BA lloon Expandable vs. SElf Expanding Transcatheter VaLve for Degenerated BioprosthesIs: Design and Rationale of the BASELINE Trial

Rutger-Jan Nuis MD, PhD , Eric van Belle MD, PhD , Rui Teles MD, PhD , Daniel Blackman MD, PhD , Verena Veulemans MD, PhD , Ignacio Amat Santos MD, PhD , Thomas Pilgrim MD, PhD , Giuseppe Tarantini MD, PhD , Francesco Saia MD, PhD , Ioannis Iakovou MD, PhD , Julia Mascherbauer MD, PhD , Flavien Vincent MD, PhD , Marcel Geleijnse MD, PhD , Janarthanan Sathananthan MD, PhD , David Wood MD, PhD , Raj Makkar MD, PhD , Nicolas M. Van Mieghem MD, PhD , On behalf of the BASELINE Investigators

PII: S0002-8703(22)00295-2
DOI: https://doi.org/10.1016/j.ahj.2022.11.013
Reference: YMHJ 6661

To appear in: *American Heart Journal*

Received date: July 3, 2022
Accepted date: November 15, 2022

Please cite this article as: Rutger-Jan Nuis MD, PhD , Eric van Belle MD, PhD , Rui Teles MD, PhD , Daniel Blackman MD, PhD , Verena Veulemans MD, PhD , Ignacio Amat Santos MD, PhD , Thomas Pilgrim MD, PhD , Giuseppe Tarantini MD, PhD , Francesco Saia MD, PhD , Ioannis Iakovou MD, PhD , Julia Mascherbauer MD, PhD , Flavien Vincent MD, PhD , Marcel Geleijnse MD, PhD , Janarthanan Sathananthan MD, PhD , David Wood MD, PhD , Raj Makkar MD, PhD , Nicolas M. Van Mieghem MD, PhD , On behalf of the BASELINE Investigators, BA lloon Expandable vs. SElf Expanding Transcatheter VaLve for Degenerated BioprosthesIs: Design and Rationale of the BASELINE Trial, *American Heart Journal* (2022), doi: https://doi.org/10.1016/j.ahj.2022.11.013

Trial Designs

BA lloon Expandable vs. SElf Expanding Transcatheter VaLve for Degenerated BioprosthesIs: Design and Rationale of the BASELINE Trial

Rutger-Jan Nuis[1], MD, PhD; Eric van Belle[2], MD, PhD; Rui Teles[3], MD, PhD; Daniel Blackman[4], MD, PhD; Verena Veulemans[5], MD, PhD; Ignacio Amat Santos[6], MD, PhD; Thomas Pilgrim[7], MD, PhD; Giuseppe Tarantini[8], MD, PhD; Francesco Saia[9], MD, PhD; Ioannis Iakovou[10], MD, PhD; Julia Mascherbauer[11], MD, PhD; Flavien Vincent[2], MD, PhD; Marcel Geleijnse[1], MD, PhD; Janarthanan Sathananthan[12], MD, PhD; David Wood[12], MD, PhD; Raj Makkar[13], MD, PhD; Nicolas M. Van Mieghem[1,*], MD, PhD; On behalf of the BASELINE Investigators

[1]Department of Cardiology, Erasmus University Medical Center, Rotterdam, Netherlands

[2]Department of Cardiology, Institut Cœur Poumon, CHU Lille, Lille, France

[3]Hospital de Santa Cruz, CHLO; Nova Medical School, CEDOC, Lisbon, Portugal

[4]Department of Cardiology, Leeds Teaching Hospitals NHS Trust, Leeds, United Kindom

[5]Division of Cardiology, Heinrich Heine University Medical Center Dusseldorf, Dusseldorf, Germany

[6]Departamento de Cardiología, Hospital Clínico Universitario, Valladolid, Spain

[7]Department of Cardiology, Bern University Hospital, University of Bern, Bern, Switzerland

[8]Department of Cardiac, Thoracic, Vascular Science and Public Health, University of Padova, Padua, Italy

[9]U.O. Cardiologia, Dipartimento Cardio-Toraco-Vascolare, Azienda Ospedaliero-Universitaria di Bologna, Policlinico S. Orsola-Malpighi, Bologna, Italy

[10]Department of Cardiology, Onassis Cardiac Surgery Center, Athens, Greece

[11]Department of Cardiology, University Hospital St. Polten, Austria

[12]Centre for Cardiovascular and Heart Valve Innovation, St. Paul's and Vancouver General Hospital, Vancouver, Canada

[13]Department of Cardiology, Cedars-Sinai Medical Center, Los Angeles, United States

[*]**Corresponding Author:** Dr. Nicolas M. Van Mieghem, MD, PhD, Department of Interventional Cardiology, Erasmus University Medical Center, Room Nt-645, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. Phone: +31(0)107035260, Email: n.vanmieghem@erasmusmc.nl

ABSTRACT

Background: Surgical aortic valve bioprostheses may degenerate over time and require redo intervention. Transcatheter aortic valve replacement (TAVR) is a less invasive alternative to redo surgery. The ***BA***lloon Expandable vs. ***SE***lf Expanding Transcatheter Va***L***ve for Degenerated Bioprosthes***I***s **(BASELINE) trial** was designed to compare the performance of the balloon-expandable SAPIEN-3 Ultra and the self-expanding EVOLUT PRO+ valve systems in symptomatic patients with a failing surgical bioprosthesis.

