocarditis	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)
Prosthetic valve thrombosis	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)
Aortic valve reintervention	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)
Rehospitalisation due to cardiovascular cause	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)
Rehospitalisation for heart failure	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)
Rehospitalisation overall	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)

Table 19 Restricted mean time survival time [ITT | AT]

Variable	Restricted to years	Difference mean (95%CI) P value	TAVI (n = XX) mean (95%CI)	SAVR (n = XX) mean (95%CI)
Time to stroke or death	0 to 1	XXX (XXX to XXX) X.XXX	XXX (XXX to XXX)	XXX (XXX to XXX)
Overall survival time	0 to 1	XXX (XXX to XXX) X.XXX	XXX (XXX to XXX)	XXX (XXX to XXX)
Time to stroke or death	0 to 5	XXX (XXX to XXX) X.XXX	XXX (XXX to XXX)	XXX (XXX to XXX)
Overall survival time	0 to 5	XXX (XXX to XXX) X.XXX	XXX (XXX to XXX)	XXX (XXX to XXX)

Time to stroke or death	1 to 5	XXX (XXX to XXX) X.XXX	XXX (XXX to XXX)	XXX (XXX to XXX)
Overall survival time	1 to 5	XXX (XXX to XXX) X.XXX	XXX (XXX to XXX)	XXX (XXX to XXX)

Table 20: Categorical secondary endpoints at 30 days and 1 year (ITT) with proportions and with odds ratios (OR) from ordinal or nominal logistic regression.

[similarly for 5 years in the second article]

End Point	***30 Days***			***12 Months***		
	TAVI n/N (%)	**SAVR n/N (%)**	**OR (95%CI)**	**TAVI n/N (%)**	**SAVR n/N (%)**	**OR (95%CI)**
Stroke			X.XX (X.XX			X.XX (X.XX
- Disabling	X/XXX (XX.X)	X/XXX (XX.X)	to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	to X.XX)
- Non-disabling	X/XXX (XX.X)	X/XXX (XX.X)		X/XXX (XX.X)	X/XXX (XX.X)	
- TIA	X/XXX (XX.X)	X/XXX (XX.X)		X/XXX (XX.X)	X/XXX (XX.X)	
Stroke			X.XX (X.XX			X.XX (X.XX
- hemorrhagic	X/XXX (XX.X)	X/XXX (XX.X)	to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	to X.XX)
- Ischemic	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX
			to X.XX)			to X.XX)
Bleeding			X.XX (X.XX			X.XX (X.XX
- None	X/XXX (XX.X)	X/XXX (XX.X)	to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	to X.XX)
- Minor	X/XXX (XX.X)	X/XXX (XX.X)		X/XXX (XX.X)	X/XXX (XX.X)	
- Major	X/XXX (XX.X)	X/XXX (XX.X)		X/XXX (XX.X)	X/XXX (XX.X)	
- Life-threatening/disabling	X/XXX (XX.X)	X/XXX (XX.X)		X/XXX (XX.X)	X/XXX (XX.X)	
Vascular and access-related complication			X.XX (X.XX to X.XX)			X.XX (X.XX to X.XX)
- None	X/XXX (XX.X)	X/XXX (XX.X)		X/XXX (XX.X)	X/XXX (XX.X)	
- Minor	X/XXX (XX.X)	X/XXX (XX.X)		X/XXX (XX.X)	X/XXX (XX.X)	
- Major	X/XXX (XX.X)	X/XXX (XX.X)		X/XXX (XX.X)	X/XXX (XX.X)	
- Percutaneous closure device failure	X/XXX (XX.X)	X/XXX (XX.X)		X/XXX (XX.X)	X/XXX (XX.X)	
Vascular and access-related complication			X.XX (X.XX			X.XX (X.XX
- Access site-related	X/XXX (XX.X)	X/XXX (XX.X)	to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	to X.XX)
- Non-access site-related	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	X.XX (X.XX to X.XX)
NYHA class			X.XX (X.XX			X.XX (X.XX
- I	X/XXX (XX.X)	X/XXX (XX.X)	to X.XX)	X/XXX (XX.X)	X/XXX (XX.X)	to X.XX)
- II	X/XXX (XX.X)	X/XXX (XX.X)		X/XXX (XX.X)	X/XXX (XX.X)	
- III	X/XXX (XX.X)	X/XXX (XX.X)		X/XXX (XX.X)	X/XXX (XX.X)	
- IV	X/XXX (XX.X)	X/XXX (XX.X)		X/XXX (XX.X)	X/XXX (XX.X)	
- dead	X/XXX (XX.X)	X/XXX (XX.X)		X/XXX (XX.X)	X/XXX (XX.X)	
Acute kidney injury in first week			X.XX (X.XX to X.XX)			
- None	X/XXX (XX.X)	X/XXX (XX.X)				
- Stage I	X/XXX (XX.X)	X/XXX (XX.X)				

