Randomized comparison of TAVI valves: The Compare-TAVI trial

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Introduction Based on technical advancements and clinical evidence, transcatheter aortic valve implantation (TAVI) has been widely adopted. New generation TAVI valve platforms are continually being developed. Ideally, new valves should be superior or at least non-inferior regarding efficacy and safety, when compared to best-in-practice contemporary TAVI valves.

Methods and analysis The Compare-TAVI trial (ClinicalTrials.gov NCT04443023) was launched in 2020, to perform a 1:1 randomized comparison of new vs contemporary TAVI valves, preferably in all comers. Consecutive cohorts will be launched with sample sizes depending on the choice of interim analyses, expected event rates, and chosen superiority or non-inferiority margins. Enrollment has just been finalized in cohort B, comparing the Sapien 3/Sapien 3 Ultra Transcatheter Heart Valve (THV) series (Edwards Lifesciences, Irvine, California, USA) and the Myval/Myval Octacor THV series (Meril Life Sciences Pvt. Ltd., Vapi, Gujarat, India) balloon expandable valves. This non-inferiority study was aimed to include 1062 patients. The 1-year composite safety and efficacy endpoint comprises death, stroke, moderate-severe aortic regurgitation, and moderate-severe valve deterioration. Patients will be followed until withdrawal of consent, death, or completion of 10-year follow-up, whichever comes first. Secondary endpoints will be monitored at 30 days, 1, 3, 5, and 10 years.

Summary The Compare-TAVI organization will launch consecutive cohorts wherein patients scheduled for TAVI are randomized to one of two valves. The aim is to ensure that the short- and long-term performance and safety of new valves being introduced is benchmarked against what achieved by best-in-practice contemporary valves. (Am Heart J 2024;274:84–94.)

Background

Transcatheter aortic valve implantation (TAVI) was invented more than 30 years ago.[1-3] TAVI has since become widespread adopted in clinical practice. Despite initially being reserved for high-risk patients who were not candidates for open heart surgery,[4] use of TAVI is now expanding to low-risk patients as well as patients with failing bio-prostheses.[5-7] An increasing number of TAVI valve platforms are available.[5,7-14] Because of continual valve refinement, most valves have only short-term outcome data available, and few have moderate-term data, whereas valves with available long-term data are often no longer on the market.[15] Ideally, the performance of new valves should always be compared head-to-head with that of best-in-practice commercially available valves.

The Compare-TAVI trial is a study framework for direct comparison of TAVI valves. The purpose is to compare the short- and long-term performance, as well as long-term durability, of various TAVI valves. Through the Compare-TAVI trial framework, patients can be randomized to different valves in different cohorts running simultaneously or sequentially. Currently, ethical approval has been obtained for the following cohorts:

Cohort A: Sapien 3/Sapien 3 Ultra (Edwards Lifesciences, Irvine, California, USA) THV series vs Acurate neo 2 (Boston Scientific, Marlborough, Massachusetts, USA) THV (not enrolling, awaiting funding).

Cohort B: Sapien 3/Sapien 3 Ultra (Edwards Lifesciences, Irvine, California, USA) THV series vs My-

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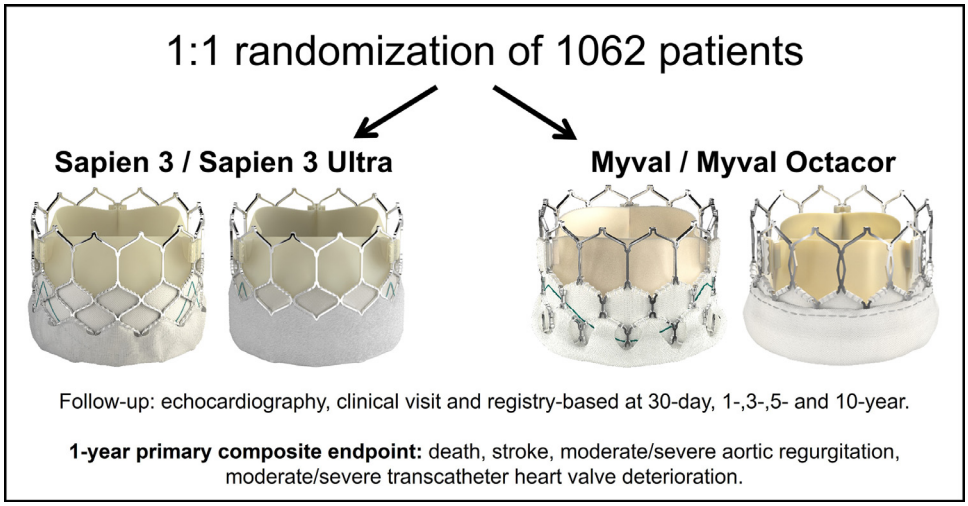
Figure 1. Compare-TAVI, cohort B.



val/Myval Octacor THV series (Meril Life Sciences Pvt. Ltd., Vapi, Gujarat, India) (Enrollment completed November 2, 2023).

