PARADIGM - PARAvalvular leak closure with the Amplatzer Valvular Plug occluDer for Interventional transcatheter closure for PVL with surgical bioloGical and Mechanical heart valve

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac valve disorders
Study type	Observational invasive

Summary

ID

NL-OMON54009

Source
ToetsingOnline

Brief title
PARADIGM

Condition

- Cardiac valve disorders

Synonym
heart valves, paravalvular leaks

Research involving
Human

Sponsors and support

Primary sponsor: St. Jude Medical
Source(s) of monetary or material Support: Abbott

Intervention

Keyword: - aortic or mitral position, - mechanical or biological heart valve, - paravalvular leaks, - transcatheter closure

Outcome measures

Primary outcome

The primary endpoint is a composite of safety and effectiveness measures

evaluating the percent of patients successfully treated with an AVP III for the

reduction of PVL, where success is defined as:

• Transcatheter placement of the AVP III in the intended location without

interfering with the surgical valve function on exit from procedure,

• Reduction in PVL by greater than or equal to two grades (defined in appendix

II of the protocol) on exit from procedure,

• Freedom from intra-procedural death, and

• Freedom from unplanned surgical procedure or transcatheter reintervention

related to the AVP III through 30 days

Secondary outcome

The descriptive safety endpoints will be the incidence of the following adverse

events:

o Early events (occurring <= 30 days post-implant):

o Life-threatening, disabling or major bleeding, or other major cardiac

complications (BARC type 3a and above)

o Major and minor vascular complications (access-site and access-related)

o Complications due to septal crossing (for trans-septal access)

o Device dislodgement, migration or embolization

o Coronary obstruction (peri-procedure)

o Unplanned surgical or interventional procedures (such as cardiopulmonary bypass or hemodynamic support response, and conversion to emergency surgery)

o Heart block requiring permanent pacemaker insertion

o Early (<=30 days) and late events (31 days to 1 year):

o Mortality (all-cause and cardiac-related)

o Endocarditis (related to the device)

o Valve dehiscence

o Hemolytic anemia (newly developed or worsening)

o Device-related hemolytic anemia (newly developed or worsening)

o Device or valve thrombosis

o Interference of AVP III with surgical valve function

o Heart failure hospitalizations

o Systemic Embolism

o Device Related Embolism

o Stroke and TIA

o Blood transfusions for treatment of hemolytic anemia

The descriptive efficacy endpoints are as follows:

o NYHA functional class at 30 days, 6 months, and 1 year, and change or no change in NYHA functional class observed between Baseline and

30 days, between Baseline and 6 months, and between Baseline and 1 year

o Improvement in Quality of life measures (Kansas City Cardiomyopathy Questionnaire (KCCQ) and EuroQol 5D (EQ-5D)) observed between Baseline and 30 days and between Baseline and 1 year

o Type and severity of PVL or freedom from residual PVL as assessed by echocardiography at Baseline, Discharge, 30 days, 6 months, and 1 year

o Transvalvular regurgitation (whether present, and severity if present) assessed by echocardiography at Baseline, Discharge, 30 days, 6 months and 1 year.

o Transvalvular mean and peak gradients assessed by echocardiography at Baseline, Discharge, 30 days, 6 months and 1 year

o Left ventricular ejection fraction assessed by echocardiography, at Baseline , Discharge, 30 days, 6 months and 1 year

Study description

Background summary

Paravalvular leak (PVL) is the presence of a regurgitant flow around a prosthetic valve when there is an incomplete seal between the prosthesis and the native valve tissue. PVL is a known potential complication after valve replacement by either a surgical or a transcatheter approach. Predisposing factors to PVL may be patient-related, such as calcification, fibrosis or infection; but may also be related technical factors such as valve debridement, valve sizing, valve suturing, and valve positioning; or even precipitated by endocarditis or generalized frail tissue.

PVLs are primarily detected by echocardiography and are graded as mild, mild to moderate, moderate, moderate to severe or severe based on echocardiographic measurements, as described by Ruiz et al.1 PVLs may be asymptomatic if small

with mild severity but can be moderate or severe and cause symptoms of heart failure (breathlessness, edema) and/or anemia due to hemolysis. A clinically significant PVL occurs with a higher severity grade of PVL (moderate or severe) and typically involves the aortic or mitral valves since both valves are on the left side of the heart where there is greater blood pressure and a higher likelihood for producing symptoms of heart failure and/or hemolysis. PVL with a severity grade of moderate or higher is considered to be representative of the target patient population who may be treated with the AVP III. Asymptomatic patients or patients with a clinically insignificant PVL with a severity grade of mild or lower are typically monitored with periodic echocardiographic evaluation and functional assessment and do not undergo surgical or transcatheter intervention to treat the PVL. Repeat open-heart surgery for moderate or severe PVL is often necessary to relieve symptoms and avoid worsening clinical outcomes, and medical therapy is considered palliative. However, repeat surgery is known to be associated with a high morbidity and mortality rates, as well as a high risk of PVL recurrence.2-4

The overall PVL incidence rate (all grades included) is cited as 7-17% in surgical mitral valve replacement (SMVR) and 2-10% in surgical aortic valve replacement (SAVR), and most occur within the first year after valve replacement.1,5,6 Based on a review of recently published literature the highest reported rate of moderate to severe PVL for a surgical valve implanted in the mitral position is 5.4% and in the aortic position is 3%.7,8