Methods: The BASELINE trial is an investigator-initiated, non-funded, prospective, randomized, open-label, superiority trial enrolling a total of 440 patients in up to 50 sites in 12 countries in Europe and North-America. The primary endpoint is device success at 30-days defined by the Valve Academic Research Consortium-3 Criteria as the composite of technical success, freedom from mortality, freedom for surgery or intervention related to

the device or to a major vascular or access-related or cardiac structural complication with an intended performance of the valve (mean gradient <20 mmHg and less than moderate aortic regurgitation). The co-primary endpoint at 1 year is defined as the composite of all-cause death, disabling stroke, rehospitalization for heart failure or valve related problems. Independent Core Laboratories will conduct uniform analyses of echocardiography (pre-, post-, 1-year post-procedure), multi-sliced computed tomography (pre-, and if available post-procedure) and cine-fluoroscopy studies.

Conclusions: The BASELINE trial is a head-to-head comparative trial investigating the two most used contemporary transcatheter heart valves for the treatment of a failing surgical aortic bioprosthesis. (ClinicalTrials.gov number NCT04843072).

Keywords: Surgical bioprosthetic valve degeneration, valve-in-valve, randomized trial, transcatheter aortic valve replacement

INTRODUCTION

Surgical aortic valve replacement (SAVR) serves many patients with aortic valve disease[1, 2], with currently more than 200.000 procedures performed annually worldwide and a predicted increase to 850.000 per year in 2050[3, 4]. Bioprosthetic valves represent the mainstream in SAVR and are increasingly used in younger patients because of a low thrombosis risk and no need for lifelong anticoagulation[4, 5]. Yet, bioprosthetic valves have limited durability, with surgical prosthetic degeneration and failure ensuing within 10 to 15 years[6]. As a result, the number of patients that outlive their prosthesis and require valve reintervention is increasing. Transcatheter aortic valve (TAV) implantation (TAVI) has emerged as a less invasive treatment option for failed surgical aortic valve (SAV) bioprostheses than redo surgery[7, 8]. Limitations of TAV-in-SAV relative to TAVI for native

aortic valve disease include an incremental risk for coronary occlusion, device malposition and prosthesis-patient mismatch (PPM)[9, 10]. Currently, the most used transcatheter heart valves for the treatment of failing SAVs are the balloon-expandable (BE) SAPIEN-3 Ultra and the self-expanding (SE) EVOLUT PRO+ systems. The balloon-expandable SAPIEN-3 Ultra is a short intra-annularly functioning TAV which is fundamentally different from the long supra-annularly functioning self-expanding EVOLUT platform. A supra-annular design may offer superior hemodynamic valve performance but may be at higher risk for paravalvular leak and/or coronary obstruction. Whether other hazards related to TAV-in-SAV therapy (e.g. conduction abnormalities, aortic rupture, bioprosthetic thrombosis) is different with either TAV platform is unsettled.

The ***BA***lloon Expandable vs. ***SE***lf Expanding Transcatheter Va***L***ve for Degenerated Bioprosthes***I***s (BASELINE) trial is a randomized controlled trial comparing device success at 30 days and clinical efficacy at 1 year between the two most used contemporary TAV-technologies for the treatment of symptomatic patients with a degenerated SAV.

MATERIALS AND METHODS

The BASELINE trial is an investigator-initiated, non-funded, prospective, randomized, multinational, multicenter, open-label, superiority trial. The primary objective is to compare TAV-in-SAV with the balloon-expandable SAPIEN-3 Ultra valve vs. the self-expanding EVOLUT PRO+ valve in terms of device success at 30 days as defined by the latest Valve Academic Research Consortium-3 Criteria[11] (**Figure 1).** Patient with a failing transcatheter aortic bioprosthesis accepted for TAVI will be followed in a nested TAV-in-TAV registry (details below).

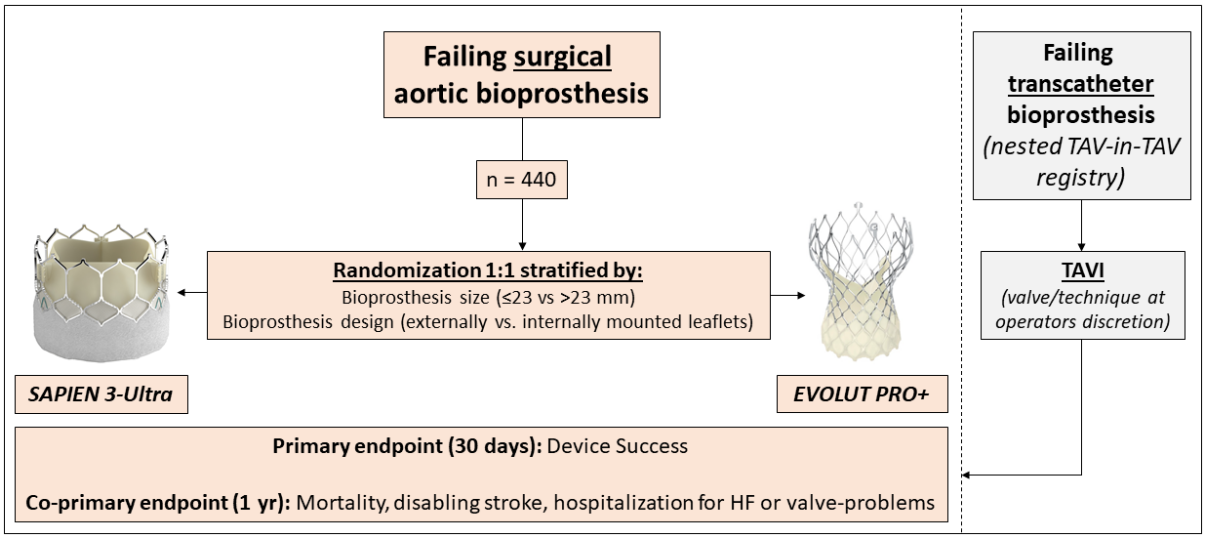

Figure 1. Study flowchart of the Baseline Trial *(This Figure requires colors upon publication)*

