Thrombus Aspiration during Percutaneous coronary intervention in Acute non-ST-elevation myocardial infarction Study (TAPAS II)-Study design

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Background and Objective. The Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS) has shown that thrombus aspiration improves myocardial perfusion and clinical outcome compared with conventional primary percutaneous coronary intervention (PCI) in patients with ST-segment-elevation myocardial infarction. Impaired myocardial perfusion due to spontaneous or angioplasty-induced embolisation of atherothrombotic material also occurs in patients with non-ST-elevation myocardial infarction (NSTEMI). The aim of this study is to determine whether thrombus aspiration before stent implantation will result in improved myocardial perfusion in patients with NSTEMI compared with conventional PCI.

Study design. The study is a single-centre, prospective, randomised trial with blinded evaluation of endpoints. The planned inclusion is 540 patients with acute NSTEMI who are candidates for urgent PCI. Patients are randomised to treatment with manual thrombus aspiration or to conventional PCI. The primary endpoint is the incidence of myocardial blush grade 3 after PCI. Secondary endpoints are coronary angiographic, histopathological, enzymatic, electrocardiographic and clinical outcomes including major adverse events at 30 days and one year.

Implications. If thrombus aspiration leads to significant improvement of myocardial perfusion in patients with acute NSTEMI it may become part of the standard interventional approach. (Neth Heart J 2009;17:409-13.)

Keywords: non-ST-elevation myocardial infarction, percutaneous coronary intervention, thrombus aspiration

The pathogenesis of acute coronary syndromes (ACS) includes the rupture or erosion of a coronary atherosclerotic plaque with variable degrees of superimposed platelet aggregation inducing a thrombus.^{1,2} ST-elevation myocardial infarction (STEMI) is often caused by a total coronary occlusion of the atherothrombotic plaque, whereas in non-ST-elevation myocardial infarction (NSTEMI) the thrombus is mainly nonocclusive or transiently occlusive causing less myocardial damage.² Conventional percutaneous coronary intervention (PCI) focuses on compressing the atherothrombotic plaque with the aim to normalise flow in the coronary artery and therefore restore perfusion of the ischaemic myocardium. However, embolisation of atherothrombotic material may occur spontaneously after plaque rupture or due to mechanical crushing of the culprit lesion during PCI.^{3,4} This results in obstruction of distal vessels or the microcirculation in the down-stream bed of the ischaemia-related artery.^{4,5} Although normal epicardial flow may be achieved, this will lead to diminished myocardial perfusion, which is associated with larger infarct size, diminished left ventricular ejection fraction and increased mortality.⁶

Antiplatelet therapy protects against thrombotic complications after PCI.⁷ Also various distal protection devices and thrombectomy devices have been developed to protect the microcirculation against embolisation of atherothrombotic material and to improve myocardial reperfusion after PCI. Several trials in patients with STEMI have shown that thrombus aspiration improves

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myocardial reperfusion compared with conventional PCI.⁸⁻¹⁰ The largest study to date, the TAPAS trial, showed that manual thrombus aspiration using the Export aspiration catheter (EAC) in patients with STEMI improves myocardial perfusion and one-year clinical outcome compared with conventional PCI.^{10,11} As a consequence of these results, thrombus aspiration has been included in the new European guidelines for patients with STEMI as a therapy to improve myocardial perfusion.¹²

In patients with NSTEMI, thrombus aspiration has shown to be feasible and safe to re-establish flow in the ischaemia-related vessel. Furthermore, a similar rate of effective thrombus aspiration (70%) was found compared with patients with STEMI.¹³ However, no study has been performed to determine whether thrombus aspiration also improves myocardial perfusion and clinical outcomes compared with conventional PCI in patients with NSTEMI.

The standard coronary angiographic technique for the assessment of myocardial perfusion is myocardial blush grade (MBG).⁶ Another method to measure the myocardial perfusion is the Quantitative Blush Evaluator (QuBE) score. This new computer-assisted myocardial blush quantification score correlates very well with MBG, ST-elevation resolution, enzymatic infarct size and one-year survival.¹⁴ Complementary markers of myocardial perfusion include the electrocardiographic (ECG) analysis of ST-segment deviation after PCI and enzymatic infarct size to determine the amount of myocardial damage.

