SMall Annuli Randomized To Evolut* or SAPIEN* Trial (SMART Trial)

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Medtronic, Inc. is sponsoring the SMART Trial, a prospective, multi-center, international, randomized controlled, post-market trial. The purpose of this trial is to generate clinical evidence on valve safety and performance of SE versus BE TAVR in...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac valve disorders
Study type	Interventional

Summary

ID

NL-OMON51976

Source
ToetsingOnline

Brief title
SMART trial

Condition

- Cardiac valve disorders

Synonym
Aortic valve stenosis, Small aortic annulus

Research involving
Human

Sponsors and support

Primary sponsor: Medtronic Trading NL BV
Source(s) of monetary or material Support: Medtronic

Intervention

Keyword: Severe native calcific aortic stenosis Small annulus, transcatheter heart valve replacement therapy.

Outcome measures

Primary outcome

The primary objectives of the trial are to demonstrate clinical non-inferiority

and hemodynamic superiority of the Evolut PRO/PRO+/Fx System when compared to

subjects treated with the SAPIEN 3/3 Ultra System at 12 months post-procedure.

Primary Endpoints

The trial will have two powered co-primary endpoints comparing the Medtronic SE

TAVs and Edwards BE TAVs to:

1. A clinical outcome composite endpoint of mortality, disabling stroke or

heart failure rehospitalization at 12 months.

2. A valve function composite endpoint of BVD at 12 months including any of the

following:

* HSVD: hemodynamic mean gradient >= 20mmHg

* NSVD: severe PPM, >= moderate AR

* Thrombosis

* Endocarditis

* Aortic valve re-intervention

Secondary outcome

The secondary objective of the trial is to generate long-term valve function

data for both SE and BE TAVR through 5 years of follow-up.

Powered Secondary Endpoints

The powered secondary endpoints for the trial comparing the SE and BE TAVR are:

- BVD in female subjects at 12 months

- HSVD at 12 months

- Hemodynamic mean gradient as continuous variable at 12 months

- Effective orifice area (EOA) as continuous variable at 12 months

- Moderate or severe prothesis-patient mismatch (PPM) at 30 days

Non-powered Secondary Endpoints pls see point 5.2.3 in CIP

Study description

Background summary

Pls see Page 17-18 of the CIP:

Transcatheter aortic valve replacement (TAVR) has been shown to be a safe and effective treatment for patients with severe aortic stenosis (AS) who are at extreme, high, intermediate or low surgical risk(1-8). Since TAVR devices became commercially available in the global market, two valve types have been widely used: self-expanding (SE) and balloon-expandable (BE). Both types of valves have different designs in expansion mode, leaflet characteristics and stent frames, which translate into different rates of procedural complications, and differences in hemodynamic function and long-term performance.
In recent years, reports from randomized trials, registry data, meta-data analysis, propensity score matched or unmatched analysis, or single-center experience have been published to provide device performance comparison of SE vs BE valves. In the CHOICE trial, a total of 241 high-risk patients were