Patients will be enrolled in up to 50 structural heart valve sites across 12 countries in Europe and North America **(Figure 2).** In November 2021 the first patient enrolled into the study; in June 2022 (date of manuscript submission) a total of 16 patients were randomized in 4 investigational sites. The study is conducted in accordance with the principles stated in the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice. There is no involvement of industry and no extramural funding was used to support this work. The authors are responsible for the design and conduction the trial, the study analyses, the drafting and editing of the manuscript and its final contents. Trial administration and data management will be carried out in the Erasmus University Medical Center, Rotterdam, Netherlands. The trial is registered under ClinicalTrials.gov number **NCT04843072**.

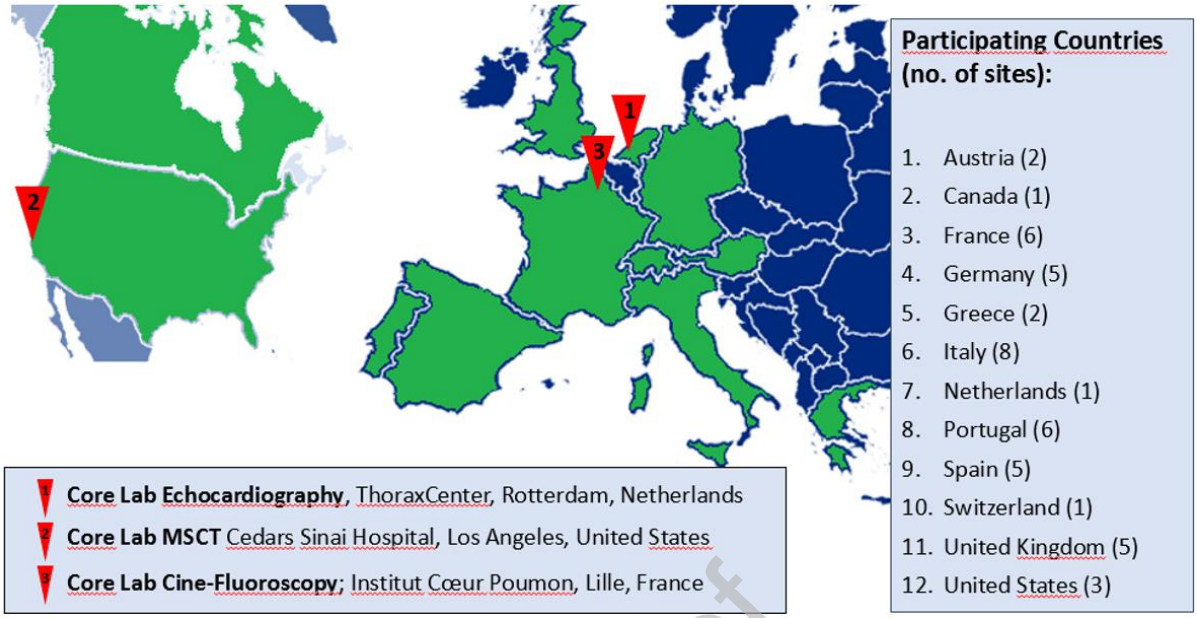

Figure 2. Geographical overview of investigational sites and imaging Core Laboratories the BASELINE Trial *(This Figure requires colors upon publication)*

STUDY POPULATION

All patients experiencing symptoms due to a failing SAV through regurgitation, stenosis or a combination and who are selected per Heart-Team consensus and conform to a set of in- and exclusion criteria will be eligible for study participation **(Table 1)**. Data of patients who are screened but not randomized will be collected in a screening log, including the reason for not entering the study (i.e. anatomical not eligible, physician's preference, formal exclusion criterion, participation in a different trial etc.). Written patient informed consent must be provided as approved by the ethical committee of the respective clinical site.

Table 1. Summary of key inclusion and exclusion criteria

Inclusion criteria
1. Age ≥ 18 years
2. 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 multi-modality
3. Written informed consent
Exclusion criteria
1. Not eligible for Transfemoral TAVI with SAPIEN-3 / Ultra and Evolut Pro+
2. Multi-valve defects requiring intervention
3. Clinically unstable and/or inotropic/vasopressor /mechanical support.
4. Known mural thrombus in the left ventricle
5. History of recent (within 1 month) stroke or transient ischemic attack

Nested TAV-in-TAV registry

Similar to the surgical population, the number of patients with valve degeneration after native TAVI is expected to increase as eligibility criteria expand to lower risk categories. Limited data indicate that TAV-in-TAV for degenerated transcatheter valves is feasible but associated with distinctive challenges. For the purpose of generating new insights on this issue, a nested TAV-in-TAV registry will be implemented thereby leveraging the existing infrastructure of the BASELINE trial **(Figure 1)**. Patients selected for enrollment in the registry follow the same study requirements as the main cohort and imaging data will be analyzed per Core Laboratory standards.

