Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Fröbert O, Lagerqvist B, Olivecrona GK, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. N Engl J Med 2013;369:1587-97. DOI: 10.1056/NEJMoa1308789

Thrombus Aspiration in ST- Elevation myocardial infarction in Scandinavia (TASTE trial)

A multicenter, prospective, randomized controlled clinical trial based on the Swedish angiography and angioplasty registry (SCAAR) platform

This supplement contains the following items:
1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

Original protocol, final protocol, summary of changes. **May 6, 2013**

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Summary of changes:

Amendment 1: additional PCI centers, addition of one more thrombus aspiration catheter (Eliminate, Terumo).

Amendment 2: additional PCI centers.

Amendment 3: additional PCI center. Precision of ECG criterion for posterior MI.

Amendment 4: (application for permission to include patients unable to give informed consent. This was declined by the review board).

Amendment 5: application for the Data Safety Monitoring Board (DSMB) to perform interim analysis due to lower than expected mortality in the overall patient cohort. We were granted permission for this.

Amendment 6: based on the DSMB recommendation, application for permission to increase the number of patients in the trial from 5000 to 7200.

Note to file 1: an additional secondary endpoint was added: “Stroke as reported in the Swedish national patient registry”.

Research Protocol, February 28, 2010

Thrombus Aspiration in ST- Elevation myocardial infarction in Scandinavia (TASTE trial)

A multicenter, prospective, randomized controlled clinical trial based on the Swedish angiography and angioplasty registry (SCAAR) platform

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1. Abbreviations

CABG	Coronary artery by-pass grafting
CPI	Coordinating principal investigator
CRF	Case report form
IEC	Independent endpoint committee
PCI	Percutaneous coronary intervention
PI	Principal investigator
SCAAR	Swedish Coronary Angiography and Angioplasty Registry
STEMI	ST-segment elevation myocardial infarction
SWEDEHEART	National Swedish registry on heart disease integrating information from four different registries: RIKS-HIA (registry on cardiac intensive care units), SEPHIA (secondary prevention of heart disease registry), the Swedish heart surgery registry and SCAAR
TAPAS	Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study
TIMI flow grade	Thrombus in Myocardial Infarction flow grade
UCR	Uppsala Clinical Research Center

2. Study rationale

2.1 Background

Percutaneous coronary intervention (PCI) is the optimal therapy in ST-segment elevation myocardial infarction (STEMI). While this treatment alleviates the major acute problem of having an occluded or highly stenosed coronary artery, distal embolization of thrombus material often precludes restoration of normal coronary artery flow [1] and thrombus material is also thought to play an important role in reperfusion injury.

Meta-analyses of randomized trials on adjunctive mechanical devices to prevent distal embolization have not demonstrated benefits in mortality, despite improvement in myocardial perfusion and reduced distal embolization [2, 3]. In fact, some mechanical thrombectomy devices may worsen outcome [4]. More recently, focus has been on aspiration thrombectomy devices. In table 1 an overview of previous trials is shown [4-14].

In the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) detailed information on all patients treated by PCI in Sweden is registered. While registry and database information by nature is retrospective, in the present study, for the first time, we will use the SCAAR as a prospective platform for conducting a randomized clinical multicenter trial. The rationale being that with standardized and validated information coupled to other health care registries by social security number almost complete follow-up can be assured and that the extra work related to actual

study conduction is very limited. Another important advantage by using SCAAR as a platform for randomization is the opportunity to include a large number of patients over a relatively short time period, thus allowing investigation of hard end points such as death, stent thrombosis, restenosis and target vessel revascularization.

Table 1. Randomized aspiration thrombectomy trial overview

First author	Source	Trial acronym	n	Device	Follow-up	MACE	Death	Myocardial blush
Haeck, J.D.E.	JACC Intv 2009;2:934	PREPARE	284	Proxis, St. Jude Medical	1 month	ns	ns	ns
Sardella, G.	JACC 2009;53:309	EXPIRA	175	Export (Medtronic)	9 months	ns	P<0.02	P=0.001
Lipiecki, J.	Am Heart J 2009;157:583		40	Export (Medtronic)	6 days	-	-	ns
Vlaar, P.J.	Lancet 2008;371:1915	TAPAS, 1 year	1071	Export (Medtronic)	12 months	ns	P=0.02	-
Svilaas, T.	N Engl J Med 2008;358:557	TAPAS	1071	Export (Medtronic)	1 month	ns	ns	P<0.001
Ikari, Y.	JACC Intv 2008;1:424	VAMPIRE	355	TVAC (Nipro)	8 months	P<0.05	ns	P<0.001
Kaltoft, A.	Circ 2006;114:40		215	Rescue (Boston Scientific)	1 month	ns	ns	-
Silva-Orrego, P.	JACC 2006;48:1552	DEAR-MI	148	Pronto (Vascular Solutions)	1 month	ns	ns	P<0.001
Burzotta, F.	JACC 2005;46:371	REMEDIA	100	Diver CE (Invatec)	1 month	ns	ns	P=0.020
Lefèvre, T.	JACC 2005;46:246	X AMINE ST	201	X-Sizer (eV3)	6 months	ns	ns	ns
Beran, G.	Circ. 2002;105:2355		66	X-Sizer (Endicor)	1 month	ns	ns	P=0.03

MACE: cardiac death, nonfatal reinfarction, and target vessel revascularization; ns: not statistically significant.

2.2 Purpose of the study

In a multicenter, prospective, randomized controlled clinical trial based on the SCAAR platform to compare all cause death, stent thrombosis and TIMI flow grade in patients with STEMI treated with PCI and manual thrombus aspiration versus PCI alone.

2.3 Hypothesis

In this trial we test the hypothesis that PCI and thrombus aspiration is superior to PCI alone in reducing death in patients with STEMI (primary end point).

Secondary end points are TIMI flow grade, time to re-hospitalization with nonfatal reinfarction, heart failure, target vessel revascularization, time to all-cause death or new myocardial infarction (first occurring), time to acute coronary occlusion,

stent thrombosis, restenosis, heart failure, complications of PCI during index hospitalization and length of hospital stay.

2.4 Clinical relevance

STEMI remains one of the leading causes of death globally. Thrombolysis was a major step forward in the treatment of STEMI [15-17] and further progress was done when primary PCI was established as a golden therapeutic standard [18]. Treatment has been further optimized with pre, peri- and post procedure platelet inhibition, statins, angiotensin converting enzyme and beta adrenoreceptor blockade. One of the most important remaining therapeutic challenges in STEMI is establishment of normal coronary flow after PCI because reduced flow is associated with death and heart failure [19 20]. Reduced flow after PCI is closely associated with the paradox that opening of an occluded coronary artery is not solely beneficial because of the so-called reperfusion injury [21]. In reperfusion injury restoration of coronary flow results in arrhythmias, contractile dysfunction, microvascular impairment and irreversible myocardial damage through apoptosis and necrosis [22].

