Non-inferiority of Angiography-derived Physiology Guidance Versus Usual Care in an All-comers PCI Population Treated With Unrestricted Use of the Healing-Targeted Supreme (HT Supreme) Drug-eluting Stent and P2Y12 Inhibitor Monotherapy After 1-month of Dual-antiplatelet Therapy: the PIONEER IV trial

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This PIONEER IV trial aims to demonstrate a non-inferiority of QFR-guidance PCI to usual care PCIwith respect to Patient oriented Composite Endpoint (PoCE) at 1 year with the unrestricted use ofHT Supreme-SES in an all-comers population (including...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON55997

Source
ToetsingOnline

Brief title
PIONEER-IV Study

Condition

- Coronary artery disorders

Synonym
Coronary artery disease

Research involving
Human

Sponsors and support

Primary sponsor: University of Galway-Prof.James Livesey (Vice President of Research)
Source(s) of monetary or material Support: De subsidising party is een bedrijf;SINOMED (zie protocol),SINOMED

Intervention

Keyword: coronary artery disease, drug-eluting stent, ischemia, quantitative flow ratio

Outcome measures

Primary outcome

The Primary Endpoint for this trial is a non-inferiority comparison of

Patient-oriented Composite Endpoint (PoCE) at 12 months post-procedure. PoCE is

a composite clinical endpoint of:

* all-cause death;

* any stroke, Modified Rankin scale, (MRS >=1);

* any myocardial infarction (periprocedural MI according to SCAI, spontaneous

according to 4th universal definition);

* any clinically and physiologically driven revascularization.

Secondary outcome

* Patient oriented composite endpoint (PoCE) at 2 and 3 years;

* Individual components of patient-oriented composite endpoint;

* Vessel-oriented composite endpoints (VoCE)

o Vessel-related cardiovascular Death1

o Target-vessel related MI

o Clinically and physiologically-oriented Target vessel revascularization

* Individual components of vessel-oriented composite endpoint;

* Device-oriented composite endpoint (DoCE) at all timepoints

o Cardiovascular Death

o Target-vessel related MI

o Clinically and physiologically-oriented Target lesion revascularization

* Individual components of device-oriented composite endpoint;

* Peri-procedural myocardial infarction according to 4th universal definition;

* Device Success Rate according to the statement from European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the European Society of Cardiology (ESC)

* Definite / Probable stent thrombosis

* Definite or probable stent thrombosis

* Target vessel failure (TVF)

o Cardiovascular Death

o Target-vessel related MI

o Clinically and physiologically-oriented Target vessel revascularization

* Individual components of target-vessel failure composite endpoint

* Bleeding according to BARC classification

Myocardial Infarction:

*SCAI consensus for peri-procedure MI <=48 hours, and Fourth Universal Definition (FUD) for spontaneous MI >48hours after index procedure.

Study description

Background summary

The CE-marked Healing-Target Supreme (HT SupremeTM) Sirolimus eluting stent or any next generation of the HT SupremeTM stent family will be used in line with their indications. The rationale for the use of HT Supreme is following:
- long drug-elution delays the healing process and may lead to incompetent healing;
- targeting a quicker return of a functional, protective endothelial layer could lead to better short-term prevention of stent thrombosis and at long-term could prevent neoatherosclerosis;
- HT Supreme has been specifically designed to allow the vessel to heal and return to its natural protective defences against thrombosis and restenosis allowing for short dual-antiplatelet therapy followed by P2Y12 inhibitor monotherapy;

Recently the sub analysis of the Global Leaders trial demonstrated that in complex procedures ticagrelor monotherapy after one month of DAPT with aspirin reduces the occurrence of death from all causes without reducing bleeding, compared to standard DAPT for one year followed by aspirin monotherapy.

QFR has been validated as an accurate alternative for iFR and FFR in several reports and has obtained Conformité Européenne (CE) mark 18-23. In the FAVOR I study, the diagnostic accuracy of QFR has been demonstrated without the need for pharmacologic hyperemia18. Thereafter, the FAVOR II China and the FAVOR II Europe-Japan study demonstrated the diagnostic accuracy of QFR for detection of functional significant lesions in comparison with 2D-QCA using FFR as reference standard 19, 23. In a systematic review and Bayesian meta-analysis, Collet et al confirmed the high sensitivity and specificity of QFR against pressure wire derived physiological assessment21. Both FAVOR III China and Europe-Japan are ongoing randomized controlled trials in stable and unstable angina. FAVOR III China study aims to demonstrate the superiority of QFR-guided PCI in terms of clinical outcome and cost-effectiveness compared to angiography-guided PCI in which no other functional tests such as FFR/iFR can be used for further assessment of the lesion before PCI. The FAVOR III China study is not able to answer the question whether QFR can replace FFR or not. On the other hand, the objective of the FAVOR III Europe-Japan study is to investigate whether a QFR-based diagnostic strategy will result in non-inferior clinical outcome after 12 months compared to an FFR-based diagnostic strategy. The FAVOR III Europe-Japan study could bring an answer to the question whether QFR as a tool for physiological assessment can replace FFR or not. However, the use of FFR in daily practice is still low, and whether routine QFR-guided PCI could improve clinical outcomes in daily practice will remain unanswered.