STUDY ENDPOINTS

Primary endpoint (30 days)

The primary endpoint is device success at 30 days defined as the composite of technical success (at exit from procedure room), freedom from mortality, freedom for surgery or intervention related to the device or to a major vascular or access-related or cardiac structural complication, intended performance of the valve (mean gradient <20

mmHg, peak velocity < 3 m/s, Doppler velocity index ≥0.25, and less than moderate aortic regurgitation)[11]. Technical success is defined as freedom from mortality at exit from procedure room with successful access, delivery and retrieval of the valve delivery system, correct valve positioning and no need for surgery or intervention related to the device or to a major vascular or cardiac related complication. The exact nature and date of death will be recorded[11].

Co-primary endpoint (1 year)

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

Secondary Endpoints

The following clinical endpoints as defined by the most recent VARC 3 criteria will be collected[11]:

1. All-cause mortality
2. Stroke (ischaemic, haemorrhagic, not otherwise specified)
3. Coronary artery obstruction requiring intervention
4. Myocardial Infarction
5. Overt bleeding type 1-4
6. Major vascular complication
7. Major Access-related non-vascular complication
8. Acute kidney injury stage III-IV
9. New Conduction disorder
10. New Pacemaker-implantation
11. Valve related dysfunction requiring repeat procedure
12. Rehospitalisation for valve-related symptoms or worsening congestive heart failure

13. All cause rehospitalisation

14. NYHA heart failure class III or IV

15. Bioprosthetic valve dysfunction categorized as:

a. structural valve deterioration (SVD: intrinsic permanent changes to the prosthetic valve)

b. non- structural valve dysfunction (NSVD: any abnormality not intrinsic to the prosthetic valve resulting in valve dysfunction such as patient-prosthesis mismatch or inappropriate positioning)

c. clinically significant valve thrombosis

d. endocarditis.

16. Hemodynamic valve deterioration stage I-III

17. Bioprosthetic valve failure stage I-III

RANDOMIZATION

Subjects will be randomized 1:1 to TAVI with the balloon-expandable or self-expanding TAV system and will be stratified by:

1. SAV labelled size (<23.0 vs ≥23 mm)
2. SAV design (with vs. without externally mounted leaflets)

The rationale for stratification is that small SAVs (<23.0 mm) yield higher risk for severe residual gradients (mean >20 mmHg) whereas SAVs with externally mounted leaflets carry significantly higher risk for coronary obstruction after TAV insertion. Both factors affect device success rates and, therefore, a balanced distribution of SAV size and design in this study is essential. Based on previous studies, the expected percentage of patients with a small SAV (<23 mm) is 19-27%[12-15]. The proportion of patients with a SAV composed of externally mounted leaflets seems less predictable (ranging between 2-42%)[16-19]. Following

screening and signing the informed consent form, patients will be electronically randomized prior to arterial access using random block size randomization, with lower boundary of 2 and upper boundary of 6.

TREATMENT AND FOLLOW-UP

The study flow chart is summarized in **Figure 1.** Patients are admitted prior to the TAVI procedure per local practice. TAVI procedure is executed per local standard using the Edwards Sapien-3 Ultra device or the EVOLUT PRO+ device. The use of ancillary devices (i.e. dedicated large-bore closure devices, cerebral embolic protection devices) and techniques (e.g. valve fracture, chimney stenting, bioprosthetic aortic scallop intentional laceration to prevent iatrogenic coronary obstruction [BASILICA]) are per operator's discretion and will be collected. TAVI is preferably performed under local anaesthesia/conscious sedation. Only transfemoral approach is allowed. Participating sites are encouraged to adhere to guidelines on antithrombotic and anticoagulant therapy. However, their use before and after the procedure is per treating physician's discretion and data on its (dis)continuation will be collected.

Data from enrolled subjects will be collected at baseline, pre-discharge, 30-days and at 1 year follow-up, including demographics, past medical history, current medications, standard laboratory data and New York Heart Association class (an extended follow-up until 5-years is currently under consideration by the steering committee). A uniform protocol for transthoracic echocardiographic acquisition of endpoint data will be used in all sites and three echocardiograms per patient (pre-procedure, pre-discharge or at 30 days, 1 year post TAVI) will be evaluated by an independent core laboratory (Erasmus Medical Center, Rotterdam, Netherlands). Similarly, all pre-procedure multi-sliced computed tomography (MSCT) images and cine-fluoroscopic images taken during the procedure will be anonymized

and evaluated by dedicated core laboratories in Cedars Sinai Hospital, Los Angeles, United States (for MSCT) and Institut Cœur Poumon, Lille, France (for cine-fluoroscopy). A post-TAVI MSCT is recommended 1 to 3 months post TAVI.

MONITORING

Prospective monitoring for the occurrence of the (co-)primary and secondary endpoints and serious adverse events starts at randomization and continues until 1 year follow-up. All study sites will be monitored periodically by and independent monitor to ensure that it is conducted, recorded, and reported in accordance with the study protocol, written procedures and the applicable regulatory requirements and standards. Monitoring and data review may occur remotely as well as during on-site visits and will be coordinated by the National Lead Investigator of each participating country (12 in total). Monitoring results will be reported to the coordinating center.

