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Study Protocol: Optimization of Commissural Alignment During Transcatheter Aortic Valve Implantation with Evolut FX+: A randomized, prospective study

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Versjon 1.2

1. Background and rationale

Transcatheter Aortic Valve Implantation (TAVI) has become a preferred treatment for patients with severe aortic stenosis who are at high or intermediate surgical risk (1). However, when compared to surgical aortic valve replacement, TAVI less often results in commissural alignment (2). Optimizing commissural alignment between the transcatheter valve and the native aortic valve is critical in preserving future coronary access, especially for younger patients and patients with known coronary artery disease that may require percutaneous coronary intervention (PCI) after TAVI (3, 4). In addition, an increasing number of patients are considered for redo-TAVI if failure of their first TAVI-valve occurs. Commissural misalignment impacts the feasibility of a redo-TAVI procedure, because of risk of sinus sequestration and coronary obstruction as well as the possibility for leaflet modification techniques of their prior TAVI valve (3). It may also have effects on valve functionality and durability (5, 6). Current implantation techniques vary in their ability to obtain commissural alignment, which impact coronary artery access and PCI after TAVI as well as redo-TAVI procedures (7, 8).

The latest-generation self-expandable Evolut FX+ TAVI valve offers potential benefits in achieving commissural alignment or later better coronary access compared to older generations of the Evolut family (3, 4). Khera et al. compared Evolut FX and Evolut PRO+ in a non-randomized trial. They concluded that the new design features of the Evolut FX system appeared to significantly improve the ability to achieve commissural alignment (4). Later, the FX+ valve has been released, which incorporates a modified frame with larger coronary

access windows to improve catheter maneuverability and access to coronary arteries. Recent work has indicated that the position of the delivery system in the descending aorta is important for commissural alignment and avoidance of coronary overlap (7). Furthermore, Konami et al recently demonstrated that rotation of the fluoroscopic “Hat” marker in the descending aorta is useful for improving commissural alignment in TAVI with Evolut devices (8). Currently, it is common that the operator rotates the delivery system in a left anterior oblique (LAO) projection to achieve that the "Hat" marker is facing the great curvature of the descending aorta before crossing the aortic arch, but at which LAO degree this should be performed has not been established.

On this background, we believe that the optimal implantation technique to obtain the best possible commissural alignment and subsequent coronary access with the Evolut FX+ for each specific patient remains unclear and warrants further investigation. This is underpinned by recent data supporting that patient-specific rotation with the self-expanding "ACURATE neo" TAVI-valve, based on computed tomography (CT)-analysis obtained before implantation, may improve the success rate of commissural alignment (9). Also, another study by Bieliauskas et al. based a patient- and valve-specific implantation technique on each patient´s pre-operative CT (three types of valves; Evolut R/PRO, ACURATE neo2, Portico), which allowed for safe and reproducible implantation (10). The purpose of the present study is to prospectively evaluate the efficacy and safety of a novel patient-specific rotation of the Evolut FX+ TAVI valve and the delivering system during the transfemoral (TF) procedure. Specifically, it aims to evaluate and compare the commonly used fluoroscopic (X-ray) LAO degree for rotation of the delivery system and more patient-specific LAO degree achieved by CT analysis prior to the procedure. The degree of alignment and coronary overlap will be measured with ECG-gated CT after the procedure. Thus, it will prospectively explore if these two techniques differ in obtaining commissural alignment, coronary overlap and safety outcomes following implantation of latest-generation Evolut FX+ valve.

2. Study objectives

In patients with severe aortic stenosis indicated for TF-TAVI with the Evolut FX+ valve after multidisciplinary heart team meeting:

Primary Objective:

- To investigate and compare commissural alignment of two rotational positioning methods based on the positioning of the fluoroscopic “Hat” marker at the descending aorta with the Evolut FX+ valve.

Secondary Objective:

- To evaluate and compare the likelihood of successful post-TAVI coronary access assessed by CT after TAVI with the Evolut FX+ valve.

