Randomized comparison of eligible TAVI-valves

The Compare-TAVI trial

Protocol v. 6.5.2023

In each country, a national investigator is responsible for ethical approval.

When filing the national ethical committee, only national co-investigators are put on the application.

Separate core labs will be established for Echo, HCT, MRI and aortography (Videodensitometry).

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The Principal Investigator and one co-investigator from each participating center will join the steering committee. The following centers and co-investigators are currently including in cohort B.

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Background: Transcatheter Aortic Valve Implantation (TAVI) is a method where an artificial heart valve is implanted through a. femoralis (the groin) or via alternative access (apical, transcaval, axillaris, direct aorta), instead of conventional surgery. TAVI is the routine treatment for in-operable and high-surgical risk patients, and is increasingly used in patients with low and intermediate surgical risk (1, 2). In Denmark, approximately 1000 TAVI valves are implanted each year. In Europe yearly implantation mounts to more than 50.000 TAVI devices. Although a considerable number of TAVI valves have been introduced, there are few direct comparisons of the valves. The 5 most widely used valves are: Sapien (Edwards)(2), Evolut (Medtronic) (3), Navitor/Portico (Abbott) (4, 5) and Acurate (Boston) (6, 7). New TAVI-valves are routinely introduced to the market. Recently, Myval (Meril) (8) and Allegra (New Valve Technology) (9) were launched.

The larger TAVI-centers are routinely using 2-4 different valves, and the majority of patients are eligible for treatment with more than one valve.

The purpose of the "Compare-TAVI" organization is to ensure a continuous comparison of the TAVI-valves implanted, and to monitor long-term valve performances.

Purpose: To compare outcome in patients randomized to treatment with one of two TAVI-valves.

Hypotheses:

1. There is no difference in the combined endpoint (death, stroke, moderate/severe para-valvular leakage, moderate/severe valve deterioration) between the two valves being compared.
2. There is no difference between valves in secondary endpoints: death, stroke, moderate/major paravalvular leakage, moderate/severe valve deterioration, new pacemaker implantation, readmission for congestive heart failure, 6-minute walk test, and degeneration of the valve as evaluated by

computerized tomography (CT), transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), or MRI.

Design: Randomized controlled trial with clinical and national registry follow-up.

Inclusion criteria:

1. Patient more than 18 years of age.
2. Patient eligible for at least 2 valves being implanted routinely at the participating center, according to a TAVI heart team conference.
3. The center experience for each of the valves considered should be more than 15 cases a year, and the treating physician should have implanted at least 15 of each valves used in the trial.
4. The center volume should be more than 75 cases a year.
5. The patient has given signed informed consent.
6. TAVI performed via the femoral artery.

Centers eligible for inclusion: Scandinavian and European centers who fulfill the above mentioned criteria.

Randomization:

Before randomizing patients, the center decides which two valves the patient is found eligible for, and enters these valves in the electronic randomization form (TrialPartner). Randomization is then performed between these two valves. A patient is only randomized if a dedicated technical TAVI conference has found the patient eligible for treatment with both valves.

Consecutive cohorts are established.

We plan to initiate the following cohorts:

Cohort A: Patients randomized to the Sapien or the Accurate neo 2 TAVI valve (Approved, not recruiting, await funding).

Cohort B: Patients randomized to the Sapien or the Myval TAVI valve (Recruiting).

Cohort C: Patients randomized to a BEV valve (To be determined whether Sapien or Myval) compared to the Navitor valve (Awaits approval and funding).

Operator requirements:

Any procedure requires that the physician has performed at least 15 implantations with the valve in use. Otherwise the procedure is performed according to the routine of the institution.

Primary endpoints, for each cohort:

1. MACE: Mortality, stroke, moderate/major PVL, moderate/severe valve deterioration at 1 year, using VARC-3 criteria (10).