- Stage II	x/xxx (xx.x)	x/xxx (xx.x)
- Stage III	x/xxx (xx.x)	x/xxx (xx.x)
- dead	x/xxx (xx.x)	x/xxx (xx.x)

Table 21: Events that may occur more than once in one patient

Event	**TAVI**	**SAVR**	**TAVI vs. SAVR**
	n/Patient-years (yearly incidence rate)	**n/Patient-years (yearly incidence rate)**	**P-value***
Myocardial infarction	XX/XXX (X.XX)	XX/XXX (X.XX)	X.XXXX
Spontaneous MI	XX/XXX (X.XX)	XX/XXX (X.XX)	X.XXXX
Stroke, disabling or non-disabling	XX/XXX (X.XX)	XX/XXX (X.XX)	X.XXXX
Stroke, disabling	XX/XXX (X.XX)	XX/XXX (X.XX)	X.XXXX
Stroke, non-disabling	XX/XXX (X.XX)	XX/XXX (X.XX)	X.XXXX
TIA	XX/XXX (X.XX)	XX/XXX (X.XX)	X.XXXX
Bleeding, major or life-threating / disabling	XX/XXX (X.XX)	XX/XXX (X.XX)	X.XXXX
Bleeding, life-threating / disabling	XX/XXX (X.XX)	XX/XXX (X.XX)	X.XXXX
Bleeding, major	XX/XXX (X.XX)	XX/XXX (X.XX)	X.XXXX
Rehospitalisation	XX/XXX (X.XX)	XX/XXX (X.XX)	X.XXXX
Rehospitalisation due to cardiovascular cause	XX/XXX (X.XX)	XX/XXX (X.XX)	X.XXXX
Rehospitalisation heart failure related	XX/XXX (X.XX)	XX/XXX (X.XX)	X.XXXX
Prosthetic valve dysfunction	XX/XXX (X.XX)	XX/XXX (X.XX)	X.XXXX
Prosthesis endocarditis	XX/XXX (X.XX)	XX/XXX (X.XX)	X.XXXX

Data shown as absolute (relative) frequencies. *Unadjusted descriptive P value from Jonckheere Terpstra test (asymptotic).

Table 22: Vital signs in AT set

	Visit	**Total**		**TAVI**		**SAVR**	
		Mean (SD)	n**	Mean (SD)	n**	Mean (SD)	n**
Systolic blood pressure (in mmHg)	Screening Final examination	XXX (XXX) XXX (XXX)	X X	XXX (XXX) XXX (XXX)	X X	XXX (XXX) XXX (XXX)	X X
Diastolic blood pressure (in mmHg)	Screening Final examination	XXX (XXX) XXX (XXX)	X X	XXX (XXX) XXX (XXX)	X X	XXX (XXX) XXX (XXX)	X X

Heart rate (in bpm)	Screening Final examination	XXX (XXX) XXX (XXX)	X X	XXX (XXX) XXX (XXX)	X X	XXX (XXX) XXX (XXX)	X X

**Number of non-missing values; mmHg: millimeters of mercury; bpm: beats per minute

14.1.5 Echocardiography

Table 23: Echocardiographic data reported by [core lab | trial sites] for the ITT data as median (quartiles). Differences rely on multiply imputed data.