Herein, the Compare-TAVI trial for randomized comparison of TAVI valves is presented in compliance with the SPIRIT 13 guidance for protocols.[16] There may be details only relevant for one cohort which is then highlighted.

Administrative information

Trial registration

Each cohort will be registered at clinicaltrials.gov when enrollment is initiated. Currently, cohort B has been registered (NCT04443023) (Figure 1).

Protocol version

Ethical approval was initially applied for on October 9, 2017, and was obtained March 3, 2018, based on a revised protocol submitted on February 25, 2018. Amendments have since been filed for approval of computerized tomography (CT) and cardiac magnetic resonance (CMR) substudies, and protocol changes to adhere to the most recent Valve Academic Research Consortium (VARC) 3 criteria.[17] The current protocol version is "Randomized comparison of TAVI valves, version 6.5.2023, amendment 10," submitted for ethical approval May 6, 2023, and approved May 30, 2023.

Funding

The study is investigator-initiated. The Danish Heart Foundation has given an unrestricted grant to the Compare-TAVI organization. Applications for funding will be sent to companies manufacturing TAVI valves. Cohort B is currently sponsored by Meril Life Sciences Pvt. Ltd., Vapi, Gujarat, India; the Central Denmark Region; and Vingmed Vicare A/S, Birkerød, Denmark.

Roles and responsibilities

The research unit at the Department of Cardiology, Aarhus University Hospital, Denmark is the sponsor and coordinating center. This unit is responsible for the electronic Case Report Form (eCRF) for the trial, collecting data, monitoring the study, the coordination of safety committee meetings, endpoint adjudication meetings, and steering committee meetings, and drafting of initial manuscripts.

For each cohort, a steering committee is established with one representative from each center randomizing patients in that cohort. A separate safety committee is established for each cohort. The members are physicians not implanting TAVI valves, and an epidemiologist and statistician from the Department of Clinical Epidemiology, Aarhus University, Denmark. An endpoint committee is established to adjudicate selected endpoints (stroke, readmission with congestive heart failure, acute myocardial infarction, and endocarditis). For adjudication of stroke, two neurologists represent the endpoint committee, according to VARC-3 recommendations.[17] For adjudication of the remaining endpoints, two cardiologists not implanting TAVI valves constitute the endpoint committee.

Monitoring of the study is performed by trained monitors following a separate monitoring plan (Appendix A).

Study setting

European centers performing more than 75 TAVI procedures per year are eligible to participate. Operators are

Table 1. Inclusion criteria for cohort B comparing Sapien 3/Sapien 3 ultra THV series vs Myval/Myval Octacor THV series balloon-expandable valves

1. Patients older than 18 years.
2. Patients eligible for treatment with both valves being compared according to a TAVI heart team conference.
3. Operator experience for each considered valve comprising more than 15 cases per year and at least 15 valves implanted before a valve can be used in the trial.
4. Center volume exceeding 75 cases per year.
5. Patient provision of signed informed consent.
6. TAVI performed via the femoral artery.

THV: Transcatheter heart valve; TAVI: transcatheter aortic valve implantation.

required to have implanted at least 15 of each valve being compared before including patients in the trial (Table 1).

Eligibility criteria

The inclusion criteria for cohort B are shown in Table 1. Cohort B is aimed at including all-comer patients. The cohort comprises only patients scheduled for transfemoral access.[6] Additional inclusion/exclusion criteria may apply to new cohorts, if one or both valves being compared are not eligible for all-comer use.

Interventions

The TAVI procedures are performed according to usual clinical practice at the participating centers.

Endpoints

Primary and secondary endpoints are presented in Table 2. Updated definitions from the VARC and Bleeding Academic Research Consortium (BARC) will be applied [6,7]. Additional endpoints may apply to new cohorts.

