Design and rationale of the COMPARE-TAVI 2 trial: An all-comers head-to-head comparison of Evolut FX+ and Sapien 3 Ultra Resilia transcatheter heart valves

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ABSTRACT

Introduction The COMPARE-TAVI trial framework was launched for direct comparison of transcatheter aortic valve implantation (TAVI) valves. The COMPARE-TAVI 1 trial, comparing Myval/Myval Octacor versus Sapien 3/Sapien 3 Ultra transcatheter heart valves (THVs), was recently published. Here, we present the design and rationale for the COMPARE-TAVI 2 trial comparing the Evolut FX+ self-expandable THV with the Sapien 3 Ultra Resilia balloon-expandable THV.

Methods and analysis In the COMPARE-TAVI 2 trial (ClinicalTrials.gov NCT06470022), patients will be randomized 1:1 between the THVs. The trial will test whether the Evolut FX+ self-expandable THV is noninferior to the Sapien 3 Ultra Resilia balloon-expandable THV in terms of the combined 1-year primary composite endpoint of all-cause mortality, stroke, moderate/severe total aortic regurgitation, or moderate/severe hemodynamic THV deterioration, according to VARC-3 criteria. If noninferiority is proven, superiority analyses may apply. Based on a power of 80%, alpha level of 0.05, 1-sided test, noninferiority margin of 4.5%, and expected event rate of 12%, the necessary sample size has been estimated to be 1,364 patients. Prespecified secondary endpoints, including long-term follow-up for 10 years, will also be investigated.

Summary The COMPARE-TAVI 2 will provide important information on the short- and long-term outcomes among patients treated with the Evolut FX+ self-expandable and the Sapien 3 Ultra Resilia balloon-expandable THVs. (Am Heart J 2026;297:107387.)

Background

The COMPARE-TAVI trial framework for direct comparison of transcatheter aortic valve implantation (TAVI) valves has previously been presented.[1] The framework allows for head-to-head comparison of transcatheter heart valves (THVs). The first head-to-head comparison of Myval/Myval Octacor versus Sapien 3/Sapien 3 Ultra THVs was recently published as the COMPARE-TAVI 1 trial.[2]

Here, we present the design and rationale for the COMPARE-TAVI 2 trial (ClinicalTrials.gov NCT06470022), comparing the Evolut FX+ self-expandable THV with the Sapien 3 Ultra Resilia balloon-expandable THV in all comers undergoing transfemoral TAVI (Graphical abstract).

Methods

Trial design and setting

Patients scheduled for transfemoral TAVI will be randomized 1:1 to treatment with either the Evolut FX+ THV or the Sapien 3 Ultra Resilia THV (Figure 1).

European centers performing more than 75 TAVI procedures per year will be eligible to participate, and op-

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Figure 1. Outline of the COMPARE-TAVI 2 trial.

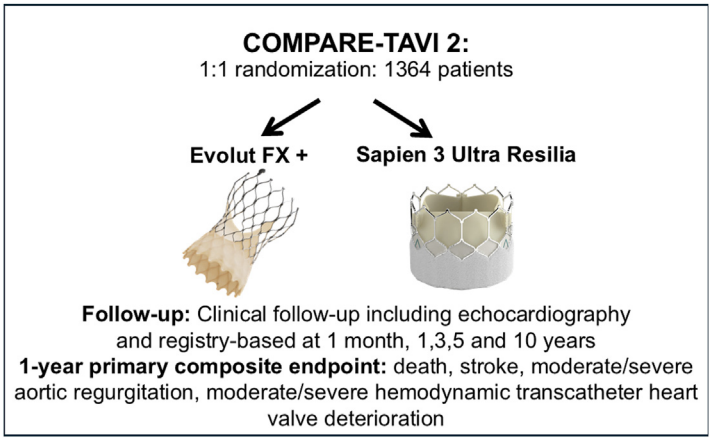
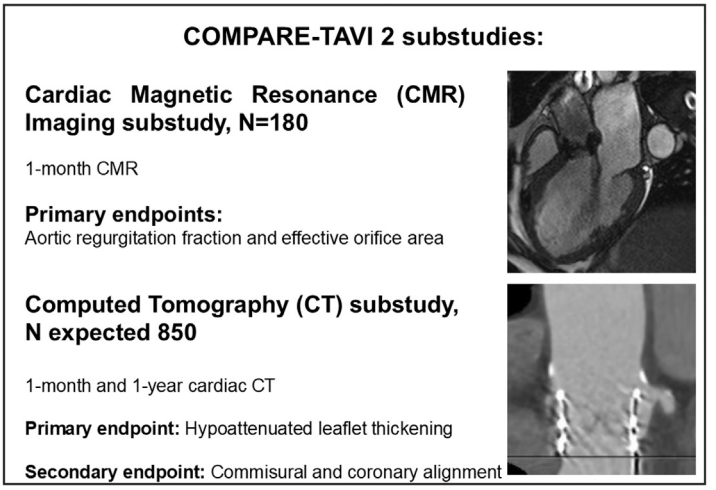