randomized to receive a self-expanding CoreValve or a balloon-expandable SAPIEN XT, and the trial concluded that clinical outcomes at 1 year including death, all stroke, repeat hospitalization were not statistically different between the two devices despite the higher device success rate with the BE valve that was attributed to lower frequency of residual more-than-mild aortic regurgitation(9-10). The SOLVE-TAVI trial randomized 447 high to intermediate risk patients to an Evolut R or SAPIEN 3 device and concluded the SE and BE devices were equivalent for the primary efficacy endpoint(11). A propensity-matched comparison from the FRANCE-TAVI Registry compared the outcomes of SAPIEN XT/ SAPIEN 3 and CoreValve in a large nationwide registry and suggested the use of the SE devices was associated with a higher risk of paravalvular regurgitation (PVR) (12). However, reports from single centers identified similar short-term outcomes between third-generation SE and BE devices and rare clinically significant paravalvular leak(13-14). A meta-data analysis conducted by Osman, et al, showed similar outcomes were seen following transcatheter aortic valve replacement with BE (SAPIEN, SAPIEN XT, and SAPIEN 3) and SE (CoreValve, Evolut-R, and Evolut PRO) devices with the exception of a higher rate of pacemaker implantation and PVL in SE valve group(15).
Though these published data are based on various generations of devices, and are primarily comprised of earlier generations of the SE technology, there appears to be consistent evidence suggesting superior hemodynamic performance of SE compared with BE, with lower aortic valve mean gradient and/or large aortic valve area(9-12,13-14,16). The difference of hemodynamic performance could be attributed to the valve design differences with the supra-annular leaflet function in SE as opposed to an intra-annular level in BE. Initial hemodynamic performance of prosthetic aortic valves has been reported to be prognostic of intermediate and longer term clinical outcomes including hemodynamic or structural deterioration(17-18), heart failure hospitalization(19), and mortality(19-21). This is likely to be particularly true for patients with a small aortic annulus who are predisposed to having PPM when implanted with an intra-annular prosthesis(22). PPM primarily affects patients with impaired preoperative left ventricular function and results in decreased survival, lower freedom from heart failure, and incomplete left ventricular mass regression(23). The SE device appears to provide better performance compared to BE in patients with small aortic valve annuli, resulting in low rates of PPM and at least comparable rates of PVR based on insights from the CHOICE Trial and the CHOICE-Extend Registry (24). OCEAN-TAVI (Optimized CathEter vAlvular iNtervention) registry reported Evolut R seems to be superior to SAPIEN 3 in hemodynamic performance for patients with small annuli and body surface area up to 1 year after TAVR, and had significantly lower moderate PPM at 1 year in the extremely small annulus cohort (aortic annulus <= 21mm)25. Better hemodynamic profile of SE has also been reported for bicuspid patients via BEAT (self-expanding versus balloon-expandable valve for the treatment of bicuspid aortic valve stenosis) registry26.
With indications of TAVR being approved for all surgical risk levels, and more TAVR devices becoming commercially available, it is critically important to generate comparative evidence for patients and physicians to consider and allow

individualized selection of the TAVR device. Both SE and BE valve platforms have evolved over the last several years. For example, the iterations of the Edwards BE valve were made to address paravalvular leak major vascular complications27 and the Medtronic SE valve iterations included repositionability, an outer pericardial wrap to enhance annular sealing to promote a decrease in paravalvular leak28, and improved implantation methods with cusp overlap(29-30) and commissural alignment31. The SMall Annuli Randomized To Evolut or SAPIEN (SMART) Trial will provide a direct comparison of safety, efficacy, hemodynamics and long-term valve performance between SE and BE valves for patients with a small aortic annulus.

Study objective

Medtronic, Inc. is sponsoring the SMART Trial, a prospective, multi-center, international, randomized controlled, post-market trial. The purpose of this trial is to generate clinical evidence on valve safety and performance of SE versus BE TAVR in subjects with a small aortic annulus and symptomatic severe native aortic stenosis.

Study design

This trial is designed as a prospective, multi-center, international, randomized controlled, post-market trial to generate clinical evidence on valve safety and performance of self-expanding (SE) versus balloon-expandable (BE) transcatheter aortic valve replacement (TAVR) in subjects with a small aortic annulus and symptomatic severe native aortic stenosis.
Approximately 700 as-treated subjects will be recruited at approximately 90 sites located in Canada, EMEA and the United States. The trial may be expanded to include additional geographies based on enrollment rates, identification of qualified sites and local device indication approval.
Subjects will be randomized on a 1:1 basis to receive either a Medtronic SE or an Edwards BE TAV, and randomization will be stratified by site and sex (Figure 3).
To ensure a widespread distribution of data and minimize trial site bias in trial results, enrollments shall not exceed 20% (approximately 140 subjects) of total as-treated subjects at any individual site. Enrollment is competitive; therefore, there is no set minimum number of subjects to be enrolled per site and sites reaching 20% should seek approval from sponsor to continue enrollment.
The trial methods include the following measures to minimize potential sources of bias:
•All sponsors and external trial personnel will be trained on the Clinical Investigation Plan (CIP) and related trial materials.
•Subjects will be screened to confirm eligibility with pre-defined inclusion and exclusion criteria prior to enrollment and randomization.
•An external, independent Clinical Events Committee (CEC) will review and adjudicate, at minimum, all deaths and endpoint related adverse events. Safety

endpoint results will be based on CEC adjudications.
•All sites will follow a standardized protocol for acquisition of echocardiographic endpoint data.
•An independent core laboratory will evaluate all echocardiograms. Echocardiographic trial endpoint results will be based on Core Lab assessments.

