The PACE NOW Trial: A Prospective, rAndomized Comparison of tEmporary transvenous pacing and leadless paciNg therapy in pOst-TAVI patients With conduction abnormalities

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The primary objective of the study is to outline the advantages of LP implantation in TAVI patients who require temporary, and possibly permanent pacing compared to the Standard of Care using TV-TP therapy. We will study whether placement of a LP...

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

Summary

ID

NL-OMON44244

Source
ToetsingOnline

Brief title
PACE NOW TRIAL

Condition

- Cardiac arrhythmias

Synonym
abnormal heart rhythm, Conduction abnormalities

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Leadless pacing therapy, Transcatheter Aortic Valve Implantation, Transvenous (temporary) pacing therapy

Outcome measures

Primary outcome

Procedure related complications:

Potential device and procedure related risks for both leadless pacemakers

include:

-Cardiac perforation

*Pericardial effusion and cardiac tamponade

*Vascular complication

-Bleeding

*Arteriovenous fistula

*Pseudoaneurysm

*Failure of vascular closure device requiring intervention

-Arrhythmia during device implantation

*Asystole

*Ventricular tachycardia or ventricular fibrillation

-Cardiopulmonary arrest during implantation procedure

-Device dislodgement

-Device migration during implantation owing to inadequate fixation

-Pacing threshold elevation with retrieval and implantation of new device

-Other

Hemothorax

Angina pectoris

Pericarditis

Acute confusion and expressive aphasia

Dysarthria and lethargy after implantation

Contrast-induced nephropathy

Orthostatic hypotension with weakness

Left-leg weakness during implantation

Probable pulmonary embolism

Ischemic stroke

Transvenous Pacing Therapy

An overview of potential risks following transvenous pacing therapy is

listed below:

-Traumatic complications

* Perforation of cardiac structure

* Pneumo(hemo)thorax

* Pericardial effusion

-Lead related complications

*Lead fractrure

*Lead dislocation or disconnection

*Insulation problem

*Infection (ie, lead endocarditis

*Stimulation threshold problem

* Diaphragm or pocket stimulation

-Pocket complications

*Hematoma

*Difficult to control bleeding

*Infection

*Discomfort due to pocket or pacemaker

*Skin erosion

-Pulse generator problems

*Problem with connection screw

*Manufacturer recall

*Reset to default settings

*Device cannot be programmed

* Pacemaker tachycardia

* Malfunction of software algorithm

Secondary outcome

Mortality (All-cause, Cardiovascular, SCD, Unexplained)

Device-related complications individually

Major Adverse Cardiac Event

Stroke ischemic or hemorrhagic: classified as disabling or nondisabling and TIA

Functional Improvement from baseline per NYHA functional classification

Left ventricular function (in LVEF).

Length of in-hospital stay and time to mobilization

Recurrent cardiovascular hospitalizations

Total hospital days from the index procedure to one-year post procedure

Composite of all-cause mortality, MACE, recurrent cardiovascular

hospitalization.

Health Related Quality of Life

Cost effectiveness

Percentage PPM implantation in TV-TP group

Percentage pacing indication persists,

Permanent pacemaker indications

Conduction disorder progression in all patients

Patient satisfaction

Study description

Background summary

In 6-28% of patients undergoing transcatheter aortic valve implantation , there is a need for temporary and subsequent permanent pacing therapy, and it is difficult to predict which patients will develop this need. Patients requiring transvenous temporary pacing (TV-TP) are mandated bed rest and therefore at risk for infections, cardiac perforation, lead malfunction, delirium, re-intervention and prolonged hospitalization. In up to 67% of these patients who received TV-TP the pacing need persists, hence requiring a second procedure, the implantation of a permanent pacemaker (PPM). TV-TP therapy complications can be reduced by replacing it with leadless pacemaker (LP) therapy, a recently introduced technology aimed to reduce complications related to conventional PPM therapy. Patients can be treated in one procedure, and potentially be mobilized and discharged earlier compared to standard of care. It is expected that LP may provide an additional treatment benefit for the elderly population by reducing re-operations and hospital stay.