Figure 2. Outline of the COMPARE-TAVI 2 trial computed tomography and magnetic resonance imaging substudies.



erators will be required to have implanted at least 15 of each valve before including patients in the trial.

Computed tomography (CT) and cardiac magnetic resonance (CMR) substudies will be conducted (Figure 2).

The trial is registered with ClinicalTrials.gov (NCT06470022).

Patients and recruitment

Patients 18 years or older who are scheduled for transfemoral TAVI will be eligible for inclusion in the trial. Patients must be candidates for treatment with both valves, according to a technical evaluation in agreement with instructions for use of the THVs.

Interventions

The TAVI procedures will be performed according to usual clinical practice at the participating centers in general agreement with the instructions for use of the THVs. Procedural characteristics will be recorded.

Endpoints and timeline

The primary and secondary endpoints are presented in Table 1. The endpoint definitions are consistent with VARC-3 and BARC criteria, as specified.[3,4]

Follow-up with clinical assessment and echocardiography will be scheduled before discharge; after 30 days; and after 1, 3, 5, and 10 years. A standardized protocol for echocardiography established by the echocardiography core laboratory will be used, and all echocardiographies are evaluated by the echocardiography core laboratory (Echo protocol, Supplementary material). Endpoints will be assessed in relation to clinical and echocardiographic follow-up, and from registries.

Table 1. COMPARE-TAVI 2 trial endpoints.

Primary composite endpoint
All-cause mortality, stroke, moderate/severe total aortic regurgitation, or moderate/severe hemodynamic transcatheter heart valve (THV) deterioration at 1 year, according to VARC-3 criteria.
The individual components of the primary outcome will be presented, to describe their contribution to the primary endpoint. The primary composite endpoint and each component will be re-analyzed at 3-, 5-, and 10-year follow-up.

Secondary safety and efficacy endpoints (Bonferroni correction for multiple testing):

1. **TAVI-related complications:** These complications comprise conversion to open surgery during implantation, unplanned use of cardiopulmonary support, coronary artery obstruction, ventricular septal defect, mitral valve apparatus damage or dysfunction, cardiac tamponade/pericardial effusion resulting in pericardiocentesis, valve embolization, valve migration, and need for TAVI-in-TAVI deployment, according to VARC-3 criteria,[10] or annulus rupture, aortic rupture/perforation, aortic dissection, or shunts other than ventricular septal defect.
2. **Proportion with successful implantation of the chosen valve.** This proportion is defined according to no need for more than 1 TAVI valve; no change to an unplanned valve during the procedure, because implanting the planned valve was impossible; and no conversion to surgery or procedure-related death.
3. **SMART criteria for bioprosthetic valve dysfunction through 1-year:** These criteria comprise (1) hemodynamic structural valve dysfunction, defined as an aortic valve mean gradient $\geq$20 mmHg at any time up to the 1-year visit echocardiography; (2) nonstructural valve dysfunction, defined as severe prosthesis-patient mismatch or moderate to severe total aortic regurgitation at any time until the 1-year visit echocardiography; (3) clinical valve thrombosis; (4) endocarditis; or (5) aortic valve reintervention.
4. **Pacemaker implantation:** New pacemaker implantation within 1 year after TAVI.

Exploratory secondary endpoints for the 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, according to VARC-3 criteria, during admission and within 30 days.
2. Major bleeding resulting in a decrease in hemoglobin level $\geq$1.86 mmol/l and/or erythrocyte transfusion $\geq$2 units, during admission and within 30 days, modified from BARC type 3 to 5 criteria. This endpoint will be adjudicated and presented as VARC-3 type 2, 3, or 4 bleeding.