Thrombus aspiration may contribute to improve coronary artery flow post PCI [5 9 10 12 14]. However, most previous studies on thrombus aspiration have not been powered for hard clinical endpoints, such as mortality. To date, the only large-scale randomized trial of thrombus aspiration for STEMI to demonstrate a survival benefit is the single-center TAPAS trial in which death was a secondary end point [7, 9]. Thrombus aspiration is easy, quickly performed and a cheap adjunct to PCI. Perhaps because of the low-tech nature and the limited possibilities of future patents and economic revenue of thrombus aspiration the interest from the medical device industry to initiate new large-scale studies in this area is low. However, only large scale randomized studies can answer the impeding question of this treatment modality: is thrombus aspiration life saving or not?

Thus, responsibility and initiative for establishing evidence of the clinical applicability of thrombus aspiration is left to the scientific community. Thrombus aspiration has been adapted by some Swedish centers as routine while others use this treatment at the discretion of the operator and others yet again use it scarcely (ref: SCAAR). In the recent guidelines from the American College of Cardiology and the American Heart Association thrombus aspiration has been upgraded to a class IIa recommendation (i.e. it is reasonable to perform the procedure) with a level of evidence:

B (i.e. limited populations evaluated) [23]. In our view, evidence needs to be established before thrombus aspiration becomes routine for some and is discarded by others because of the uncertainty related to evidence this far.

By purpose, the present protocol is planned to be very close in design to the TAPAS trial – only with fewer exclusion criteria to investigate the real world applicability of TAPAS.

3. Patients and methods

3.1 Patients

A total of 5000 patients will be included in the study.

3.1.1 Patient inclusion

Individuals for inclusion will be recruited among the patients referred to the participating centers for PCI because of STEMI (Figure 1). The patients will not receive any honorarium for participation.

3.1.2 Inclusion criteria

- Patients with a diagnosis of STEMI as defined by chest pain suggestive for myocardial ischemia for at least 30 minutes before hospital admission, time from onset of symptoms of less than 24 hours, and an ECG with new ST-segment elevation in two or more contiguous leads of ≥0.2 mV in leads V2-V3 and/or ≥0.1 mV in other leads or a probable new-onset left bundle branch block.
- Correspondence between ECG findings and culprit artery pathoanatomy
- A minimum of 50% stenosis in culprit artery by visual estimate
- Possibility to perform thrombus aspiration

3.1.3 Exclusion criteria

- Need for emergency coronary artery bypass grafting
- Inability to provide informed consent
- Age below 18 years
- Previous randomization in the TASTE trial

3.2 Consort patient flow chart

Before study start, each of the hospitals entering data in SCAAR has to decide whether or not to participate in the trial (for Danish centers data entry will be done in a separate database with a graphical design identical to SCAAR). The understanding will be that all

PCI operators in the participating hospitals will actively attempt to include all eligible patients in the study period.

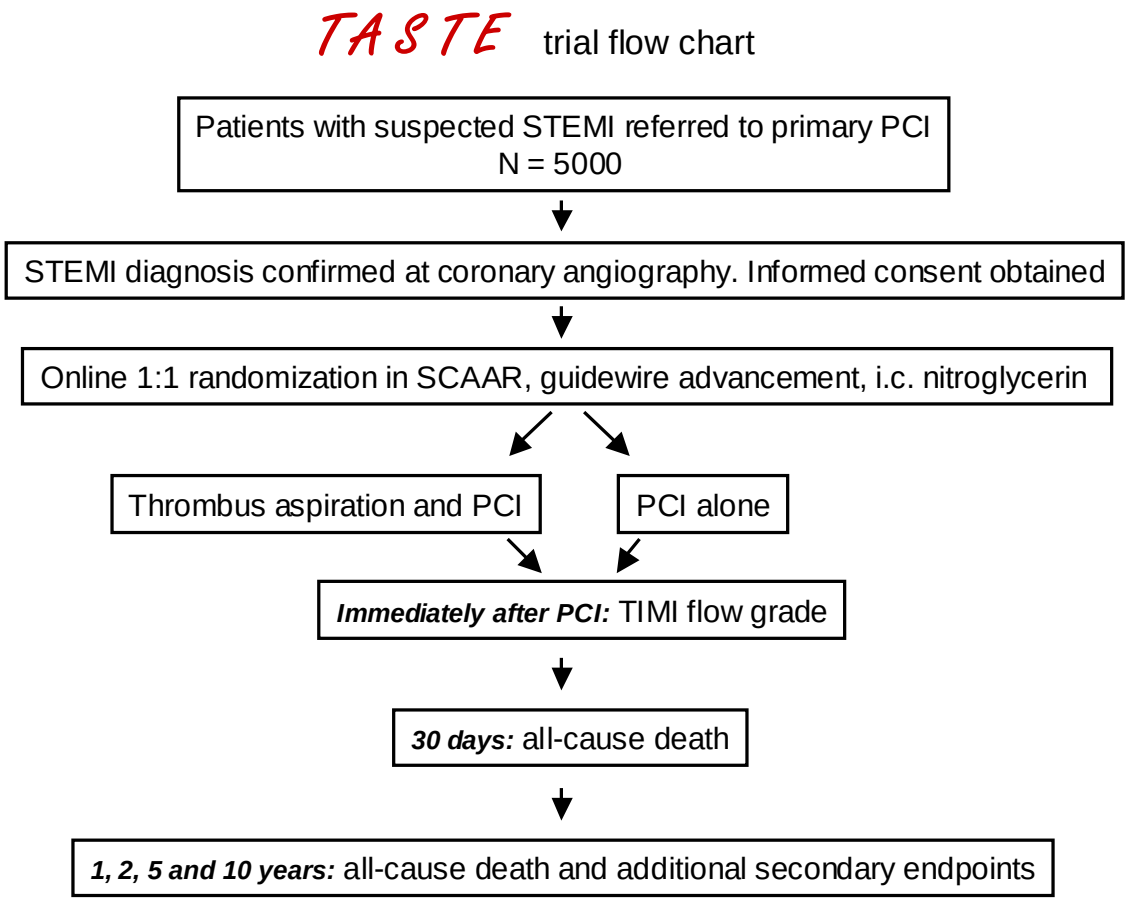

Figure 1. **Flow chart of study design**
i.c. : intracoronary; PCI: percutaneous coronary intervention; SCAAR: Swedish Coronary Angiography and Angioplasty Registry; STEMI: ST-elevation myocardial infarction.

In the SCAAR there is a prospective registration of all patients with STEMI. In all participating centers, reasons for not including particular patients will be documented on an electronic consort patient flow chart.

