IMPACT

Imaging and Modeling to investigate the mutual relationship of Plaque growth and biomechanical parameters in human coronary arteries

- Correction April 2014: section 11.5: The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection ~~6~~ 9 of the WMO

IMPACT: Imaging and **M**odeling to investigate the mutual relationship of **P**laque growth and biomechanical **p**arameters in human **c**oronary arteries

Protocol ID	**IMPACT**
Short title	Imaging and **M**odeling to investigate the mutual relationship of **P**laque growth and biomechanical **p**arameters in human **c**oronary arteries
EudraCT number	***Not applicable***
Version	**2.0**
Date	**08-11-2016**
Coordinating investigator/project leader	***Dr.ir. Jolanda Wentzel*** ***Thoraxcentrum BME, Ee23.22*** ***Postbus 2040, 3000CA, Rotterdam*** ***010-7044044***
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder) ***<Multicenter research: per site>***	***Dr. J. Daemen*** ***Cardiologie, Ad 342*** ***3000 CA Rotterdam*** ***Dr. ir. Jolanda Wentzel*** ***Thoraxcentrum BME, Rotterdam*** ***Not applicable***
Sponsor (in Dutch: verrichter/opdrachtgever)	***Erasmus MC (Investigator driven)*** ***Prof. dr. F. Zijlstra*** ***Thoraxcentrum, Ba-595*** ***Postbus 2040*** ***3000 CA Rotterdam***

Subsidising party	***ERC grant Agreement n. 310457***
Independent expert (s)	**Dr. O.C. Manintveld**
Laboratory sites <*if applicable*>	***Not applicable***
Pharmacy <*if applicable*>	***Not applicable***

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Sponsor or legal representative: **Erasmus MC (investigator driven)** **Head of Department:** ***Prof. Dr. F. Zijlstra*** ***Head Thorax center***		10/11/16
[Coordinating Investigator/Project leader/Principal Investigator]: ***Dr.ir. Jolanda Wentzel*** ***Thoraxcentrum BME, Ee23.22*** ***Postbus 2040, 3000CA, Rotterdam*** ***010-7044044*** ***Dr. J. Daemen*** ***Cardiologist***		10. 11. 16

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
ACS	**Acute Coronary syndrome**
AE	**Adverse Event. Any undesirable experience occurring to the subject, during the clinical trial, whether or not considered related to the investigational product(s). An adverse event is defined as serious whenever the event is fatal, life-threatening, disabling or results in in-patient hospitalization or prolongation of hospitalization**
AMI	**Acute myocardial infarction**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CK	**Creatine Kinase**
CK - MB	**Creatine Kinase - Muscle Brain**
CRF	**Case Report Form. A record of the data and other information on each subject in a trial as defined by protocol.**
CTA	**Computed Tomography Angiography**
CV	**Curriculum Vitae**
DEATH	**All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established.**

DSMB	**Data Safety Monitoring Board**
ECG	**Electrocardiography**
EMBOLIZATION	**An acute disruption of the contrast medium opacification of the coronary artery distal to the site of treatment caused by dislodged tissue and blood clot.**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
FEA	**Finite Element Analysis**
FSI	**Fluid Structure Interaction**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IVUS	**Intravascular ultrasound**
IVUS-VH	**Intravascular ultrasound virtual histology**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
MACE	**Major adverse cardiac events**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
MLA	**Minimal luminal area**
MYOCARDIAL INFARCTION	**Diagnosis based on 2 of the following 3 conditions -clinical symptoms, ECG and enzyme changes (more than double upper normal limits of creatine kinase (CK) and/or presence of CK-MB)**
NIRS	**Near infrared spectroscopy**

NSTEMI	**Non-ST segment elevation myocardial infarction**
OCT	**Optical Coherence Tomography**
PERFORATION	**Perforation of the target vessel wall as classified below:**

Type 0	***Absent***
Type 1	***Wire Exit - wire is outside the true lumen penetrating the arterial wall (intima, adventitia, media) without extravasation***
Type 2	***Blushing - Extravasation of contrast into the vascular wall which clears following the injection***
Type 3	***Staining - Extravasation of contrast into the vascular wall or localized epicardial structures which persists following the injection***
Type 4	***Extravasation - Extravasation of contrast into the pericardial free space as demonstrated by angiography.***