Secondary endpoints, for each cohort:

1. MACE: Mortality, stroke, moderate/major PVL, moderate/severe valve deterioration at 30-day, 3-year, 5-year and 10-year, using VARC-3 criteria (10).
2. Mortality: 30-day, 1-year, 3-year, 5-year and 10-year.
3. Stroke: During admission, 30-day, 1-year, 3-year, 5-year and 10-year, using VARC-3 criteria (10).
4. Moderate or severe PVL: 30-day, 1-year, 3-year, 5-year and 10-year, using VARC-3 criteria (10).
5. Moderate or major valve deterioration: 30-day, 1-year, 3-year, 5-year and 10-year, using VARC-3 criteria (10).
6. Pacemaker-implantation: during admission, 30-day, 1-year, 3-year, 5-year and 10-year.
7. Major bleeding resulting in drop in hgb-level ≥1.86 mmol/l and/or erythrocyte transfusion ≥ 2 units: during admission, 30-day, 1-year, 3-year, 5-year and 10-year, modified from BARC type 3-5 criteria (11, 12).
8. 6-minute walk test: baseline, 30-day, 1-year, 3-year, 5-year and 10-year.
9. Other TAVI-related complications: conversion to open surgery during implantation, unplanned use of cardiopulmonary support (CPS), coronary artery obstruction, ventricular septal perforation, mitral valve apparatus damage or dysfunction, cardiac tamponade, valve embolization, valve migration, need for TAVI-in-TAVI deployment, using VARC-3 criteria (10).
10. Other TAVI-related complications: Annulus rupture, Aortic rupture.
11. Endocarditis, 30-day, 1-year, 3-year, 5-year, 10-year.
12. Proportion with successful implantation of the chosen valve. This means no need for more than 1 TAVI valve, no change to another valve than planned during the procedure because it was impossible to implant the valve planned, and no conversion to surgery or procedure-related death.
13. Major vascular access site and access-related complications resulting in endovascular or open surgery using VARC-3 criteria during admission and at day 30 (10).
14. Occurrence of valve thrombosis or severe stenosis (confirmed by TEE, TTE or CT), 30-day, 1-year, 3-year, 5-year and 10-year.
15. Readmission for congestive heart failure: 30-day, 1-year, 3-year, 5-year or 10-year.
16. Increase in renal creatinine level more than to ≥200% (AKIN stage 2-3, VARC-3 criteria) or resulting in dialysis (AKIN stage 4) according to VARC-3 criteria: during admission and at day 30 (10).

17. Severity of PVL stratified according to level of annular calcium on CT (low/medium/high) at day 30.
18. Gradient (AO) stratified according to level of annular calcium on CT (low/medium/high) at day 30.
19. Prosthesis-patient mismatch (EOA/body surface area). Severe PPM≤0.65 cm2/m2. Moderate PPM≤0.85 cm2/m2, 30-day, 1-year, 3-year, 5-year and 10-year according to VARC-3 criteria (10).
20. Effective orifice area and volume of aortic regurgitation measured by MRI at 1 month (only patients included in MRI sub-study).
21. Leaflet thickening (hypoathenuated leaflet thickening = HALT) or reduced leaflet motion or thrombus assessed by HCT at 1 month and 12 month (only patients included in HCT sub-study).
22. Proportion with moderate or major commissural misalignment on 1 month HCT (only patients included in the HCT sub-study)
23. AMI, 30-day, 1-year, 3-year, 5-year and 10-year according to VARC-3 criteria (10).
24. PCI (not scheduled before TAVI), 30-day, 1-year, 3-year, 5-year and 10-year according to VARC-3 criteria (10).
25. CABG (not scheduled before TAVI), 30-day, 1-year, 3-year, 5-year and 10-year according to VARC-3 criteria (10).
26. Reoperation (TAVR,SAVR,BAV), 30-day, 1-year, 3-year, 5-year and 10-year according to VARC-3 criteria (10).
27. Newly diagnosed atrial fibrillation/flutter, 30-day, 1-year, 3-year, 5-year and 10-year according to VARC-3 criteria (10).

Registration of endpoints:

The majority of endpoints are collected from national registries. An echo core-lab is established to evaluate echo parameters (degree of PVL moderate/severe, valve deterioration, thrombosis). A CT core-lab is established to evaluate CT parameters (leaflet thickening, reduced leaflet motion, leaflet thrombosis, coronary alignment). An MRI core lab is established to evaluate MRI parameters (EOA and volume of aortic regurgitation). A separate core lab is established for analysis of aortaograms (videodensitometry) following TAVI. Procedure-related complications are manually collected from electronic patient files. At each follow-up (1-month, 1-year, 3-year, 5-year, 10-year) each site also monitor events and file them in the ECRF, thus both site-reporting and registry-validation of events. Selected endpoints are adjudicated by an endpoint committee (Stroke, AMI, readmission with heart failure, endocarditis).