STATISTICAL CONSIDERATIONS

All patients who are eligible and enrolled in the study prior to TAVI will be included in the analysis. Primary analysis is based on the intention-to-treat sample. Sample size calculation was based on prior observational studies evaluating TAV-in-SAV with the balloon-expandable and self-expanding TAV-systems. VARC-3-defined device success has not been reported previously. Instead, most studies described the component endpoints of device success **(Table 2)**. The component endpoints seem equally frequent with BE and SE TAV systems, except for the rate of severe residual gradients (>20 mmHg) which vary between 34-38% after BE valves [10, 12-14, 20] and between 16-21% after SE valves[10, 12, 13, 19]. Of note, in patients with small surgical prostheses (≤23 mm labelled size), severe residual gradients have been reported in up to 62% after BE vs. 21% after SE valves. We estimated that the absence of device success will be 30% with balloon-expandable and 18% with self-expanding

valves. On the basis of these assumptions, a sample size of 200 patients per group (i.e. 400 in total) is needed for 80% power using an alpha of 0.025 (two-sided). The sample size was rounded up to 440 patients to accommodate dropouts etc.

DISCUSSION

Surgical aortic bioprosthetic failure represents a growing health issue as bioprosthetic valves are increasingly implanted in younger patients. TAV-in-SAV has become an established and often preferred strategy for patients with a failing aortic bioprosthesis who are by default at elevated operative risk because of the need for a re-sternotomy. In a matched comparison of high-risk patients from a nationwide study, TAV-in-SAV conferred an advantage over repeat-SAVR in terms of 30-day mortality, morbidity and bleeding complications[8]. Also in comparison with conventional TAVI, STS/ACC data indicate that TAV-in-SAV is associated with superior mortality and morbidity rates[7]. Nonetheless, despite these favorable results, TAV-in-SAV has been associated with an increased likelihood of coronary occlusion, device malposition, residual regurgitation and prosthesis-patient mismatch as compared to native TAVI[9]. In absence of robust randomized data, it is uncertain how different TAV systems affect procedural outcome. Recently, a small randomized study (LYTEN trial, n=98 patients) demonstrated that, in patients with small failed surgical bioprostheses (≤23 mm), self-expandable valves are associated with improved (echo-derived) valve hemodynamic performance as compared to balloon-expanding valves[10]. We designed the BASELINE trial (n=440 patients) to compare the performance of the self-expanding EVOLUT valve versus the balloon-expandable SAPIEN3 Ultra valve in patients with degenerated surgical bioprostheses. These comparative data will inform interventionalists in selecting which TAV will best fit the individual patient while it may serve surgeons with the

possibility to modify their SAVR technique and/or SAV choice for the benefit of future TAV-in-SAV procedures.

The premise of the BASELINE trial is that the self-expanding supra-annular functioning EVOLUT PRO+ is superior to the balloon expandable SAPIEN3 Ultra valve in terms of device success at 30 days (primary endpoint). Device success represents an accurate indicator of immediate procedural success addressing short-term procedure- and valve-related issues in addition to early hemodynamic performance of the valve[11]. In the context of TAV-in-SAV, the lower devices success rate with the BE valve is expected to result from higher transvalvular gradients as compared to the SE device. Data from the VIVID registry, PARTNER 2 and a large multicenter study found that the rate of severe residual gradients ≥20 mmHg range between 34-40% after BE-in-SAV while it varies between 16-21% after SE-in-SAV[12-14, 19, 20]. An overview of previously published studies reporting TAV-in-SAV outcomes stratified by TAV-device is shown in **Table 2.**

Irrespective of TAV-choice, however, final hemodynamic performance after TAV-in-SAV mostly depends on the characteristics of the failing surgical prosthesis. Pre-existing PPM of the surgical prosthesis as well as its design (stented>stentless), mode of failure (stenosis>regurgitation) and size play an important role[21]. Small SAVs have been associated with small effective orifice areas and high mean gradients and even mortality after TAV-in-SAV[7, 13, 19, 21, 22]. For these reasons, patients in this study will be stratified according to SAV size (<23 mm vs. ≥23 mm) to avoid imbalances between treatment groups that could bias study results. The use of pre- and/or post-dilatation with or without advanced techniques that facilitate optimal hemodynamic outcome such as prosthesis-ring fracturing are allowed as per discretion of the treating operator. Regardless of the use of these measures, however, balloon-expandable Sapien3 valve in this study most likely will be associated with

higher residual gradients and thus lower device success rates in comparison to the self-expanding Evolut system. In the subset of patients with a small surgical prosthesis (≤23 mm labelled size), severe residual gradients (>20 mmHg) were reported in 62% after balloon-expandable valve implantation (vs 21% after self-expanding valves)[10]. The clinical impact of higher than desirable residual gradients after TAV-in-SAV is currently unknown. Abbas et al[23, 24] recently found that invasively measured and echocardiography-derived transvalvular mean gradients correlate well in native aortic valve stenosis but weakly after TAVI for native valves and failed bioprosthetic valves. Echocardiography overestimates transvalvular mean gradients compared with invasive measurements, a discordance that was most profound in association with small BE devices[10]. Echocardiographic gradient assessment is based on the assumption that the maximal velocity is captured and converted to a pressure gradient using the Bernoulli equation. An inherent limitation is that these measurements record the maximal gradient immediately distal to the prosthesis and overestimate the gradients assessed more distally which are typically lower due to pressure loss recovery[25]. Also, the measurements assume laminar flow which is disturbed when 1 or 2 prosthetic valves are in situ. Conversely, invasive hemodynamic measurements are also limited by methodological issues such as time of measurement immediate post TAVI. Early changes in flow and/or other hemodynamic valve adaptions may explain the unreliability of hemodynamic measurements immediately after TAVI. How echocardiographic and invasive gradient measurements relate to one another before and after TAV-in-SAV, and how these indices affect 1-year clinical outcome (co-primary endpoint) will be investigated in the Baseline Trial. It requires uniform echocardiographic imaging interpretation and analysis which will be facilitated by a dedicated echocardiography core laboratory.