PCI	**Percutaneous Coronary Intervention**
PTCA	**Percutaneous transluminal coronary angioplasty**
QCA	**Quantitative Coronary Angiography performed at Angiographic Core Laboratory.**
(S)AE	**(Serious) Adverse Event**
SAP	**Stable angina pectoris**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SS	**Shear Stress is the frictional, longitudinal force of blood against**

	the arterial wall.
STEMI	**ST segment elevation myocardial infarction**
TCFA	**Thin cap fibroatheroma**
TIMI CLASSIFICATION (CORONARY FLOW)	**TIMI 0** **No perfusion.** **TIMI 1** **Penetration with minimal perfusion. Contrast fails to opacify the entire bed distal to the stenosis for the duration of the cine run.** **TIMI 2** **Partial perfusion. Contrast opacifies the entire coronary bed distal to the stenosis. However, the rate of entry and/or clearance is slower in the coronary bed distal to the obstruction than in comparable areas not perfused by the dilated vessel.** **TIMI 3** **Complete perfusion. Filling and clearance of contrast equally rapid in the coronary bed distal to stenosis as in other coronary beds.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UAP	**Unstable angina pectoris**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)**
WS	**Wall Stress is the stress in the arterial wall, caused by the blood pressure.**

SUMMARY

Rationale: Myocardial infarction is mainly caused by atherosclerotic plaque rupture and subsequent atherothrombosis in the coronary arteries. Evidence is accumulating for a role of plaque composition in this process. Biomechanical parameters are known to play an essential role in atherosclerotic plaque formation, but not much information is available on its involvement in plaque growth and changes in plaque composition, so called plaque destabilization, over time. Two biomechanical parameters are of importance in the vasculature: shear stress of the blood at the vessel wall, and wall stress, the stress inside the vessel wall. Assessment of these factors over time is of utmost importance to further gain insight in the process that are involved in plaque growth and destabilization and might aid in improvement of risk prediction for MACE and ultimately, in improved, risk-adapted, "personalized" patient care.

Objective: To investigate the association between shear stress and plaque growth and plaque composition changes over time. Furthermore, it will be investigated how these plaque changes influence the local wall stress.

Study design: Prospective, longitudinal, observational study

Study population: A total of 70 patients with documented acute coronary syndrome admitted for PCI treatment and who meet all inclusion/exclusion criteria, will be included.

Intervention (if applicable): *Not applicable*

Main study parameters/endpoints:

Our primary endpoints to be investigated:

*1) Association between shear stress **at baseline** and plaque geometry and composition **at baseline** (including wall thickness, cap thickness and lipids).*

*2) Association between shear stress **at baseline** and plaque geometry and composition **changes over time** in (including wall thickness, cap thickness and lipids).*

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

Intravascular coronary imaging is often part of the clinical routine in PCI as it can help the operator to achieve an optimal stent result. The burden of this study to the patient at baseline and follow-up is the additional imaging of non-culprit coronaries, which adds extra time to the total procedural time and a very small risk of coronary complications associated with introduction of a guide wire and imaging catheter in the coronary artery (less than 1 promille). The patient might potentially benefit from the invasive imaging in two ways. First, invasive imaging might help to reach optimal treatment of the culprit lesion and at follow up the treatment location will be investigated for restenosis, and if necessary treated. Secondly, thorough evaluation of the non-culprit vessel might reveal additional, significant, but

angiographically silent lesions warranting treatment. Recently the failure rate of angiography to visualize such additional lesions causing clinical events in the near future, has been reported as high as 15% (PROSPECT).

1. INTRODUCTION AND RATIONALE

Biomechanical parameters play an essential role in atherosclerotic plaque initiation and formation, however not much information is available on its involvement in atherosclerotic growth and changes in the plaque composition, the so called plaque destabilization, over time in the coronary arterial wall in patients. The latter can be explained by the fact that biomechanical parameters cannot easily be assessed and advanced imaging is needed to obtain information on the wall composition. In order to study the mutual interaction between biomechanical parameters and plaque characteristics over time, we propose a clinical trial (IMPACT) in which new imaging techniques will be applied, that allow assessment of the wall composition and dimensions, which will be combined with computations for biomechanical characterization of the vessel wall. This will be further explained in section 1.3.

1.1 Atherosclerotic disease burden

Atherosclerosis is a major health care burden, responsible for nearly 40% of the mortality in Europe. Atherosclerotic coronary artery disease, often complicated by (athero) thrombosis leading to acute myocardial infarction. Risk factors for atherosclerosis include gender, age, cholesterol, hypertension, smoking, obesity and diabetes mellitus [1]. Despite these risk factors are systemic in nature, plaques are often localized at specific regions in the vasculature for instance in the inner curves and close to side branches, where the shear stress of the blood is low.

