REduction or eLimination of mItral rEgurgitation in degenerative or Functional mitral regurgitation with the CardiAQ-Edwards* Transcatheter Mitral Valve

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The objectives of this study are to evaluate the safety and performance of the valve and delivery systems for the treatment of symptomatic moderate to severe degenerative or functional mitral regurgitation in a prohibitively high risk patient...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Cardiac valve disorders
Study type	Interventional

Summary

ID

NL-OMON43333

Source
ToetsingOnline

Brief title
The RELIEF Trial

Condition

- Cardiac valve disorders

Synonym
leaky heart valve, mitral regurgitation

Research involving
Human

Sponsors and support

Primary sponsor: Edwards Lifesciences LLC.
Source(s) of monetary or material Support: Edwards Lifesciences LLC.

Intervention

Keyword: implantation, mitral valve, regurgitation, transcatheter

Outcome measures

Primary outcome

Freedom from MACCE (defined as all-cause mortality, myocardial infarction, stroke, renal failure, and conversion to surgery per MVARC definitions) at 30 days.

Secondary outcome

Safety Endpoints

* Freedom from composite MACCE at three (3), six (6) and twelve (12) months

* Freedom from the following events (refer to MVARC definitions) at 30 days, three (3), six (6) and twelve (12) months:

o All-cause mortality

o Procedure-related death

o Non-cardiovascular mortality

o Rehospitalization for heart failure

o Bleeding complications

o Vascular and access complications

o Stroke and other cerebrovascular events

o Myocardial infarction

o Acute kidney injury/progression of chronic kidney disease

o Arrhythmia and conduction system disturbances

o Unplanned mitral valve surgery due to device/procedure failure or malfunction

o Requirement/insertion of biventricular pacemaker for CRT

* Freedom from all individual adverse events related to the device or procedure at 30 days, three (3), six (6) and twelve (12) months.

* All adverse events, including the MACCE composite, will be evaluated as time dependent events.

Valve Performance

Valve performance improvements at 30 days, three (3), six (6) and twelve (12) months compared to baseline. The valve will be assessed by echocardiography for reduction in mitral regurgitation by quantitative measures (including but not limited to LVEDV, LVESV, regurgitant fraction, regurgitant volume, MR grade, vena contracta width, EROA).

Functional Improvements

Functional improvements at 30 days, three (3), six (6) and twelve (12) months as compared to baseline for New York Heart Association (NYHA) classification, Exercise tolerance (Six Minute Walk Test) and Quality of Life evaluation (Minnesota Living with Heart Failure; EQ-5D; SF-12).

Technical, Device, Procedure and Patient Success (MVARC)

Technical Success

* Technical success, which is assessed at exit from OR/cath lab, is defined as

below:

a. Alive, with

b. Successful access, delivery and retrieval of the transcatheter valve

delivery system, and

c. Deployment and correct positioning of the single intended device, and

d. No need for additional emergency surgery or re-intervention related to the

device or access procedure

* Device Success (measured at 30 days and all later post-procedural intervals),

is defined as below:

a. Alive, with

b. Proper placement and positioning of the device, and

c. Freedom from unplanned surgical or interventional procedures related to the

device or access procedure, and

d. Continued intended safety and performance of the device, including:

o No evidence of structural or functional failure

o No specific device-related technical failure issues and complications

o Reduction of MR to either optimal or acceptable levels without significant

mitral stenosis and with no greater than mild (+1) paravalvular MR

* Expected hemodynamic performance is MR < 2+, EOA > 2.0 cm2; MV gradient < 5

mmHg

* No para-device complications (i.e., no effect on coronary circulation or need

for PPM; LVOT gradient > 25 mmHg from baseline)