3.3 Follow-up

Patients in the main study will not be followed-up. The primary end point will be monitored using national registries and the secondary end points will be monitored using national registries and the SCAAR and Swedeheart databases.

In a magnetic resonance imaging (MRI) sub-study, 150 patients will be followed by MRI at day 4±2. Please refer to details under caption 9 – sub-studies.

3.4 Endpoints

3.4.1 Primary endpoint

- The primary endpoint is time to all-cause death at 30 days. These data will be obtained from national health registries.

3.4.2 Secondary endpoints

- Time to all-cause death after 1year, 2 years, 5 years and 10 years.

- Time to re-hospitalization with nonfatal reinfarction, heart failure and target vessel revascularization after 30 days and 1 year, 2 years, 5 years and 10 years.

- Time to all-cause death or new myocardial infarction (first occurring) after 30 days, 1 year, 2 years, 5 years and 10 years.

- Time to acute coronary occlusion, stent thrombosis and restenosis in treated lesions as reported in SCAAR.

- Reported heart failure and complications of PCI during index hospitalization as reported in SWEDEHEART.

- Length of hospital stay as reported in SWEDEHEART.

- TIMI-flow grade.

3.4.4 Endpoint definition

TIMI-flow grade after PCI is defined as: grade 0 denoted an absence of antegrade flow beyond the point of occlusion; grade 1, partial penetration of contrast agent beyond the obstruction but incomplete distal filling; grade 2, patency with opacification of the entire distal vessel but with delayed filling or washout of contrast agent; and grade 3, normal flow [16, 24]. Coronary artery bypass surgery after randomization and re-hospitalization after index procedure are collected by merging SCAAR with national registries. Myocardial infarction is defined as ICD codes I21 and I22, heart failure as I50. New PCI are followed in SCAAR. Target lesion revascularization is defined as a new therapeutic PCI in the same coronary segment as the index procedure or coronary artery bypass surgery after the index procedure.

3.5 Treatment strategies

In all patients, initially a guidewire is passed through the culprit lesion.

3.5.1 PCI

For patients randomized to conventional PCI, guidewire advancement is followed by balloon dilatation, balloon dilatation and stenting or direct stenting to achieve antegrade flow. Post-dilatation of stents is optional.

3.5.2 Thrombus aspiration and PCI

For patients randomized to thrombus aspiration, guidewire passing will be followed by thrombus aspiration with an Export aspiration catheter (Medtronic Inc., Santa Rosa, USA). Continuous manual suction is performed using a proximal-to-distal approach, which is defined as active aspiration during initial passage of the lesion. In lesions that cannot initially be passed with the thrombus aspiration catheter it is permitted to dilate the lesion with an angioplasty balloon up to a maximal nominal diameter size of 2.0 mm and attempt to advance the thrombus aspiration catheter for a second time. After thrombus aspiration PCI is done as described above.

3.5.3 Post-procedure platelet inhibition

After the index PCI, lifelong acetylsalicylic acid in a dose of 75-160 mg per day will be prescribed. Duration of glycoprotein 2b/3a inhibitor treatment, clopidogrel or other P2Y12 inhibitor is left to the discretion of the treating physician.

4. Statistics and data management

The data management work and statistical analyses will be performed at Uppsala Clinical Research Center (UCR), Uppsala University Hospital, Sweden.

4.1 Statistical analysis

Differences between groups in time-to-event endpoints will be assessed with the log-rank test (for the primary endpoint, patients will be censored at 30 days; analyses at other time points will be handled in a similar way). Survival probabilities will be displayed and calculated using Kaplan-Meier methodology. Hazard ratios between groups will be calculated using Cox proportional hazard model. Differences between group means will be assessed with the two-tailed Student's t-test. Chi-square analysis or Fisher's exact test will be used to test differences between proportions. A two-tailed P-value <0.05 is considered statistically significant. All in accordance with the TAPAS study [7].

4.2 Safety

A maximum of 3 months following inclusion of the first 1500 patients and again following 3000 patients an independent endpoint committee (IEC) will monitor study endpoints. Premature termination of the study will be mandated in the event that one of the treatment strategies shows statistically significant inferiority in a degree exceeding figures to be expected from previous clinical trials.

4.3 Analysis population

The results will be analyzed according to the intention-to-treat principle, i.e. patients randomized to a certain group will be followed and assessed irrespectively of the actual treatment. Protocol violations will be monitored continuously and the responsible centers notified.

4.4 Sample size calculations

Sample size is calculated on the basis of two sources. We used cardiac death at 1 year in TAPAS which demonstrated a hazard ratio of 1.93 for conventional PCI compared to the thrombus aspiration group [7]. In addition we used available data from 2005-2007 in the SCAAR, which showed an overall one-year mortality of 9.0% in PCI treated STEMI patients (approx 6 500 PCI in STEMI/year).

If the hazard ratio (relative risk) of conventional PCI patient per thrombus-aspiration and PCI patient is set to 1.3 in this trial, and the 1 year mortality is estimated at 9.7% we will need to study 2334 conventional PCI patients and 2334 thrombus-aspiration + PCI patients to be able to reject the null hypothesis that the experimental and control survival curves are identical with a probability (power) of 0.80. The Type I error probability associated with testing of this null hypothesis is 0.05 [25]. In order to control for dropouts, crossing from one group to the other, and aspiration device failure, 5000 patients will be included.

4.5 Randomization procedure

Following written informed consent by the patient, the randomization procedure will be performed online in the SCAAR database using a 1:1 ratio. There will be a stratified randomization according to centre.

4.6 Case Report Form

An electronic case report form (CRF) will be generated automatically based on the ordinary SCAAR/SWEDEHEART registration form and stored at UCR for each patient

included. The patient's identity will always be confidential. All information in the CRF will be in English. The investigators are responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the CRFs.

5. Monitoring

The study will be monitored using the ordinary SCAAR monitoring system by independent professionals. During the study period, monitors will have regular contact with the participating departments to ensure that the trial is conducted in compliance with the protocol and applicable regulatory requirements. The monitors will ensure that the used products are all right and will review source documents for verification of consistency with the data recorded in the CRFs. The monitors will also provide information and support to the investigator(s).

Investigators and other responsible personnel must be available during the monitoring visits, audits and inspections and should devote sufficient time to these processes. Because the data recorded in the CRFs are recognized as source data there will be no need for consistency control.

6. Administration

6.1 Organization

Swedish, Danish and Icelandic PCI centers with experience and interest in thrombus aspiration and willingness to randomize all eligible STEMI patients during the study period can participate in the study.

There will be a country coordinating principal investigator (CPI) for each participating country and a principal investigator (PI) for each centre. The CPIs will be responsible for the study in the respective countries. Further, they will be key members of the steering committee * of the study, and in charge of the study. The PIs will take care of the study at centre level.