Participant timeline

Patients with symptomatic aortic stenosis or failing aortic bioprostheses planned to undergo TAVI are screened for study eligibility. Eligible patients provide oral and written consent to participate in the main trial and substudies. Currently, a CT substudy and a CMR substudy are approved for cohort B (Table 2, Figure 2). Randomization is performed as close to the time of treatment as possible, preferably on the day of valve implantation. Clinical and echocardiographic evaluation is performed at baseline, before discharge, and after 30 days, 1, 3, 5, and 10 years (Table 2). A standardized protocol for echocardiography was established by the echocardiography core laboratory (Appendix B). Endpoints are assessed in relation to clinical and echocardiographic follow-up, and from registries (Table 2). In the current CT substudy, CT is performed at the 30-day and 1-year follow-up (Figure 2). In the current CMR substudy, CMR is performed at the 30-day follow-up (Figure 2).

Sample size

A steering committee determines the size of each cohort (randomized comparison between two valves). In the initial cohorts (A+B), a non-inferiority design was chosen for comparison of the 1-year primary composite safety and efficacy endpoint (death, stroke, moderate-severe aortic regurgitation, and moderate-severe valve deterioration). The study size depend on expected event rate, chosen non-inferiority margin, number of interim analyses, and expected drop-out (Table 3). Registry data (from national reports from The Western Denmark Heart Registry and The Danish Heart Registry) have indicated a 1-year mortality rate of 6%, 1-year stroke rate of 2%, and moderate-severe aortic regurgitation rate of 1.5% in the unselected cohort of patients treated with TAVI. No data are available on moderate-severe THV deterioration at 1-year, but we assumed that this rate would also be <1.5%. Because of competing risk, and because event rates are usually lower in patients consenting to trial participation, we anticipated an overall 1-year event rate for the primary composite endpoint of approximately 9%. When designing the study, the steering committee advocated for a higher sample size and two interim analyses in cohort A, planning for inclusion of self-expandable valves, because several studies had indicated higher rates of aortic regurgitation with the use of self-expandable valves.[8,9,18] Accordingly, in cohort A, 1346 patients were scheduled for enrollment to allow for two interim analyses, and a non-inferiority margin of 4%, 4.4%, or 4.7%, if the final event rate was 9%, 11%, or 13%, respectively. For cohort B, the initial sample size was set to 1062, to allow for a non-inferiority margin of 4%, 4.5%, or 5% if the event rates were 7, 9, or 11%, respectively (Table 3). Many previous non-inferiority trials have experienced event rates lower than expected.[19] If the final event rate differs significantly from the expected rate, the steering committee may decide to adjust either the non-inferiority margin or the sample size accordingly (Table 3). If two interim analyses are chosen, the safety committee must compare the primary safety and efficacy outcome after inclusion of approximately 1/3 and 2/3 of patients. If one valve is not clearly inferior, randomization will continue until the complete cohort is included. If no interim analyses are chosen, the safety committee will still have full access to the data, but no pre-specified comparison of the primary safety and efficacy outcome will be performed. The safety committee will provide recommendations to the

Table 2. Study endpoints implemented in cohort B comparing Sapien 3 / Sapien 3 Ultra THV series versus Myval/Myval Octacor THV series balloon expandable valves.

Primary composite safety and efficacy endpoint for main study (non-inferiority analyses, see power calculation):

1. Mortality, stroke, moderate-severe aortic regurgitation, or moderate/severe THV deterioration at 1 year, according to VARC-3 criteria

The composite endpoint will be re-analyzed after 3-, 5- and 10-year. Separate analyses of each component of the primary outcome will be presented, to better understand their contribution to the primary endpoint.

Secondary safety and efficacy endpoints for main study (Bonferroni correction, multiple comparisons):

1. TAVI-related complications: conversion to open surgery during implantation, unplanned use of cardiopulmonary support, coronary artery obstruction, ventricular septal perforation, mitral valve apparatus damage or dysfunction, cardiac tamponade, valve embolization, valve migration, or need for TAVI-in-TAVI deployment, according to VARC-3 criteria, or annulus rupture, aortic rupture/perforation, aortic dissection, other shunts than VSD.
2. Proportion with successful implantation of the chosen valve, i.e., no need for more than one TAVI valve, no change to an unplanned valve during the procedure because implantation of the planned valve was impossible, and no conversion to surgery or procedure-related death.
3. Pacemaker implantation: New pace-maker implantation either prophylactic before TAVI (<1 month before) or within 1-year following TAVI.

Exploratory secondary endpoints (hypothesis generating only):Procedural and early in-hospital complications:

1. Major vascular access site and access-related complications resulting in endovascular or open surgery, according to VARC-3 criteria during admission and within 30 days.
2. Major bleeding resulting in a decrease in Hgb level ≥1.86 mmol/l and/or erythrocyte transfusion with ≥ 2 units, during admission: 30 day, according to BARC type 3 or 5 criteria corresponding to type 2–4 VARC-3 criteria.

