REPRISE III: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus* Valve System - Randomized Clinical Evaluation

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The objective of the REPRISE III trial is to evaluate the safety and effectiveness of the Lotus* Valve System for transcatheter aortic valve replacement (TAVR) in symptomatic subjects with calcific, severe native aortic stenosis who are considered...

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

Summary

ID

NL-OMON44639

Source
ToetsingOnline

Brief title
REPRISE III

Condition

- Cardiac valve disorders
- Cardiac therapeutic procedures

Synonym
Narrowed aortic heart valve., Symptomatic aortic heart valve stenosis

Research involving
Human

Sponsors and support

Primary sponsor: Boston Scientific Cooperation International
Source(s) of monetary or material Support: Boston Scientific Corporation.

Intervention

Keyword: Aortic Lotus Valve System, Percutaneous, Replacement, Repositionable

Outcome measures

Primary outcome

Primary Safety Endpoint: Composite of all-cause mortality, stroke,

life-threatening and major bleeding events, stage 2 or 3 acute kidney injury,

or major vascular complications at 30 days.

Primary Effectiveness Endpoint: Composite of all-cause mortality, disabling

stroke, or moderate or greater paravalvular aortic regurgitation (based on core

lab assessment) at 1 year.

Secondary outcome

Secundary endpoint: moderate or greater paravalvular aortic regurgitation

(based on core lab assessment) at 1 year.

Study description

Background summary

The incidence of aortic stenosis (AS), which most commonly occurs in the very elderly, is increasing due to the aging of the world-wide population and the lack of drug therapies to prevent, halt, or effectively slow the stenotic process. It is estimated that nearly 5% of elderly >=75 years of age have AS and its prevalence is expected to increase as a result of an aging population. Aortic stenosis is associated with high rates of death and complications after the appearance of symptoms.

The standard of care for AS in patients who do not have serious comorbidities is surgical aortic valve replacement (SAVR), which has been shown to reduce symptoms and improve survival. Between 1999 and 2011, the rate of surgical AVR for elderly subjects in the United States has increased and outcomes have improved. However, up to one-third of patients with severe AS are not treated with SAVR because of their comorbidities and consequent peri-operative risk (e.g., advanced age, left ventricular dysfunction, etc.). With standard medical therapy, mortality after 1 year among these patients may be as high as 50%. Percutaneous transluminal aortic valvuloplasty, which was introduced as an alternative to SAVR in elderly and/or high-surgical-risk subjects, can provide symptomatic relief and/or temporary improvement but does not provide definitive treatment in subjects with severe calcific AS. It is also associated with relatively high mortality and complication rates.

Transcatheter aortic valve replacement (TAVR) has recently emerged as a less invasive treatment strategy in subjects who are not suitable candidates for open-heart surgery and more than 60,000 transcatheter aortic valve prostheses have been implanted worldwide. Patients with severe aortic stenosis undergo a joint interdisciplinary screening process, including comprehensive multimodality imaging, prior to procedure recommendation. Because existing surgical risk scores imperfectly characterize risk, center Heart Teams also consider other co-morbidities and patient frailty. While not captured well by any of the standard risk scores, these added measures help to more fully characterize a patient population that potentially benefits from TAVR.

Transcatheter aortic valve replacement was initially performed through a retrograde transfemoral approach and an antegrade transapical approach. Two additional retrograde approaches, transaortic through the ascending aorta and trans-subclavian, were subsequently described. Evidence of the safety of the procedure using either a balloon expandable or a self-expanding bioprosthetic heart valve has rapidly accumulated through observational studies, device-specific registries, and national registries. In the randomized Placement of Aortic Transcatheter Valves (PARTNER) trial, patients unsuitable for surgical valve replacement who underwent TAVR with a balloon-expandable device experienced significant reductions in mortality and repeat hospitalization compared to those receiving conventional medical therapy at 1 and 2 years and high-surgical-risk patients receiving either TAVR or surgical replacement had a similar mortality risk. In the randomized U.S. CoreValve High Risk Study, TAVR with a self-expanding transcatheter aortic-valve bioprosthesis was associated with a significantly higher rate of survival at 1 year compared to SAVR.

A recently published expert consensus document lists TAVR as a reasonable alternative to SAVR in AS patients with high surgical risk and a subsequent consensus document outlines patient selection for TAVR. The potential of TAVR to be a treatment option for a considerable number of patients with AS has resulted in significant advances in the technology aiming to simplify the

procedure and minimize adverse events. Standardized endpoint definitions were published by the Valve Academic Research Consortium (VARC) in 2011 (VARC-170) and updated in 2012 (VARC-271).