Study objective

The primary objective of the study is to outline the advantages of LP

implantation in TAVI patients who require temporary, and possibly permanent pacing compared to the Standard of Care using TV-TP therapy. We will study whether placement of a LP system following TAVI procedure is superior to TV-TP therapy with respect to intervention-related complications. Secondary objectives are the evaluation of: all-cause mortality, major adverse cardiac event, stroke, NYHA functional classification, left ventricular systolic function, duration of hospitalization, time to mobilization, recurrent hospitalization due to cardiovascular event, Health Related Quality of Life, cost-effectiveness, percentage patients requiring PPM following TV-TP, percentage need for pacing therapy in all PM patients, determine conduction disorder progression, and patient satisfaction.

Study design

This will be a prospective, randomized, multicenter, interventional two-arm trial to claim superiority of an intervention (LP) over a SOC strategy (TV-TP) in selected TAVI patients on intervention-related complications. Patients will be randomized in two arms on a 1:1 basis (block randomization):

1) Interventional arm: implant of LP therapy in TAVI-patients who are indicated for temporary pacing therapy post-TAVI implantation.
2) Control arm: standard TV-TP therapy in TAVI-patients who are indicated for temporary pacing therapy post-TAVI implantation, and subsequent conventional transvenous PPM therapy if applicable.

We will select up to 10 centers, 6 from The Netherlands (including University and Non-University Hospitals) and 4 from European countries with similar health care systems. There are additional requirements for site selection. In section 4.1 the site selection requirements are reported.

This study will include 210 patients with a follow-up of 12 months. With 2 x 105 (including 5% attrition) randomized patients the trial has 90% power to claim superiority of the interventional arm (LP) with respect to the primary endpoint of difference in intervention-related complications in comparison to the conventional arm (TV-TP therapy) at 12 months from randomization. The complete sample size calculation is discussed in 4.4.

Pilot/ First phase interim analysis
We will start with the pilot, a prospective, randomized, monocenter, interventional two-arm trial, including 20 patients (2x10 patients per treatment arm) with a follow-up of 30 days. This pilot will be executed in the Academic Medical Center to determine feasibility and logistics of the study design. If deemed necessary in additional Dutch medical centers will be asked to participate. These 20 patients will be included in the total study population of the subsequent international multicenter study.

Intervention

The patients who are allocated to the interventional arm are implanted with a leadless pacemaker, preferably within the same procedure as the TAVI, but must be implanted with a leadless pacemaker within 12 hours after randomization. These patients will receive standard care for leadless pacemaker implantation. The LP will be implanted under fluoroscopic guidance, using a percutaneous, transfemoral approach with a 18F introducer sheath (Nanostim LP) or 27F introducer sheath (Micra TPS). The LP will be implanted in the right ventricular apicoseptal region. After electrical testing, the LP will be released, and the delivery catheter will be removed from the groin. The expected fluoroscopy time will be expected to be less than 5 minutes (3.5-4.0 mSv). The implant procedure of the LP is described in section 6 of the study protocol in more detail.
The patient has to undergo one procedure when radomised in the interventional arm in comparison to two procedures with standard of care. There are two types of leadless pacemakers: the Micra (Medtronic) and the Nanostim (Abbott). The choise for leadless pacemaker will be based on availability and patients/ implanting physicians.

Study burden and risks

In TAVI patients who develop a need for pacing due to conduction abnormalities secondary to the TAVI implant, transvenous temporary pacing (TV-TP) therapy is provided as a bridge to PPM. In some patients the need for pacing is only temporary. Guidelines recommend to implant a PPM within 7 days if the conduction abnormalities persist. TV-TP therapy requires monitoring, often in the cardiac care unit, resulting in prolonged hospital stay providing a significant economical and logistic burden. To attain deeper knowledge on TV-TP our research group performed a scoping review in order to give an up-to-date overview on complications, need for subsequent PPM of all available studies until December 2016. In 17 out of 31 studies the need for PPM placement following TV-TP was documented. In 57.4% of patients subsequent PPM was required after TV-TP therapy.

Previously reported complication rates are high with a mean of 26.5%, but ranging from 10-60%. These complications are often related to the temporary pacing lead (i.e. dislodgement, malfunction, perforation, infection) or to the venous access (i.e. pneumothorax, venous thrombosis, access site bleeding, hematomas). Since the reported complication rates were so high and varied widely we evaluated this problem in our scoping review. We observed a total complication rate ranging from 0.8% to 80.5%. The weighted mean complication rate of all included studies was 30.7%.