3. Study hypotheses

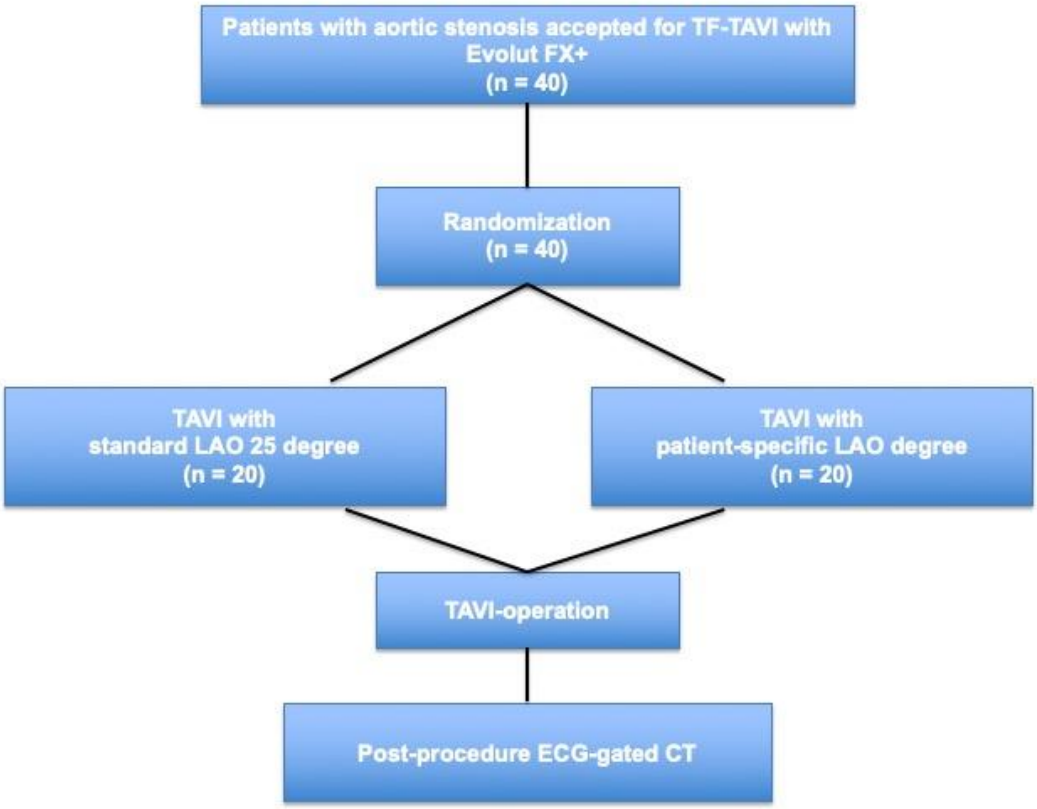
In patients with severe aortic stenosis indicated for TF-TAVI with the Evolut FX+ valve after heart team meeting:

1. A strategy of patient-specific rotation will be superior to a generalized approach in obtaining commissural alignment.

2. A strategy of patient-specific rotation will increase the likelihood of successful post-TAVI coronary access assessed by CT after TAVI with the Evolut FX+ valve.

4. Overview of study design

- Randomized, prospective, single-center observational study.



5. Study sample

5.1. Target enrollment: 40 patients.

5.2 Inclusion criteria:

- Patients with severe aortic stenosis indicated for TAVI after heart team meeting.
- Age ≥65 years.
- Patients planned by the TAVI team to receive a self-expandable valve (Evolut FX+ valve).
- Patients providing informed consent.

5.3 Exclusion criteria:

- Severe peripheral vascular disease preventing transfemoral access.
- Prior aortic valve replacement or bicuspid valve.
- Severely reduced kidney function (estimated glomerular filtration rate <30).

6. Randomized treatments

Subjects will be randomized to a patient-specific rotational method or a conventional generalized rotational method before the procedure.

7. Study procedures

7.1 Overview of study procedures

Pre-procedural (standard) assessment

- Baseline CT scan to evaluate aortic root anatomy by using 3mensio analysis software.
- Clinical and echocardiographic assessment (left ventricular function, aortic valve area, mean gradient).
- Coronary angiography to assess native coronary anatomy.
- Blood tests.

Procedural steps

- Valve implantation: The Evolut FX+ valve will be implanted using standard transfemoral access under fluoroscopic guidance.
- Rotational positioning methods:
    - **Method 1** (generalized approach): The “Hat” marker positioned in the descending aorta with fluoroscopy at 25 degrees left anterior oblique.
    - **Method 2** (patient-specific approach): The “Hat” marker positioned in the descending aorta with fluoroscopy at the pre-procedural identified degree at which the right and non-coronary cusp overlap (from CT analysis).