The computational pressure-flow dynamics derived FFR (caFFR) (RainMed Ltd,

Suzhou, China) is another well validated alternative to traditional FFR and iFR. This method is based on computational pressure-fluid dynamics, in conjunction with thrombolysis in myocardial infarction (TIMI) frame count, applied to coronary angiography simulated three-dimensional (3D) mesh reconstruction of the coronary artery, without using pressure wire or hyperemia state The calculation of caFFR requires a specialized pressure transducer (FlashPressure, RainMed Ltd, Suzhou, China) to extract the aortic pressure. CaFFR was first validated in 323 patients of the FLASH FFR study which showed the diagnostic accuracy of 95.7% as compared with invasive FFR. Ai et al. further showed the high level of agreement between caFFR and invasive FFR in both pre-PCI and post-PCI stages. In addition, multiple studies have demonstrated the independent prognostic value of post-PCI caFFR for clinical outcomes in ACS and CCS populations and several trials are ongoing with the technology. The cut-off value for higher target vessel failure was caFFR<0.90 in a cohort of 136 patients, while the cut-off value of post-PCI caFFR was <=0.83 in 65 patients for predicting VOCE.Thus, the cut off value of caFFR still requires further research.

Study objective

This PIONEER IV trial aims to demonstrate a non-inferiority of QFR-guidance PCI to usual care PCI
with respect to Patient oriented Composite Endpoint (PoCE) at 1 year with the unrestricted use of
HT Supreme-SES in an all-comers population (including HBR patients) treated post PCI with one month
DAPT followed by 11-month of P2Y12 inhibitor monotherapy.

Patients with blocked or narrowed blood vessels will be treated with the Healing-Targeted Supreme stent (HT-SupremeTM). This stent is covered with a drug layer (Sirolimus) which reduces the chances of narrowing or blockage in that part of the vessel again. This drug layer is biodegradable and is slowly absorbed by your body and disappears completely from the stent. It has been approved by the authorities to treat a narrowing of the coronary artery. This study aims to study the efficacy and performance of the HT supreme in all patients treated.

This clinical trial will also compare two diagnostic techniques. The first technique uses imaging software QFR (Quantitative Flow Ratio) from Medis or caFFR from RainMed in providing information on the blockage/narrowing in your blood vessel(s) and provides guidance on how to best treat your vessels. The Medis and RainMed assessment software is non-invasive, which means nothing will enter your body, and has been approved by the authorities. The other technique are local routine diagnostic procedures (LRDP) already used at your hospital (e.g. visual assessment and/or invasive wire-based techniques (iFR and FFR), which have also been approved by the authorities.

In this trial two anticoagulants (antiplatelet inhibitors) are prescribed for the duration of one month. This is shorter than usual, but treatment guidelines are currently moving towards this recommendation, based on new clinical data. The anticoagulant medication reduces the risk of blood clots forming in the doped blood vessel after your PCI procedure. The risk of blood clotting decreases, but this increases the risk of heavier bleeding if you cut yourself, for example.
After this month, only ticagrelor is prescribed for the duration of another 11 months.