Bioprosthetic valve dysfunction:

1. Endocarditis, 30 day, 1, 3, 5 and 10 years.
2. Reoperation (TAVR, SAVR, or BAV), 30 day, 1, 3, 5, and 10 years, according to VARC-3 criteria.
3. Moderate/severe prosthesis-patient mismatch: effective orifice area/body surface area ≤0.70 cm^2/m^2 if BMI≥ 30 kg/m^2 and ≤0.85 cm^2/m^2 if BMI<30 kg/m^2, at 30 day, 1, 3, 5 and 10 years, according to VARC-3 criteria.

Readmissions, clinical and paraclinical findings:

1. Pacemaker implantation: during admission, 30 day, 1, 3, 5 and 10 years.
2. Readmission for congestive heart failure: 30 day, 1, 3, 5 and 10 years.
3. AMI: 30 day, 1, 3, 5 and 10 years, according to VARC-3 criteria.
4. PCI or CABG (not scheduled before TAVI): 30 day, 1, 3, 5 and 10 years, according to VARC-3 criteria.
5. Newly diagnosed atrial fibrillation/flutter: 30 day, 1, 3, 5 and 10 years, according to VARC-3 criteria
6. Increase in renal creatinine level to ≥200% (AKIN stage 2–3, VARC-3 criteria) or dialysis (AKIN stage 4): during admission and within 30 days.
7. 6-minute walk test: 30 day, 1, 3, 5 and 10 years.

Primary outcome for CT substudy:

1. HALT assessed by CT at 30 days and 12 months.

Secondary outcome for CT substudy:

1. Commisural and coronary alignment

Primary outcomes for CMR substudy:

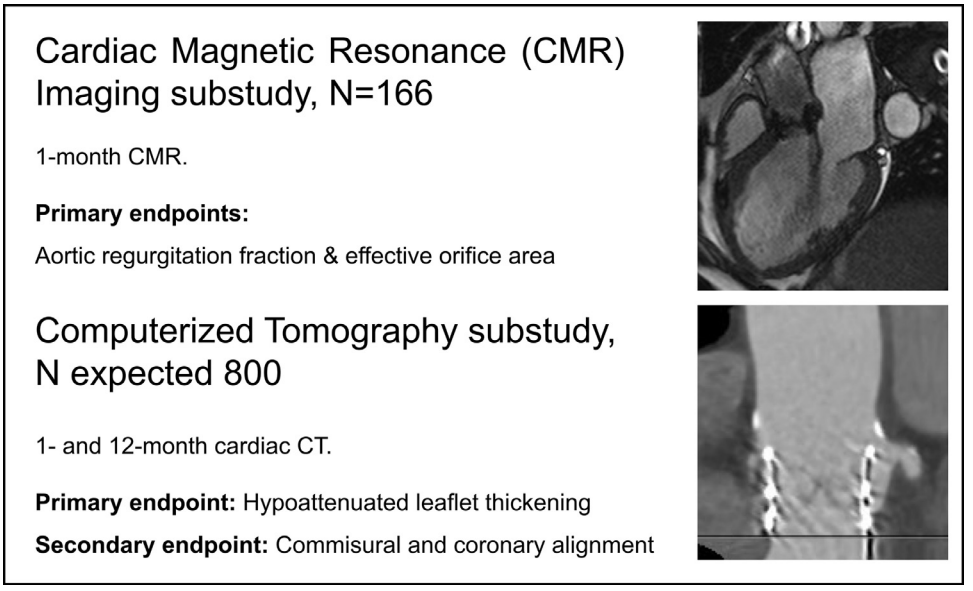
1. Aortic regurgitation fraction and Effective orifice area measured by CMR at 30 days.

AKIN: acute kidney injury. AMI: acute myocardial infarction. BARC: Bleeding Academic Research Consortium. BAV: balloon aortic valvuloplasty. CABG: coronary artery bypass grafting. CMR: cardiac magnetic resonance imaging. CT: computerized tomography. HALT: hypoattenuated leaflet thickening. PCI: percutaneous coronary intervention. SAVR: surgical aortic valve replacement. TAVI: transcatheter aortic valve implantation. THV: transcatheter heart valve. VARC-3: Valve Academic Research Consortium.

steering committee if serious safety issues are expected to arise. For each cohort, the maximal inclusion period is 3 years, and the first interim analysis (if planned according to the steering committee) will be performed no later than 2 years after inclusion. A cohort will also be closed for inclusion, if one of the study valves is removed from the market. The steering committee decides whether the study should be terminated, if one of the valves being compared is replaced by a new generation of the device.