Bioprosthetic valve dysfunction:

1. Endocarditis at 30 days, and 1, 3, 5, and 10 years.
2. Reoperation (TAVI, surgical aortic valve replacement, or balloon aortic valvuloplasty) at 30 days, and 1, 3, 5, and 10 years, according to VARC-3 criteria.
3. Moderate/severe prosthesis-patient mismatch: Effective orifice area (EOA)/body surface area $\leq$0.85 cm^2/m^2 if BMI $<$30 kg/m^2 or $\leq$0.70 cm^2/m^2 if BMI $\geq$30 kg/m^2, at 30 days, according to VARC-3 criteria.
4. EOA at 30 days, and 1, 3, 5, and 10 years, as evaluated by the echocardiography core laboratory.
5. Mean gradient at 30 days, and 1, 3, 5, and 10 years, as evaluated by the echocardiography core laboratory.

Readmissions, and clinical and paraclinical findings:

1. Pacemaker implantation at 30 days before TAVI; during admission; and 30 days, and 3, 5, and 10 years after TAVI.
2. Readmission for congestive heart failure at 30 days, and 1, 3, 5, and 10 years, according to VARC-3 criteria.
3. AMI at 30 days, and 1, 3, 5, and 10 years, according to VARC-3 criteria.
4. Revascularization with percutaneous coronary intervention (not scheduled before TAVI) or coronary artery bypass grafting (not scheduled before TAVI) at 30 days, and 1, 3, 5, and 10 years, according to VARC-3 criteria.
5. Newly diagnosed atrial fibrillation/flutter at 30 days, and 1, 3, 5, and 10 years, according to VARC-3 criteria.
6. Increase in renal creatinine level to $\geq$200% (AKIN stage 2-3, VARC-3 criteria) or resulting in dialysis (AKIN stage 4), according to VARC-3 criteria, during admission and at 30 days.

CT substudy, *N* = 850:

1. Coprimary endpoint: Hypoattenuated leaflet thickening (HALT) or reduced leaflet motion or thrombus, assessed by HCT at 1 month and 1 year.
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. Secondary endpoint: EOA.

In the CT substudy, CT will be performed at 30-day and 1-year follow-up. A standardized protocol for CT, established by the CT core laboratory, will be used, and all CT scans will be evaluated by the CT core laboratory.

In the CMR substudy, CMR will be performed at the 30-day follow-up. A standardized protocol for CMR, established by the CMR core laboratory, will be used, and all CMR scans will be evaluated by the CMR core laboratory.

Allocation and blinding

Patients are randomized through an online portal for medical research enabling both randomization and data registration. Randomization is stratified by sex and center. Center and sex are potential confounders, and while other potential confounders may exist, we did apply further stratification to minimize the risk of overstratification.

Because blinding will not be achievable, the trial should be considered open label. The patient records indicate the implanted valve, and, although the core laboratories evaluate images without information on the implanted valve, the valves have different appearances on imaging, thus making blinding impossible.

Data collection, management, and monitoring

The electronic case report form (eCRF) will contain all patient and procedure characteristics and imaging analyses, as well as follow-up data and events. Data in the eCRF are encrypted, and all access events or attempts to access data are logged and monitored. The system has been approved by the Danish Data Protection Agency.

Monitoring of the study will involve a combination of on-site monitoring and remote monitoring, including through the eCRF. The monitors will follow a specific monitoring plan (Monitoring and event adjudication plan, Supplementary material). Sites will be continually provided with updates on data completeness.

The following serious adverse events will be filed with the ethical committee on occurrence: (1) structural THV deterioration resulting in repeated TAVI or surgical aortic valve replacement 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 1 valve during index treatment). As of July 1, 2025, ethical regulations were changed in Denmark, such that only serious adverse events associated with the device must be reported to the ethical committee expedited, whereas remaining events will be reported once yearly. Same approach has since been adapted in Finland and will be proposed for Ireland.

The ethical committee can choose to undertake auditing at any time. In this event, the committee will be granted access to all data. The sponsor may perform on-site audit, in which event access to source data is needed.

Statistical analyses and sample size considerations

Data will be analyzed according to the intention-to treat principle. If there are any cases of cross-over, per-protocol analyses will also be performed.

Regarding the primary endpoint, a noninferiority analysis will be conducted. Separate analyses of each component of the primary outcome will be presented in accordance with FDA (Multiple Endpoints in Clinical Trials) and EMA (Points to consider on multiplicity issues in clinical trials) guidelines. Regarding the secondary safety and efficacy endpoints, Bonferroni correction will be used for multiple testing (Figure 3). Additional secondary endpoints will be explorative and should be considered hypothesis generating. A detailed statistical analysis plan that also specifies planned subgroup analyses is provided (Statistical analysis plan, Supplementary material).