	n	TAVI (n = XX)	n	SAVR (n = XX)	Difference Median (95%CI)
Aortic valve effective orifice area – cm2					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Aortic valve mean gradient – mmHg					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Aortic valve maximum gradient – mmHg					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Aortic valve regurgitation					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Aortic valve paravalvular regurgitation					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
LV ejection fraction					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Mitral valve regurgitation					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)

1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Mitral valve stenosis					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Mitral valve mean gradient					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Tricuspid valve regurgitation					
Baseline	XXX	XXX (XX.X%)	XXX	XXX (XX.X%)	XX.X (XX.X;XX.X)
Discharge	XXX	XXX (XX.X%)	XXX	XXX (XX.X%)	XX.X (XX.X;XX.X)
1 Year	XXX	XXX (XX.X%)	XXX	XXX (XX.X%)	XX.X (XX.X;XX.X)
LV enddiastolic volume – ml					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
LV endsystolic volume – ml					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Stroke volume – ml					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
TAPSE - mm					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
30 Days	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
LVEDD					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
IVS					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
PW					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)

1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
E					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
A					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
E'					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
E/E'					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
LVOT Vmax					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
LVOT Vmean					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
LVOT PGmax					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
LVOT PGmean					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
LVOT VTI					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
AV Vmax					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Aortic valve Vmean					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
AAV VTI					

Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
PAP					
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)	XX.X (XX.X;XX.X)

Table 24: Echocardiographic data reported by [*core lab* | *trial sites*] *as n (%) of available data and odds ratio (OR) from ordinal logistic regression with 95% confidence interval (95%CI). OR rely on multiply imputed data.*

Prosthetic dysfunction	n	TAVI n (%)	n	SAVR n (%)	OR (95%CI)
Baseline	XXX		XXX		X.XX (X.XX to X. XX)
Grade 1		XXX (XX.X%)		XXX (XX.X%)	
Grade 2		XXX (XX.X%)		XXX (XX.X%)	
Grade 3		XXX (XX.X%)		XXX (XX.X%)	
Discharge	XXX		XXX		X.XX (X.XX to X. XX)
Grade 1		XXX (XX.X%)		XXX (XX.X%)	
Grade 2		XXX (XX.X%)		XXX (XX.X%)	
Grade 3		XXX (XX.X%)		XXX (XX.X%)	
1 Year	XXX		XXX		X.XX (X.XX to X. XX)
Grade 1		XXX (XX.X%)		XXX (XX.X%)	
Grade 2		XXX (XX.X%)		XXX (XX.X%)	
Grade 3		XXX (XX.X%)		XXX (XX.X%)	

14.1.6 Laboratory analysis

Troponin I will be reported only, if valid standardizations between laboratories are available by the time of analysis.
Variables reported using other units than stated here, are transformed by program code using the established transformations.

Table 25: Laboratory analysis in the ITT data as median (quartiles)

	n	**TAVI**	**n**	**SAVR**
Hemoglobin – g/dL				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Erythrocytes – 10^12/l				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Hemoglobin – g/dL				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
WBC – 10^9/l				

Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Thrombocytes – 10^9/l				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
NA – mmol/l				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
KA – mmol/l				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Serum-Creatinine – µmol/L				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
GFR (CKD-EPI) - ml/min/1.73m^2				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Urea – mg/dl				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Albumin – g/L				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Bilirubin – µmol/l				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
ASAT/GOT – U/l				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
ALAT/GPT – U/l				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
LDH – U/l				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)

Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
CRP – mg/l				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
NT-proBNP – ng/L				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Troponin T – ng/L				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Troponin I – ng/L				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
CK total – U/l				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
CK-MB – U/l				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Cholesterol total – mmol/l				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
INR				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
PTT – s				
Baseline	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
Discharge	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)
1 Year	XXX	XX.X (XX.X;XX.X)	XXX	XX.X (XX.X;XX.X)

14.1.7 Quality of life and health care utilization

Table 26: Quality of life at [1 | 5] years in [ITT | AT] data. Differences rely on multiple imputation. Asterisks denote estimates adjusted for sex and STS PROM.