Patients who receive TV-TP are required to remain bed rested in order to minimize risk of lead dislocation or perforation. Not only is this not

comfortable for the patients, especially the elderly TAVI population is at high risk for development of muscle atrophy, hospital acquired pneumonia , and delirium (in 10-40%) which is often associated with adverse short- and long-term health implications.

Recently, LP therapy has been introduced aimed to reduce complications related to conventional PPM therapy (e.g. lead fractures, pocket infection, pacemaker endocarditis, pneumothorax).There are currently two LP available an used in clinical practice: 1) The nanostim LP (15) and 2) the Micra transcatheter pacing system (TPS). First studies showed safety and efficacy of these devices. For the Nanostim LP, complication rates ranged from 4-6% and were almost all related to the implant procedure (i.e. perforation, dislocation, venous access site bleeding). Major device-related complications occurred in 25 (3.4%) of the 725 patients following Micra TPS. No reports of infection of the both devices have been reported in the patient cohort with the longest follow-up of 12 months. Outside of the investigational setting, recent results of the acute performance of the Micra TPS from a worldwide Post-Approval Registry were presented at EHRA Cardiostim Congress June 2017 in Vienna. The device was successfully implanted in 792 of 795 registry patients (99.6%) by 149 implanters at 96 centers in 20 countries. Through 30 days post implant, a total of 13 major complications occurred in 12 patients, for a major complication rate of 1.51% (95% confidence interval, 0.78%-2.62%). Major Early pacing capture thresholds were low and stable.

Patients will be randomised to either routine therapy with (temporary) tranvenous pacing therapy, or to treatment with a leadless pacemaker. Patients in the leadless pacemaker arm will be subjected to additional follow-up visits compared to routine therapy. However, this is standard care following leadless pacemaker implantation, and not be considered additional burden.Patient with leadless pacemaker implantation in whom the pacing indication disappears, are subjected to an extra procedure, namely the leadless pacemaker implant. However, results from our scoping review showed that in 56%, patients will develop a permanent pacing indication. In patients who do not require the need for pacing, it is recommended to leave the LP implanted and program the pacemaker to a lower rate of 30 BPM VVI to prevent against SCD or/and treat future progression of conduction disorders.

There are risk associated with both therapies which are:

Potential device and procedure related risks for both leadless pacemakers include:
-Cardiac perforation
*Pericardial effusion and cardiac tamponade
*Vascular complication
-Bleeding
*Arteriovenous fistula
*Pseudoaneurysm

*Failure of vascular closure device requiring intervention
-Arrhythmia during device implantation
*Asystole
*Ventricular tachycardia or ventricular fibrillation
-Cardiopulmonary arrest during implantation procedure
-Device dislodgement
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Hemothorax
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*Infection
*Discomfort due to pocket or pacemaker
*Skin erosion
-Pulse generator problems
*Problem with connection screw
*Manufacturer recall
*Reset to default settings
*Device cannot be programmed
*Pacemaker tachycardia

* Malfunction of software algorithm

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

- Patients * 18 years
- TAVI patients that have a need for temporary pacing therapy, defined as:
1) intra-procedural or post-procedural (up to 48 hours) high degree AV block
2) intra-procedural or post-procedural (up to 48 hours) (sinus) bradycardia
3) intra-procedural or post-procedural (up to 48 hours) new onset of 1st degree AV block, RBBB, LBBB

Exclusion criteria

-Patients with pre-existing pacing or defibrillation leads
-Patients with current ICD implant
-Patients with current pacemaker implant
-Patients with pacemaker syndrome, has retrograde AV conduction, or suffers a drop in arterial blood pressure with the onset of ventricular pacing apart from rapid pacing during the TAVI implant procedure*
-Patients who are allergic or hypersensitive to <1mg of dexamethasone sodium phosphate (DSP)*
-Patients with a mechanical tricuspid valve prosthesis
-Patients with implanted vena cava filter
-Patients with a serious known concomitant disease with a life expectancy of less than one year
-Patients with a cardiac contractility modulator
-Patients with circumstances that prevent follow-up
-Patients who are unable to give informed consent
-Patents who cannot be implanted within 12 hours after randomization with a leadless pacemaker due to any logistical issues

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):	18-07-2018
Enrollment:	150
Type:	Actual

Medical products/devices used

Generic name:	Cardiac device implantation
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	18-12-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL62264.018.17