Acute myocardial infarctions are mainly triggered by rupture of so-called vulnerable plaques in the coronary arteries. Vulnerable plaques that cause cardiac events can be histopathologically characterized by: a mildly stenotic, positively remodeled, eccentric lesion, containing a lipid-rich necrotic core under a thin fibrous cap that is weakened by inflammation, also denoted as thin-cap fibroatheromas (TCFA) [2]–[5]. A large patient study (PROSPECT TRIAL) confirmed that the presence of coronary lesions with the following characteristics, namely TCFAs, as diagnosed based on virtual histology, minimal luminal area (MLA) ≤ 4 mm2 and plaque burden (PB) ≥ 70 %, increase the risk of Major Adverse Cardiovascular Events (MACE) [6]. However, these new criteria based on virtual histology only predicted 18% of the MACE in a follow-up period of 3.4 years, indicating that further research is needed to better estimate the risk for MACE.

The exact process of the development of a plaque causing clinical sequelae and MACE is still unknown. Known is that biomechanics are involved in plaque initiation and growth, but unknown is how these relate to plaque composition. Assessment of these factors over time is of utmost importance to further gain insight in the process that are involved in plaque growth and destabilization, might aid in improvement of risk prediction for MACE and ultimately, in improved, risk-adapted, "personalized" patient care.

1.2 Biomechanics behavior, plaque composition and plaque growth

The origin of acute myocardial infarctions is rupture of so-called vulnerable plaques in the coronary arteries. Unraveling the mechanisms that influence plaque growth, plaque composition changes and rupture is of eminent importance for detection of these rupture prone vulnerable plaques.

The force of the blood flow along the endothelial cells of the vessel wall is defined as *shear stress (SS)*. Low shear stress is found close to side branches or in the inner curvature of the coronary arteries [7], [8], whereas high shear stress can be found in the outer curve or at the carina of a coronary bifurcation. Multiple studies have shown that low/oscillatory shear stress promotes plaque initiation [7], [9], [10]. For instance, in the coronary arteries a correlation is observed between wall thickness and average low SS locations[7]. The Erasmus MC Biomechanics Laboratory (Biomedical Engineering department) was the first to show this relationship in human coronary arteries in vivo. In addition, we and others in the field showed that low endothelial shear stress plays also an important role in the development of plaques and might be involved in changes in plaque composition [7]–[9], [11]. However plaque development studies that include plaque composition are performed in atherosclerotic animal models. The only known patient study investigating plaque composition uses IVUS-VH with limited accuracy in plaque composition especially in calcified regions [12].

To an extent the arterial wall can adapt the to the plaque area increase and maintain the same lumen area the plaque will then develop outwards, this phenomenon is called remodeling [13]. At a certain moment the plaques start to encroach into the lumen and are thereby exposed to high shear stress at the upstream side of the plaque [14], [15]. Evidence is accumulating for a role of high shear stress in plaque composition changes i.e. cap thinning, this phenomenon is also called plaque destabilization [12], [15]–[18]. Ruptures of plaques were in 70% of the cases observed at the upstream, supposedly high shear stress, region of the plaque [19]. These were also the regions where the plaque composition was more vulnerable than downstream [19], [20]. Since shear stress is very small in magnitude it is unlikely that it will cause plaque rupture by its imposed force, but it may initiate various biological processes that lead to local weakening of the cap [14]. Thus, shear stress potentially contributes to plaque destabilization and thus future risk at plaque rupture.

Another biomechanical force is the wall stress, i.e. the stress inside the vessel wall imposed by the blood pressure, defined as *wall stress (WS).* Rupture of a plaque will occur if the stress in the vessel wall, exceeds the strength of the different plaque components [21]. Wall stresses are very much dependent on the local plaque composition; an inverse relationship is observed between wall stress and cap thickness. High wall stress in the fibrous cap of the

plaque can lead to rupture. Rupture of the plaque can trigger local thrombosis formation and may lead to myocardial infarction. However, subclinical plaque rupture, will result in thrombus organization which in turn will lead to further plaque growth. Therefore, repeated subclinical plaque ruptures on a smaller scale, can thereby lead to rapid plaque growth. Thus high wall stress potentially identifies plaques currently at risk to grow or rupture leading to myocardial infarction.

1.3 Intracoronary imaging of atherosclerosis

Intravascular and minimal/ non-invasive imaging technologies that are currently available to allow assessment of the lumen and the plaque size and composition are reviewed in this paragraph.

1.3.1 Minimal/ non-invasive imaging techniques

Angiography is an imaging technique which visualizes the lumen, by injecting a contrast agent during X-ray imaging. This technique has provided important insights when treating acute infarct angioplasty [22]. However when using angiography only the lumen of the arteries are captured in 2D, therefore side vessels can be erroneous projected. Furthermore angiography does not allow visualization of the wall and thus plaque composition.

