Impact of Vascular Reparative Therapy on Vasomotor Function and Myocardial Perfusion: a randomized H215O PET/CT Study

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The objective of the proposed study is to determine the impact of VRT, in comparison with conventional drug-eluting stenting, on endothelium dependent vasodilation and maximal hyperemic myocardial perfusion using H215O PET.

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

Summary

ID

NL-OMON39000

Source
ToetsingOnline

Brief title
VANISH

Condition

- Coronary artery disorders

Synonym
coronary arteriosclerosis, Obstructive coronary artery disease

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: Abbott,Bijdrage Farmaceutisch bedrijf; Abbott

Intervention

Keyword: bioresorbable scaffolds, H215O PET, myocardial perfusion, revascularization

Outcome measures

Primary outcome

MBF measurements: resting MBF, during endothelial dependent vasodilation provoked by cold-pressor-testing (CPT), and during (endothelial dependent and independent) maximal vasodilation by infusion of adenosine intravenously

Secondary outcome

Obstructive coronary lesions on control invasive coronary angiogram that may affect the MBF measurements.

Study description

Background summary

More than three decades ago, percutaneous coronary intervention (PCI) was introduced as a means to restore myocardial perfusion in the presence of an obstructive epicardial coronary stenosis. Initially, coronary angioplasty consisted solely of mechanical dilatation of the stenotic lesion by balloon inflation. Notwithstanding the clinical groundbreaking success of this therapeutic avenue, now referred to as *plain old balloon angioplasty* was associated with feared short-term complications such as elastic recoil, dissection, and intraparietal hematoma that led to acute coronary occlusion in a not inconsequential number of patients. (Gruntzig A, Lancet 1978) Furthermore, angioplasty was associated with re-stenosis of the dilated coronary segment due to constrictive remodeling and neointimal hyperplasia in the ensuing months after treatment. The introduction of stenting coronary lesions with a metallic scaffold dramatically counteracted these aforementioned acute hazardous complications. (Serruys et al, NEJM 1994) Cytostatic drug coating of these metallic stents, which inhibit neointimal proliferation, thereafter largely antagonized the issue of intra-stent re-stenosis. (Morice MC et al, NEJM 2002) Due to these advances in interventional cardiology, PCI for

stable coronary artery disease (CAD) in the current era is characterized by a low complication rate and good long-term outcome.
Nonetheless, implantation of a permanent metallic device has several proven and hypothesized caveats. First, the uncovered and/or malapposed struts of the endoluminal prosthesis may offset a thrombotic cascade that can result in subacute or late stent thrombosis. The latter phenomenon is particularly relevant with drug- eluted stents that interfere with the endothelialization process thereby demanding prolonged dual anti-platelet therapy. (Finn AV et al, Circulation 2007) Second, permanent caging of the coronary artery with a rigid stent alters vessel geometry indefinitely and induces changes in flow, shear stress, and cyclic strain patterns throughout the cardiac cycle. These permanent changes may interrupt physiological cellular signaling pathways, through lack of what is called *mechanotransduction*, and promote the process of atherosclerosis. (Slager CL et al, Nat Clin Pract Cardiovasc Med 2005)
These issues have propelled the development of a biodegradable scaffold that instantly and safely treats a stenotic coronary stenosis but thereafter ultimately dissolves and may facilitate restoration of normal coronary physiology, abolishing the long-term detrimental effects of a traditional coronary stent implantation. (Waksman R, J Invasive Cardiol 2006) Indeed, preliminary studies have revealed that vasomotor function of the neo-intima gradually returns, as tested by intraluminal administration of acetylcholine, throughout the degrading process of the scaffold. (Serruys PW, JACC 2011) Apparently, the newly formed endothelial layer can regain the capacity to respond to pharmacologically induced stimuli. This form of therapy is therefore also ambitiously labeled as *vascular reparative therapy* (VRT). (Serruys PW et al, Eur Heart J 2012)
Eventhough the implantation of these drug-eluting bioresorbable scaffolds (BRS) appears to be safe in selected cohorts of human subjects, their hypothesized superiority over conventional drug-eluting stents has yet to be proven. (Serruys PW et al, Lancet 2009) Currently, randomized trials are ongoing to further clarify this issue. These trials, however, are predominantly targeted to document clinical end- points (e.g. target vessel revascularization, myocardial infarction, and death). Given the low event rate of patients who are treated by PCI for stable CAD in the current era, such trials demand inclusion of large numbers of patients to be sufficiently powered to detect potential differences between treatment strategies and will require long-term follow-up. These results, therefore, will not become available within the next coming years. Furthermore, these studies will reveal little about the potential beneficial physiological aspects of VRT. Ultimately, the primary goal of any PCI is not to relief the anatomical blockage of a coronary artery per se but to restore downstream myocardial perfusion. In fact, the level of impairment of myocardial perfusion reserve is one of the most important independent prognostic predictors for death in patients with ischemic heart disease. (Murthy VL et al, Circulation 2011) Consequently, enhancement of flow reserve and alleviation of significant ischemic burden is associated with a more favorable prognosis. (Shaw LJ et al, Circulation 2008) In theory, the potential beneficial effect of VRT on vasomotor function, e.g. by flow mediated coronary

