LANDMARK trial: Update in statistical analytical plan and protocol for the one-year report

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PII: S0002-8703(24)00035-8
DOI: https://doi.org/10.1016/j.ahj.2025.04.008
Reference: YMHJ 7166

To appear in: *American Heart Journal*

Please cite this article as: Akihiro Tobe MD , Yoshinobu Onuma MD, PhD , Niels van Royen MD, PhD , Ignacio J Amat-Santos MD, PhD , Ashokkumar Thakkar MD, PhD , Udita Chandra MD , Sanaa Ansari M.Pharm , Kasala Latheef PhD , Andreas Baumbach MD , Patrick W Serruys MD, PhD , LANDMARK trial: Update in statistical analytical plan and protocol for the one-year report, *American Heart Journal* (2025), doi: https://doi.org/10.1016/j.ahj.2025.04.008

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Word count: manuscript excluding references and Table 293 words

(There is no clear word count, but should be brief.)

The LANDMARK trial demonstrated the non-inferiority of the Myval transcatheter heart valve (THV) series compared to contemporary standard THVs (Sapien and Evolut series) with respect to the composite of safety and effectiveness endpoint at 30 days in patients with symptomatic severe aortic stenosis.[1-3] The primary results at 30 days were published in The Lancet in May 2024.

For the upcoming 1-year report, the steering committee and sponsor have decided to update the statistical analytical plan before analyzing the 1-year outcomes to ensure alignment with VARC-3 recommendations.[4] The clinical efficacy endpoint at 1 year is a composite of freedom from all-cause mortality, all stroke, or procedure- or valve-related hospitalization. Non-inferiority will be tested in the intention-to-treat population. Assuming an event rate of 27.23% based on previous studies,[5-7] with a total of 768 patients (384 per group) and a non-inferiority margin of 10.89% (40% of the assumed event rate), the calculated power under these conditions is 94%, with a one-sided alpha of 0.05. The window period for 1-year follow-up is between day 335 and day 395. Given the substantial number of censoring events within this period, Kaplan-Meier estimates at day 335 will be reported as the 1-year outcome.

Additionally, a clinical efficacy endpoint incorporating quality of life assessment has been added according to the VARC-3 recommendation. This composite endpoint includes all-cause mortality, all stroke, procedure- or valve-related hospitalization, and a decrease of ≥2.5 points

in the physical and mental domains of the SF-12 compared to pre-procedure values. Multiple imputation by chained equation will be used for missing SF-12 data.

This protocol update was implemented on 18th Februrary 2025, prior to the 1-year outcomes analysis. All clinical events are adjudicated by an independent committee using VARC-3 criteria.

The 1-year report of the LANDMARK trial will be presented soon.

Table. Clinical efficacy composite endpoint at one year*

Clinical efficacy at 1, 3 and 5 years (Kaplan-Meier estimate)
Composite of freedom from 1. All-cause mortality 2. All stroke 3. Procedure- or valve-related hospitalization
Clinical efficacy with quality of life assessment at 1 year (binary proportion)
Composite of freedom from 1. All-cause mortality 2. All stroke 3. Procedure- or valve-related hospitalization 4. A decrease of 2.5 poitns or more in physical and mental domains of SF-12 compared with pre-procedure values

*According to the VARC-3 definition.

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