Coronary CT angiography (coronary CTA) permits visualization of the coronary artery lumen and detection of coronary artery stenosis. In addition, non-stenotic coronary atherosclerotic plaques can be depicted. In contrast to 'calcium screening', coronary CTA also allows visualization and, to some extent, quantification and characterization of non-calcified plaque deposits, but the outer wall quantification is still a challenge. However, all of this requires excellent image quality without artefacts. Also CT enables a full 3D representation of the lumen of coronary arteries.

1.3.2 Invasive imaging techniques

Intravascular ultrasound (IVUS) uses sound waves to penetrate the tissue. Due to attenuation, reflection and scattering of the sound an image is obtained. This technique as opposed to angiography can visualize more structures than solely the lumen, including calcium and the transition from media to adventitia. Interpretation of IVUS gray scale data has a high specificity for calcification only; it cannot distinguish lipids or other soft components in the wall.

A post processing IVUS technique of raw frequency (RF) data, intravascular ultrasound virtual histology, IVUS-VH, shows potential to distinguish different types of components in the plaque [23]. However, discrimination between lipid-containing and mixed (fibro-lipidic) plaque, labeled as a region of low-density in gray scale IVUS remains difficult to achieve. Besides, analysis of tissue behind a calcification is difficult because of signal attenuation [23].

A new technique the NIRS (Near Infrared Reflection Spectroscopy), provides a probability map (chemo gram) for the presence of lipids based on spectroscopy and is thereby able to identify the angle in the plaque that contains lipid [24]. A new system is developed, LipidScanTM (infraReDx Inc), that is able to perform NIRS and IVUS simultaneously. In this way information on both the geometry as well as presence of lipids is available. A drawback of this technique is that only the angular extent within the vessel circumference and not to the exact size and location of the lipids within the plaque can be captured.

OCT is similar to IVUS with the major difference that it is based on light reflection instead of sound. The resolution of this technique is much higher than IVUS and it is able to distinguish the fibrous cap thickness [25] and the location of certain plaque components including the lipid and calcium. However the penetration depth of this technique is less than IVUS and therefore does not permit visualization of media and adventitial layer.

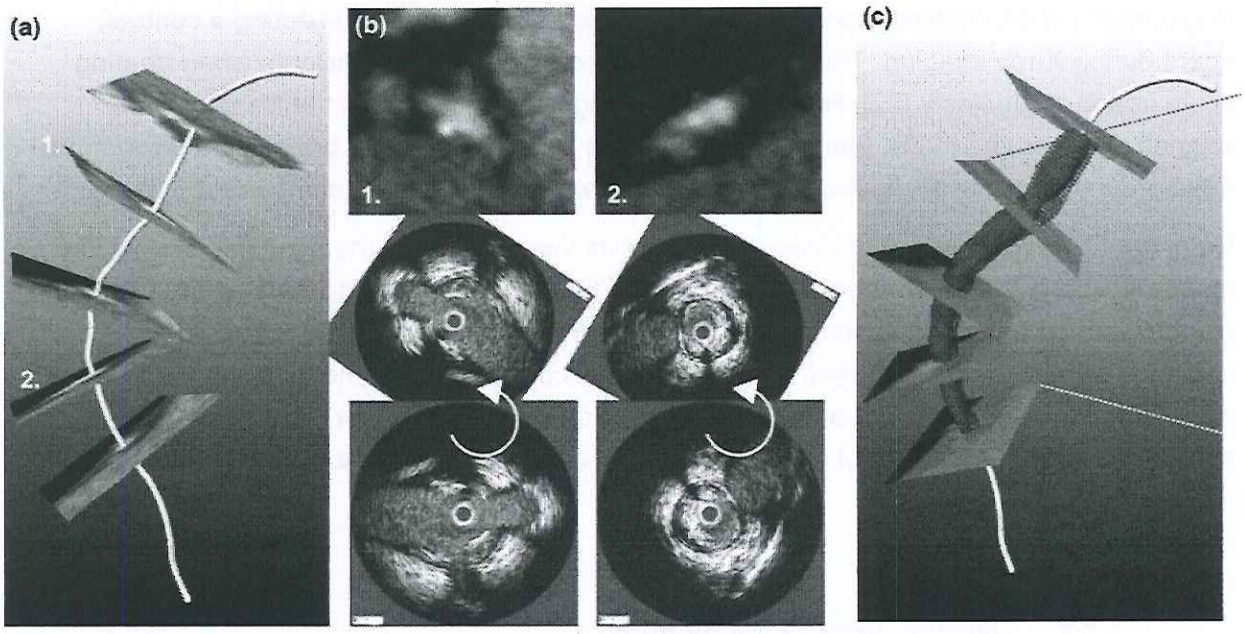

Figure 1: Fusion. The white line indicates the centerline (a) of the diseased artery obtained from CT. Perpendicular to the centerline are the IVUS images (b, 1 and 2). The CT images were matched to landmarks. Thereafter the 3D geometry (c) is obtained [26].