The efficacy of thrombus aspiration in reducing the amount of atherothrombotic material in the ischaemia-related lesion can be evaluated by methods that assess the residual load before and after stenting. Optical coherence tomography (OCT) is an intravascular high-resolution imaging modality that is based on the reflection of infrared light. OCT is currently the most sensitive imaging modality to identify plaque characteristics.¹⁵⁻¹⁷ Kubo et al. have documented intracoronary thrombus in all patients with acute myocardial infarction with OCT.¹⁵ No previous study has reported the difference in residual atherothrombotic load assessed by OCT after thrombus aspiration or conventional PCI. Kubo et al. describe that the prevalence of plaque characteristics in patients with acute myocardial infarction is similar to the prevalence found in pathological studies in patients with coronary artery disease who died suddenly.^{1,15,18} Our study can compare characteristics of the atherothrombotic material *in vivo* determined by OCT images with the pathohistological findings of the aspirated atherothrombotic material.

In this trial, we will evaluate the effect of the EAC in improving myocardial blush grade in patients with acute NSTEMI compared with conventional PCI. If thrombus aspiration significantly improves myocardial perfusion, it may become a standard part of the treatment in patients with acute NSTEMI.

Study objectives

The primary objective is to investigate the effect of thrombus aspiration with the EAC on the incidence of MBG 3 after PCI in patients with acute NSTEMI. Secondary objectives are to establish the effect of thrombus aspiration on enzymatic infarct size, coronary angiographic, electrocardiographic and clinical outcomes up to one year. Furthermore, histopathological characteristics of all retrieved atherothrombotic material will be analysed. In the substudy with OCT, we will evaluate the residual atherothrombotic load.

Study design

This is a single-centre, prospective, randomised, open trial with blinded evaluation of endpoints. The study will be performed in the University Medical Center of Groningen, a high-volume PCI centre working in close cooperation with the department of cardiothoracic surgery in a thoraxcentre. Patient recruitment started in 2007 and will continue until 540 patients with acute NSTEMI have been included. Patients will be randomised after the initial coronary angiogram to one of the two procedures: thrombus aspiration followed by stenting or conventional PCI. The substudy of OCT imaging will include 120 consecutive patients who are also participating in the main study. Both studies have been approved by the institutional review board.

Study population

All patients with acute NSTEMI admitted or referred to our hospital who are candidates for urgent PCI will be considered for participation in the study.

Inclusion criteria

- Diagnosis of acute NSTEMI defined by:
 - Chest pain suggestive of myocardial ischaemia for at least 30 minutes
 - Time from onset of symptoms of less than 72 hours
 - ECG with ST-segment shifts (depression of >0.1 mV in at least two contiguous leads or transient ST-segment elevation >0.1 mV in at least two contiguous leads for less than 30 minutes) and/or T-wave changes (inversion of >0.15 mV in at least two contiguous leads)
 - Positive cardiac troponin T >0.01 µg/l.
- Clinical indication for urgent PCI of the ischaemia-related target lesion as identified at coronary angiography

Exclusion criteria

- Persistent ST elevation of more than 0.1 mV in two or more leads
- Presence of cardiogenic shock
- Inability to obtain informed consent
- Known existence of a life-threatening disease with a life expectancy of less than six months

Randomisation

Following coronary angiography and informed consent, eligible patients will be randomised to thrombus aspiration followed by stenting or conventional PCI of the ischaemia-related artery. Sealed randomisation envelopes will be used, prepared in blocks of four and six patients to achieve a balanced allocation for therapy. Registration of baseline characteristics, randomisation outcome and angiographic data will be performed by means of a computerised documentation form filled in by the interventional cardiologist directly after PCI.

Treatment and devices

Pharmacotherapy

Pharmacotherapy will be according to current international guidelines.^{2,12} All patients will receive aspirin (a bolus of 300 mg), intravenous heparin (5000 IU), clopidogrel (a bolus of 600 mg), β -blockers and nitrates before PCI unless contraindicated. At the discretion of the clinical cardiologist, some patients will receive an intravenous bolus and infusion of tirofiban (0.4 μ g/kg/min for 30 minutes followed by 0.15 μ g/kg/min). All patients not using tirofiban will receive abciximab (0.25 mg/kg bolus) during PCI. Furthermore, additional heparin guided by activated clotting time measurements will be administered during PCI. Standard therapies after PCI include aspirin 100 mg, clopidogrel 75 mg, β -blockers, lipid-lowering agents, and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.