Questionnaire	Difference			TAVI			SAVR		
	n	Meandiff [95%CI]	Mediandiff [95%CI]	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)

EQ-5D-5L Index (Utility Score)									
Baseline	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]
Discharge	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]
30 Days	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]
1 Year	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]
1 Year*	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]						
QALY*									
[1 | 5] Year [s]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]
EQ5D-Visual Analogue Scale (VAS)									
Baseline	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]
Discharge	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]
30 Days	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]	XX	XX (XX.X)	XX [X.XX;X.XX]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]
1 Year	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]	XX	XX (XX.X)	XX [X.XX;X.XX]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]
1 Year*	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]						
VAS-AL*									
[1 | 5] Year [s]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]
CES-D Score									
Baseline	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]	XX	XX (XX.X)	XX [X.XX;X.XX]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]
30 Days	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]	XX	XX (XX.X)	XX [X.XX;X.XX]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]
1 Year	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]	XX	XX (XX.X)	XX [X.XX;X.XX]	XX	XX [X.XX;X.XX]	XX [X.XX;X.XX]

SD = standard deviation, meandiff = difference of means, mediandiff = difference of medians, CI = confidence interval, EQ5D-5L = quality of life in 5 dimensions on 5-point scales, QALY = quality index adjusted life years adjusted for sex and STS PROM, VAS-AL = visual-analogue scale adjusted life years adjusted for sex and STS PROM..

Table 27: Health care utilization during the first [5] year[s] from ITT data as median (quartiles)

Characteristic	**TAVI (n = XX)**	**SAVR (n = XX)**
Hospitalizations	XXX (XXX; XXX)	XXX (XXX; XXX)
Hospitalizations not for COVID19	XXX (XXX; XXX)	XXX (XXX; XXX)
Days in hospital	XXX (XXX; XXX)	XXX (XXX; XXX)
Days in hospital not for COVID19	XXX (XXX; XXX)	XXX (XXX; XXX)
Days in ICU	XXX (XXX; XXX)	XXX (XXX; XXX)
Days in ICU not for COVID19	XXX (XXX; XXX)	XXX (XXX; XXX)
Days in rehab	XXX (XXX; XXX)	XXX (XXX; XXX)
Days in nursing homes	XXX (XXX; XXX)	XXX (XXX; XXX)
Ratio of days alive out of hospital to total days alive	XXX (XXX; XXX)	XXX (XXX; XXX)

14.1.8 Subgroup analyses

Table 28: Subgroup analyses by unadjusted cox regression explaining times to [stroke or death | death] in [ITT | as treated] data with [1|5] years of follow-up.

Subgroup	TAVI n/N (%)	SAVR n/N (%)	HR [95% CI]	P-value*
Age				X.XXX
>=75 years	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
70 to <75 years	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
< 70 years	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX; X.XX]	
Sex				X.XXX
Female	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX; X.XX]	
Male	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX; X.XX]	
BMI				X.XXX
>=30 kg/m^2	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
25 to <30 kg/m^2	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
< 25 kg/m^2	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX; X.XX]	
STS-PROM				X.XXX
≤ 2	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
>2	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
NYHA class				X.XXX
≤ 2	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
>2	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
Coronary artery disease				X.XXX
Yes	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
No	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
Previous myocardial infarction				X.XXX
Yes	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
No	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
Previous Stroke				X.XXX
Yes	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
No	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
Cerebrovascular disease				X.XXX
Yes	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
No	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
Peripheral vascular disease				X.XXX
Yes	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
No	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
COPD				X.XXX
Yes	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
No	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
Diabetes mellitus				X.XXX
Yes	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
No	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
Atrial fibrillation				X.XXX
Yes	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
No	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
Permanent Pacemaker				X.XXX

Yes	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
No	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
Pulmonary hypertension				X.XXX
Yes	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
No	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
Left ventricular ejection fraction				X.XXX
≥ 50%	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
< 50 %	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
GFR				X.XXX
≥ 60 ml/min/1.72m2	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
< 60 ml/min/1.72m2	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
Amendment				X.XXX
<2	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
3	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
4	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
Concomittant procedures				X.XXX
Yes	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
No	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
COVID Lockdown at admittance				X.XXX
Yes	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	
No	XX/XXX (XX.X)	XX/XXX (XX.X)	X.XX [X.XX ;X.XX]	

HR = *hazard ratio, CI = confidence interval, p-value* = p value from interaction between treatment variable and subgroup variable.*