Power calculations:

For each cohort (randomized comparison between two valves) the steering committee decides to perform the study with or without interim analyses. In case interim analyses is chosen, a safety committee will compare outcome after inclusion of approximately 1/3 and 2/3 of patients (interim analyses). If one valve is

not clearly inferior, randomization will continue until the complete cohort is included. The size of the cohort is dependent of expected event-rate, chosen non-inferiority margin, number of interim analyses and expected drop-out. See table below. With 2 interim analyses and a non-inferiority margin of 4%, event rate 9% and expected drop out of 5% the sample size should be 1346 patients. If including 1062 patients as planned in cohort B, and with no interim analyses and 5% drop-out, the non-inferiority margin would be 4% if the event-rate is 7% and 4.5% if the event rate is 9%. If the observed event-rate differ significantly from the expected, the steering committee should consider adjusting sample size or non-inferiority margin (see table below).

Table: Various 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. Alfa=0.05.

Event rate	Non-inferiority margin	Relative non-inferiority margin	No drop-out, No interim-analysis	No drop-out, 2 interim-analyses	5% drop-out, no interim-analyses	5% drop-out, 2 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	1009	1017	**1062**	1071
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 1345, With interim analyses and 5% drop-out (As planned in cohort A)						
7	≈3.6	0.52	**1268**	**1279**	**1336**	**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

For the MRI-substudy evaluating the hemodynamics (EOA, aortic regurgitation fraction), the expected EOA is 1.5 (SD 0.54) cm2, and the expected regurgitation fraction 0.14 (SD expected to be 0.09). A total of 148 patients are needed to document a difference of 0.25 cm2 in EOA (1.5 to 1.25 cm2) and 102 patients to document a difference of 0.05 in expected regurgitation fraction (0.14 to 0.09). The initial plan was to include 166 patients with an expected drop-out of 10% of patients. After inclusion of the first 166 patients in the MRI-substudy, inclusion was on hold for 1 year, and Myval was replaced by Myval Octacor. It was therefore decided to include another cohort in the MRI-substudy, comparing Sapien with Myval Octacor. To account

for higher than expected drop-out, the ethical committee was applied and approved that the MRI-substudy cohort was increased up to 360 patients. A HCT-substudy is performed with expected 850 patients evaluating occurrence of HALT at 1-month and 1-year. This substudy is descriptive.

Criteria used to perform interim analysis before planned or terminate the study before planned:

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 after no later than two years of inclusion. A cohort will also be closed for inclusion, if one of the study valves is retracted from the market or replaced by a new generation of the device.

Number of centers and procedures per center: The prerequisite for initiating a comparison between two valves is that at least 3 centers will randomize from the beginning, that at least 10 centers are expected to randomize in each cohort, and that each center aims at including at least 50 patients per year.

Statistics: Data will be analyzed according to the intention-to-treat principle. Continuous data will be presented as mean ± SD, and compared using a t-test, if data are normally distributed. If data are not normally distributed the Mann Whitney U test will be used. Categorical variables will be compared using Fischers exact test or Chi-square test as appropriate, and data presented as numbers and percentages. Significance level is $p<0.05$ (double sided). When comparing primary endpoints, a non-inferiority analysis will be used. When comparing secondary endpoints, Cox regression and logistic regression analyses will be used, as appropriate. Kaplan-Meir curves will be used for graphical presentation of time to events.

Data management: Data will be collected and stored according to the Danish data protection legislation. TrialPartner will be used for the Electronic Case Report form (ECRF). Patient and procedural characteristics will be entered in the ECRF following the procedure and at time of discharge. Follow-up (30-day, 1-year, 3-year, 5-year and 10-year) will be conducted mainly registry based (CPR-registry, National patient registry, Invasive registry), but at each follow-up the site will also check for events, and file them in the ECRF. This will ensure two sources for event-registration. Regarding moderate and severe PVL, moderate and severe aortic stenosis, and presence of thrombus or leaflet thickening, data will be entered by the Echo and HCT core labs. MRI findings will be entered by the MRI core lab. TrialPartner is approved by the Danish data regulative, and data entry and access will be logged. When a cohort is terminated, data will be merged and anonymized and a key stored with the CPR-number.