6.2 Economy

The TASTE trial is an academic study, conceived and conducted by cardiovascular interventionalists in the respective countries. The study is independent of commercial interests. Study logistics, handling of data and statistical assessments will be financed by the UCR and the Department of Cardiology, Örebro University Hospital, Sweden. The steering committee will apply for grants from public funds and from manufacturers

of thrombus aspiration catheters used in the study. Possible external sponsors will have no influence on the conduct of the study.

* Members of the steering committee are Stefan James (chairman), Ole Fröbert (CPI, entire study and Sweden), Bo Lagerqvist (vice CPI, entire study and Sweden), Leif Thuesen (CPI, Denmark), Torarinn Gudnasson (CPI, Iceland) and Göran Olivecrona (substudy organizer)

7. Ethical considerations

The study will be conducted in accordance with the protocol, applicable regulatory requirements and the ethical principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964 and subsequent versions. The study will be initiated, when the Medical Ethical Committee of Uppsala, Sweden has approved the protocol. In the study, we compare two well-known treatments; PCI alone with thrombus aspiration followed by PCI. Both treatment regimens are used routinely and interchangeable globally and this, in our view, eliminates severe ethical considerations in conducting the study. One ethical aspect is that the STEMI patient has to be asked for study participation after diagnostic coronary angiography in the catheterization laboratory. This will of course be demanding for the patient in an already stressful situation. However, this study design is well tested and has been implemented in ongoing [26] and previous studies [27] in Scandinavia.

7.1 Risks, side-effects, advantages and disadvantages in participation

Patients randomized to PCI alone will be treated according to standard clinical praxis. We expect that patients in the thrombus aspiration and PCI arm of the study will benefit from less no-reflow phenomena, less heart failure and reduced risk of death although this cannot be guaranteed. Previous reports of mechanical thrombectomy devices which may worsen outcome [4] are judged to be irrelevant for the present study using different technology where such reports have not been published. If manual thrombus aspiration and PCI is not statistically superior compared with PCI alone (the study hypothesis) we estimate that this adjunctive treatment will be neutral on outcome.

7.2 Biological material

Biological material will not be collected or stored in the study [to be determined].

7.3 Guidelines for obtaining informed consent

Patients will enter the study after signing the informed consent form. Candidate participants will receive written information of the study, and they will receive oral information by medical doctors participating in the study. The information will be given in the catheterization laboratory following diagnostic coronary angiography.

7.4 Withdrawal

A patient can be withdrawn from the study at any time, if it is the wish of the patient, or if it is medically indicated, as judged by the investigator. A patient's participation in the study will be discontinued, if any of the following criteria applies: a) the patient's general condition contraindicates continuing the study, b) non-eligible patient, c) protocol violation.

8. Publication

Results, positive as well as negative, will be published in an international cardiovascular journal. Publication and author issues will be decided by the steering committee on basis of general involvement in the study (drafting of protocol, core laboratory. function, endpoint committee membership, etc.) and on number of included patients. The sequence of additional authors will be determined by the inclusion rates of the participating centers.

9. Sub-studies

9.1 MRI Follow-up

An MRI sub-study assessing infarct size and area at risk will be done in selected centers. Patients will be asked to participate in an MR imaging study on day 4±2 following PCI. MR imaging is performed on a 1.5 T Philips Intera CV system (Philips, Best, the Netherlands) with a cardiac synergy coil. The examination is performed with subjects in the supine position. After defining the left ventricular (LV) long-axis orientation, gradient-recalled echo (GRE) cine images are acquired in long- and short-axis planes of the LV to enable evaluation of LV function. After intravenous administration of a gadolinium-based contrast agent, segmented inversion-recovery (IR) GRE images are acquired in the corresponding planes of the LV, enabling detailed characterization of the area of infarction. The cine GRE and the IR GRE acquisition are undertaken during breath hold. In addition, a GRE velocity-mapping sequence is used

to acquire flow-sensitive images perpendicular to the ascending aorta. From these images the LV stroke volume and consequently the cardiac output can be determined with high accuracy and precision. All image acquisition is triggered by ECG. T2 weighted cardiac MRI will be performed to determine area at risk according to published procedures [28] [29, 30].

Initiation of additional sub-studies are encouraged, but should be accepted by the steering committee. No sub-studies are part of the primary application for ethical approval of the TASTE study.

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UCR

Uppsala Clinical Research Center

Till
Regionala etikprövningsnämnden i Uppsala
Box 1964
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Uppsala 2010-07-05

Dnr: 2010/111
Protokollnr: U-10-001
Projekttitel: Thrombus Aspiration in ST- Elevation myocardial infarction in Scandinavia (TASTE)

Amendment 1 till TASTE-studien (Trombsugning vid akut hjärtinfarkt i Skandinavien (godkänd 2010-04-07)

Härmed ansöker vi om tillstånd för ett tillägg till TASTE-studien (huvudprövare Ole Fröbert, Universitetssjukhuset Örebro). Detta tillägg innebär att:

- ytterligare 19 PCI-centra i Sverige ansluts till studien
- rekommendation av ytterligare katetertyper för trombsugning
- mindre omformuleringar av patientinformationen

Följande bilagor medföljer ansökan

Bilaga 1: Amendment 1, 2010-06-22
Bilaga 2:1-19: Resursintyg
Bilaga 3: Patientinformation med markeringar

Avgiften om 2000 kr har erlagts.

Svar skickas till:
Dr Ole Fröbert
Kardiologiska kliniken, Universitetssjukhuset
701 85 Örebro

Med vänliga hälsningar

Elisabeth Palmcrantz Graf

Elisabeth Palmcrantz Graf
Projektledare, UCR
på uppdrag av Ole Fröbert

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Bilaga 1

UCR
Uppsala Clinical Research Center

CONFIDENTIAL

Clinical Trial Protocol Amendment

Amendment Number:	1		
Date:	5 July, 2010	X	To be implemented only after documented approval of the *IRB / IEC / Competent Authorities*
EudraCT No.:			To be implemented immediately after *IRB / IEC / Competent Authorit* have been notified of change
Sponsor Project No.:	U-10-001		
Investigational Product(s):	Method Thrombus Aspiration		Can be implemented without *IRB / IEC / Competent Authority* approval as changes involve
Title:	**Thrombus Aspiration in ST- Elevation myocardial infarction in Scandinavia (TASTE trial)**		
Change:	19 Swedish sites will be affiliated to the study. Several types of catheters for thrombus aspiration instead of one are recommended.		