dilatation, could contribute to a more substantial restoration of long-term myocardial perfusion. Documented late luminal gain by VRT in comparison with conventional stent implantation may also add to this hypothesized favorable effect on perfusion. (Onuma Y et al, Circulation 2010) Data to substantiate these postulated effects are, however, lacking.
Positron emission tomography (PET) enables to noninvasively quantify biological processes in vivo. In fact, PET in conjunction with the flow tracer oxygen-15-labeled water (H215O) is considered the gold standard to noninvasively assess myocardial blood flow (MBF) in man. (Knaapen et al, Basic Research Cardiol 2009) Moreover, the short physical half-life of this tracer (120 seconds) allows to perform multiple measurements within a single scanning session at low radiation burden for the patient. Thus, this imaging technique allows to study the effects of VRT on downstream myocardial perfusion using different physiological and pharmacological stimuli.

Study objective

The objective of the proposed study is to determine the impact of VRT, in comparison with conventional drug-eluting stenting, on endothelium dependent vasodilation and maximal hyperemic myocardial perfusion using H215O PET.

Study design

Type of study
The study is designed as a single center single-blind randomized clinical trial and will be conducted at the VU University Medical Center in Amsterdam.

Summary of the study design
Sixty patients accepted for this study will be randomized to implantation of a drug-eluted stent (Xience Prime) or BRS (Absorb). H215O PET will be performed one month (reference scan), one year, and three years after the PCI procedure (resolution of BRS is generally complete within a three year period). The PET protocol will consist of three MBF measurements: resting MBF, during endothelial dependent vasodilation provoked by cold-pressor-testing (CPT), and during (endothelial dependent and independent) maximal vasodilation by infusion of adenosine intravenously. After three years a control invasive coronary angiogram will document any potential obstructive coronary lesions that may affect the MBF measurements.

Duration of the study
Inclusion rate will be 1-2 patients weekly and therefore the inclusion period is estimated to be one year. The follow-up period is three years, therefore the entire study will be conducted over a four-year period.

Intervention

Patients will be randomized to implantation of a drug-eluted stent (Xience Prime) or BRS (Absorb).

Study burden and risks

PET/CT scans will be planned one month, one year, and three years after PCI, each with exposure to an effective dose equivalent of 2 mSv. Every PET/CT will take approximately one hour inclusive patient preparation. Adenosine will be infused intravenously during PET/CT, which may induce transient AV-conduction delay or bronchospasm. Investigator will be present to monitor any adverse events. Patient will have to place their hand in ice-water for a few minutes depending on endurence. This might cause unplaesant feelings. The patient is able to remove their hand from the ice-water at any time.
After three years control angiography will be performed during one day hospitalization with exposure to an effective dose equivalent of 4mSv, depending on patient habitus. Risk of caronary angiography is comparable with clinical control coronary angiography with an event rate of less than 0,5%.
Patient-benefit consists of a potentially improved treatment and close monitoring of patient treatment and symptoms. There is benefit for good clinical practice because of an improved determination of indications for BRS. An other possible benefit will exists of documentation of microvascular function (PET).

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 with documented obstructive CAD by invasive coronary angiography resulting in myocardial ischemia (either documented by invasive (i.e. fractional flow reserve, FFR) or noninvasive imaging techniques (e.g. exercise ECG, myocardial perfusion imaging, or inducibility of wall motion abnormalities during dobutamine stress).
- Presence of a single, de-novo lesion in a native coronary artery (type A or B1), with a reference vessel diameter of at least 3.0 mm and a diameter stenosis of 50% or more and less than 100%, with a thrombolysis in myocardial infarction (TIMI) flow grade of at least 2. Coronary lesion must be amendable for successful treatment with one of the following BRS device dimensions: length 18 or 28 mm, diameter 3.0 or 3.5 mm.
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Exclusion criteria

- refusal or inability to provide written informed consent
- other than single CAD
- abnormal echocardiographic findings (i.e. wall motion abnormalities, ventricular hypertrophy, valvular disease etc.)
- complex coronary lesion characteristics (e.g. lesions located in the left main coronary artery, lesions involving a side branch more than 2 mm in diameter, and the presence of thrombus or another clinically significant stenosis in the target vessel)
- poor kidney function defined as an eGFR < 30 ml/min
- astma or chronic obstructive pulmonary disease
- other than sinus rhythm
- pregnancy
- bail out stenting after placement of the study device

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-08-2013
Enrollment:	60
Type:	Actual

Medical products/devices used

Generic name:	Bioresorbable scaffold (ABSORB)
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	23-05-2013
Application type:	First submission
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	NL43796.029.13