Randomized comparison of Evolut FX versus Sapien 3 Ultra Resilia. The Compare-TAVI trial

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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 have currently agreed to participate the current Compare TAVI cohort (Evolut FX vesus Sapien 3 Ultra Resilia).

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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 1200 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 most 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 of present study:

To compare outcome in patients randomized to treatment with Evolut FX versus Sapien 3 Ultra Resilia.

Hypotheses:

1. Evolut FX is non-inferior to Edwards Sapien 3 Resilia with regard to the combined endpoint (death, stroke, moderate/severe aortic regurgitation, moderate/severe valve deterioration) between the two valves being compared.

2. There is no difference between valves in secondary safety and efficacy endpoints (see below)

3. There is no difference in Aortic Regurgitation fraction (ARF) and Effective Orifice Area (EOA) measured by CMR (CMR-substudy, N=166)

4. There is no difference in EOA measured invasively during dobutamine stress (hemodynamic substudy, N=440).

5. There is no difference in occurrence of Hypoathenuated Leaflet Thickening (HALT) measured by CT (CT-substudy, N=778).

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 valve 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.

Operator requirements:

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

Primary composite endpoints, for each cohort:

Primary composite endpoint (outcome): Mortality, stroke, moderate/major aortic regurgitation, moderate/severe THV deterioration at 1 year, using VARC-3 criteria [10].

Analyses of the primary composite endpoint and each component of the primary endpoint:

The primary composite endpoint is at one-year, and a non-inferiority test is performed. See separate statistical analysis plan. Separate analyses of each component of the primary outcome will be presented, in accordance with the FDA guidelines and EMA guidelines, i.e. mortality, stroke, moderate/severe aortic regurgitation and moderate/severe THV deterioration to better understand their contribution to the primary endpoint. If non-inferiority is proven for the primary composite endpoint, a split alfa is used to test for superiority if possible (alfa=0.025) and to test secondary safety and efficacy endpoints (Total alfa=0.025 for these). The composite endpoint will be re-analyzed after 3-, 5- and 10-year as superiority analyses.

<u>Secondary safety and efficacy endpoints (Bonferoni correction for multiple testing):</u>

1. **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 / pericardial effusion resulting in pericardiocentesis, valve embolization, valve migration, need for TAVI-in-TAVI deployment, using VARC-3 criteria [10], or annulus rupture, aortic rupture/perforation, aortic dissection, or other shunts than VSD.

2. **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.

3. **SMART criteria for bioprosthetic valve dysfunction through 12 months**: composed of the following components: (1) hemodynamic structural valve dysfunction, defined as aortic valve mean gradient ≥ 20 mmHg at any time up to the 12-month visit echo; (2) nonstructural valve dysfunction, defined as severe prosthesis-patient mismatch or ≥ moderate total aortic regurgitation at any time up to the 12-month visit echo; (3) clinical valve thrombosis; (4) endocarditis; or (5) aortic valve reintervention.

4. **Pacemaker-implantation:** New pace-maker implantation within 1-year following TAVI.

Exploratory secondary endpoints for main trial (hypothesis-generating only):

Procedural and early in-hospital complications:

1. Major vascular access site and access-related complications resulting in endovascular or open surgery using VARC-3 criteria during admission and within 30-days [10].
2. 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].

Bioprosthetic valve dysfunction:

1. Endocarditis, 30-day, 1-year, 3-year, 5-year, 10-year.
2. Reoperation (TAVR,SAVR,BAV), 30-day, 1-year, 3-year, 5-year and 10-year according to VARC-3 criteria [10].

3. Moderate/severe prosthesis-patient mismatch: EOA/body surface area ≤0.85 cm2/m2 if BMI<30 kg/cm2 or <=0.70 cm2/m2 if BMI>=30 kg/cm2., at 30-day, 1-year, 3-year, 5-year and 10-year according to VARC-3 criteria [10].
4. Effective orifice area, 30-day, 1-year, 3-year, 5-year and 10-year as evaluated by Echo Core-lab.
5. Mean gradient, 30-day, 1-year, 3-year, 5-year and 10-year as evaluated by Echo Core-lab.

Readmissions, clinical and paraclinical findings:

1. Pacemaker-implantation: 30-day prior to TAVI, during admission, 30-day, 3-year, 5-year and 10-year following TAVI.
2. Readmission for congestive heart failure: 30-day, 1-year, 3-year, 5-year or 10-year according to VARC-3 criteria.
3. AMI, 30-day, 1-year, 3-year, 5-year and 10-year according to VARC-3 criteria [10].
4. Revascularization with PCI=percutaneous coronary intervention (not scheduled before TAVI) or CABG =Coronary Artery Bypass Grafting (not scheduled before TAVI), 30-day, 1-year, 3-year, 5-year and 10-year according to VARC-3 criteria [10].
5. Newly diagnosed atrial fibrillation/flutter, 30-day, 1-year, 3-year, 5-year and 10-year according to VARC-3 criteria [10].
6. 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].