SIGNATURE PAGE(S)

Chairman, steering committee
TASTE

11-07-05
Date

Stefan James, MD/PhD

Section 3.5.2 Thrombus aspiration and PCI

Old text:

For patients randomized to thrombus aspiration, guidewire passing will be followed by thrombus aspiration with an Export aspiration catheter (Medtronic Inc., Santa Rosa, USA).

New text:

For patients randomized to thrombus aspiration, guidewire passing will be followed by any thrombus aspiration catheter that is 6-French compatible, simple and low profile in design and meant for manual aspiration. Eliminate (Terumo) and Export (Medtronic) are recommended.

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Uppsala 2010-09-29

Dnr: 2010/111
Protokollnr: U-10-001
Projekttitel: Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE)

Amendment 2 till TASTE-studien (Trombsugning vid akut hjärtinfarkt i Skandinavien, godkänd 2010-04-07)

Härmed ansöker vi om tillstånd för yttterligare ett tillägg till TASTE-studien (huvudprövare Ole Fröbert, Universitetssjukhuset Örebro). Detta tillägg innebär att ytterligare 4 svenska PCI-centra ansluts till studien, samt att ett ord ("dödsregister" kallas i stället "befolkningsregister") bytts ut i patientinformationen.
Följande bilagor medföljer ansökan

Bilaga 1:1-4 Resursintyg för Sunderbyn, Danderyd, Malmö och Sahlgrenska

Bilaga 2: Aktuell patientinformation

Avgiften om 2000 kr har erlagts.

Svar skickas till:
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701 85 Örebro

Med vänliga hälsningar

Elisabeth Palmcrantz Graf
Projektledare, UCR
på uppdrag av Ole Fröbert

BESLUT
Datum: 2010-10-28
Godkännes som ändring till av EPN i Uppsala tidigare godkänd forskning enligt beslut
datum ..... i ärende .....

Ordf

Vet sekr

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2000 kr
22/11

UCR

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Uppsala 2010-11-15

Dnr: 2010/111
Protokollnr: U-10-001
Projekttitel: Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE)

Amendment 3 till TASTE-studien (Trombsugning vid akut hjärtinfarkt i Skandinavien, godkänd 2010-04-07)

Härmed ansöker vi om tillstånd för ytterligare ett tillägg till TASTE-studien (huvudprövare Ole Fröbert, Universitetssjukhuset Örebro). Detta tillägg innebär att Skövde, som sista ännu ej anslutna svenska PCI-center ansluts till studien, inklusionskriterium nr 1 justeras och ytterligare en kateter omnämns som möjlig att använda i studien.

Följande bilagor medföljer ansökan

Bilaga 1: Resursintyg för Skövde

Bilaga 2: Amendment 3

Avgiften om 2000 kr har erlagts.

Svar skickas till:
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Kardiologiska kliniken, Universitetssjukhuset
701 85 Örebro

Med vänliga hälsningar

Elisabeth Palmcrantz Graf

Elisabeth Palmcrantz Graf
Projektledare, UCR
på uppdrag av Ole Fröbert

BESLUT
Datum: 2010-11-25

Godkännes som ändring till av EPN i Uppsala tidigare godkänd forskning enligt beslut datum 2010-04-07 **i ärende** 2010/111

Ordf ERIK LEMPERT **Vet sekr** Bengt Simonsson

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Clinical Trial Protocol Amendment

Amendment Number:	3		
Date:	15 November, 2010	X	To be implemented only after documented approval of the *IRB / IEC / Competent Authorities*
EudraCT No.:			To be implemented immediately after *IRB / IEC / Competent Authorit* have been notified of change with request for approval.
Sponsor Project No.:	U-10-001		
Investigational Product(s):	Method Thrombus Aspiration		Can be implemented without *IRB / IEC / Competent Authority* approval as changes involve
Title:	**Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE trial)**		
Change:	One Swedish site (Skövde) will be affiliated to the study. Inclusion criterium 1 is adjusted. Another specified type of catheter for thrombus aspiration is added.		

SIGNATURE

Coordinating Investigator
TASTE

December 15, 2010
Date

Ole Fröbert, MD, PhD

New PCI center

The last Swedish PCI center not yet affiliated to the TASTE study (Skövde) , will now be included.

3.1.2 Inclusion criteria

Old text:

-Patients with a diagnosis of STEMI as defined by chest pain suggestive for myocardial ischemia for at least 30 minutes before hospital admission, time from onset of symptoms of less than 24 hours, and an ECG with new ST-segment elevation in two or more contiguous leads of ≥0.2 mV in leads V2-V3 and/or ≥0.1 mV in other leads or a probable new-onset left bundle branch block.

New text:

- Patients with a diagnosis of STEMI as defined by chest pain suggestive for myocardial ischemia for at least 30 minutes before hospital admission, time from onset of symptoms of less than 24 hours, and an ECG with new ST-segment elevation in two or more contiguous leads of =0.2 mV in leads V2-V3 and/or =0.1 mV in other leads (including posterior leads) or a probable new-onset left bundle branch block.

3.5.2 Thrombus aspiration and PCI

Old text:

For patients randomized to thrombus aspiration, guidewire passing will be followed by any thrombus aspiration catheter that is 6-French compatible, simple and low profile in design and meant for manual aspiration. Eliminate (Terumo) and Export (Medtronic) are recommended.

New text:

For patients randomized to thrombus aspiration, guidewire passing will be followed by any thrombus aspiration catheter that is 6-French compatible, simple and low profile in design and meant for manual aspiration. Eliminate (Terumo), Export (Medtronic) and Pronto (Vascular Solutions) are recommended.

Uppdaterat följebrev med Ole Fröbert underskrift. Original skickat till EPN 2011-03-08

UCR

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Till
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Uppsala 2011-02-17

Dnr: 2010/111
Protokollnr: U-10-001
Projekttitel: Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE)

Amendment 4 till TASTE-studien (Trombsugning vid akut hjärtinfarkt i Skandinavien, godkänd 2010-04-07)

Härmed ansöker vi om tillstånd för ytterligare tillägg till TASTE-studien (huvudprövare Ole Fröbert, Universitetssjukhuset Örebro). Tillägget innefattar två punkter:

1. I samband med PCI-ingreppet ges muntligt samtycke av patienten till deltagande i TASTE, skriftligt samtycke ges i efterhand. Denna procedur beskrivs under punkt 4 "Information och samtycke" i ansökningsblanketten. Därmed faller patienter som är för sjuka för att ge muntligt samtycke bort. Konsekvensen av detta bortfall beskrivs i bilaga 1. Vi vill med denna ansökan få tillstånd att inkludera dessa svårast sjuka patienter utan krav på muntligt samtycke, och endast samla in skriftligt samtycke i efterhand.