PCI procedure and devices

The EAC (Medtronic) is a 6F thrombus aspiration catheter and is currently used in routine clinical practice. The total usable length is 145 cm and the aspiration lumen is 0.041 inch. The catheter contains a radio-opaque marker located 2 mm from the distal tip. Advanced over the guidewire, the catheter will be placed proximally of the target lesion. Continuous manual suction during advancement through the lesion segment is provided by a lockable 20 ml syringe, which allows an aspiration rate of 1 ml/s. The syringe will be emptied in a filtering cup to separate the aspirated fragments from blood. All participating interventional cardiologists are experienced with the use of the EAC. In both arms of the trial balloon angioplasty will be performed when necessary for stent delivery and optimal deployment. One or more stents will be placed whenever possible.

OCT (0.016-inch, LightLab Imaging Inc., Westford, Massachusetts) is an intravascular imaging modality that will be used in the substudy. The technique of intravascular OCT imaging has been described.¹⁶ In short, the EAC is placed proximally of the target lesion. The OCT imagewire is placed in the aspiration lumen of the EAC and advanced distally of the lesion. Through flushing with contrast solution a clear view is obtained. An image of the whole lesion is

recorded through automatic pullback of 55 mm in 3 mm/sec. A second image is recorded of the residual atherothrombotic load after thrombus aspiration or balloon angioplasty. After stent implantation, a final image is recorded to determine the presence of residual atherothrombotic material in the stented segments.

Endpoints

Primary endpoint

The primary endpoint is the incidence of MBG 3 after PCI.

Secondary endpoints

Secondary endpoints include the following:

- Coronary angiographic outcomes: TIMI flow, MBG, computerised myocardial perfusion score assessed by Quantitative Blush Evaluator (QuBE), presence of thrombus, TIMI thrombus score and evidence of distal embolisation
- Histopathological outcomes: size and composition of retrieved atherothrombotic material
- Enzymatic infarct size
- Electrocardiographic outcomes: persistent ST-T segment deviation and new Q waves.
- Clinical outcomes: target-vessel revascularisation, reinfarction and cardiovascular as well as total mortality at 30 days and one year.

Additional endpoints in OCT substudy

- Residual atherothrombotic load before and after stenting
- Characteristics of the atherothrombotic material on OCT images compared with the histopathological findings.

Outcome characteristics

Coronary angiographic outcomes

The coronary angiograms at baseline and after PCI will be analysed by two independent investigators. The following baseline and postprocedural angiographic features will be recorded: ischaemia-related artery, length and diameter of the stenosis, number of diseased vessels, TIMI flow, MBG, presence of thrombus, TIMI thrombus score and evidence of distal embolisation. Thrombus is defined as the presence of an intraluminal central filling defect or lucency surrounded by contrast material seen in multiple projections with the absence of calcium within the defect and persistence of contrast material within the lumen.¹⁹ The thrombus load will be graded from 0 to 5 according to the TIMI thrombus score.²⁰ Distal embolisation is defined as circumscribed filling defects and/or abrupt cut off of a vessel distal to the target lesion on the angiogram after PCI.²¹

Quantitative Blush Evaluator (QuBE) score is a new computerised myocardial perfusion score that will be assessed using the same myocardial blush frames of the postprocedural coronary angiogram.¹⁴ The in-

investigator will select the dedicated coronary angiogram that contains the ischaemia-related artery and will encircle this area with a polygonal shape. The QuBE score is corrected for panning motions for each frame. The QuBE score is defined as the sum of the maximum increase in contrast density.

The OCT image that is recorded before the procedure will be analysed for atherothrombotic characteristics as described by Jang et al.²² These characteristics will be compared with the histopathological findings. The residual atherothrombotic load quantified on the OCT image after thrombus aspiration will be compared with the load after balloon angioplasty. The final OCT image will be analysed for the presence of residual atherothrombotic material after stent implantation.