Study objective

The objective of the REPRISE III trial is to evaluate the safety and effectiveness of the Lotus* Valve System for transcatheter aortic valve replacement (TAVR) in symptomatic subjects with calcific, severe native aortic stenosis who are considered at extreme or high risk for surgical valve replacement.

Study design

REPRISE III is a prospective, multicenter, 2:1 randomized (Lotus Valve System versus a commercially available CoreValve Transcatheter Aortic Valve Replacement System), controlled trial designed to evaluate the safety and effectiveness of the Lotus Valve System for TAVR in symptomatic subjects who have calcific, severe native aortic stenosis and who are at high or extreme risk for surgical aortic valve replacement (SAVR).

There will be a non-randomized roll-in phase with only the test device for centers that do not have previous experience implanting the Lotus Valve;each of these centers will perform at least 2 roll-in cases before commencing randomization. Data from roll-in subjects will be summarized separately from the randomized population. Roll-in subjects will not be included in the endpoint analyses.

Intervention

The randomized group will consist of two groups: One group will be eligible for TAVR with the Lotus Valve and the other group will be eligible for TAVR with the CoreValve. On average, 2 of every 3 patients will be in the Lotus group. The other patients will be in the CoreValve group.

Study burden and risks

The burden of participating in this trial could be related to the yearly follow-up visit throughout 5 years after the implantation. On the one hand these planned follow-up visits are positive for the patients since they will be followed very closely, on the other hand these yearly follow-up visits can be experienced as a burden since they are planned up to 5 years after the implant in a strict timewindow. Patients will also be requested to complete on regular timepoints (baseline, 30 days, 6 month, 1 year, 3 year and 5 year) Quality of Life questionnaires.

This can also be experienced as a burden for
the patients enrolled in the study. The burden of other planned examinations depends on routine practice within the
hospital. As far as planned examinations per study protocol are part of the routine examinations in daily practice, they are
no extra burden for the patients enrolled in the trial. The possible risks and side effects of taking part in this study are
listed above in section E. Patients who take part in this study are subject to similar risks shared by all patients who receive
a similar type of device but are not in this study. There may also be additional risks or side effects which are unknown at
this time. As a result of the complications listed above, you may require medical, percutaneous or surgical intervention,
including re-operation and replacement of the Lotus* Valve. Such complications can be fatal. As the Lotus* Valve is an
investigational device, uncertainty remains over risks of experiencing some or all of the complications listed above. There
may be risks that are unknown at this time.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

IC1. Subject has documented calcific, severe native aortic stenosis with an initial AVA of <=1.0 cm2 (or AVA index of <=0.6 cm2/m2) and a mean pressure gradient >=40 mm Hg or jet velocity >=4.0 m/s, as measured by echocardiography and/or invasive hemodynamics.
IC2. Subject has a documented aortic annulus size of >=20 mm and <=27 mm based on the center*s assessment of pre-procedure diagnostic imaging (and confirmed by the Case Review Committee [CRC]) and is deemed treatable with an available size of both test and control device.
IC3. Subject has symptomatic aortic valve stenosis with NYHA Functional Class >= II.
IC4. There is agreement by the heart team (which must include a site investigator interventionalist and a site investigator cardiac surgeon) that subject is at high or extreme operative risk for surgical valve replacement (see note below for definitions of extreme and high risk, the required level of surgical assessment, and CRC confirmation) and that TAVR is appropriate. Additionally, subject has at least one of the following.
• Society of Thoracic Surgeons (STS) score >=8% -OR-
• If STS <8, subject has at least one of the following conditions:
o Hostile chest
o Porcelain aorta
o Severe pulmonary hypertension (>60 mmHg)
o Prior chest radiation therapy
o Coronary artery bypass graft(s) at risk with re-operation
o Severe lung disease (need for supplemental oxygen, FEV1 <50% of predicted, DLCO <60%, or other evidence of severe pulmonary dysfunction)
o Neuromuscular disease that creates risk for mechanical ventilation or rehabilitation after surgical aortic valve replacement
o Orthopedic disease that creates risk for rehabilitation after surgical aortic valve replacement
o Childs Class A or B liver disease (subjects with Childs Class C disease are not eligible for inclusion in this trial)
o Frailty as indicated by at least one of the following: 5*meter walk >6 seconds, Katz ADL score of 3/6 or less, body mass index <21, wheelchair bound, unable to live independently
o Age >=90 years
o Other evidence that subject is at high or extreme risk for surgical valve replacement (CRC must confirm agreement with site heart team that subject meets high or extreme risk definition)
IC5. Heart team (which must include a cardiac interventionalist and an experienced cardiac surgeon) assessment that the subject is likely to benefit from valve replacement.
IC6. Subject (or legal representative) understands the study requirements and the treatment