2. Studieprotokollet beskriver under avsnitt 9.1 en uppföljande magnetresonansundersökning. Som tillägg till detta avsnitt beskriver vi mer detaljerat hur denna uppföljning genomförs i formen av ett substudieprotokoll som biläggs som Appendix 1 till huvudstudiens protokoll.

Koordinerande huvudprövare i TASTE-studien är undertecknad (Dr Ole Fröbert, Örebro), och koordinerande prövare för beskrivna substudie är Dr Göran Olivecrona, Lund.

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Följande bilagor medföljer:

Bilaga 1:	Ändring i rekryteringsproceduren – endast skriftligt samtycke för de svårast sjuka
Bilaga 2:	Substudieprotokoll för magnetresonansundersökning 16 feb 2011- Appendix 1 till TASTE-protokollet
Bilaga 3:	Patientinformation magnetresonansundersökning, 16 feb 2011
	Som extra information medföljer även:
Bilaga 4:	TASTE studieprotokoll (redan godkänt)

Avgiften om 2000 kr har erlagts.

Svar skickas till:
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Kardiologiska kliniken, Universitetssjukhuset
701 85 Örebro

Med vänliga hälsningar

Ole Fröbert
/Huvudprövare

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Bilaga 2

CLINICAL STUDY PROTOCOL

Thrombus Aspiration in ST- Elevation myocardial infarction in Scandinavia with MRI to evaluate reduction in infarct size sub study

The TASTE MRI sub study

Protocol Version. 16 February, 2011

Investigational Strategy: Thrombus aspiration in primary PCI with the use of The Eliminate catheter

Coordinating Investigator: **Goran K. Olivecrona,** MD, PhD
Department of Cardiology
Skane University Hospital
SE- 221 85 Lund
SWEDEN
+46 46 17 30 53 (Telephone)
+46 46 17 60 11 (Fax)

Signature:

The clinical study will be conducted, and essential documentation archived, in compliance with UCR SOPs and standards, which incorporate the requirements of the ICH Guideline for Good Clinical Practice.

2010/111 ändring 1915

UCR Uppsala Clinical Research Center

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Uppsala 2011-05-25

Dnr: 2010/111
Protokollnr: U-10-001
Projekttitel: Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE)

Amendment 5 till TASTE-studien (Trombsugning vid akut hjärtinfarkt i Skandinavien, godkänd 2010-04-07)

Härmed ansöker vi om tillstånd för en ändring av protokolltexten avseenden en interimsanalys i TASTE. Denna analys är planerad att genomföras av en oberoende data safety monitoring board (DSMB) för att utvärdera säkerhetsvariabler. Därmed är den ursprungliga formuleringen i protokollet felaktig och vi önskar rätta till texten så att den beskriver vad man planerar att göra.

Eftersom rekryteringen går relativt snabbt och vi beräknar att planerat antal patienter har inkluderats under andra kvartalet 2012, anser vi att en interimsanalys, i stället för två, när ca hälften av patienterna (2500) inkluderats är tillräcklig.

Vidare information se bilaga 1, Amendment 5.

Avgiften om 2000 kr har erlagts.

Svar skickas till:
Dr Ole Fröbert
Kardiologiska kliniken, Universitetssjukhuset
701 85 Örebro

Med vänliga hälsningar

Ole Fröbert
Koordinerande huvudprövare, TASTE

BESLUT
Datum: 2011-06-07

Godkännes som ändring till av EPN i Uppsala tidigare godkänd forskning enligt beslut datum 2010-04-07 Lärende 2010/111

Ordf LEIF GRANGETH Vet sekr PER BLOMSTRÖM

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Clinical Trial Protocol Amendment

Amendment Number:	5		
Date:	25 May, 2011	X	To be implemented only after documented approval of the *IEC*
EudraCT No.:			To be implemented immediately after *IEC* has been notified of change with request for approval.
Sponsor Project No.:	U-10-001		
Investigational Product(s):	Method Thrombus Aspiration		Can be implemented without *IEC* approval as changes involve logistical or administrative aspects only
Title:	**Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE trial)**		
Change:	Change of interim analysis		

SIGNATURE

Chairman steering committee

27/5 2011 — *Date*

Stefan James, MD PhD

Coordinating Investigator

_____ — *Date*

Ole Fröbert, MD PhD

Statistician

2011-05-25 — *Date*

Ollie Östlund, PhD

Clinical Trial Protocol Amendment

Amendment Number:	5		
Date:	25 May, 2011	X	To be implemented only after documented approval of the *IEC*
EudraCT No.:			To be implemented immediately after *IEC* has been notified of change with request for approval.
Sponsor Project No.:	U-10-001		
Investigational Product(s):	Method Thrombus Aspiration		Can be implemented without *IEC* approval as changes involve logistical or administrative aspects only
Title:	**Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE trial)**		
Change:	Change of interim analysis		

SIGNATURE

Chairman steering committee

	Date	Stefan James, MD PhD
Coordinating Investigator	27/5 2011	
	Date	Ole Fröbert, MD PhD
Statistician		
	Date	Ollie Östlund, PhD

Section 4.2 Safety

Old text:

A maximum of 3 months following inclusion of the first 1500 patients and again following 3000 patients an independent endpoint committee (IEC) will monitor study endpoints. Premature termination of the study will be mandated in the event that one of the treatment strategies shows statistically significant inferiority in a degree exceeding figures to be expected from previous clinical trials.

New text:

At a maximum of 3 months following inclusion of the first 2500 patients, a data safety monitoring board (DSMB) will monitor study data to look for specific safety concerns. The DSMB will define what safety concerns should be considered and may recommend the TASTE steering committee to terminate the study only due to these specific safety concerns. Premature termination due to differences in efficacy will not be considered.

Reason for change:

The interim analysis, as being described under section 4.2 "Safety", was originally planned for safety reasons. Looking for statistically significant inferiority for one of the treatment strategies would cause a loss in power for the final study results and is not seen as necessary in this study, where the treatment strategies compared are already used in clinical praxis.

The recruitment period is relatively short and inclusion in TASTE is estimated to stop during the second quarter of 2012. Therefore it is believed that one safety interim analysis is enough.

F1: 631

J.

ÖREBRO LÄNS LANDSTING
USÖ
2012 -06- 05
Centrala diariet
12ou2812-1

INKOMMEN
Regionala etikprövningsnämnden i Uppsala
2012 -05- 24
Dnr 2010/111/6

UCR

Uppsala Clinical Research Center

2000:- inb. 28/5

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Uppsala 2012-05-16

Dnr: 2010/111
Protokollnr: U-10-001
Projekttitel: Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE)

Amendment 6 till TASTE-studien (Trombsugning vid akut hjärtinfarkt i Skandinavien, godkänd 2010-04-07)

Härmed ansöker vi om tillstånd för att utöka patientantalet från 5 000 till 7 200 i TASTE-studien, med en interimanalys vid 5000 patienter för att ha möjligheten att stoppa inklusionen vid 5 000 som ursprungligen planerat.

