BASELINE trial: update in study design

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The study design of the BASELINE trial (The BAlloon Expandable vs. Self-Expanding Transcatheter VaLve for Degenerated Bioprosthesis) was published in the American Heart Journal (NCT04843072) in February 2023.[1] It was designed as an investigator-initiated, nonfunded, prospective, randomized, multinational, multicenter, open-label, superiority trial. The original objective of the trial was to compare the balloon-expandable Sapien3 Ultra with the self-expanding Evolut R/PRO/PRO+ valve systems in symptomatic patients with a failing surgical aortic bioprosthesis. Since then, the protocol has been updated. The purpose of this letter is to inform the Journal readership and interventional cardiology community on the updated BASELINE trial protocol.

The protocol amendments for the BASELINE Trial study design are presented in the Table 1.

Investigational device

The original study design compared balloon-expanding transcatheter heart valves (THVs) using the SAPIEN3 Ultra valve with self-expanding THVs using the Evolut R/PRO/PRO+ valve systems. In the latest protocol, the Myval™ THV (Meril Life Sciences Pvt. Ltd., Vapi, Gujarat, India) has been introduced into the study. As a result, the primary objective has been updated to compare valve-in-valve transcatheter aortic valve replacement (VIV-TAVR) using all commercially available iterations of Sapien/Myval THV series with the Evolut THV series in symptomatic patients with a failing surgical bioprosthesis. Once randomized to receive the balloon-expandable THV, the choice between the Sapien or Myval THV is at the discretion of the investigational site.

Myval is a new-generation balloon-expandable THV system that has demonstrated favorable procedural and clinical outcomes across various subpopulations.[2,3] Transcatheter VIV/valve-in-ring Myval THV implantation for failed left side heart bioprosthesis presented a high success rate, low early and mid-term mortality and morbidity in a 1-year follow-up study.[4] In alignment with results of previous studies in native aortic stenosis patients, a 2-year follow-up after Myval implantation demonstrated a high device success rate along with no vascular complications, a very low rate of pacemaker implantation and no signs of structural valve deterioration.[5] Recently, the LANDMARK trial demonstrated noninferiority of Myval valve in terms of safety and effectiveness to contemporary valves (Sapien and Evolut series).[6,7] Low rates of moderate to severe paravalvular leak and permanent pacemaker insertion have also been reported with the Myval and Myval Octacor THV systems.[8] These study findings indicate that TAVI with the Myval technology achieves satisfactory safety and efficacy. Hence, to make the trial contemporary by reflecting the results of recent trials, the decision was made to include Myval THV series in this trial.

Eligibility criteria

The age limit for participation in the trial was originally set at ≥65 years. In contemporary practice, however, the number of patients with a failing surgical bioprosthesis accepted for VIV-TAVR under the age of 65 years is increasing. Regardless of patient age, heart-teams encounter similar challenges and uncertainties when using balloon- vs self-expanding THVs for failing surgical bioprostheses. Therefore, it was decided to lower the age cutoff from 65 to 18 years and leave study eligibility to the discretion of the local heart-team, in accordance with the other in- and exclusion criteria.

Primary endpoint modification

The primary endpoint (VARC-3 defined device success)[9] has been modified to include severe prosthesis patient mismatch (PPM) as an additional indicator of early hemodynamic valve performance. The rationale for adding this component to the primary endpoint is that, unlike TAVR for native aortic stenosis, VIV-TAVR carries a higher risk for severe PPM which may affect prognosis. Adopting the modified primary endpoint (defined in Table 1) does not affect the expected event rates or sample size (n = 440). This is because the power calculation is based on the anticipated number of patients with high

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Table 1. Protocol amendments in BASELINE TRIAL

Protocol updates	Original study design	Updated study design
Study design	1:1 Randomization (Sapien 3/Ultra vs Evolut R/Pro)	1:1 Randomization (Sapien/ Myval THV Series vs Evolut THV series)
Inclusion	Age ≥65 years	Age ≥18 years
Primary endpoint	Device success, VARC 3 definition: "device success" definition in new version 3.0 (red was added): a) Absence of procedural mortality AND b) Technical success at exit from procedure room defined as freedom (a) from mortality, (b) successful access, delivery of the devices, and retrieval of the delivery system, (c) correct positioning of a single prosthetic heart valve into the proper anatomical location and (d) freedom from surgery or intervention related to the device or to a major vascular or access-related, or cardiac structural complication AND c) Intended performance of the prosthetic heart valve (no severe prosthesis-patient mismatch and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, Doppler velocity index ≥0.25, no moderate or severe prosthetic valve regurgitation).	Device success, VARC 3 **modified** definition: "device success" definition in new version 3.0 (red was added): a) Absence of procedural mortality AND b) Technical success at exit from procedure room defined as freedom (a) from mortality, (b) successful access, delivery of the devices, and retrieval of the delivery system, (c) correct positioning of a single prosthetic heart valve into the proper anatomical location and (d) freedom from surgery or intervention related to the device or to a major vascular or access-related, or cardiac structural complication AND c) Intended performance of the prosthetic heart valve (no severe prosthesis-patient mismatch and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, Doppler velocity index ≥0.25, no moderate or severe prosthetic valve regurgitation). **Clinically significant prosthesis patient mismatch is defined by EOAi ≤0.65 cm2 /m2 (≤0.55 if BMI ≥30 kg/m2)[11].**
Secondary endpoint		Novel secondary endpoints: Prosthetic valve function, as measured by invasive hemodynamic assessment after implantation of the transcatheter heart valve: – Peak gradient (mmHg) – Mean gradient (mmHg) – Aortic regurgitation index calculated as: ([diastolic aortic blood pressure—left ventricular end-diastolic blood pressure] / systolic aortic blood pressure) x 100