Procedure Success (measured at 30 days):

a. Device success (either optimal or acceptable), and

b. Absence of major device or procedure related serious adverse events, including:

o Death

o Stroke

o Life-threatening bleeding (MVARC scale)

o Major vascular complications

o Major cardiac structural complications

o Stage 2 or 3 acute kidney injury (includes new dialysis)

o Myocardial infarction or coronary ischemia requiring PCI or CABG

o Severe hypotension, heart failure, or respiratory failure requiring intravenous pressors or invasive or mechanical heart failure treatments such as ultrafiltration or hemodynamic assist devices [except for temporary support immediately post-procedure], including IABP or LV/bi-ventricular assist devices, or prolonged intubation > 48 hours

o Any valve-related dysfunction, migration, thrombosis, or other complication requiring surgery or repeat intervention

* Patient Success (measured at 1 year):

a. Device success (either optimal or acceptable) and

b. Patient returned to the pre-procedural setting and

c. No rehospitalizations or reinterventions for the underlying condition; or a reduction of hospitalization days for the underlying condition compared to prior year and

d. Improvement from baseline in symptoms (NHYA functional class improvement by > 1 functional class); and

e. Improvement from baseline in functional status (6MWT improvement by > 50m)

and

f. Improvement from baseline in quality of life measures

o MLHFQ improvement by a decrease of 15 or more points

o SF-12v2 physical and mental improvement more than 5 points

o EQ5D-5L index score improvement of more than 0.05

Study description

Background summary

Today*s standard of care for mitral valve replacement is open-heart surgery. But, open-heart surgery can involve serious risks for patients who are older, have other heart disease, or have general health problems. Edwards Lifesciences LLC. has developed the CardiAQ-Edwards TMVI System to replace a patients mitral valve without the need for open-heart surgery. Instead, the CardiAQ-Edwards Valve is implanted using a procedure called a transcatheter mitral valve implantation (TMVI).

Study objective

The objectives of this study are to evaluate the safety and performance of the valve and delivery systems for the treatment of symptomatic moderate to severe degenerative or functional mitral regurgitation in a prohibitively high risk patient population.

Study design

A multi-center, prospective, single-arm, and non-randomized study without concurrent or historical controls to evaluate the safety and performance of the CardiAQ-Edwards* Transcatheter Mitral Valve (TMV) with Transapical and Transseptal Delivery Systems in a prohibitively high risk patient population. Access approach (transapical or transseptal) will be determined by the Heart Team, which includes at a minimum, one cardiac surgeon and one interventional cardiologist. The inclusion of an echocardiologist on the Heart Team is strongly recommended.

Intervention

Transcatheter Mitral Valve Implantation

Study burden and risks

The potential risks (listed below) that the subject may encounter by participating in this study are similar to the risks associated with standard cardiac catheterization, the use of anesthesia and mitral valve replacement (MVR). The implantation procedure and/or investigational device itself has the potential to cause some side effects or reactions. As the CardiAQ-Edwards* Transcatheter Mitral Valve (TMV) is an investigational device, there may also be additional risks or side effects, which are unknown at this time. Possible outcomes of these risks and side effects could include reoperation, surgical removal of the device, permanent disability or death.
The experience in treating actual patients with the CardiAQ-Edwards* Transcatheter Mitral Valve (TMV) is very limited. Therefore, the estimated occurrence in possible risks and side effects of taking part in the study is based on results of similar transcatheter devices that are used to replace the aortic valve (instead of the mitral valve), where there is significant experience, surgical mitral valve replacement, and commercial transcatheter mitral valve repair. These risks will be explained to the subject by the study doctor. Should any side effects occur, they will be fully assessed and the subject will be monitored closely.