Intervention

All randomized and treated subjects will undergo a 5*year follow*up period. For each subject, data will be collected at pre* and post*procedure, at discharge, at 30 days and once a year until the 5*year follow*up is completed.
Main collected data will be:
• Baseline subject demographics, medical history, anatomical eligibility, MDCT, and Society of Thoracic Surgeons*Predicted Risk or Mortality (STS* PROM) score at Screening
• Procedural/discharge evaluations
• Clinical assessment at Screening, Baseline, Discharge, 30*day, 12*month, 2* year, 3*year, 4*year and 5*year follow*up visits
• Transthoracic echo at Screening, Discharge, 30*day, 12*month, 2*year, 3* year, 4*year and 5*year follow*up visits
• 12*lead ECG at Pre* and post*procedure, Discharge, 30*day and 12* month follow*up visits
• NYHA at Screening, Baseline, Discharge, 30*day, 12*month, 2*year, 3*year, 4* year and 5*year follow*up visits
• Quality of Life assessments at Baseline, 30*day, 12*month, 2* year, 3*year, 4* year and 5*year follow*up visits
• 6*minute walk test at Baseline, 30*day, 12*month, 2*year, 3*year, 4*year and 5*year follow*up visits

Study burden and risks

TAVR is now established as having an acceptable safety profile and is considered an effective treatment option for subjects with symptomatic severe native aortic stenosis who are at low to extreme risk for surgical aortic valve replacement. The Medtronic CoreValve* system, the Evolut R system, the Evolut PRO system, and the Evolut PRO+ system (referred jointly as Medtronic TAVR) have been in widespread use since the first generation received CE Mark in 2007, and there is now extensive published experience demonstrating the Medtronic TAVR system is fulfilling its intended role with a favorable risk/benefit ratio.(35-38) Rigorous clinical trials have established its safety and effectiveness, with improved mortality and quality of life compared with medical therapy in extreme, high, intermediate and low risk subjects. (1-4) Appropriate risk management activities have been performed for the Evolut PRO, Evolut PRO+, SAPIEN 3, and/or SAPIEN 3 Ultra system resulting in a positive risk-to-benefit rationale given the products have received local regulatory body approval. Other than a subset of subjects that will undergo a stress

echocardiogram at selected sites, the risks and potential benefits are identical for subjects implanted as part of this trial when compared to the commercial setting.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

I1. Symptomatic subjects with predicted risk of operative mortality < 15% at 30-days per multidisciplinary local heart team assessment
I2. Severe aortic stenosis, defined as: Aortic valve area <=1.0 cm2 (or aortic valve area index of <=0.6 cm2/m2), OR mean gradient >=40 mmHg, OR maximal aortic valve velocity >=4.0 m/sec by transthoracic echocardiography at rest
I3. Aortic valve annulus area <= 430 mm2 based on Multi- detector computed tomography (MDCT)
I4. Subject's anatomy is appropriate for both Medtronic TAV and Edwards TAV

systems, used within in the conduct of the trial.
I5. Subject*s anatomy is suitable for TAVR via transfemoral vessel access
I6. Commercial indication for transcatheter aortic valve replacement (TAVR), in conformity with both local regulations and Instructions for Use (IFU)
I7. Subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits

Exclusion criteria

E1. Estimated life expectancy of less than 2 years
E2. Multivessel coronary artery disease with a Syntax score >32 and/or unprotected left main coronary artery.
E3. Participating in another trial that may influence the outcome of this trial
E4. Need for an emergent procedure for any reason
E5. Contraindicated for treatment with the Medtronic and Edwards TAV systems in accordance with the Instructions for Use
E6. Other medical, social, or psychological conditions that in the opinion of the Investigator precludes the subject from appropriate consent or adherence to the protocol required follow-up exams
E7. Pregnant, nursing or planning to be pregnant.
E8. Subject is less than legal age of consent, legally incompetent, unable to provide his/her own informed consent, or otherwise vulnerable
E9. Subject has an active COVID-19 infection or relevant history of COVID-19. Note: An active COVID-19 infection is defined as a positive Polymerase Chain Reaction (PCR) result. Relevant history of COVID-19 is defined as availability of a positive COVID-19 test with sequela or hospitalization for treatment of COVID-19 that was less than 3 months prior to enrollment. Subjects with a positive COVID-19 test who were asymptomatic or had mild symptoms should be excluded only if the positive test was less than 3 months prior to enrollment.
E10. Previous aortic valve replacement

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-11-2021
Enrollment:	150
Type:	Actual

Medical products/devices used

Generic name:	Medtronic Evolut PRO;Evolut PRO+ Transcatheter Aortic Valve (TAV) Systems and Evolut FX* transkat
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	28-05-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	17-03-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	28-04-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	12-08-2024
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT04722250
CCMO	NL75851.058.21