The CMR substudy is initiated for each cohort, with the aim of evaluating effective orifice area (EOA), aortic regurgitation fraction (ARF), and aortic regurgitation volume 30 days after TAVI. If the expected EOA is 1.5 (SD 0.54) cm^2, and the expected ARF is 0.14 (SD 0.09), 148 patients are needed to document a 0.25 cm^2 difference

Figure 2. Pre-specified computerized tomography (CT) and cardiac magnetic resonance (CMR) imaging substudies for Compare-TAVI.



in EOA, and 102 patients are needed to document a 0.05 difference in expected ARF. We plan to include 166 patients, with an expected drop-out of 10% of patients. In the CT substudy, we aim to include as many patients as possible from each cohort, to evaluate the occurrence of HypoAttenuated Leaflet Thickening (HALT) after 30 days and 1 year. This substudy is descriptive.

Recruitment

The prerequisite for initiating a comparison between two valves is that at least 3 centers will randomize from the beginning of the study period, that at least 10 centers are expected to randomize in each cohort, and that each center aims to include at least 50 patients per year, to achieve an active inclusion period shorter than 3 years.

In general, centers including patients in the study are recommended to include all eligible patients willing to provide informed consent to participate. The aim is to obtain a study population as close to an all-comer population as possible.

Methods: Assignment of interventions

Allocation

Patients are randomized with www.corolog.net, an online portal for medical research enabling randomization and data registration. Randomization is stratified by sex and center.

Blinding

The trial is not blinded (open label). The patient records indicate the implanted valve. Core laboratories evaluate echocardiography, CMR, and CT data without information on the implanted valve. However, different valves may have differing appearances on imaging, thus potentially making truly blinded analyses impossible.

Methods: Data collection, management, and analysis

Data collection methods

The website www.corolog.net is used for the eCRF. Patient and procedural characteristics as well as follow-up data and events will be entered in the eCRF. Follow-up visits are planned at 30 days, 1, 3, 5, and 10 years. When possible, depending on the participating centers and countries, events will also be collected from registries. For cohort B, only including patients in Denmark, events are also collected from the Danish Civil Registration registry (daily update of vital status for all citizens), the Danish National Patient Registry, and The Western Denmark Heart Registry, and cross-checked against the events registered at follow-up.[20-22] Events of moderate-severe aortic regurgitation, moderate-severe THV deterioration, EOA, ARF, presence of thrombus, or HALT will be registered by the echocardiography, CMR and CT core laboratories. Event committees adjudicate the following events: stroke, AMI, readmission with congestive heart failure, and endocarditis, according to VARC-3 criteria.[17] Procedure-related complications will be manually collected from electronic patient files. Because of the use of comprehensive Danish registries, and access to clinical follow-up data in electronic patient files, loss to follow-up is expected to be low in cohort B. When launching

Table 3. Event rates, non-inferiority margins, and sample sizes estimated for non-inferiority studies with and without drop-out, and with and without interim analyses. Power = 0.80. Alpha = 0.05

Event rate	Non-inferiority margin	Relative non-inferiority margin	No drop-out, no interim analysis	No drop-out, two interim analyses	5% drop-out, no interim analyses	5% drop-out, two interim analyses
		Closest non-inferiority margin (1.decimal) if no. of included patients is 1062, without interim analyses and with 5% drop-out (as planned in cohort B)				
7	~4.0	0.57			1062	
9	~4.5	0.50				
11	~5.0	0.45				
13	~5.3	0.41				
		Closest non-inferiority margin (1.decimal) if no. of included patients is 1346, with two interim analyses and 5% drop-out (as planned in cohort A)				
7	~3.6	0.52				1346
9	~4,0	0.44				
11	~4,4	0,40				
13	~4,7	0,36				
			Study size if fixed non-inferiority margin = 4%			
7	4	0.57	1008	1017	1062	1070
9		0.44	1268	1279	1335	1346
11		0.36	1514	1527	1594	1607
13		0.31	1750	1764	1843	1857
			Study size if fixed non-inferiority margin = 4.5%			
7	4.5	0.64	796	803	838	845
9		0.50	1002	1011	1055	1064
11		0.41	1198	1208	1262	1272
13		0.35	1382	1394	1455	1467
			Study size if fixed non-inferiority margin = 5.0%			
7	5.0	0.71	646	651	680	685
9		0.56	812	818	855	862
11		0.45	970	978	1021	1029
13		0.38	1120	1129	1179	1188

future cohorts, we aim to include centers who have similar registries, to ensure complete follow-up.