Potential Risks
Estimated to occur in 10 to 20 out of 100 patients
* Bleeding/Anemia (Bleeding that requires 4 or more units of blood transfusion)

Estimated to occur in 5 to 9 out of 100 patients
* Conduction System Injury (defect) which may require pacemaker (abnormal heart rhythm requiring implantation of a medical device that uses electrical pulses to create a normal heart rate)
* Pleural Effusion
* Renal Failure or Insufficiency (Kidneys do not filter the blood well enough)
* Vascular trauma, dissection or occlusion

Estimated to occur in less than 5 out of 100 patients
* Abnormal Lab Values
* Allergic Reaction to Anesthetic (Anesthesia), Anti-coagulant Therapy (Medication to thin out your blood), Contrast Media (Dye fluid) or Nitinol (the metal that the valve is made from)
* Anaphylactic Shock or Toxic Reaction (Severe, potentially life-threatening allergic reaction)
* Angina (Chest pain or discomfort)
* Aortic Valve Impairment/Damage
* Arrhythmia (Irregular heartbeat)
* Atrial Fibrillation (Irregular and often rapid heart rate that can cause poor blood flow to the body)

* Atrioventricular Groove Disruption or Mitral Valve Annulus Rupture (Hole or rip in the heart)
* Atrio-ventricular Node Block (Passage of electrical signal from the top to the bottom of the heart is delayed or interrupted)
* Bleeding diathesis (Increased susceptibility to bleeding)
* Cardiac Arrest
* Cardiac Failure or Decompensation (Inability of the heart to maintain adequate circulation)
* Cardiac Perforation (Tearing a hole in the heart)
* Cardiac Tamponade (pressure on the heart that occurs when blood or fluid builds up in the space between the heart muscle (myocardium) and the outer covering sac of the heart (pericardium).
* Cardiogenic shock (Loss of blood circulation)
* Chordal Rupture
* Conversion to Open Sternotomy (Conversion to open heart surgery)
* Coronary Artery Obstruction (Blockage in one of the major blood vessels that supplies blood, oxygen and nutrients to the heart)
* Dissection, Any Vessel (A cut inside of one of the blood vessels)
* Dyspnea (Difficulty in breathing or shortness of breath)
* Edema (Swelling caused by excess fluid trapped in the blood vessels)
* Electrolyte Imbalance
* Electro-mechanical Dissociation (heart not pumping blood)
* Embolization including air, particulate, calcific material, or thrombus
* Emergent Percutaneous Coronary Intervention (PCI) (Inserting a catheter or long tube and Inflating a balloon to fix a blockage and possibly implanting a metal stent)
* Emergent Cardiac Surgery (e.g. Coronary Artery Bypass, Valve Replacement with open heart surgery)
* Endocarditis (An infection of the inner lining of the heart)
* Esophagus Irritation/Perforation - TEE related (Tear or irritation of the esophagus from one of the instruments that is used to look inside the heart)
* Fever
* Frame Strut Fracture (Break in the metal frame of the valve)
* GI Bleeding (Bleeding in the digestive track)
* Heart Failure (Heart can't pump enough blood to keep up with the needs of the other organs)
* Hematoma (Localized collection of blood outside a blood vessel)
* Hemolysis (Breaking down of the red blood cells)
* Hemolytic Anemia (Body does not have enough healthy red blood cells)
* Hemorrhage (Bleeding)
* Infection at the Access Site (Infection in or around the skin or deeper tissue at the incision site)
* Inflammation (significant enough to affect the function of the valve)
* Leaflet tearing
* Left Ventricle Failure (The main pumping chamber of the heart does not circulate enough blood)
* Local and Systemic Infection (infection at one part (local) or throughout