procedures, and provides written informed consent.
IC7. Subject, family member, and/or legal representative agree(s) and subject is capable of returning to the study hospital for all required scheduled follow up visits.
Note: Extreme operative risk and high operative risk are defined as follows:
Extreme Operative Risk: Predicted operative mortality or serious, irreversible morbidity risk >=50% at 30 days.
High Operative Risk: Predicted operative mortality or serious, irreversible morbidity risk >=15% at 30 days.;Risk of operative mortality and morbidity must be assessed via an in-person evaluation by a center cardiac surgeon and must be confirmed by the CRC (which must include an experienced cardiac surgeon).

Exclusion criteria

EC1. Subject has a congenital unicuspid or bicuspid aortic valve.
EC2. Subject has had an acute myocardial infarction within 30 days prior to the index procedure (defined as Q-wave MI or non-Q-wave MI with total CK elevation >= twice normal in the presence of CK-MB elevation and/or troponin elevation).
EC3. Subject has had a cerebrovascular accident or transient ischemic attack within the past 6 months prior to study enrollment.
EC4. Subject has end-stage renal disease or has GFR <20 (based on Cockcroft-Gault formula).
EC5. Subject has a pre-existing prosthetic aortic or mitral valve.
EC6. Subject has severe (4+) aortic, tricuspid, or mitral regurgitation.
EC7. Subject has a need for emergency surgery for any reason.
EC8. Subject has a history of endocarditis within 6 months of index procedure or evidence of an active systemic infection or sepsis.
EC9. Subject has echocardiographic evidence of new intra-cardiac vegetation or intraventricular or paravalvular thrombus requiring intervention..
EC10. Subject has Hgb <9 g/dL, platelet count <50,000 cells/mm3 or >700,000 cells/mm3, or white blood cell count <1,000 cells/mm3.
EC11. Subject requires chronic anticoagulation therapy after the implant procedure and cannot be treated with warfarin (other anticoagulants are not permitted in the first month) for at least 1 month concomitant with either aspirin or clopidogrel.
EC12. Subject has had a gastrointestinal bleed requiring hospitalization or transfusion within the past 3 months, or has other clinically significant bleeding diathesis or coagulopathy that would preclude treatment with required antiplatelet regimen, or will refuse transfusions.
EC13. Subject has known hypersensitivity to contrast agents that cannot be adequately pre-medicated, or has known hypersensitivity to aspirin, all P2Y12 inhibitors, heparin, nickel, tantalum, titanium, or polyurethanes.
EC14. Subject has a life expectancy of less than 12 months due to non-cardiac, comorbid conditions based on the assessment of the investigator at the time of enrollment.
EC15. Subject has hypertrophic obstructive cardiomyopathy.
EC16. Subject has any therapeutic invasive cardiac or vascular procedure within 30 days prior to the index procedure (except for balloon aortic valvuloplasty or pacemaker implantation, which are allowed).

EC17. Subject has untreated coronary artery disease, which in the opinion of the treating physician is clinically significant and requires revascularization.
EC18. Subject has severe left ventricular dysfunction with ejection fraction <20%.
EC19. Subject is in cardiogenic shock or has hemodynamic instability requiring inotropic support or mechanical support devices.
EC20. Subject has severe vascular disease that would preclude safe access (e.g., aneurysm with thrombus that cannot be crossed safely, marked tortuosity, significant narrowing of the abdominal aorta, severe unfolding of the thoracic aorta, or symptomatic carotid or vertebral disease).
EC21. Subject has thick (>5 mm) protruding or ulcerated atheroma in the aortic arch
EC22. Subject has arterial access that is not acceptable for the test and control device delivery systems as defined in the device Instructions For Use.
EC23. Subject has current problems with substance abuse (e.g., alcohol, etc.).
EC24. Subject is participating in another investigational drug or device study that has not reached its primary endpoint.
EC25. Subject has untreated conduction system disorder (e.g., Type II second degree atrioventricular block) that in the opinion of the treating physician is clinically significant and requires a pacemaker implantation. Enrollment is permissible after permanent pacemaker implantation.
EC26. Subject has severe incapacitating dementia.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-05-2015
Enrollment:	20
Type:	Actual

Medical products/devices used

Generic name:	Lotus Valve system
Registration:	No

Ethics review

Approved WMO Date:	19-12-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-08-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-05-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
CCMO	NL50236.078.14