Data management

An online research portal used for randomization and data management (www.corolog.net), has been approved by the Danish Data Protection Agency. Data entry and access will be logged.

Statistical methods

Data will be analyzed according to the intention-to-treat principle, but per-protocol analyses will also be performed if cross-over is observed.[19] In the comparison of primary endpoints, a non-inferiority analysis will be used for the current cohorts A and B. In the comparison of secondary safety and efficacy endpoints, Bonferroni correction will be used for multiple testing. Additional secondary endpoints are explorative and thus hypothesis-generating only (Table 2). Continuous data will be presented as mean ± SD if normally distributed, and otherwise as median (IQR). Comparison will be made with the Student t-test or Mann-Whitney U test, as appropriate. Categorical variables will be compared with Fisher's exact test or chi-square test, and data will be presented as numbers and percentages. The significance level is $P < .05$ (two sided). Cox regression and logistic regression analyses will be used as appropriate. Kaplan-Meier curves will be used for graphical presentation of time to events.

Methods: Monitoring

Data monitoring

Monitoring of the study will involve a combination of on-site monitoring and central monitoring. The monitors will follow a separate monitoring plan (Appendix A). The

sponsor will regularly provide sites with lists of "missing data."

Harms: The following events are filed to the Ethical Committee: (1) structural THV deterioration resulting in repeated TAVI or SAVR within 3 years, (2) death within 3 years, (3) endocarditis within 30 days, (4) stroke within 30 days, (5) vascular surgery associated with the access site within 30 days, and (6) device failures (embolization or use of more than one valve during index treatment).

Auditing: The Ethical Committee can choose to undertake auditing; in which case the Committee will be granted access to all data.

Ethics and dissemination

Research ethics approval

For all centers participating in a cohort, ethics committee approval will be obtained before the inclusion of participants. Any important protocol modifications will be sent to the ethics committee for approval. After approval, these modifications will be directly communicated to investigators.

Consent

Patients admitted for a TAVI procedure will be approached for inclusion in the study. The treating physician, or personnel delegated by the treating physician, as instructed by the primary investigator, will be responsible for inclusion of patients. Patient information will be provided in written and oral forms. Patients will be informed that they have time to consider inclusion, and that a relative or a third person may participate when information regarding the study is provided.

Patients are informed that they can withdraw their consent at any time. If consent is withdrawn, patients will be asked whether previously collected data can be used. If not, the data will be deleted. A patient's decision to withdraw consent will be filed in the patient record.

Confidentiality

All data in the eCRF are encrypted. Any access or attempt to access data will be logged. Investigators will allow for monitoring or auditing by the ethical committee or the data protection agency, as well as the national board of health. Investigators are responsible for ensuring that all patients have given written consent to access source data (the patient record). When a cohort is terminated, data will be merged and anonymized in compliance with Danish legislation. Data from Danish patients will be uploaded to the Secure Research Platform at the Danish Health Data Authority to allow for merging of data with data in the national registries.

Dissemination policy

Data for each cohort will be published after inclusion of the complete cohort, regardless of the final findings. If a valve is removed from clinical use, or the safety committee advocates for pre-term termination of patient randomization and the steering committee agrees, inclusion will be stopped, and the collected data will be published.

All individuals designated as authors will meet all four International Committee of Medical Journal Editors criteria for authorship. No professional writers will be used. The authors are solely responsible for the design and conduct of this study, all analyses, the drafting and editing of the paper and its final contents.

A separate publication is planned for 1, 3, 5, and 10-year data. For each cohort, substudies may be described and published. At the 30-day follow-up, only secondary outcomes are collected, but the steering committee may also decide to publish 30-day results.

Discussion

New TAVI valves are continually being introduced for commercial use, based on limited short-term performance data and no data on long-term durability. The Compare-TAVI organization was launched with the aim of comparing new generation TAVI valve with contemporary TAVI valves, to ensure that patients receive the best available valves, and that new valves are only accepted for routine clinical use if they demonstrate superiority or at least non-inferiority to the performance of best-in-class contemporary TAVI valves.