Vidare information se bilaga 1, Amendment 6.

Avgiften om 2000 kr har erlagts.

BESLUT
Datum: 2012-05-30

Godkännes som ändring till av EPN i Uppsala tidigare godkänd forskning enligt beslut datum 2010-03-10 i ärende 2009/417

Ordf Vet sekr

Erik Lampa

Svar skickas till:
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Med vänliga hälsningar

Stefan James, STEFAN JAMES, Chairman

~~Ole Fröbert~~
~~Koordinerande huvudprövare, TASTE~~

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Clinical Trial Protocol Amendment

Amendment Number:	6		
Date:	16 May, 2012	X	To be implemented only after documented approval of the *IEC*
EudraCT No.:			To be implemented immediately after *IEC* has been notified of change with request for approval.
Sponsor Project No.:	U-10-001		
Investigational Product(s):	Method Thrombus Aspiration		Can be implemented without *IEC* approval as changes involve logistical or administrative aspects only
Title:	**Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE trial)**		
Change:	Increased sample size from 5000 to 7200, and a new interim analysis with the opportunity to stop enrolment after about 5000 patients		

SIGNATURE

Chairman steering committee

May 17, 2012 — *Date*

Stefan James, MD PhD

Coordinating Investigator

May 17, 2012 — *Date*

Ole Fröbert, MD PhD

Statistician

May 22, 2012 — *Date*

Ollie Östlund, PhD

3. Patients and methods

3.1 Patients

Old text:

A total of 5000 patients will be included in the study.

New text:

A total of 7200 patients will be included in the study. An interim analysis will give the opportunity to stop enrolment after inclusion of about 5000 patients.

Reason for change:

The sample size calculation has been updated to reflect the primary endpoint of the study, and to take into account a lower overall mortality than expected, as revealed by a blinded interim review as per January 15, 2012. This increases the time until the study results are available to the public, for which reason a formal interim analysis is introduced with the potential of making the results available earlier.

4. Statistics and data management

4.1 Statistical analysis

Old text:
Differences between groups in time-to-event endpoints will be assessed with the log-rank test (for the primary endpoint, patients will be censored at 30 days; analyses at other time points will be handled in a similar way). Survival probabilities will be displayed and calculated using Kaplan-Meier methodology. Hazard ratios between groups will be calculated using Cox proportional hazard model. Differences between group means will be assessed with the two-tailed Student's t-test. Chi-square analysis or Fisher's exact test will be used to test differences between proportions. A two-tailed P-value <0.05 is considered statistically significant. All in accordance with the TAPAS study.

New text:
General considerations
Differences between groups in time-to-event endpoints will be assessed with the log-rank test. For the primary endpoint, patients will be censored at 30 days (where the day of PCI is day 0); analyses at other time points will be handled in a similar way. Survival probabilities will be displayed and calculated using Kaplan-Meier methodology. Hazard ratios between groups will be calculated using Cox proportional hazard model. Differences between group means will be assessed with the two-tailed Student's t-test. Chi-square analysis or Fisher's exact test will be used to test differences between proportions. Estimates will be presented with nominal 95% confidence limits and nominal 2-tailed p-values.

Change of study design to group-sequential
To declare statistical significance for the primary variable, a group-sequential design will be employed. The group-sequential design was introduced in a protocol amendment, after a blinded interim analysis revealed a lower overall mortality rate than expected, which necessitated a revision of the sample size necessary to reach the intended 80% power. The study design changes and sample size update were decided on by study team members with access to data on overall mortality rate, but without access to any data that allowed treatment comparisons. See also the section on sample size calculation.

Interim analysis plan
The interim analysis for efficacy will be performed after 30 days follow-up on all-cause death has been obtained for at least 4800 patients. The data safety monitoring board (DSMB) will be entrusted to either declare that a statistically significant treatment difference has been detected for the primary variable and that enrolment will stop, recommend that the study is terminated due to a low confidence in the possibility to detect a meaningful treatment difference after 7200 patients have been included (futility), or recommend that the study continues until 7200 patients have been included.

Statistical significance at the interim analysis will be defined by $p<0.01$ (two-sided). If significance is not obtained, the DSMB will have the opportunity to recommend stopping the study due to a low confidence in the possibility to detect a meaningful treatment difference. The recommended, non-binding, criterion for futility stopping is that the interim analysis gives $p>0.49$, based on a spending of beta=0.05. To aid the decision, the conditional probability of obtaining a significant result at 7200 patients, and the estimated hazard ratio with 95% confidence interval, will be calculated.

If the study is not discontinued after the interim analysis, statistical significance at the final analysis, even if the goal of 7200 patients is not reached, will be defined by $p<0.0471$ (two-sided), to ensure that the total type I error rate is below 5%. The p-value boundaries were calculated based on interpolated alpha- and beta-spending methodology, using East version 5.4.2.0 (Cytel, Inc., Cambridge, MA, USA), for a comparison of the proportion patients that die within 30 days. By estimating the expected accumulated information fraction by the number of patients, these boundaries are valid for the primary analysis, time to death within 30 days. In the event that more than 7300 patients are included in the final analysis, the p-value for declaring statistical significance will be recalculated using Haybittle-Peto alpha-spending, based on 4800 patients in the interim analysis and the actual number of patients in the final analysis, with expected information fractions estimated using the number of patients.

Dissemination of interim analysis results
The interim analysis will be performed by an unblinded UCR statistician, and the data and results delivered to the DSMB by encrypted e-mail. Here unblinded means having access to data that allows treatment comparisons. Interim study data, analysis results and the interim report will be kept in a restricted area of the UCR computer system, with access only for the unblinded UCR study statistician(s) and the UCR registry data manager that extracts the interim data from the registry. Unblinded personnel will not be involved with any decisions

on the study design. Care will be taken that no interim analysis results are disseminated to other persons involved in the study.

Final analysis
After termination of enrolment, whether the study is terminated at the interim analysis or not, the necessary data for the primary variable will be collected for all patients. For Swedish patients, data on death is updated from the population registry at monthly scheduled time points, and the final analysis data set will be based on such an update, at least two calendar months after enrolment is terminated to ensure sufficient reporting of 30 day mortality. For non-Swedish patients, data on deaths, death times, and censoring times, will be collected with similar quality. Since the Swedish data is easier to obtain, the latest available scheduled update of Swedish patients at time of data base lock will be used.

At the final analysis, the treatment hazard ratio will be presented with its nominal 95% confidence interval, and nominal p-value from the log-rank test. Statistical significance will be determined using the appropriate p-value limit as by the interim analysis plan. As a supplementary analysis, the proportion patients that died before or on day 30 after PCI will be tabulated and analysed using logistic regression, and the odds ratio presented with nominal 95% confidence interval, and p-value from the Pearson chi-square test.