During planning of COMPARE-TAVI 2, the 1-year primary endpoint for COMPARE-TAVI 1 was unknown, and the event rate was expected to be 12% in COMPARE-TAVI 2. However, the 1-year primary endpoint rates reached 13% and 14% in the 2 arms in COMPARE-TAVI 1.[2] Therefore, the steering committee for COMPARE-TAVI 2 on June 11, 2025, proposed that when 25% of patients included in COMPARE-TAVI 2 reach 1-year follow-up (May 19, 2026), a blinded event rate will be calculated (for both groups combined), and if the event rate exceeds 12%, the sample size will be increased according to the estimates in Table 2. Changes were filed as amendment 14 to the ethical committee in Denmark and as amendment 1 to the ethical committee and FIMEA in Finland. The sample size estimate is based on a power of 80%, alpha level of 0.05, and noninferiority margin of 4.5%. For a 12% event rate, the sample size has been increased to reach 1,364 patients (determined with a Farrington-Manning Score test) instead of the initially planned 1,346 patients (determined with a Pearson chi-square test). If the initial enrollment of the planned 1,364 (previously 1,346) patients is completed before May 19, 2026, then enrollment will continue until a final sample size decision is made on May 19, 2026. After May 19, 2026, enrollment will continue until a potential new target sample size has been reached.

The noninferiority margin of 4.5% was evaluated as clinically relevant since it only allows for a risk-difference up to around 1.5% to accept noninferiority. With higher risk-differences the lower confidence interval would cross the noninferiority margin, and noninferiority would not be claimed. The noninferiority margin of 4.5% corresponds to a relative noninferiority margin of 37.5% at an event rate of 12% down to 30% at an event rate of 15%. The rationale for the noninferiority margin has also been addressed in the design paper for COMPARE-TAVI 1.[1]

For the CT substudy, follow-up will be performed after 1 and 12 months, to evaluate the occurrence of hypoattenuated leaflet thickening (HALT). On the basis of

Figure 3. Statistical analyses in the COMPARE-TAVI 2 trial.

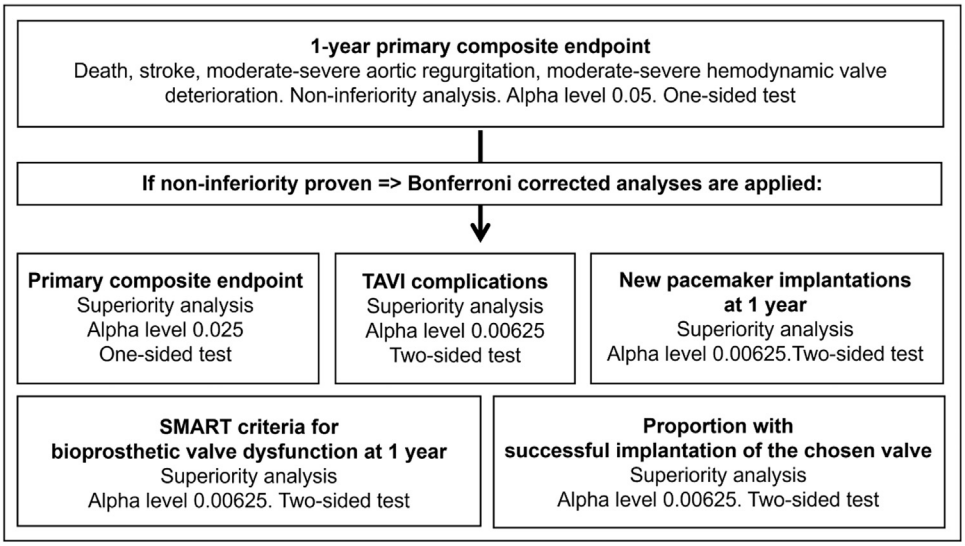


Table 2. Sample size based on expected event rates, with a power of 80%, alpha of 5%, and noninferiority margin of 4.5%.

Expected event rate	Sample size	Sample size, anticipating 4% drop-out
12%	1,308	1,364
13%	1,398	1,458
14%	1,484	1,546
15%	1,570	1,636

COMPARE-TAVI 1 (unpublished data), we expected a 12-month HALT incidence of 24%. With a beta of 0.80 and alpha level of 0.05, a total of 778 patients will be needed to detect an 8% difference in HALT. With the inclusion of 850 patients, a drop-out rate as high as 9% could be accommodated.