Previous randomized head-to-head comparisons of TAVI-valves have been hampered by very high non-inferiority margins, short follow-up, highly selected patients (eg, inclusion of less than 1 patient per site per month on average), and extensive exclusion criteria (Table 4).[8,9,18] Short follow-up and highly selected populations result in lower event rates than observed in daily clinical practice. A lower-than-expected event rate and/or a high non-inferiority margin often results in conclusions of non-inferiority among the THVs being compared, despite numerical differences in outcomes.[19] Such findings may be in the companies' interest and may convince clinicians to use new valves, even though the chosen non-inferiority margin is not clinically acceptable. A consensus agreement among the cardiac societies is warranted to guide the choice of clinically acceptable non-inferiority margins. The margin depends on the expected number of events included in the primary composite endpoints. Many studies have a large number of components in the primary endpoint to increase event rates and allow for shorter follow-up and smaller sample size. The inherent risk is that important endpoints like mortality is given same importance as non-fatal events. Given the current favorable outcome in patients treated with TAVI, a 2% difference in mortality or stroke between valves would probably be unacceptable, while acceptable for aortic regurgitation or new pacemaker implantations. For Compare-TAVI cohort B, we chose a

Table 4. Previous and ongoing randomized head-to-head comparison of TAVI valves

Trial	THVs being compared	Primary endpoint	Event rate	NI or EQ margins	Conclusion	No. patients per site per month (mean)	Bicuspid and ViV included
PORTICO-IDE,[9] *N* = 750	Portico vs Sapien or Evolut	Death, disabling stroke, life-threatening bleeding requiring transfusion, acute kidney injury requiring dialysis, or major vascular complications at 30 days	13.8 vs 9.6%	NI = 8.5	Non-inferiority not met for Portico	0.4	No
REPRISE-III,[26] *N* = 912	Lotus vs Evolut	Death, stroke, life-threatening/major bleeding, stage 2/3 acute kidney injury, and major vascular complications at 30 days.	20.3 vs 17.2%	NI = 10.5	Non-inferiority met for Lotus	1.1	No
SCOPE-I,[8] *N* = 739	Acurate vs Sapien	Death, stroke, life-threatening or disabling bleeding, major vascular complications, coronary artery obstruction requiring intervention, stage 2 or 3 acute kidney injury, rehospitalization for valve-related symptoms or congestive heart failure, THV dysfunction requiring repeated procedure, moderate-severe PVL, or moderate-severe THV stenosis within 30 days	23.7% vs 16.5%	NI = 7.7	Non-inferiority not met for Acurate. Superiority met for Sapien.	1.5	No
SCOPE-II,[18] *N* = 796	Acurate vs Evolut	Death or stroke at 1 year	15.8% vs 13.9%	NI = 6.0	Non-inferiority not met for Acurate	1.4	No
SOLVE-TAVI,[27] *N* = 438	Evolut vs Sapien	Mortality, stroke, moderate-severe PVL, or permanent pacemaker implantation at 30 days	28.4% vs 26.1%	EQ = 10%	BEV and SEV equivalent	2.6	Yes
SMART,[28] *N* = 716	Evolut vs Sapien	Mortality, disabling stroke, readmission with congestive heart failure at 1-year.	9.4 % vs 10.6%	NI = 8.0	SEV non-inferior	0.6	Yes
LANDMARK,[11] *N* = 768	Myval vs Sapien or Evolut	Death, stroke, life-threatening or disabling bleeding, stage 2 or 3 acute kidney Injury, major vascular complications, moderate-severe PVL, or new pacemaker implantation at 30 days		NI = 10.4	Inclusion finalized	NA	No
Compare-TAVI cohort B, *N* = 1062[29]	Myval vs Sapien	Death, stroke, moderate-severe aortic regurgitation, or moderate-severe THV deterioration at 1 year		NI = 4.5 if event rate 9%.	Inclusion finalized	NA	Yes
BEST trial, *N* = 1862[30]	Evolut vs Sapien	Mortality at 90 days		NA	Ongoing	NA	Not ViV

BEV: balloon expandable valves; EQ: equivalence; NA: Not available; NI: non-inferiority; PVL: paravalvular leakage; SEV: self-expandable valves; THV: transcatheter heart valve; ViV: valve-in-valve; TAVI: Transcatheter Aortic Valve Implantation.

non-inferiority margin of 4.5% (expected event rate 9%) which is the lowest non-inferiority margin in any head-to-head comparisons of THVs to date (Table 4). Importantly, the non-inferiority margin represents the upper confidence interval of the observed difference in event rate, ie, to demonstrate non-inferiority, the observed difference in event rate should be considerably lower than the 4.5% non-inferiority margin. Predicting the event rate is challenging, and thus the observed and expected event rates often differed in previous studies. In COMPARE

TAVI cohort B, the estimated event rates were based on national registries. However, since no previous study included THV deterioration in the composite primary endpoint the expected event rate of this component is unknown. If the observed event rates in the COMPARE TAVI studies differ significantly from what expected, the steering committee may consider changing either the sample size or the non-inferiority margin.