Post-procedural assessment

- CT imaging:
    - Assessment of commissural alignment post-TAVI.
    - Coronary ostial relationship with the implanted valve.
- Clinical and echocardiographic assessment (left ventricular function, aortic valve area, mean gradient).
- Blood tests.
- Hospital chart review for safety endpoints.

Table of study procedures				
	Baseline		TAVI-operation	Follow-up
Eligiblity assessment	X			
Informed consent	X			
Randomization	X			
Patient demographics	X			
Clinical assessment and medications	X			
Medical history	X			
Blood tests	X			X
ECG	X			X
Echocardiography	X			X
CT	X			X
Complications				X

7.2. Screening and recruitment

All patients with severe aortic stenosis indicated for TAVI with the Evolut FX+ valve after heart team meeting at Oslo University Hospital (OUS) Ullevål will be screened for eligibility and screening logs will be registered during the whole study period. Potential participants will be identified after the heart and TAVI meetings have been completed, as only those who receive a decision for Evolut FX+ will be asked to participate in the study (there are always two operators from the intervention group present and all operators at the section (5 operators) will be involved in the recruitment by notifying the study group if patients have been approved for TAVI with Evolut FX+. The participants will then receive written and verbal information from one of the individuals in the study group or one of the treating physicians at the department (either in-hospital during their pre-operative evaluation so that they will have time to evaluate over days/weeks before they possibly consent to inclusion, or alternatively early during admission for surgery so that patients will have sufficient time to evaluate if they want to participate (at least the day before)). All participants will meet and receive information from a study group member (Cecilie Egeland, Ahmed Al-Ani, Trygve Sundby Hall, Tonje Amb Aksnes, Jørgen Gravning) before giving consent, and this study group member will not be in a "treatment relationship" with the patient (ref. 7.3 and paragraph 13 of the Health Research Act) .

7.3. Informed consent

Written informed consent after oral information and reading relevant documents will be obtained before the procedure. A copy of the signed consent document will be given to the patient and the original will be retained by the study personnel. The informed consent will be obtained in accordance with paragraph 13 of the Health Research Act. This means that the informed consent and signature will be obtained by a "neutral" person that is not involved in the treatment of the patient.

7.4. Randomization

Randomization will be performed using sealed envelopes, each containing a pre-determined treatment assignment, that are opened sequentially as participants are enrolled. This process helps to maintain allocation concealment and reducing the potential for selection bias.

7.5. Follow-up

Following the operation routine clinical follow-up will be performed as part of the standard procedure for all patients that are operated in our hospital. Standard clinical assessment, blood tests and safety endpoints will be reviewed and registered from the hospital chart. An ECG-gated CT scan of the heart after the TF-TAVI procedure will be performed during or a few days after the hospital stay.

7.6 Variable list

A detailed variable list is attached as supplementary information to the present protocol.

8. Study outcomes

8.1 Primary efficacy outcomes

- Proportion of patients achieving commissural alignment post-TAVI (measured by CT-analysis after TAVI).
- The relationship between alignment and rotational positioning method after TAVI.

8.2 Secondary efficacy outcome

- The likelihood of successful coronary access assessed by CT after TAVI.

8.3 Safety outcomes

- Pacemaker, vascular complications, pericardial effusion, open surgery, valve embolization, stroke, peri-procedural MI, kidney failure and death.

9. Data management

- All data will be de-identified and registered in “Medinsight”. Data will be obtained from hospital records reporting investigations that are performed in their usual clinical pathway. The only additional investigation that will be performed will be an additional CT-scan after the TAVI.

10. Withdrawal of participants

Participants may withdraw consent to participate at any stage of the study and for any reason.

11. Statistical considerations

- Commissural alignment will be reported and statistically compared by use of the proportion of patients achieving alignment (defined as 0 degrees to 15 degrees being commissural alignment, 15.1 degrees to 30.0 degrees being mild commissural misalignment, 30.1 degrees to 45.0 degrees being moderate commissural misalignment and 45.1 to 60.0 degrees being severe commissural misalignment) (3).

- Coronary access feasibility will be reported and statistically compared by use of proportion of patients achieving coronary access feasibility (defined as severe coronary overlap (within 0 degrees to 15 degrees) and less severe coronary overlap (>15 degrees)) (4).
- Safety outcomes will be reported and statistically compared by use of the proportion of patients with occurrence of each safety outcome.
- Categorical variables will be presented as numbers and/or percentages, and continuous variables will be presented as means (standard deviation) or medians (quartiles 1 to 3). Continuous variables will be compared with the t-test (if normally distributed) or the Mann-Whitney U test (if skewed). Categorical variables will be compared by using the Pearson chi square test or Fischer's exact test (if any field included <6). A p-value of < 0.05 will be regarded statistically significant, and all hypothesis testing will be two tailed.
- The potential difference in proportion of commissural alignment between the two techniques is unknown and thus no power calculation has been done. Comparisons between groups will therefore be descriptive and mainly hypothesis-generating.