(systemic) the body)
* LVOT Obstruction (Blood flow is blocked on the inside of the main pumping chamber of the heart)
* Mal-positioning of Prosthesis (Valve is in the wrong position)
* Multi-system Failure (Two or more systems in the body are failing)
* Myocardial Infarction (Heart Attack)
* Nausea
* Pannus Formation (Abnormal layer of scar tissue forming on the valve)
* Papillary Muscle Damage
* Pericardial Effusion (Blood or fluid builds up around the heart)
* Peripheral Ischemia (Not enough blood flow to the limbs)
* Pneumonia (Lung Infection)
* Prosthesis Dislodgement, Migration or Embolization (Movement of the implanted valve)
* Prosthesis Leaflet Entrapment (Implanted valve leaflets being jammed closed and not properly opening)
* Prosthesis Paravalvular Leak (Blood leak between the implanted valve and the heart tissue)
* Prosthesis Regurgitation (Implanted valve does not close tightly, allowing blood to flow backward in the heart)
* Prosthetic Valvular Endocarditis (Infection of the implanted valve)
* Prosthetic Valvular Thrombosis (Blood clot attached to or near the implanted valve)
* Pseudo-aneurysm (Injury causing blood to leak and pool outside of the artery's wall)
* Pulmonary Edema
* Pulmonary Vein Obstruction
* Reintervention or reoperation (Another surgical procedure)
* Retroperitoneal Bleed
* Respiratory Failure (Not enough oxygen passes from the lungs into the bloodstream)
* Septicemia (Blood infection)
* Stroke or Other Neurological Event (Blood flow to the brain is stopped)
* Structural Deterioration (Parts of the implanted valve break)
* Systolic Anterior Motion (The Mitral valve opens at the wrong time and blocks blood flow from the heart)
* Thromboembolism (Blood clot moves from one place and blocks blood flow into a blood vessel)
* Valve Stenosis
* Ventricular Perforation by Frame (Tearing of heart tissues caused by the implanted valve)
* Vessel Spasm (Narrowing and constriction of the blood vessels, preventing blood flow)
* Wound Dehiscence (the wound ruptures along sutures)

Pregnancy Risks
Women who are pregnant may not participate in this study. The effects of this

treatment and follow*up requirements to an embryo or fetus are currently unknown. If the subject is a woman of child*bearing potential, and are not sterile, a small amount of blood or urine will be collected, to confirm the subject is not pregnant before the study procedure. If the subject becomes pregnant anytime during study participation, the subject will be exited from the study.

WHAT ARE THE POSSIBLE RISKS AND SIDE EFFECTS ASSOCIATED WITH MEDICATIONS BEFORE
AND AFTER THE TMVR PROCEDURE?
The subject will be asked to take medications before and after the procedure. These medications are intended to help prevent clots from forming on the new heart valve. They are standard medications given to patients following implantation of a number of cardiac devices. There are increased risks of bruising and or bleeding complications related to these medications. They also can cause diarrhoea, nausea, digestive disturbances, vomiting, lack of appetite, and skin rash.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART?
There is no guarantee that participating in this study will help the subject. The subject's condition might not improve or might get worse while the subject is in this study; however, the information that is learned from this study may benefit other patients who have the same health condition. It is possible that the collection of information on during this clinical study of the device will allow early detection of unforeseen problems.

The CardiAQ-Edwards* Transcatheter Mitral Valve may provide one or more of these benefits:
* Mitral valve replacement without open heart surgery
* Mitral regurgitation reduction or elimination that improves the blood flow through the heart
* Improved quality of life by reducing some of the physical limitations
* Reduced discomfort or tiredness when performing certain physical activities

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

General
1. * 18 years old.
2. Willing and able to comply with all required follow-up evaluations and assessments.
3. Patient or authorized representative has read the informed consent, agrees to comply with the requirements, and has signed the informed consent to participate in the study.
Heart Failure Status
4. New York Heart Associate Classification * II
5. Left Ventricular Ejection Fraction * 30%.
6. Mitral regurgitation (MR) * Grade 3+ (moderate/severe, or severe per Appendix D).
7. Patient is determined to be prohibitively high surgical risk per MVARC definition as assessed by the site*s Heart Team (a minimum of one Cardiac Surgeon and one Interventional Cardiologist).
Anatomical
8. Left atrial height * 4 cm.
9. Mitral valve major annulus diameter meets the range of 35-45 mm via CT.
10. Angle of mitral valve axis to aortic valve axis is deemed unlikely to be obstructive by the Investigator.
11. Suitable left ventricular anatomy for delivery system access per the medical opinion of the Investigator (Transapical Only).
23. Absence of CRT with Class I indication criteria for biventricular pacing
24. Hypotension (systolic pressure <90mmHg) or requirement for inotropic support or mechanical hemodynamic support.
25. Hypertrophic cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, or any other structural heart disease causing heart failure other than dilated cardiomyopathy of