Hemodynamic substudy, N=440:

1. Coprimary endpoint: EOA and peak gradient during rest and dobutamine stress immediately following TAVI measured invasively using Gorlin formula (Hemodynamic substudy, see below).
2. Secondary endpoint: Cardiac output by thermodilution during dobutamine stress following TAVI.

CT-substudy, N=850:

1. Coprimary endpoint: Leaflet thickening (hypoathenuated leaflet thickening = HALT) or reduced leaflet motion or thrombus assessed by HCT at 1 month and 12 months.
2. Secondary endpoint: commissural and coronary alignment and THV implantation depth.

CMR-substudy, N=166

1. Coprimary endpoint: Aortic regurgitation fraction (ARF) and aortic regurgitation volume measured by CMR at 1 month.
2. Seondary endpoint: Effective orifice area.

Registration of endpoints:

Most endpoints are collected from national registries. An echo core-lab is established to evaluate echo parameters (degree of aortic regurgitation, valve deterioration, thrombosis, EOA, peak and mean gradients, LVEF). A CT core-lab is established to evaluate CT parameters (HALT, reduced leaflet motion, coronary alignment). A CMR core lab is established to evaluate CMR parameters (EOA, ARF and volume of aortic regurgitation). A Hemodynamic core lab is established do determine EOA immediately following the

procedure based on invasive measurements during dobutamine stress, including cardiac output measurements using thermodilution. 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 screens for events, and file them in the ECRF. Thus, both site-reporting and registry-validation of events occur. See monitoring plan for events to be reported. A monitor will also monitor the following events in all patients: 1) death (up to 10 years), 2) stroke, TIA or retinal occlusion (up to 10 years), 3) endocarditis (up to 1 year), 4) readmission with CHF (up to 10 years), 5) reoperation (TAVR, SAVR, BAV up to 10 years), 6) drop in hgb Hgb ≥ 1.86 mmol/l, within 30 days, 7) erythrocyte transfusion ≥2 units, within 30 days, 8) vascular complications: any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, aortic pseudoaneurism, or vascular complications related to access site resulting in surgery or endovascular intervention, within 30 days., 9) Valve thrombosis by CT (HALT) or TEE, within 10 years, 9) Complications related to TAVI procedure resulting in: Pacemaker, annulus rupture, aortic rupture, conversion to surgery, conversion to alternate access, non-planned use of CPS, coronary artery obstruction, VSD, mitral valve damage or dysfunction, pericardial effusion resulting in tamponade and/or pericardiocentesis, within 30-days of the procedure, 13) valve embolization, valve migration resulting in TAVI-in-TAVI, other need for TAVI-in-TAVI). In a random sample of paitents more extensive monitoring is done for alle events (See separate monitoring plan). Selected endpoints are adjudicated by an endpoint committee (Stroke, AMI, readmission with heart failure, endocarditis, HALT/thrombosis by HCT/TEE).

Hemodynamic Assessment Following TAVR:

Post-implantation hemodynamic assessment of the aortic valve (AV) is conducted following the TAVI in patients participating in the hemodynamic substudy (N=440). Using a standard retrograde approach, a coronary pressure wire is positioned within the left ventricle (LV), while a 6-French catheter is positioned in the ascending aorta. In tandem, cardiac output is measured by thermodilution (average of 3 measurements with less than 10% variation) via a thermodilution catheter inserted into the pulmonary artery. This dual-measurement technique facilitates the construction of precise pressure loss versus flow rate curves for each individual valve. Given the unpredictable hemodynamic behavior of the newly implanted AV under varying flow conditions, a standard dobutamine stress test will be performed. Dobutamine stress is initiated at 5 mcg/kg/min, increased to 10 mcg/kg/min, and ultimately to 20 mcg/kg/min in 3-minute intervals. At baseline and each level of dobutamine, pressures in the LV, ascending aorta, pulmonary artery, and pulmonary artery wedge are recorded. Cardiac output by thermodilution is also measured at each stress level.

The stress test is terminated in case of LV outflow tract obstruction, indicated by the Brockenbrough sign, which is the systolic anterior motion of the anterior mitral valve leaflet, or in the presence of arrhythmias or hemodynamic instability.

The stress test will allow us to monitor the valve's response, specifically changes in the pressure gradient (ΔP) relative to flow rate (ΔQ) after implantation [13]. The calculation of the aortic valve area will employ the updated Gorlin formula [14, 15]: Aortic valve area = CO (mL)/(systolic ejection period × heart rate × 44.3 × √mean gradient).

Data will be archived for offline analysis, utilizing the Philips Hemo system and stored on the Philips Xper IM server.