residual gradients (mean gradient >20 mmHg), which is the main driver of PPM risk.

Novel secondary endpoints

In addition to echocardiographic assessment of hemodynamic valve performance, the BASELINE trial also provides data on invasive hemodynamic performance before and after VIV-TAVR. Given the discrepancy between echo-derived and invasive measures for assessing normal bioprosthetic valve functioning, and with some reports even cautioning against the use of echo-derived valve assessment post-TAVR and post-VIV-TAVR,[10] it was decided to select invasive hemodynamic parameters as new secondary endpoints in the updated protocol. The 3 novel secondary endpoints include: post-VIV-TAVR invasively measured peak gradient, mean gradient and aortic regurgitation index, which is calculated as ([diastolic aortic blood pressure—left ventricular end-diastolic blood pressure] / systolic aortic blood pressure) x 100.

The new protocol (Table 2) aims to improve the clinical-scientific value of the trial and enhance the transcatheter management of degenerative surgical bioprosthetic valve disease.

Table 2. Updated protocol

Updated protocol

Objective
The primary objective is to compare safety and efficacy of balloon vs. self-expanding THV for the treatment of a failing surgical aortic bioprosthesis.

Study design
1:1 randomization to TAVI with Sapien/Myval Series or Evolut THV Series.

Inclusion criteria
In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- Age ≥18 years
- Failing surgical aortic bioprosthesis requiring valve replacement and eligible for transfemoral TAVI with balloon expandable or self-expanding platform per heart team consensus based on multimodality imaging assessment (including echocardiography and multidetector CT).
- Written informed consent

Exclusion criteria
A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Not eligible for Transfemoral TAVI with Sapien/Myval and/or Evolut.
- Multivalve defects requiring intervention in 1 procedure.
- Clinically unstable and/or inotropic/vasopressor /mechanical support.
- Known mural thrombus in the left ventricle.
- Presence of a mechanical aortic valve.
- History of recent (within 1 month) stroke or TIA.

Primary endpoint is device success by VARC-3 at 30 days.
- Absence of procedural mortality AND
- Technical success at exit from procedure room defined as freedom (a) from mortality, (b) successful access, delivery of the devices, and retrieval of the delivery system, (c) correct positioning of a single prosthetic heart valve into the proper anatomical location and (d) freedom from surgery or intervention related to the device or to a major vascular or access-related, or cardiac structural complication AND
- Intended performance of the prosthetic heart valve (no severe prosthesis- patient mismatch and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, Doppler velocity index ≥0.25, no moderate or severe prosthetic valve regurgitation). Clinically significant prosthesis patient mismatch is defined by EOAi ≤0.65 cm^2/m^2 (≤0.55 if BMI ≥30 kg/m^2). (15)

Safety endpoint at 1 year defined by the composite of all-cause death, disabling stroke, rehospitalization for heart failure or valve related problems.

Secondary endpoints
- All-cause mortality.
- Any stroke.
- Life threatening bleeding.
- Acute kidney injury.
- Coronary artery obstruction requiring intervention.
- Major vascular complication.
- Valve related dysfunction requiring repeat procedure.
- Rehospitalization for valve-related symptoms or worsening congestive heart failure.
- All cause rehospitalization.
- Valve-related or Heart-failure related rehospitalization.
- New Conduction disorder.
- New Pacemaker-implantation.
- Myocardial Infarction.
- NYHA heart failure class III or IV.
- Prosthetic valve function, as measured by trans thoracic echocardiography and evaluated by an independent core lab:
  - √ Left ventricular ejection fraction (%).
  - √ Peak velocity (m/s).
  - √ Mean gradient (mmHg).
  - √ Effective orifice area (cm^2).
  - √ Indexed effective orifice area (m^2/cm^2).
  - √ Prosthetic aortic valve regurgitation.

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Table 2. (*continued*)

Updated protocol

- Prosthetic valve function, as measured by invasive hemodynamic assessment after implantation of the transcatheter heart valve and after valve optimization manoeuvre (ie, postdilatation, if applicable):
  - √ Peak gradient (mmHg).
  - √ Mean gradient (mmHg).
  - √ Aortic regurgitation index calculated as: ([diastolic aortic blood pressure—left ventricular end-diastolic blood pressure] / systolic aortic blood pressure) x 100.

Declaration of competing interest

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