either ischemic or nonischemic etiology.
26. Untreatable hypersensitivity or contraindication to any of the following:
* Aspirin and Clopidogrel and Ticlopidine,
* Heparin and Bivalirudin,
* Warfarin, Nitinol alloys (nickel and titanium), contrast media, glutaraldehyde or bovine tissue.
27. Bleeding diathesis or coagulopathy, or patient refuses blood transfusion.
28. Active peptic ulcer or GI bleeding.
29. Fixed pulmonary artery systolic pressure >70 mmHg.
30. Severe right ventricular systolic dysfunction.
31. Severe tricuspid valve regurgitation requiring intervention.
32. Pulmonary function FEV1 (< 750 cc).
33. Patients with renal insufficiency (creatinine > 2.2 mg/dL) on lab test * 48 hours prior to scheduled implant procedure and not already receiving dialysis.
34. Liver disease, cirrhosis of the liver (CTP B or C) or significantly abnormal liver function test results.
35. Co-morbid condition(s) that, in the opinion of the Investigator, limit life expectancy to < 12 months.
36. Active infection that requires antibiotic therapy (if temporary illness, patients may enroll 2 weeks after discontinuation of antibiotics). Patients must be free from infection prior to treatment. Any required dental work should be completed a minimum of 3 weeks prior to treatment.
37. Pregnant or planning pregnancy within 12 months after enrollment.

Exclusion criteria

General
1. Currently participating in another investigational drug or device study.
2. Need for emergent or urgent surgery for any reason.
3. Any condition that, in the opinion of the Investigator, could interfere with patient participation, confound the study results or interfere with study compliance.
Anatomical
4. Lack of chordal support of the mitral valve (i.e., ruptured papillary muscle or secondary chords).
5. Severe calcification of any component of the mitral valve, including one or both of the mitral leaflets.
6. Myocardial infarction within the previous 6 weeks.
7. Intra-cardiac thrombus, mass or vegetation.
8. Aneurysmal dilatation of the left ventricular apex (Transapical Only).
9. Need for native aortic, tricuspid or pulmonic valve repair or replacement.
10. History of atrial septal repair (Transseptal Only).
11. Implanted inferior vena cava (IVC) filter (Transseptal Only).
Existing Co-morbidities
12. Any prior surgical or transcatheter repair (excluding balloon valvuloplasty) or replacement of the mitral valve.

13. Pre-existing mechanical prosthetic valve in the aortic position.
14. Pre-existing device in the LV apex (Transapical Only).
15. History of cardiac transplantation.
16. Any history of ilio-femoral deep vein thrombosis (Transseptal Only).
17. Clinically significant, untreated coronary artery disease.
18. Percutaneous coronary intervention, TAVR, carotid surgery, CRT, CRT-D, ICD or pacemaker within the prior 30 days.
19. Contraindication to Transesophageal Echocardiography (TEE).
20. Active endocarditis or rheumatic heart disease within the previous 3 months.
21. Stroke or TIA within the previous 3 months.
22. Uncontrolled atrial fibrillation.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	28
Type:	Anticipated

Medical products/devices used

Generic name:	the CardiAQ-Edwards Transcatheter Mitral Valve (TMV)
Registration:	No

Ethics review

Approved WMO

Date:	20-01-2017
Application type:	First submission
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
ClinicalTrials.gov	NCT02722551
CCMO	NL57127.078.16