1.3.3 Imaging used in this study

In this study we chose to use OCT and NIRS IVUS. OCT is able to capture the local cap thickness and presence of lipids. Furthermore, due to its low penetration depth the lipids can only be captured at the front side of lipids. NIRS is not limited by the penetration depth and is therefore able to provide additional information on the location of lipids. Since NIRS comes in combination with IVUS also wall thickness information is available. Since OCT and NIRS-IVUS are imaging modalities that visualizes the cross section of the vessel only, these

imaging modalities do not provide information on the 3D geometry, which is needed for our modeling techniques. Therefore, fusion of these intravascular imaging modalities with CT, which by nature is 3D is required for our study, see Figure 1 [26].

1.4 Modeling

In order to assess the shear stress and wall stress computational methods can be applied. Computational methods, also known as Finite element analysis (FEA), uses the 3D geometry of the lumen and/or wall geometry and composition. The composition and 3D-geometry can be obtained via fusion of (intravascular) imaging techniques and CT, see section 1.3. Subsequently, the 3D reconstructed geometry is divided in many elements, which are used to perform the computations on the shear stress or wall stress. Each element is assigned with material properties, defining material behavior. Using finite element analysis different deformations and stresses can be modeled. For example the shear stress of the blood at the arterial wall can be calculated at each location of the vessel wall for which information of the blood flow is required. For calculation of the stress inside the vessel wall, the properties of the different vessel wall components are used. Depending on the modeling objective pressure and flow measurements are needed for model input, both require separate intravascular measurements.

2. OBJECTIVES

The objective of this study is to investigate the association between biomechanical parameters (e.g. shear stress) and plaque geometry and composition and changes over time. This study has a large potential in finding new parameters that give novel insights in vulnerable plaque development, which might play a role in identification of patients at risk in the future.

Our primary endpoints are:

1) *Association between shear stress **at baseline** and plaque geometry and composition **at baseline** (including wall thickness, cap thickness and lipids).*
2) *Association between shear stress **at baseline** and plaque geometry and composition **changes over time** in (including wall thickness, cap thickness and lipids).*

Therefore we will use advanced intravascular imaging techniques in combination with state-of the-art finite element modeling to assess the shear stress and wall stress and plaque geometry and composition.

3. STUDY DESIGN

This is a single-center, investigator-initiated, prospective, observational, longitudinal- study. A total of 70 patients with documented acute coronary syndrome admitted for PCI and who meet all inclusion/exclusion criteria, will be included. The culprit vessel is treated according to local standards. At least two coronary arterial segments of at least 30mm in length will be imaged, that were not treated. The imaging will be performed with intravascular imaging (OCT and NIRS-IVUS) at the index procedure and at one year follow-up. Besides the intravascular imaging techniques a CT at baseline will be made before or shortly after the culprit vessel is treated. All patients will be enrolled in the Thoraxcenter, Erasmus MC, Rotterdam.

4. STUDY POPULATION

4.1 Population (base)

A total of 70 patients with documented acute coronary syndrome who are admitted for PCI treatment and who meet all inclusion/exclusion criteria, will be included.

4.2 Inclusion criteria

- Patient eligible for PCI of a native coronary artery
- Written informed consent obtained
- Study coronary artery must be accessible to the OCT /NIRS-IVUS catheters;

4.3 Exclusion criteria

- Unable to provide informed consent
- Under 18 years of age
- Hemodynamic instability
- Cardiogenic shock
- TIMI 0 flow at target lesion site
- Lesion beyond acute bends or in a location within the coronary anatomy where the catheter cannot transverse
- Bypass graft as target vessel
- Ejection fraction less than 30%
- Contra-indication to emergency coronary artery bypass surgery
- No access to cardiac surgery
- Contra-indication to treatment with aspirin, ticlopidine, clopidogrel, prasugrel, ticagrelor, or heparin
- Renal insufficiency (creatinine clearing < 50ml/min)
- Pregnancy or inadequate anticonception
- History of bleeding diathesis or coagulopathy.
- History of stroke within the past year
- History of significant gastrointestinal bleed within the past month