Coronary obstruction represents a potentially devastating complication of TAV-in-SAV procedures associated with mortality rates of up to 50%[17, 26]. The risk is approximately two-to-four times higher as compared to native TAVI, but can be 8-times higher in patients carrying a SAV with externally mounted leaflets as compared with SAVs with internally mounted leaflets[17]. The two main mechanisms relate to the expansion of the TAV-frame within the SAV with subsequent displacement of the SAV leaflets towards:

(i) the coronary ostium causing direct leaflet-ostium contact and obstruction, or

(ii) the sinotubular junction with formation of a cylinder causing sequestration of the sinus of Valsalva and subsequent impaired coronary filling.

The mechanisms imply that the risk of coronary obstruction is universal to all TAV designs as it mainly depends on the characteristics of the SAV and the relationship of its leaflets with the coronary ostiae and/or surrounding aortic structures (sinotubular junction). Observational studies indeed report similar rates of coronary complications with self- vs. balloon-expandable TAV-in-SAV procedures (0.8-3.8%[12-15, 20] vs. 0.9-3.2%[12, 13, 19], respectively). Nevertheless, TAV-systems with an extended sealing cuff, less predictable implantation depth and/or no repositioning or retrievability features might be associated with an increased risk for coronary complications. Also, in the event of coronary flow impairment, the BE-TAV may provide easier accessibility compared to the SE-TAV. The Baseline Trial will provide comparative insights on this matter. To ensure fair comparison between study-groups, stratified randomization based on the presence of externally mounted SAV leaflets will be performed. All MSCT's will undergo uniform and centralized analyses in a Core Laboratory to investigate the interaction between the TAV and SAV frames relative to surrounding anatomical structures. In approximately 50% of the patients

(n=∼200) a post-procedural MSCT will be available which allows for an in-vivo appreciation of key TAV-SAV interactions.

The post-procedural MSCT scans will also be analyzed for presence of hypoattenuated leaflet thickening (HALT) and reduced leaflet motion (RLM) as measures of (subclinical) leaflet thrombosis, a finding that has been suggested to be more common in valve-in-valve procedures as compared to native TAVI[27, 28]. In TAV-in-SAV, the immobilized and upward-oriented SAV-leaflets may act as a divider separating blood flow from the "sinus" and the "neo-sinus", leading to stasis of blood and potential valve thrombosis. However, data from the RESOLVE/SAVOURY registry could not confirm that there is an increased risk of leaflet thrombosis associated with TAV-in-SAV[29]. Conflicting data on this subject have led to heterogeneous policies including vitamin K antagonist, non-vitamin K antagonist oral anticoagulants or single antiplatelet agents after TAV-in-SAV procedures[30]. In the Baseline Trial, direct comparative data for contemporary TAV-devices in conjunction with pre- and post-procedure MSCT assessment of the prosthesis and surrounding anatomy will generate new insights on the incidence and mechanisms of TAV-in-SAV thrombosis.

Other safety issues such as the risk of stroke, paravalvular leak and need for new pacemaker seem less frequent after TAV-in-SAV as compared to after native TAVI[9]. Yet, compared to BE-in-SAV, SE-in-SAV has been associated with numerically higher rates of ≥moderate regurgitation (SE: 0-8.9% vs. BE: 0-2.5%) and pacemaker need (SE: 0-12.2% vs. BE: 0-5%) whereas stroke rates seem similar (SE: 0-1.6% vs. BE 0-2.7%, **Table 2)**.

Conclusion

The Baseline Trial is an international, prospective, multicenter, randomized-controlled trial comparing the two most used TAV systems for the treatment of failing surgical bioprosthetic valves. Insights on TAV-SAV interactions that determine clinical

outcome will help optimize patient selection, procedural planning and TAV selection in a more patient-tailored approach.

Declaration of Competing Interest

R Nuis: nothing to declare

E van Belle: nothing to declare

R Teles: nothing to declare

D Blackman: nothing to declare

V Veulemans: received consulting fees, travel expenses, or study honoraria from Medtronic, Edwards Lifesciences, and Boston Scientific.

I Amat Santos: proctor for Medtronic, Boston Scientific, Meril Life, and Products&Features

T Pilgrim: nothing to declare

G Tarantini: consulting fees, travel expenses, or study honoraria from Medtronic, Edwards Lifesciences, and gada

F Saia: advisory Board and Lecture Fees from Abbott, Medtronic, Edwards

I Iakovou: nothing to declare

J Mascherbauer: consulting fees, travel expenses, unrestricted grants from Medtronic, Edwards Lifesciences, Boston Scientific, Abbott.