For the CMR substudy evaluating the hemodynamics (effective orifice area [EOA] and aortic regurgitation fraction [ARF]), the expected EOA is 1.5 (SD 0.54) cm^2, and the expected ARF is 0.14 (SD expected to be 0.09). A total of 150 patients will be needed to document a difference of 0.25 cm^2 in EOA (1.5 to 1.25 cm^2), whereas 160 patients will be needed to document a difference of 0.04 in expected ARF (0.14 to 0.10). We aim to include 180 patients, with an expected drop-out rate of 10% of patients, beta of 0.80, and alpha level of 0.05.

Ethical considerations

At the participating centers, ethics committee approval will be obtained before the start of patient inclusion. Any protocol modifications will be sent to the ethics committee for approval. The COMPARE-TAVI organization for head-to-head comparison was approved on March 8, 2018. Amendments 2 to 10 covered COMPARE-TAVI 1. The COMPARE-TAVI 2 trial was approved in Denmark as amendment 11 on May 16, 2024. The HCT and CMR substudies were approved as amendment 12 on August 22, 2024. A separate hemodynamic substudy was approved as amendment 13 on March 11, 2025, but the idea for this study was later abandoned. On July 1, 2025, amendment 14 was approved, to allow for an increase in sample size to a maximum of 1,636 patients if the blinded event rate exceeds the initially expected 12%. Separate approval was obtained from the ethical committee and FIMEA in Finland for the Helsinki, Oulu, and Turku university hospitals on April 28, 2025. Amendment 1 was submitted in Finland to include Kuopio Hospital and a sample size increase to a maximum of 1,636 patients if the blinded event rate exceeds 12%, and was approved by the ethical committee on August 27, 2025, and by FIMEA on September 22, 2025. It is expected that application for ethical approval will be filed in Ireland December 2025.

Patients are asked to participate before the TAVI procedure and must provide verbal and written consent before participating. Physicians involved in treatment are responsible for obtaining patient consent. Patients are informed that they can withdraw their consent at any time.

The trial findings will be published regardless of the outcome. In the event of trial termination before the final inclusion rates are met, e.g., termination advised by the safety committee, the collected data will be published.

Data safety monitoring board

An independent data safety monitoring board (DSMB) will have full access to all data. The committee comprises a statistician, an epidemiologist, and 2 cardiologists not involved in the trial. The DSMB is expected to report on progress and potential safety issues after enrollment of one-third and two-thirds of the patients. Because the composite endpoint cannot be evaluated until patients have reached the 1-year follow-up, no prespecified interim analyses will be conducted. The DSMB files reports with the steering committee, which decides whether to continue inclusion, adjust the sample size, or terminate inclusion.

Steering committee

The steering committee has the overall responsibility for conducting the trial, and whether to finalize enrollment, adjust the sample size, or terminate enrollment before planned. The steering committee comprises one co-investigator from each site actively enrolling patients.

Endpoint committees

Two endpoint committees have been established. One endpoint committee comprises 2 neurologists not involved in the trial, who adjudicate all strokes and transitory ischemic attacks. The other endpoint committee comprises 2 cardiologists not actively participating in the trial, who adjudicate the following events: cause of death, acute myocardial infarction, endocarditis, readmission with congestive heart failure, atrial fibrillation, revascularization (percutaneous coronary intervention or coronary artery bypass grafting), TAVI device clinical thrombosis, and bleeding events. A separate plan for adjudication of events according to VARC-3 criteria is available (Monitoring and event adjudication plan, Supplementary material).

Local practice differences across the participating centers regarding pacemaker after TAVI may exist although guidelines are followed in general.[5] This is a potential limitation, but it should be mitigated by stratification by center in the randomization.

Study monitoring

Trained monitors will monitor all events according to a separate monitoring plan (Monitoring and event adjudication plan, Supplementary material) and will file reports with the sponsor.

Current trial status

COMPARE-TAVI 2 started enrollment in Aarhus, Denmark, on August 12, 2024, in Odense, Denmark, on November 27, 2024, in Oulu, Finland, on May 14, 2025, in Aalborg, Denmark, on September 2, 2025, in Turku, Finland, on September 24, 2025, and in Helsinki, Finland on September 25, 2025. As of October 29, 666 patients have been randomized. Additional sites (Kuopio in Finland, Dublin in Ireland, and Rigshospitalet in Denmark) are expected to start enrollment from Q1 of 2026. Patient inclusion in the main study and the CT substudy is ongoing. Inclusion in the CMR substudy has been completed. The DSMB concluded on September 23: "The independent Data and Safety Monitoring Board (DSMB) has completed its scheduled interim review of the COMPARE-TAVI 2 trial based on patients enrolled before July 1, 2025. After examining available safety and efficacy data, the DSMB recommends that the study continue as planned, with no changes to the protocol, eligibility criteria, or randomization".