4.4 Sample size calculation

In this study we are interested in the mutual interaction between plaque (composition) changes and biomechanical parameters. IVUS studies on plaque progression are summarized by Hartmann et al. [27] showing that plaque progression is linearly dependent on the lipid concentration. Furthermore, plaque progression measured in plaque area was shown to be dependent on baseline plaque burden [28] or the baseline remodeling index [29] ranging from 0.5±1.5 mm^2 to 1.1 ± 1.4 mm^2 per year. In another serial IVUS study by the group of Nissen a plaque area difference of 0.4 mm^2/year was found under aggressive lipid lowering treatment [30]. Moreover, a small 6 month follow up study by Corban et al [31] showed the highest plaque progression (0.68 +/-1.05 mm^2/year) at locations with low shear stress and having plaque burden>40% contrasting the locations with only low shear stress (0.10±0.71 mm^2/year). Taken together, plaque progression depends on lipid concentration, baseline plaque burden, baseline remodeling index and shear stress. Considering current

effective lipid lowering treatment as standard health care for patients with elevated cholesterol levels, we choose a relative small target difference of 0.45 mm^2 / year with a standard deviation of 1.0 mm^2. Furthermore we assume an alpha of 0.05, two sided test with a power of 90%. Our sample size needed to detect this difference will be $n = std^2 * ((z\beta+z\alpha)^2) / target^2 = 1.0^2 * ((1.28+ 1.96)^2) / 0.45^2 = 52$. We expect a follow up fall out of 25% of the patients of interest. Therefore 52/0.75=69.3 subjects are needed, therefore 70 subjects are included in this study

5. TREATMENT OF SUBJECTS

Not applicable.

6. INVESTIGATIONAL PRODUCT

Not applicable

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

Our primary endpoints to be investigated:

1) *Association between shear stress **at baseline** and plaque geometry and composition **at baseline** (including wall thickness, cap thickness and lipids).*

2) *Association between shear stress **at baseline** and plaque geometry and composition **changes over time** in (including wall thickness, cap thickness and lipids).*

8.1.2 Secondary study parameters/endpoints (if applicable)

- Association between change in plaque geometry and composition (e.g. wall thickness, cap thickness and lipids) and wall stress changes.
- Association between change in plaque geometry and composition (including wall thickness, cap thickness and lipids) and change in shear stress.

8.1.3 Other study parameters (if applicable)

Association between change in shear stress, plaque composition and blood parameters representing inflammation (for instance CD40, MPO and MMP9) .

8.2 Randomisation, blinding and treatment allocation

Not applicable.

8.3 Study procedures

The patient will be screened if the patient meets all the inclusion and exclusion criteria. Prior to inclusion in the study each patient (or the patient's legally authorized representative) will be given full and adequate verbal and written information regarding the objective and the study-specific tests, procedures, and blood sample collection, including the possible risks involved. The patient will be informed about his/her right to withdraw from the study at any time and for any reason without sanction, penalty or loss of benefit to which the patient is otherwise entitled and that withdrawal from the study will not jeopardize their future medical care. By signing the informed consent form the patient is included in the study. Prior to all procedures information about the history of the patient is obtained.

A CT scan of the coronary arteries is made before or after the treatment of the culprit vessel, the CT enables fusing of the OCT and NIRS-IVUS. The CT research protocol will assess 3 different scans: (1) CTCA for the evaluation of the coronary anatomy looking for significant coronary stenoses (clinical care); (2) Dynamic myocardial perfusion imaging for the

assessment of ischemia; (3) Delayed enhancement CT. During CT angiography contrast will be injected and the CT scan will be started once the contrast agent enters the aortic arch.

After an arterial sheath is placed, blood samples will be taken for assessment of cholesterol levels (HDL and LDL). Subsequently, the patient will undergo angiography and treatment for his/her culprit vessel, according to standard operating procedure.

During the treatment a CE marked guide wire allowing for assessment of intracoronary pressure and flow will be used (Volcano combiwire). This wire will give us information about the flow and pressure which is of imminent importance for biomechanical characterization.