F Vincent: nothing to declare

M Geleijnse: nothing to declare

J Sathananthan: consultant to Edwards, Medtronic and Boston scientific

D Wood: nothing to declare

R Makkar: nothing to declare

N Van Mieghem: received research grants from Edwards, Medtronic and Boston scientific

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;70(2):252-289.
2. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur J Cardiothorac Surg 2021;60(4):727-800.
3. Bax JJ, Delgado V. Bioprosthetic Heart Valves, Thrombosis, Anticoagulation, and Imaging Surveillance. JACC Cardiovasc Interv 2017;10(4):388-390.
4. Brown JM, O'Brien SM, Wu C, Sikora JA, Griffith BP, Gammie JS. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. J Thorac Cardiovasc Surg 2009;137(1):82-90.
5. Isaacs AJ, Shuhaiber J, Salemi A, Isom OW, Sedrakyan A. National trends in utilization and in-hospital outcomes of mechanical versus bioprosthetic aortic valve replacements. J Thorac Cardiovasc Surg 2015;149(5):1262-9 e3.
6. Dvir D, Bourguignon T, Otto CM, Hahn RT, Rosenhek R, Webb JG, et al. Standardized Definition of Structural Valve Degeneration for Surgical and Transcatheter Bioprosthetic Aortic Valves. Circulation 2018;137(4):388-399.

7. Tuzcu EM, Kapadia SR, Vemulapalli S, Carroll JD, Holmes DR, Jr., Mack MJ, et al. Transcatheter Aortic Valve Replacement of Failed Surgically Implanted Bioprostheses: The STS/ACC Registry. J Am Coll Cardiol 2018;72(4):370-382.

8. Hirji SA, Percy ED, Zogg CK, Malarczyk A, Harloff MT, Yazdchi F, et al. Comparison of in-hospital outcomes and readmissions for valve-in-valve transcatheter aortic valve replacement vs. reoperative surgical aortic valve replacement: a contemporary assessment of real-world outcomes. Eur Heart J 2020;41(29):2747-2755.

9. Edelman JJ, Khan JM, Rogers T, Shults C, Satler LF, Ben D, II, et al. Valve-in-Valve TAVR: State-of-the-Art Review. Innovations (Phila) 2019;14(4):299-310.

10. Rodes-Cabau J, Abbas A, Serra V, Vilalta V, Nombela-Franco L, Regueiro A, et al. Balloon- Versus Self-Expanding Valve Systems for Treating Small Failed Surgical Aortic Bioprostheses: The LYTEN Trial. J Am Coll Cardiol 2022.

11. Varc-3 Writing C, Genereux P, Piazza N, Alu MC, Nazif T, Hahn RT, et al. Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research. J Am Coll Cardiol 2021;77(21):2717-2746.

12. Dvir D, Webb J, Brecker S, Bleiziffer S, Hildick-Smith D, Colombo A, et al. Transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: results from the global valve-in-valve registry. Circulation 2012;126(19):2335-44.

13. Dvir D, Webb JG, Bleiziffer S, Pasic M, Waksman R, Kodali S, et al. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. JAMA 2014;312(2):162-70.

14. Webb JG, Mack MJ, White JM, Dvir D, Blanke P, Herrmann HC, et al. Transcatheter Aortic Valve Implantation Within Degenerated Aortic Surgical Bioprostheses: PARTNER 2 Valve-in-Valve Registry. J Am Coll Cardiol 2017;69(18):2253-2262.

15. Ye J, Cheung A, Yamashita M, Wood D, Peng D, Gao M, et al. Transcatheter Aortic and Mitral Valve-in-Valve Implantation for Failed Surgical Bioprosthetic Valves: An 8-Year Single-Center Experience. JACC Cardiovasc Interv 2015;8(13):1735-44.

16. Tchetche D, Chevalier B, Holzhey D, Harnath A, Schafer U, Teiger E, et al. TAVR for Failed Surgical Aortic Bioprostheses Using a Self-Expanding Device: 1-Year Results From the Prospective VIVA Postmarket Study. JACC Cardiovasc Interv 2019;12(10):923-932.

17. Ribeiro HB, Rodes-Cabau J, Blanke P, Leipsic J, Kwan Park J, Bapat V, et al. Incidence, predictors, and clinical outcomes of coronary obstruction following transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: insights from the VIVID registry. Eur Heart J 2018;39(8):687-695.

18. Ferrari E, Stortecky S, Heg D, Muller O, Nietlispach F, Tueller D, et al. The hospital results and 1-year outcomes of transcatheter aortic valve-in-valve procedures and transcatheter aortic valve implantations in the native valves: the results from the Swiss-TAVI Registry. Eur J Cardiothorac Surg 2019;56(1):55-63.

19. Deeb GM, Chetcuti SJ, Reardon MJ, Patel HJ, Grossman PM, Schreiber T, et al. 1-Year Results in Patients Undergoing Transcatheter Aortic Valve Replacement With Failed Surgical Bioprostheses. JACC Cardiovasc Interv 2017;10(10):1034-1044.

20. Webb JG, Murdoch DJ, Alu MC, Cheung A, Crowley A, Dvir D, et al. 3-Year Outcomes After Valve-in-Valve Transcatheter Aortic Valve Replacement for Degenerated Bioprostheses: The PARTNER 2 Registry. J Am Coll Cardiol 2019;73(21):2647-2655.

21. Bleiziffer S, Erlebach M, Simonato M, Pibarot P, Webb J, Capek L, et al. Incidence, predictors and clinical outcomes of residual stenosis after aortic valve-in-valve. Heart 2018;104(10):828-834.

