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LANDMARK trial: Update in study protocol

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Since the publication of the design paper of the LANDMARK trial (a randomized clinical trial comparing safety and efficacy of Myval transcatheter heart valve versus contemporary transcatheter heart valves in patients with severe symptomatic aortic valve stenosis) by Kawashima et al[1] in the American Heart Journal (NCT 04275726) in February 2021, the European Society of Cardiology guidelines,[2] Medical Device Coordination Group guidance as well as Valve Academic Research Consortium (VARC)[3] have been updated. The recruitment of the LANDMARK trial started in January 2021 and lasted for 3 years. To keep the trial contemporary by reflecting the European clinical practice and using the newest definitions, the protocol has been updated twice during the enrollment phase. Prior to the primary report of this randomized controlled trial, we would like to provide the readership of the journal and the community of the interventional cardiology with a comprehensive overview of the updated protocol.

The updated eligibility criteria were implemented in October 2021 and are presented in the Table. Instead of itemized and detailed eligibility criteria initially included in the first protocol,[1] the new eligibility criteria made the local heart team responsible for the assessment of the indication for TAVI. This allows the investigators to recruit TAVI candidates in line with the latest guidelines for management of the severe symptomatic aortic stenosis.

The randomization scheme remained as the covariate-adaptive 1:1 randomization between Myval and contemporary THV. This randomization scheme is appropriate to test the primary hypothesis of noninferiority of Myval THV series to contemporary valves (combined Sapien and Evolut THV series). However, the equal allocation within the contemporary THV series (50% Sapien THV series and 50% Evolut THV series) was removed. Accordingly, the secondary hypothesis of the respective noninferiority of Myval to Sapien and Evolut THV series were also removed.

To simplify the baseline and follow-up assessment, EuroSCORE II and Frailty index were excluded from mandatory items in electronic case report form. The definition of a treated population was added to address the crossover and/or deviations from the assigned treatment protocol; the analysis enables us to evaluate the performance of the devices according to the actual treatment.

A nested registry for the large size Myval (30.5 mm and 32 mm) was initiated to evaluate the outcome of the patients who were excluded from the randomization due to the large size of annulus (≧ 30 mm).

Table. Updated eligibility criteria, randomization sheme and primary endpoint.

Inclusion criteria
1. Patient ≥ 18 y of age. 2. Patient or their legal representative has provided written informed consent as approved by the Institutional Review Board (IRB)/Ethics Committee of the investigational site to participate in the study. 3. As per local Heart Team assessment, patient is eligible for TAVI and the patient is suitable for implantation with all three study devices.
Exclusion criteria
1. Patients who are not willing to provide an informed consent form, or whose legal heirs object to their participation in the study. 2. Any condition, which in the Investigator's opinion, would preclude safe participation of patient in the study.
Randomization scheme
Covariate-adaptive 1:1 randomisation between Myval and contemporary THV
Primary composite endpoint*
Composite of • All-cause mortality • All stroke • Bleeding (Type 3 and 4) • Acute kidney injury (stages 2, 3, and 4) • Major vascular complications • Moderate or severe prosthetic valve regurgitation • Conduction system disturbances resulting in a new permanent pacemaker implantation

* According to the VARC-3 definition.

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The updated primary endpoint is presented in the Table. The primary composite endpoint remained consistent with the original version of the protocol, but the definition of the component of the composite was updated according to the VARC-3 criteria.[3] This change was implemented in June 2023 and all adjudications of clinical events by the independent committee are performed using VARC-3 criteria.

The enrollment of the LANDMARK trial concluded in December 2023 and the primary outcome at 30 days will be soon available. With the amended protocol, the LANDMARK trial investigates the validity of primary clinical hypothesis in population close to European practice with contemporary standardized clinical endpoints.

Conflicts of Interest

Akihiro Tobe received a grant from Fukuda foundation for medical therapy. Andreas Baumbach received lecture fees from Astra Zeneca and Microport. Andereas Baumbach is a participant of advisory board of Pi-Cardia and Faraday. Patrick W Serruys received consulting fees from Philips/Volcano, SMT, Novartis and Xeltis.

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