Transcatheter (percutaneous) PVL closure (TPVLC) emerged as an alternative to open cardiac surgical repair of PVL in the early 1990*s. Hourihan et al. described TPVLC in 1992 via arterial and venous femoral access using occluders originally designed for patent ductus arteriosus, septal defects and patent foramen ovale closure.9 The transapical route for TPVLC was later described by Lim in 2008 using Amplatzer occluders.10 Since its first description two decades ago, TPVLC has further been developed as a completely transvascular approach and is now an accepted less invasive alternative to surgery for high-risk patients and for patients who refuse additional surgery. As an increasing number of reports have been published on TPVLC, the 2017 EACTS/ESC guidelines for the management of valvular heart disease state that TPVLC may be considered for PVL with clinically significant regurgitation in surgical high-risk patients11, and the AHA/ACC guideline for management of patients with valvular heart disease grants a IIa level recommendation, suggesting TPVLC is beneficial to treat high-risk symptomatic patients who have PVL, and anatomic features suitable for TVPLC at experienced surgical centers.12 Finally, in recognition of the increasing adoption of TPVLC as an alternative therapeutic approach to address a clinically significant PVL, the PVL Academic Research Consortium (PVL-ARC) published in 2017 the first guideline document describing the clinical incidence and impact of PVL. The guideline document also provides definitions and methodology for assessing PVL and suggests endpoints for clinical trials of PVL closure devices.1

Despite the increasing off-label utilization of commercially available occluders that are approved for other indications for TPVLC, there is limited availability of approved transcatheter occluders indicated for PVL. No device is approved for this indication in the United States (US). Some physicians have adopted off-label use of transcatheter vascular occlusion devices for TPVLC. In particular, use of the Abbott nitinol occluders in the AMPLATZER family of devices for TPVLC has been documented in the literature.13-16 According to published data, the AVP III is a favored occlusion device for TPVLC in geographies where it is available.14 The AVP III is oblong rather than circular in cross-section design, relatively short, with a low profile, and extended rims, and is thought to better fit the common semilunar shape of a defect causing PVL than circular devices.15

Study objective

The rationale for conducting the PARADIGM study is to evaluate the safety and effectiveness of the AVP III for closure of PVLs. Until recently, current treatment in the US and OUS included off-label use of various occluder devices. The study will collect safety and effectiveness data to support FDA approval and post market clinical follow-up (PMCF) requirements in Europe as a condition for CE Mark approval.

Study design

This is a prospective, multi-center, single arm study to demonstrate the safety and effectiveness of the AVP III for closure of PVL following surgical valve replacement in either the mitral or the aortic position.

Study burden and risks

Most risks associated with participation in this trial are similar to the risks associated with commercially available AVP procedures. Study specific assessments contain the following risks:

TTE : TTE does not have additional risks for the subject, only a burden in time.

Physical exam: (weight, blood pressure, heart rate measurement) does not provide additional risks, only a burden in time

Bloodwithdrawal: There is a minor risk associated with collection of blood required per the protocol and include discomfort from needle stick, a small risk of infection, bruising, swelling and bleeding or fainting. These risks are minimized by cleaning the site carefully prior to obtaining blood by a qualified person.

Questionnaires: No risks, only a burden in time

TEE: For subjects who have multiple plugs implanted during the procedure, a TEE will be requested at the 6-month follow-up visit for the study. The TEE can be experienced as unpleasant by the subject because it requires a sedation or a full anesthesia. Discomfort can also be experienced when making a trans-oesophageal ultrasound. The most common discomforts are gagging and sore throat. Less common discomforts include vomiting and pain when swallowing. Rare discomforts include bleeding, difficulty breathing, heart problems, tooth injuries, and damage to the esophagus.

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

1. Subject is implanted with a mechanical or biological surgical valve in the aortic or mitral position. Note: Subjects in European countries can only be implanted with a mechanical valve in the aortic or mitral position
2. Subject has a clinically significant paravalvular leak with a severity grade of moderate or higher, associated with signs of heart failure and/or hemolysis necessitating recurring blood transfusions.
3. Subject has one PVL defect that can be closed with a single AVP III as assessed pre-procedurally
4. Subject has provided written informed consent
5. Subject is >=18 years old

Exclusion criteria

1. Subject has a rocking valve or extreme dehiscence of the prosthetic valve involving more than 40% of the sewing ring.
2. Subject*s PVL(s) originates from a transcatheter aortic or mitral valve replacement, or from rapid deployment or sutureless surgical replacement valves
3. Subject has multiple clinically significant PVL defects adjacent to a single prosthetic valve, or a prosthetic aortic valve and prosthetic mitral valve which both have a clinically significant paravalvular leak.
4. Subject who is hemodynamically unstable or who cannot undergo an elective procedure
5. Subject with known or suspected active endocarditis or other active infection
6. Subject has within the last 6 months a previously documented intracardiac mass, vegetation, tumor, or thrombus which would interfere with placement of the AVP III
7. Subject has inadequate vasculature for delivery of the AVP III
8. Subject has unsuitable anatomy for PVL closure using the AVP III (such as a PVL associated with an abscess cavity or a pseudoaneurysmal sac) or anatomy where the AVP III would interfere with other intracardiac or intravascular structures (such coronary ostia)
9. Subjects who are unable to receive intraprocedural anticoagulant therapy
10. Pregnant or nursing subjects or subjects who plan pregnancy during the clinical investigation follow-up period.
11. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator*s opinion, could limit the subject*s ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results.
12. Life expectancy is less than 1 year in the opinion of the Investigator
13. Incapacitated individuals, defined as persons with mental illnesses or

handicaps that impair their ability to provide informed consent, or individuals without legal authority to provide informed consent.
14. Individuals who are currently participating in an investigational drug or device study.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-02-2023
Enrollment:	40
Type:	Actual

Medical products/devices used

Generic name:	Amplatzer Valvular Plug III (AVPIII)
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	14-01-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-08-2022
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-02-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-06-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	NCT04489823
CCMO	NL75026.100.20