Study design

The PIONEER IV study is a prospective, single-blind (patient), randomized, 1:1, controlled, multi-centre trial comparing clinical outcomes between angiography-derived physiology guidance to usual care in an all-comers patient population undergoing PCI with unrestrictive use of HT Supreme sirolimus-eluting stent.
All patients should receive dual anti-platelet therapy (DAPT), being aspirin (ASA) and ticagrelor for 1 month, followed by 11 months of ticagrelor monotherapy only. After that, ticagrelor monotherapy is replaced by aspirin monotherapy at 1 year or according to standard of care.
Of note: ticagrelor is the default P2Y12 (highly recommended) in Acute Coronary Syndromes (ACS) and chronic coronary syndromes (CCS). For additional information/recommendation refer to section 11.12.
Patient will be randomized either to angio-based physiology guidance or usual care.
Angio-based physiology guidance cohort Preprocedural guidance:
* Patient undergo PCI using HT Supreme stent in all flow limiting lesions (QFR<0.80) due to significant stenosis/occlusion;
* on-line assessment of QFR is performed to evaluate the functional severity of the lesion(s). If QFR is <=0.80, PCI is performed with the HT Supreme stent. If QFR is >0.80, the treatment of the lesion is deferred.
Post-stenting assessment:
After stenting, QFR is repeated in the stented vessel(s). In case distal QFR is <0.91 or delta QFR (across the stent is >0.05), post-dilatation of stented segment or additional stenting is recommended. Post-stent IVUS/OCT assessment and guidance for further treatment (to elucidate the cause of non-normalisation of QFR and to guide the treatment) are optional at the discretion of the investigator.
Usual care cohort Presence of one or more coronary artery stenosis (*50%) by visual assessment in a native coronary artery or coronary artery bypass graft (venous or arterial) suitable for coronary stent implantation.

HT Supreme stent will be implanted in all lesions. Non-invasive and invasive assessment of the
physiological severity of the lesion, prior or at the time of the treatment, is left at the discretion of

the operator.
All patients will be (at minimum) contacted via visit at 30 days (±7 days) and 12 months (±30 days)
and by phone contact at 6 months (±14 days), 24 months (±30 days) and 36 months (±45 days) post
index procedure to assess clinical status and adverse events.

Intervention

a. If randomized to QFR guidance:
perform QFR on the diagnostic angiogram from referral site (if analysable* and in the absence of positive non-invasive test). In case the clinical presentation changed since the diagnostic angiography (e.g. CCS to ACS), the diagnostic angiography should be repeated to document the intercurrent change in anatomy/QFR.
1 if QFR of all lesions -on the referral angio- are negative and in the absence of a prior positive non-invasive test, the patient will not be admitted to the cathlab/will not undergo PCI. The patient will stay in the study (deferred PCI for all lesions) with a clear explanation to the patient and to the referring physician
2 if QFR of all lesions -on the referral angio- are negative but in presence of a prior positive non-invasive test, the negative QFR should be challenged by wire-derived FFR/iFR during the procedure.
*if QFR on diagnostic angio is not analysable, patient will be admitted to the cathlab and will undergo QFR.
b. If randomized to usual care: -> patient will be admitted to the cathlab for the PCI (as requested by the referral site).

Study burden and risks

Coronary stenting with both BMS and DES has been performed successfully for several decades and is considered a standard treatment for coronary artery disease. Furthermore, there is extensive clinical and commercial experience worldwide with cardiac catheterisation and interventional procedures and it is expected that the procedural risks in this study and existing stenting procedure will not be significantly different. Possible benefits may be found for future patients treated with HT SupremeTM. PCI and functional guidance (QFR) based upon results of this study.

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. Male or female patient >=18 years of age;
2. Patient has chronic stable angina, acute coronary syndromes or silent ischemia;
3. Presence of one or more coronary artery stenoses of >=50% (by visual assessment) in a native coronary artery (with or without prior stent/other device treatment) or in a saphenous venous or arterial bypass conduit suitable for coronary stent implantation;
4. The vessel should have a reference vessel diameter of at least 2.25 mm by visual assessment (no limitation on the number of treated lesions, vessels, or lesion length);
5. Patient has been informed of the nature of the study and agrees to its provisions and has provided written informed consent as approved by the Ethical Committee and is willing to comply with all protocol-required (follow-up) evaluations.

Exclusion criteria

1. Patient is a woman who is pregnant or nursing (a pregnancy test must be performed within 7 days prior to the index procedure in women of child-bearing potential according to local practice);
2. Known intolerance to cobalt chromium, and medications such as sirolimus, aspirin, heparin, bivalirudin or P2Y12 inhibitors;
3. Planned major elective surgery requiring discontinuation of (D)APT within 12 months of procedure;
4. Concurrent medical condition with a life expectancy of less than 3 years;
5. Currently participating in another trial and not yet at its primary endpoint;
6. Active pathological bleeding;
7. History of intracranial haemorrhage.

Study design

Design

Study type: Interventional

Masking:	Single blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	27-01-2022
Enrollment:	595
Type:	Actual

Medical products/devices used

Generic name:	HT Supreme sirolimus eluting stent
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	22-11-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-05-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-09-2023
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	NCT04923191
CCMO	NL78434.100.21