Funding sources

The COMPARE-TAVI organization was supported by a grant from The Danish Heart Foundation. The COMPARE-TAVI 2 trial was supported by an unrestricted grant from Medtronic Bakken Research Center, Maastricht, Netherlands.

The study is investigator initiated and driven. Funding parties have no influence on study design or conduct. The ethical committees will be informed of 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. Grants will be used to conduct the study (e.g., data handling, and salaries for study personnel) and to present the data.

Discussion

Use of the Evolut and Sapien THV platforms for treatment of patients with significant aortic stenosis is well-documented in inoperable patients and operable patients with high to low perioperative risk.[6–13] The latest iterations of the valves have not previously undergone head-to-head comparison in a large all-comer randomized trial.

The Evolut THV is self-expandable and supraannular, whereas the Sapien is balloon-expandable and intraannular. These design differences might have different potential benefits in different patient subsets.[14,15] Assumptions in this regard may or may not hold, and would be best tested in large-scale studies including all comers. The exclusion of certain subsets of patients during a trial precludes testing of these assumptions and might introduce important bias.

Previous head-to-head comparisons of Sapien and Evolut THVs were small, implemented previous iterations of the THVs, and either showed equivalence or favored the Sapien THV with regard to death, stroke or aortic regurgitation.[16–19] The more recent SMART-trial favored Evolut

regarding hemodynamic parameters in a highly selected patient cohort as the trial enrolled patients with small annuli only[20] French registry studies reflecting daily clinical use of the THVs, however, have indicated higher mortality and higher degree of aortic regurgitation with the previous iterations of Evolut compared to Sapien THVs, but whether differences were causal or due to selection of higher risk patients for Evolut valves are uncertain.[21–23] Both the Sapien and Evolut THVs have made recent changes in design. Sapien introduced Resilia technology and claimed it improved hemodynamic performance. Evolut FX+ introduced large cells to facilitate easier coronary artery access. As the majority of previous studies have been in favor of Sapien regarding aortic regurgitation, we chose Sapien Ultra 3 Resila as the reference THV in COMPARE-TAVI 2, and a noninferiority analysis was prioritized with the possibility to perform superiority analyses if noninferiority was proven.[21–23]

Randomized head-to-head comparisons in all-comers should be considered mandatory in the future, as registry studies may be hampered by confounding, which was seen in the previous evaluation of the Acurate THVs. A number of registry studies continued to favor the Acurate THV, but repeatedly randomized trials failed to document noninferiority of the Acurate THVs compared to other contemporary valves.[24–26] For this reason, long-term use of any THVs should be based on head-to-head comparisons with other contemporary THVs, and any new THVs introduced to the market should be compared to best-in-class contemporary THVs.

COMPARE-TAVI provides a framework for testing valves in all comers and COMPARE-TAVI 2 will provide important information regarding the performance of the latest iterations of the Evolut and Sapien THV platforms, i.e., Evolut FX+ and Sapien 3 Ultra Resilia, across all patient subsets.

Declaration of competing interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2026.107387.

CRediT authorship contribution statement

Troels Thim: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Henrik Nissen:** Writing – review & editing, Conceptualization. **Matti Niemelä:** Writing – review & editing. **Ashkan Eftekhari:** Writing – review & editing, Conceptualization. **Mikko Jalanko:** Writing – review & editing. **Mikko Savontaus:** Writing – review & editing, Conceptualization. **Pertti Jääskeläinen:** Writing – review & editing. **Mark Hensey:** Writing – review & editing. **Rebekka Vibjerg Jensen:** Writing – review & editing. **Bjarne Linde Nørgaard:** Writing – review & editing. **Christian Alcaraz Frederiksen:** Writing – review & editing. **Henrik Ølholm Vase:** Writing – review & editing. **Lars Pedersen:** Writing – review & editing, Formal analysis. **Henrik Toft Sørensen:** Writing – review & editing. **Evald Høj Christiansen:** Writing – review & editing, Conceptualization. **Christian Juhl Terkelsen:** Writing – review & editing, Writing – original draft, Visualization, Funding acquisition, Formal analysis, Conceptualization.

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