Histopathological outcome

Aspirated atherothrombotic material will first be stored at -80 °C until histopathological analysis is performed. During macroscopic examination, the size will be measured. The aspirate will then be embedded in paraffin. Histological sections will be cut and stained with haematoxylin eosin for examination with a light microscope. Additional immunostaining will be performed when applicable to optimise visualisation of smooth muscle cells and macrophage foam cells. Aspirated material will be categorised into three groups: white platelet aspirate defined as material composed only of platelets, red erythrocyte-rich aspirate defined as material with layers of coagulated erythrocytes and aspirate with plaque when any fragment of vessel wall, cholesterol crystals, inflammatory cells or collagen tissue is identified. Thrombus aspiration will be classified as effective when atherothrombotic material is identified in the aspirate.

Enzymatic infarct size

Enzymatic infarct size is defined as the area under the curve of serial measurements of creatinine kinase (CK) and myocardial band fraction of CK (CK-MB). Furthermore, the peak of troponin T will be determined.

Electrocardiographic outcome

The time interval between the obtained ECGs before and 30 to 60 minutes after PCI will be calculated. The ECG after PCI will be categorised into total normalisation of ST-T-segment shifts, partial normalisation of ST-T-segment and persistent ST-segment deviation defined as cumulative ST depression of >0.2 mV in ischaemia-related leads. The magnitude of ST-segment deviation is measured 60 ms from the J point. New Q waves will be assessed on the ECG after PCI defined as an initial negative deflection of the QRS complex of >0.1 mV and >40 ms in an ECG lead related to the myocardial area involved in the NSTEMI. Furthermore, all the pathological Q waves associated with prior myocardial infarction will be assessed.²³

Clinical outcome

Ischaemia-driven target-vessel revascularisation, re-infarction and death will be recorded at 30 days and at one year. Death is regarded as cardiac death unless a non-cardiac cause of death was known. These data will be obtained from hospital records, written correspondence and/or telephone interviews with the patient and the municipal population registry.

Statistics

Sample size calculation

The sample size to detect differences between the thrombus aspiration group and the conventional PCI group has been calculated based on previous results on the incidence of MBG 3 after PCI in patients with STEMI (45.7% vs. 32.2%) and NSTEMI (45.7% after thrombus aspiration).¹⁰⁻¹³ We have estimated an increase in the primary endpoint of 30% after thrombus aspiration. With a power of 80% and a two-sided significance level of <0.05 we have calculated a target sample size of 540 subjects.

No previous study has reported the difference in residual atherothrombotic load obtained by OCT after thrombus aspiration or balloon dilatation. We know that intracoronary thrombus is seen in all patients with STEMI by OCT,¹⁵ but there are no reports on patients with NSTEMI. In our previous reports on thrombus aspiration, we have shown that in 44 to 51% of the patients with STEMI and NSTEMI, thrombus is seen on the initial coronary angiogram and that in 70 to 73% of the patients with STEMI and NSTEMI thrombus is effectively aspirated. Based on these data and unpublished data of angiographic evidence of thrombus before and after procedure in patients with STEMI, we estimate a difference of 45% in atherothrombotic load seen by OCT after thrombus aspiration and balloon angioplasty. We have calculated a target sample size of 120 subjects with a power of 80% and a two-sided significance level of <0.05.

Statistical analysis

Analysis of data will be based on the intention-to-treat principle. An analysis per protocol will also be performed. For continuous variables, differences between group means will be assessed using the two-tailed Student's t test if normally distributed and the Mann-Whitney U test if distribution is skewed. For categorical variables, the χ^2 analysis or Fisher's exact test will be used. Survival will be calculated by the Kaplan-Meier product-limit method. The log-rank test will be used to evaluate differences in survival and cardiovascular events between the two treatment groups. Logistic regression analysis will be performed to analyse associations between the endpoints and baseline characteristics. Statistical significance is considered as a two-tailed p value <0.05. The Statistical Package for the Social Science (SPSS Inc, Chicago, IL, USA) version 16.0 will be used for all statistical analysis.

Subgroups

The primary and secondary endpoints will also be evaluated in prespecified subgroups:

- Patients with last-symptoms-to-PCI interval of less versus more than three hours
- Patients with versus without diabetes mellitus
- Patients with multivessel disease versus single-vessel disease
- Patients with TIMI flow 0 or 1 versus TIMI flow 2 or 3 on initial coronary angiogram
- Patients with versus without coronary angiographic evidence of thrombus on the initial angiogram

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