Power calculations:

For each cohort (randomized comparison between two valves) launched in the COMPARE TAVI trial the steering committee decides to perform the study with or without interim analyses and decide sample size according to accepted non-inferiority margins (Randomized comparison of TAVI valves: The Compare-TAVI trial - PubMed (nih.gov). For the comparison of Evolut FX and Sapien 3 Ultra Resilia no interim analyses are planned, the expected event rate is 12% (As observed in the just finalized COMPARE TAVI cohort B comparing Sapien 3 / Sapien 3 Ultra versus Myval / Myval Octacor). With Beta=0.80 and alfa=0.05, a non-inferiority margin of 4.5%, and up to 4% drop-out (Less than 1% withdrawal in first COMPARE TAVI cohort), we plan to include 1346 patients. The 4.5% non-inferioirty margin correspond to a relative non-inferiority margin of 0.375. If the overall observed event rate is higher than expected the steering committee has to decide whether to increase either sample size or the non-inferiority margin.

For the CMR-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). We aim to include 166 patients with an expected drop-out of 10% of patients. Beta=0.80 and alfa=0.05.

A CT-substudy is performed with 1- and 12-month HCT follow-up to evaluate HALT. Based on Compare-1 we expect a 12-month incidence of HALT of 24%. With Beta=0.80, alfa=0.05 a total of 778 patients are needed to document an 8% difference in HALT. With inclusion of 850 patients there is room for up to 9% drop-out.

An invasive hemodynamic study is performed, where patients are subjected to dobutamine stress immediately following the TAVI-procedure, while cardiac output is measured with thermodilution and pressure gradients measured (pressure in ventricle and ascending aorta) to determine AVA using Gorlin fomula. Do document a 15% difference in AVA, if the mean AVA during stress is 2.31 and the standard deviation 1.24 (approximated from Johnson et al by dividing IQR with 1.35) [13], a total of 396 patients are needed in the substudy. To account for drop-out, we aim to include 440 patients in this substudy.

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

For each cohort the maximal inclusion period is 3 years. The safety committee analyses are expected after inclusion of 1/3 and 2/3 of patients but the first safety committee analyses have to be performed no later than two years of inclusion (if slow recruitment). The safety committee will report to the steering committee who decide whether to continue inclusion, adjust sample size or terminate 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. For details regarding analyses of primary and secondary endpoints see the separate Statistical Analysis Plan.

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 after randomization, 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, medication, clinical status (NYHA,CCS) and file them in the ECRF. This will ensure two sources for event-registration. Regarding moderate and severe aortic regurgitation, moderate and severe valve deterioration, 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. Hemodynamic findings will be entered by the Hemodynamic 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). Sponsor will then reimburse each site according to fees in table 1.

Table 1: Reimbursement in upcoming cohorts

	Fee to sponsor from funding sources (expected to be covered by companies manufacturing the TAVI valves).	Reimbursement to site from sponsor
Compare-TAVI main study, N=1346		
Inclusion, entering data in eCRF	1100 euro	850 euro
Transfer of baseline Echo to core-lab	220 euro	170 euro
Transfer of post-procedure Echo to core-lab	220 euro	170 euro
1 month clinical follow-up and entering data in eCRF	170 euro	120 euro
Transfer of 1 month Echo to core-lab	220 euro	170 euro
12 month clinical follow-up and entering data in eCRF	170 euro	120 euro
Transfer of 12 month Echo to core-lab	220 euro	170 euro
3 year clinical follow-up and entering data in eCRF	170 euro	120 euro
Transfer of 3 year Echo to core-lab	220 euro	170 euro
5 year clinical follow-up and entering data in eCRF	170 euro	120 euro
Transfer of 5 year Echo to core-lab	220 euro	170 euro
10 year clinical follow-up and entering data in eCRF	170 euro	120 euro
Transfer of 10 year Echo to core-lab	220 euro	170 euro
CMR-substudy, one month CMR, N=166	450 euro	350 euro
CT-substudy, one month CT, N=850	350 euro	250 euro
CT-substudy, 1 year CT, N=850	350 euro	250 euro
Hemodynamic substudy, N=440	1000 euro	800 euro

The maximum fee for a patient with complete 10-year follow-up in the main study will be 3490 euro. Since not all patients will survive to complete follow-up, we expect the average fee per patient to be around 2750 euro for 10-year follow-up in the study, or an estimated total cost of 3.701.500 euro in 10 years, if 1346 patients are included. Three substudies are launched, the CMR-substudy with 166 patients and a total cost of 166*450=74.700 euro, the CT-substudy with 850 patients and a total cost of 850*2*350=595.000 euro, and the hemodynamic substudy with 440 patients and a total cost of 440*1000=440.000 euro.

Publications:

The cohort will be published after inclusion of 1.346 patients. Results will be published 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. A separate publication will be performed for 1-year, 3-year, 5-year and 10-year data. Substudies on MRI and hemodynamic can be published after 30 days.

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