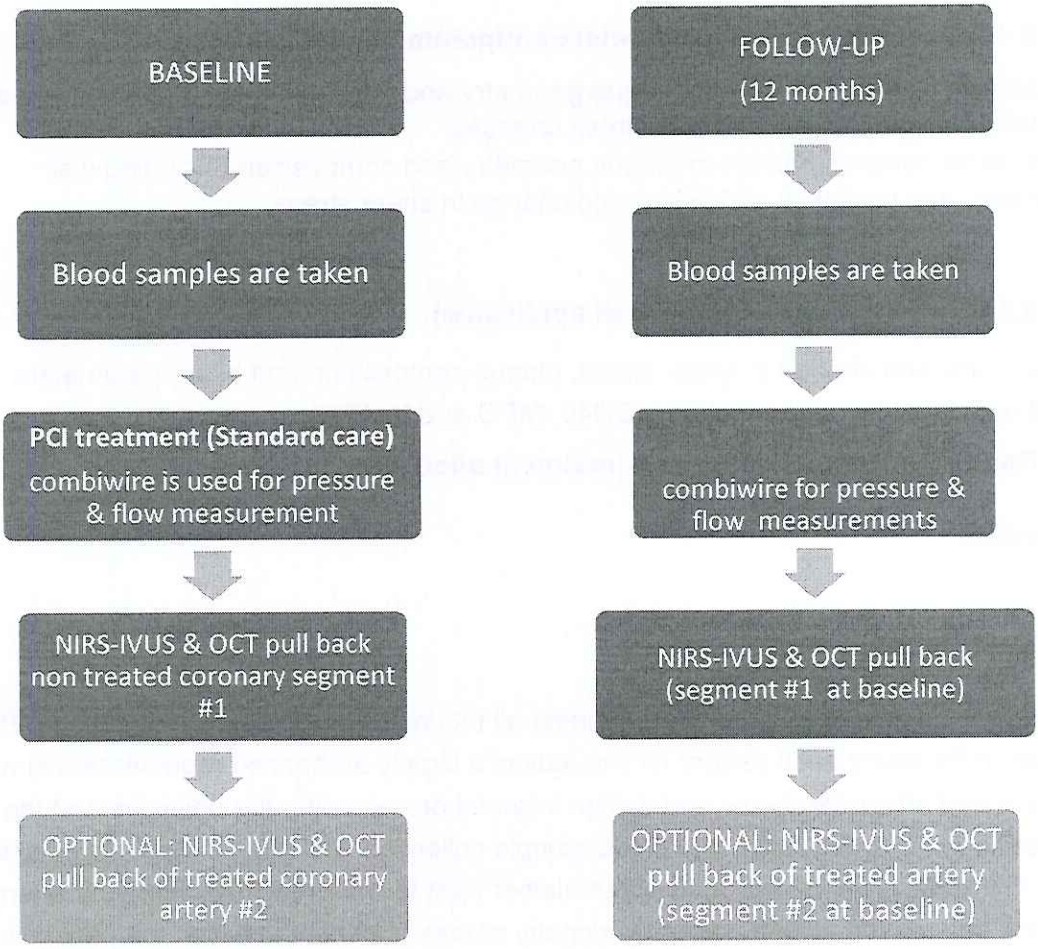

Figure 2: Schematic overview of all the invasive measurements at baseline and follow-up

Following successful PCI, imaging of 1 untreated coronary artery with a length of at least 30 mm is performed with pull backs using OCT and NIRS-IVUS catheters. From each pull back start and end positions of the catheter are documented using angiography. The combiwire is used to measure flow and pressure at a number of locations. For a schematic flow chart of all the invasive measurements see Figure 2. Upon the discretion of the operator all intravascular imaging as described previously also treated vessel can be imaged.

After 1 ± 1 months, 6 ± 1 months, and 11 ± 1 months the patient will be contacted and asked about the wellbeing, general medicine intake, and SAE and MACEs. The investigator will report any SAE or MACE within 3 days and to fill out the SAE and MACE form and check-up form (part of the CRF).

Follow up will take place 12 ± 1 months after PCI. The invasive procedure consists of similar procedures as baseline, see also Figure 2, including imaging of the treated part of the vessel.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable

8.5 Replacement of individual subjects after withdrawal

If patients indicate before the PCI that they withdraw, or other reasons prevent them to participate (e.g. severe illness or death) in this study other subjects can be included.

8.6 Follow-up of subjects withdrawn from treatment

Not applicable.

8.7 Premature termination of the study

If the disadvantages of participation in this study are significantly greater than was foreseen in the research proposal the study can be terminated. Termination of this study does not affect the healthcare/well-being of the patient, since this is an observational study.

9. SAFETY REPORTING

9.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse events.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first

knowledge of the adverse event. This is for a preliminary report with another 8 days for completion of the report.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

9.3 Annual safety report

Not applicable

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

Not applicable.

10. STATISTICAL ANALYSIS

Descriptive statistics

Categorical variables will be described as frequencies and percentages. The normal distribution of continuous variables will be assessed by the Shapiro-Wilk test and data will be presented as medians (25^{th} – 75^{th} percentile) or means ± one standard deviation, as appropriate. If normality is required by statistical tests or models, non-normal continuous variables will be log-transformed.