Previous and other ongoing head-to-head comparisons have implemented a wide range of events in the primary composite endpoint. All trials have consistently indicated that death and stroke should be included in a combined safety and efficacy endpoint, given that these complications are the most feared among patients. For low-risk patients, a tendency to focus not only on these hard clinical endpoints but also on longer-term prosthetic valve function has been suggested.[17] Therefore, we chose to combine mortality, stroke, moderate-severe aortic regurgitation, and moderate-severe THV deterioration in the combined safety and efficacy endpoint. Assessment of THV deterioration requires at least 1-year follow-up, according to the VARC-3 criteria.[17] Event components such as, eg, bleeding, pacemaker implantation, and other complications may not to a similar degree reflect long-term THV performance or impact outcome, hence we decided not to include these in the composite primary.

The Compare-TAVI organization was facilitated by a yearlong history of conducting head-to-head comparisons of stents in the Danish SORT-OUT organization.[23,24] It was further supported by experiencing suboptimal moderate- and long-term durability of a surgical valve which previously won a tender in Denmark.[25] Finally, the most recent tender conducted in western Denmark was won partly by a THV that soon thereafter was found to be inferior in a head-to-head comparison with another valve.[8] These findings support during a tender process the need for a proper balance to be struck between economic interests and the documented quality of the THVs in question. The introduction of new THVs should be possible, but only if their performance is compared with that of the best-in-practice contemporary valves. Based on prior head-to-head comparisons,[8,9,18] the Sapien 3 THV series was acknowledged as first-in-class, and therefore was selected as the comparator in the first COMPARE TAVI cohorts launched.

We aimed to include all-comers in COMPARE TAVI cohort B, hence a limited number of selection criteria was included. Moreover, any patient found to be eligible for treatment with a Sapien 3/Sapien 3 Ultra THV should be eligible for inclusion and randomization to a Myval/Myval Octacor THV. Notably, patient selection is not based on valve anatomy (eg, bicuspid and valve-in valve TAVI procedures also qualified for inclusion), or timing of procedure (eg, subacute and in-hospital cases were also eligible). The limited number of selection criteria has also resulted in a very high inclusion rate. The present study design contrasts with the majority of prior and ongoing head-to-head THV comparisons excluding these patient categories, thereby limiting findings to selected low-risk patients rather than reflecting daily clinical practice[8,9,11,18] (Table 4). Accordingly, the Compare-TAVI cohort B will be the first all-comer head-to-head comparison of two THVs.

Summary

The Compare-TAVI organization will launch consecutive cohorts, wherein patients scheduled for TAVI are randomized to receive one of two valves. The aim is to ensure that the short- and long-term performance and safety of new valves being introduced are benchmarked against the performance of best-in-practice contemporary valves.

Disclosures

CJT reports previous proctoring or lecture fees from Boston, Edwards, Meril, and Terumo, and research grants from Meril and Terumo. EHC reports previous proctoring or lecture fees from Boston, Edwards, Meril, and Abbott, and research grants from Abbott. HNI report previous proctoring or lecture fees from Edwards and Meril. PF report proctoring or lecture fees from Abbott, Edwards, and Meril, and research grants from Astra Zeneca. TT reports lecture fees from Chiesi and Terumo. The other coauthors have no disclosures.

Declaration of competing interest

Funding parties, including companies producing TAVI valves, will have no influence on study design or conduct. The ethical committees will be informed of any study support, and any contract regarding financial support must be approved by institutional legal departments. No honoraria will be given to the patients, or to the physicians or investigators responsible for the study. Grants will be used to conduct the study (eg, data handling, and salaries for study personnel) and to present the data.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2024.05.003.

CRediT authorship contribution statement

Christian Juhl Terkelsen: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Troels Thim:**

Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Philip Freeman:** Writing – review & editing, Project administration, Investigation, Data curation. **Jordi Sanchez Dahl:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Bjarne Linde Nørgaard:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Won-Yong Kim:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Mariann Tang:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Henrik Toft Sørensen:** Writing – review & editing, Supervision, Methodology, Formal analysis. **Evald Høj Christiansen:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Henrik Nissen:** Writing – review & editing, Resources, Project administration, Investigation, Funding acquisition, Data curation.

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