14.1.9 Exploratory analyses

Table 29: Exploratory analyses by Cox regression on treatment adjusted for the stated variables without interactions [analysis set]

Event time	Prognostic variables	HR for treatment [95% CI]
SFS	Treatment (time dependent)	X.XX [X.XX; X.XX]
SFS	Treatment, STS PROM	X.XX [X.XX; X.XX]
SFS	Treatment (time dependent), STS PROM	X.XX [X.XX; X.XX]
SFS	Treatment, STS PROM, age and STS PROM-age interaction	X.XX [X.XX; X.XX]
OS	Treatment (time dependent)	X.XX [X.XX; X.XX]
OS	Treatment, STS PROM	X.XX [X.XX; X.XX]
OS	Treatment (time dependent), STS PROM	X.XX [X.XX; X.XX]
OS	Treatment, STS PROM, age and STS PROM-age interaction	X.XX [X.XX; X.XX]

DFS = disease-free survival; OS = overall survival; HR = hazard ratio, CI = confidence interval.

14.2 Planned listings

14.2.1 Incomplete treatments, drop-outs, incomplete observation, and protocol deviations

Listing 1: Protocol deviations

Center	Treatment	PID*	Category	Visit	Date of monitoring visit	Date of protocol deviation	Description	Procedure	Minor/major protocol deviation
Center A	TAVI								
	SAVR								
…									

*Personal identification.

Listing 2: Protocol deviations – [Category Y]

Center	Treatment	PID*	Visit	Date of monitoring visit	Date of protocol deviation	Description	Procedure	Minor/major protocol deviation
Center A	TAVI							
	SAVR							
…								

*Personal identification.

Listing 3: Listing of patients who discontinued study after randomization

Center	Treatment	PID*	Last visit	Reason for discontinuation
Center A	TAVI			
	SAVR			
…				

*Personal identification.

14.2.2 Subject disposition

See Listing 3

.

14.2.3 Safety

Listing 4: Deaths

Center	PID	Age (years)	Weight*	Height*	Description						Date of onset	Duration of treatment until date of onset	Duration of SAE (in days)	Severity	Causal relationship	Action taken	Date of death
					SOC	HLGT	HLT	PT	LLT	Reported Term							
Center A																	
...																	

*Measured at screening,
PID = personal identification, SOC = system organ class, HLGT = high level group term. HLT = high level term, PT = preferred term, LLT = low level term, SAE = serious adverse event.

14.3 Planned figures

The following figures will be created.

14.3.1 Subject disposition

Figure 1: CONSORT-Flowchart

14.3.2 Baseline

Figure 2: Distribution of quantitative variables STS PROM and age are classed as in the inclusion criteria at different points in time for these plots

Figure 3: Distribution of valve prostheses implant sizes.

14.3.3 Primary and secondary endpoints

14.3.3.1 Survival endpoints

Figure 4: Cumulative incidence functions for the primary outcome time from randomization to stroke or death and its components from Cox regression stratified by STS PROM class and corresponding pointwise 95% confidence intervals for each treatment group. Inset are the same curves with zoomed-in y-axis, as events were few in the ITT data. Mortality was a competing risk for stroke in the curve for stroke.

14.3.3.2 Echocardiography and functional assessment

Echocardiography results are reported twice, one figure reports core lab adjudicated data, the other uses trial site reported data. Diagrams overlay results for mean transvalvular gradient and EOA.

Figure 5: Echocardiographic parameters at baseline and discharge by treatment as means and 95%-confidence intervals of non-missing data.

Figure 6: Echocardiographic parameters at baseline, discharge, and follow-up by treatment as expected values with 95%-confidence intervals estimated after multiple imputation to reduce bias by missingness of measurements in the deceased.

Figure 7: Relative frequencies of NYHA classes at baseline, 30 days, 1 year and eventually 5 years.

Figure 8: Six-minute walking distances by treatment at baseline, 30 days, and 1 year as grouped boxplots with means as overlaid symbols.

14.3.4 Subgroup analyses

Figure 9: Forest plot for subgroup analyses of (stroke-free) survival in the [ITT | as treated] data.