Recruitment of patients and informed consent: Patients admitted for a TAVI procedure will be asked for inclusion in the study. No announcement will be performed. There is no economical compensation to the patients, except that transportation expenses can be covered for the follow-up visits. Patients will receive information regarding the study either in the out-patient clinic, or when they are admitted for preoperative assessment. The information will be given by a nurse, instructed by the investigator, or by the treating physician. Patient information will be written and oral. The patient will be informed that they may have time to consider inclusion, that a relative or a third person may participate, when information regarding the study is given. The patient is informed, that they may withdraw their consent at any time. All patients have been given written and oral information regarding the purpose, procedure, risk and benefit with the study. On

arrival to the operating room, the patient again will be given time to ask any question. A written informed consent is required before randomization.

Withdrawal from the study: A patient can at any time without reason withdraw their consent. The patient will be asked, if previously collected data can be used, and whether it is acceptable to follow them in the registries, even though they don't want to meet to follow-up visits. Otherwise data will be deleted. The patient's decision to withdraw will be filed in the patient record.

Ethical aspects, risk, side effects, benefit and harm when participating in the study:

It is not expected that any risk is associated with participation in the study. The procedures compared are routine procedures and only high-volume centers will participate, and patients will only be included if a heart team conference have found them eligible for treatment with the study valves.

None the less it is important to continuously monitor safety and quality of the valves. The present study will ensure continuous head-to-head comparisons of valves used routinely. There is no potential benefit for the single patient when participating. Scientifically, the benefit is quality assessment of the valves used routinely and publication of long-time follow-up. In case a valve performs inferior to its comparator, appropriate consequences will be taken. Historically, there are examples (Mitroflow surgical valve) that valves used for several years degenerated earlier than expected.

Biobank: No biobank is collected.

Blinding: The study is not blinded.

Data from patient records: As part of the study data on previous disease (hypertension, diabetes, stroke, myocardial infarction, congestive heart failure), age, sex, Echocardiographic findings, HCT-findings will be collected from the patient records. These data will only be used for study purposes, and will be anonymized when the study is terminated. In situations where these data cannot be collected from registries, they will be retrieved from patient records. The purpose is to use these data in anonymous form when publishing the final results.

Data management and approvals: The Danish Data protection legislation will be followed. The study will be filed to the Danish Data protection agency and the local Ethical committee, and filed to www.clinicaltrial.gov before inclusion starts. In Denmark the national board of health will applied for data from the CPR-registry and the national patient registry. Data can be shared in anonymous form for research purposes.

Access to data: Data is stored in TrialPartner. All data is encrypted. Any access or attempt to access data will be logged. Investigator/Institution will allow monitoring or audit from the ethical committee or the data protection agency as well as the national board of health who will be given access to source data and patient records. Investigator is responsible for ensuring that any patient has been given written consent to access source data (patient record).

Safety committee:

A separate safety committee is established for each cohort. The members are physicians not implanting TAVI-valves.

Event committee:

A separate event committee is established to adjudicate selected endpoints (Stroke, AMI, endocarditis, readmission with CHF).

Steering committee:

For each cohort a steering committee is established with one representative from each of the centers randomizing patients in this cohort. The chair is the physician who from the beginning is responsible for this cohort.

Coordinating center:

The research department at Aarhus University Hospital will be the coordinating center, and responsible for establishing a digital CRF for the trial, and responsible for collecting data, monitoring, coordinating safety committee, event committee and steering committee meetings and publications.

Economy/Funding:

Funds will be applied for support of the study. Each of the company's manufacturing TAVI valves will be applied for support. The companies will have no influence on the design or conduction of the study. If a grant is given the Ethical committee will be informed and any contract should be approved by Aarhus University Hospital. No honorary is given to the patients nor to the physicians responsible for the study. Any grant will be used to the conduct of the study, salary to study nurses/secretaries and presentation of data.

So far cohort B has been sponsored by Meril, The Danish Heart Foundation and Vingmed Vicare.

For new cohorts, the company providing the comparator valve will be applied for a grant to sponsor to cover all expenses in the study (payment of site, monitoring, various committee meetings, core-labs).

Publications:

Each cohort will be published after inclusion of 1.346 patients in case interim analysis is decided or 1.062 patients if no interim analysis is decided, independent of the final findings. If a valve is retracted from clinical use, or the safety committee advocates for pre-term termination of randomization, data will be published at this time. First authorship is given to the center with the highest number of included patients. Number of co-authorships to each center is given according to number of included patients. Core-labs are acknowledged with co-authorships. For each cohort, one physician is responsible for initiating the cohort and senior author on the paper. A separate publication will be performed for 30-day, 1-year, 3-year, 5-year and 10-year data.

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