22. de Freitas Campos Guimaraes L, Urena M, Wijeysundera HC, Munoz-Garcia A, Serra V, Benitez LM, et al. Long-Term Outcomes After Transcatheter Aortic Valve-in-Valve Replacement. Circ Cardiovasc Interv 2018;11(9):e007038.

23. Abbas AE, Mando R, Hanzel G, Gallagher M, Safian R, Hanson I, et al. Invasive Versus Echocardiographic Evaluation of Transvalvular Gradients Immediately Post-Transcatheter Aortic Valve Replacement. Circ Cardiovasc Interv 2019;12(7):e007973.

24. Abbas AE, Mando R, Kadri A, Khalili H, Hanzel G, Shannon F, et al. Comparison of Transvalvular Aortic Mean Gradients Obtained by Intraprocedural Echocardiography and Invasive Measurement in Balloon and Self-Expanding Transcatheter Valves. J Am Heart Assoc 2021;10(19):e021014.

25. Herrmann HC, Laskey WK. Pressure loss recovery in aortic valve stenosis: Contemporary relevance. Catheter Cardiovasc Interv 2022;99(1):195-197.

26. Bernardi FLM, Dvir D, Rodes-Cabau J, Ribeiro HB. Valve-in-Valve Challenges: How to Avoid Coronary Obstruction. Front Cardiovasc Med 2019;6:120.

27. Jose J, Sulimov DS, El-Mawardy M, Sato T, Allali A, Holy EW, et al. Clinical Bioprosthetic Heart Valve Thrombosis After Transcatheter Aortic Valve Replacement: Incidence, Characteristics, and Treatment Outcomes. JACC Cardiovasc Interv 2017;10(7):686-697.

28. Abdel-Wahab M, Simonato M, Latib A, Goleski PJ, Allali A, Kaur J, et al. Clinical Valve Thrombosis After Transcatheter Aortic Valve-in-Valve Implantation. Circ Cardiovasc Interv 2018;11(11):e006730.

29. Chakravarty T, Sondergaard L, Friedman J, De Backer O, Berman D, Kofoed KF, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. Lancet 2017;389(10087):2383-2392.

30. Bapat V. Technical pitfalls and tips for the valve-in-valve procedure. Ann Cardiothorac Surg 2017;6(5):541-552.

Table 2. TAV-in-SAV outcomes stratified for balloon- and self-expanding transcatheter valve systems

				surgical bioprosthesis		TAV-in-SAV Outcome								
Study	No. patients (study period)	Age (yrs)	STS (%)	% stented /stentless	% small label size (definition in mm)	No technical success (Embolization/ device retrieval / need 2nd valve)	coronary occlusion	Major Stroke	Pacemaker (%)	Mean gradient >20 mmHg (%)	severe PPM (%)	≥moderate AR (%)	30-day mortality	1-year mortality

Balloon-Expandable Valves														
Dvir et al. 2012 VIVID Registry	78 (2010 - 2012)	78	10%	87% / 13%	21% (≤19 mm)	13%	3.8%	2.6%	5%	38%	not reported	2.5%	10.3	18%
Dvir et al. 2014 VIVID Registry	246 (2007 - 2013)	78	9%	87% / 13%	26% (≤21 mm)	4.1% 2nd valve	2%	2.4%	4.9%	not reported	44%	2.4%	8%	19%
Webb et al. 2017 PARTNER	365 (2012 - 2014)	79	9%	92% / 6%	27% (≤21 mm)	1.9% 2nd valve	0.8%	2.2%	1.9%	34%	58%	1.9%	2.7%	12.4%

2 ViV Registry														
Ye et al. JACC Intv 2015 Single-center study	42 (2007-2013)	81	10%	not reported	19% (≤21 mm)	4.7%	2%	0%	0%	not reported	not reported	0%	1.4%	10%
Rodes Cabau et al. 2022 11-center	46 (2017-2022)	80	5%	100% / 0%	100% (≤23 mm)	0%	0%	0%	0%	62%	39%	0%	0%	Not reported

RCT														
Self-Expanding valves														
Dvir et al. 2012 VIVID Registry	124 (2010 - 2012)	77	13%	70% / 30%	28% (≤19 mm)	17%	3.2%	1.6%	9%	21%	not reported	6.5%	7.3%	11%
Dvir et al. 2014 VIVID Registry	213 (2007 - 2013)	78	11%	71% / 29%	32% (≤21 mm)	10% device retrieval 7.5% second valve	2%	0.9%	12.2%	not reported	15	8.9%	7%	15%
Deeb	227	7	9	82% /	33%	2.2%	0.9%	0	8.1%	17	not	3.5	2.2%	14.6

et al. 2017 Core Valve U.S. Expanded Use Study	(2013 - 2015)	7	%	12%	(≤21 mm)	ectopic valve 4.4% valve-in-valve		.4 %		%	reported	%		%
Tchetchet et al.2019 VIVA Postmarket Study	202	79	6.6 %	93% / 7%	42% (≤21 mm)	2% retrieval 1% 2nd valve 3% malposition	2%	0 %	8%	not reported	not reported	3.8 %	2.5%	8.8 %
Rode	52	8	5	100% /	100	0%	0%	0	0%	21	20%	0%	0%	Not

s Caba u et al. 2022 11-cent er RCT	(2017 - 2022)	0	%	0%	% (≤23 mm)			%		%				rep orte d