12. Study organization

The study organization will be comprised of study coordinator Cecilie Egeland, primary investigator MD Ahmed Al-Ani and project leader MD PhD Trygve Sundby Hall. The study group will also include MD PhD and section leader of cardiac intervention at OUS, Ullevål Tonje Amb Aksnes and Professor and section leader of the echocardiography department at OUS, Ullevål Jørgen Gravning. The TAVI-team at the section of cardiac intervention at OUS, Ullevål supports the study and will assist in recruiting patients. The study will be part of an ongoing PhD-project at the University of Oslo that is supervised by MD PhD Trygve Sundby Hall, MD PhD Anders Opdahl, Professor Jørgen Gravning and Professor Thor Edvardsen.

13. Ethical considerations

- The study will be conducted according to the principles of the Declaration of Helsinki and the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors.
- We will seek approval in our hospital's local ethics committee and the privacy protection act supervisor.

- We will seek approval from the Norwegian Regional Committees for Medical and Health Research Ethics (REK).
- Informed consent will be obtained from all participants.
- Data confidentiality will be maintained according to Good Clinical Practice (GCP) guidelines.
- We consider the study to be a pilot study as this specific approach to patient-specific rotation has not been investigated previously. However, similar studies have been conducted on different rotation methods that have improved commissural alignment of current and previous generations of TAVI valves. Based on the findings found in these studies, we believe that a further patient-specific approach to the degree of rotation in the descending aorta could improve commissural alignment and potentially facilitate subsequent access to the coronary arteries by angiography/PCI, as well as improve the results of “redo TAVI” and valve functionality/durability. However, we believe it is ethically sound practice to initially evaluate whether differences in commissural alignment will be observed and, if so, how large this is, as well as to conduct CT-based analysis for the likelihood of coronary access after implantation. We have opted not to test coronary access after surgery with selective coronary angiography as this procedure does not have sufficient benefit and only imposes additional risk to the patients included. As various rotation techniques are currently performed based on the operator's own judgment, we believe it is appropriate to initially investigate the approach scientifically, prospectively and systematically in a study. Based on the observations from the study, it will be easier to assess whether it is appropriate to conduct a larger study to evaluate whether the method will actually improve coronary access in future clinical events and the results of "redo TAVI" in those patients who need this in the years after the first implantation.
- The study will assess and compare two techniques that in daily clinical practice may be used according to operator preference. Thus, the consequences of participating in the study are minimal for each patient, since the only additional investigation will be a post-TAVI CT-scan. However, this CT-scan may also be an advantage for the included patients as information obtained from this CT will be informative for future investigations and if PCI is needed during follow-up. Therefore, we believe that both the potential benefit and the potential risk for each study participant is limited. The observations from the study may inform and better define if there should be a preferred implantation technique in the future.

14. Estimated timeline

OUS Ullevål hospital performs about 200 TAVIs per year, of which approximately 60% (n = 120) are performed with the Evolut FX+ valve. We aim to continuously include patients from September 2025 until the target inclusion of 40 patients is reached (estimated to be around January-May 2026). After final inclusion, the data will be analysed and used for research until May 2031 (project period end). After May 2031, the data will be stored for five years until May 2036 (for control purposes and no active research will be done after project period end May 2031).

15. Purpose and implications

We anticipate that the patient-specific implantation techniques may:

- Improve commissural alignment, leading to better coronary access and a higher degree of success in redo TAVI-procedures.
- Reduce procedural complexity for future diagnostic angiography/PCI/redo TAVI-procedures.
- Contribute to refining best practices for Evolut FX+ valve implantation in TAVI patients.

16. Financial aspects and disclosures

- The study will be financed in full by Oslo University Hospital. Dr. Al-Ani disclose that he serves as a proctor (interventional cardiologist) for Medtronic, which has manufactured the Evolut FX+ valve. Medtronic will have no involvement in the study. The other study personnel have no disclosures to report.

17. Publication plan

- The observations from this study will be reported in peer-reviewed medical journals and at national/international conferences.

18. References

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