Study endpoints and inferences

We aim to study associations between the geometry/composition of coronary arteries and their characteristics. The data may consist of multiple measurements within a subject (multiple coronary arteries) obtained at two different time points (baseline and follow-up). We will apply linear mixed modelling to account for the clustering of the data within subjects. The mixed model also accounts for missing data.

10.1 Primary endpoints

1) *Association between shear stress **at baseline** and plaque geometry and composition **at baseline** (including wall thickness, cap thickness and lipids).*

2) *Association between shear stress **at baseline** and plaque geometry and composition **changes over time** in (including wall thickness, cap thickness and lipids).*

We will divide the coronary geometry in three areas dependent on the shear stress (low (1-33%), intermediate(34-66%) and high (67-100%) shear stress). Per shear stress category at baseline the A) average geometry parameters, average composition parameters and area positive for lipids will be determined, as well as B) the changes in average geometry parameters, composition parameters and area positive for lipids.

Primary endpoint 1: The association between shear stress (determinant) and plaque geometry/ composition (dependent variable) will be studied adjusted for risk factors (for instance age of the patient or cholesterol levels).

Primary endpoint 2: The association between shear stress (determinant) and change in plaque geometry/ composition (dependent variable) will be studied adjusted for the risk factors (for instance age of the patient or cholesterol levels)

10.2 Secondary endpoints

1) *Association between **change** in plaque geometry and composition (including wall thickness, cap thickness and lipids) and wall stress **changes**.*

Per coronary artery, the mean change in plaque geometry, composition, 99 percentile wall stress is determined. A linear mixed model will be used to study the association between change in wall stress (determinant) and change in plaque geometry/composition (dependent variable), adjusted for risk factor (for instance cholesterol levels).

2) *Association between **change** in plaque geometry and composition (including wall thickness, cap thickness and lipids) and **change** in shear stress.*

Per coronary artery, the mean change in plaque geometry, composition, the change in minimum shear stress is calculated. A linear mixed model will be used to study the association between change in shear stress (determinant) and change in plaque geometry/composition (dependent variable), adjusted for risk factor (for instance cholesterol levels).

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study will be conducted in accordance with the World Medical Association Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

ACS subjects are recruited among patients who are scheduled for PCI. They will be informed about the study and asked for consent. Patients are given several hours to until a day consider their decision.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

11.4 Benefits and risks assessment, group relatedness

The patients will benefit of study participation because also the non-culprit vessels are imaged with OCT and NIRS-IVUS. When serious (re)-stenosis (either baseline or after 12 months) or other alarming factors are seen in the non-culprit the physician will intervene in an appropriate way.

Cardiac CT is associated with radiation exposure to the patient.. Several radiation reduction techniques will be applied to minimize radiation exposure, e.g. prospective tube modulation during CTCA. The overall radiation dose is estimated between 13 and 17 mSv including all three scans. The radiation dose related to the myocardial perfusion imaging CT is in the range of a nuclear medicine scan used for the same purpose. An extra dose of 50 ml of iodinated contrast material will be administered to the patient. This extra amount does not increase the risk for contrast allergy reaction. To minimize the risk of renal damage patients with a reduced renal function (GFR<50 ml/min) will be excluded from the study. The risk inherent in administration of low dose of adenosine is minimal. A physician trained in CPR will always be present during the scan. The ECG and the blood pressure of the patient will be always monitored during the scan. Nitroglycerin will be present if the patient will show symptoms compatible with angina pectoris.

The OCT pullback takes about 3 seconds to complete. Published research shows that the complication rate of intracoronary imaging is small, compared to the risks of routine PCI. Imola et al. reported a safety study on OCT imaging in 90 patients; 16 pre-, 50 post-,and 24 pre- and post-intervention, with a total of 114 pullbacks. One complication (<1%) was recorded and no MACE [32].

A similar study was performed on the Erasmus MC OCT database. 1142 patients were included.In total 7 imaging related adverse findings were reported and no major adverse cardiac events[33]. Therefore OCT is safe and feasible in unselected patients

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study

11.6 Incentives (if applicable)

All travel expenses will be reimbursed for visitation of the research centre to undergo follow up imaging.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

All data collected in this study will be backed up on DVD, organized per imaging session. An anonymized copy will be transferred to the Biomedical Engineering for analysis and storage immediately after acquisition. For safety reasons a key file with source data and codes for anonymisation are stored at the catherization lab.

12.2 Monitoring and Quality Assurance

See monitoring plan.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

All substantial amendments will be notified to the METC and to the competent authority.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

All data resulting this study well be published in peer reviewed journals and or presented at (inter)national conferences by a representative of the Thoraxcenter, Erasmus MC from Rotterdam.

13. STRUCTURED RISK ANALYSIS

Not applicable

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