If the study is terminated early for significance, the primary analysis will be based on the final data set, including overrunning and non-Swedish patients. The interim analysis results will be given for comparison. In the unlikely event that the p-value is above the formal significance level p=0.01 in the final analysis, statistical significance will still be considered to be shown unless there are substantial discrepancies in the estimated hazard ratios.

To assess possible impact of the design changes on the interpretation of the results, if the study continues after the interim analysis, a comparison of treatment hazard ratios based on the primary variable will be presented, comparing patients enrolled up to the date that the interim analysis data was extracted from the registry, to patients enrolled after that date. This analysis will be based on a Cox model with factors treatment, study period, and interaction.

Reason for change:
The sample size is increased in this amendment from 5000 to about 7000 patients, based on a blinded review of the actual event rage. This increases the time until the study results are available to the public, for which reason a formal interim analysis is introduced with the potential of making the results available earlier. To avoid ambiguity, the day for censoring is further clarified.

4.2 Safety

Old text (from Amendment 5):

At a maximum of 3 months following inclusion of the first 2500 patients, a data safety monitoring board (DSMB) will monitor study data to look for specific safety concerns. The DSMB will define what safety concerns should be considered and may recommend the

TASTE steering committee to terminate the study only due to these specific safety concerns. Premature termination due to differences in efficacy will not be considered.

New text (additional):
When 30 days follow-up data has been obtained for at least 4800 patients, the DSMB will conduct an interim analysis based on the primary variable, to either declare statistical significance, recommend early termination of the study because of a low probability to obtain a statistically significant result at the end of the study, or to recommend that the study is continued until 7200 patients have been enrolled. Actions will be taken to ensure that information from the interim analysis, beyond the stop/continue decision, cannot influence any additional changes to the study design.

Reason for change:
The sample size is increased in this amendment from 5000 to 7200 patients, based on a blinded review of the actual event rage. This increases the time until the study results are available to the public, for which reason a formal interim analysis is introduced with the potential of making the results available earlier.

4.4 Sample size calculations

Old text:

Sample size is calculated on the basis of two sources. We used cardiac death at 1 year in TAPAS which demonstrated a hazard ratio of 1.93 for conventional PCI compared to the thrombus aspiration group [7]. In addition we used available data from 2005-2007 in the SCAAR, which showed an overall one-year mortality of 9.0% in PCI treated STEMI patients (approx 6 500 PCI in STEMI/year).

If the hazard ratio (relative risk) of conventional PCI patient per thrombus-aspiration and PCI patient is set to 1.3 in this study, and the 1 year mortality is estimated at 9.7% we will need to study 2334 conventional PCI patients and 2334 thrombus-aspiration + PCI patients to be able to reject the null hypothesis that the experimental and control survival curves are identical with a probability (power) of 0.80. The Type I error probability associated with testing of this null hypothesis is 0.05 [25]. In order to control for dropouts, crossing from one group to the other, and aspiration device failure, 5000 patients will be included.

New text:
The original sample size calculation was based on one-year mortality, and the study was planned to include 5000 patients to be able to detect a hazard ratio of at least 1.3, based on time to death within one year, at the 5% confidence level with 80% power. This calculation was updated in a protocol amendment to reflect the pre-defined primary outcome, which is time to death within 30 days. In addition, the updated sample size calculation accounts for a lower overall mortality rate than expected as revealed by a blinded interim analysis, and the introduction of a formal interim analysis with possible stopping for efficacy.

A blinded interim analysis was performed to estimate the overall all-cause death proportion at 30 days after randomization. With blinded is meant that an overall estimate of the all-cause mortality rate for the total group of patients in the study was determined while keeping the treatment group allocation blinded, and no statistics by randomized treatment group was calculated. Actions were taken to ensure personnel involved in the sample size calculation and calculation of the overall mortality rate had no access to treatment group allocation.

The blinded interim analysis, as per January 15, 2012, resulted in an overall rate of 2.9% (the Kaplan-Meier estimate). The all-cause mortality proportion at 30 days was estimated to 3.5% for patients randomized to conventional PCI by assuming a difference at 30 days between patients randomized to conventional PCI and thrombus-aspiration + PC corresponding to an odds ratio of 1.5 (based on previous study TAPAS).

Assuming a 3.5% 30-day mortality rate for conventional PCI, odds ratio at least 1.5 (conventional PCI/ thrombus-aspiration + PCI), overall type I error 0.05, and an interim analysis at 67% of the total sample size, with interim stopping for significance with $p<0.01$, and interim stopping for futility with $p>0.493$ (non-binding), a total of 7138 patients would give 80% power of obtaining a significant result at the 5% level using 2-sided tests for the odds ratio of death within 30 days. The power for the log-rank test of time to death within 30 days is assumed to be similar. 7138 is rounded upwards to 7200 patients. The calculations were done using interpolated alpha- and beta-spending methodology using East version 5.4.2.0 (Cytel, Inc., Cambridge, MA, USA).

Reason for change:
The primary endpoint of the study is time to death within 30 days, while the power calculation was based on 1 year mortality. The sample size calculation is updated to reflect the primary endpoint of the study. In addition the updated sample size calculation account for a lower overall mortality rate than expected as revealed by a blinded interim analysis. Since the revision based on blinded interim data increases the sample size from 5000 patients to about 7000 patients, the time until the study results are available to the public increases, for which reason a formal interim analysis is introduced with the potential of making the results available earlier. This design change is also incorporated in the updated sample size calculation.

Note to File no 1, TASTE trial

Study Protocol: Thrombus Aspiration in ST- Elevation myocardial infarction in Scandinavia (TASTE trial), Feb 28, 2010

In the Study Protocol, section 3.4.2 a new secondary endpoint was added:
"Stroke as reported in the Swedish national patient registry"

The steering committee for the TASTE trial judged this change as minor, not requiring an amendment. The change is therefore documented as a Note to File.

Örebro 2011-11-

Ole Fröbert
/Coordinating Investigator

Uppsala 2011-11-

Stefan James
/Chairman Steering Committee

Statistical Analysis Plan

Study Code: TASTE

Study Title: Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia

Based on protocol version and date:
February 28, 2010, with amendments up to Amendment 6

SAP version: 1.0

Biostatistician: Ollie Östlund, from april 2011.
Nils Åsenblad, responsible for sample size reestimation and design change to group-sequential, blinded to randomised treatment data

Clinical Data Manager: Elisabet Ärnström

Clinical Project Leader: Elisabeth Palmcranz-Graf

Data safety monitoring board: Lars Grip, Hans Wedel

Other relevant personnel: Ole Fröbert
Stefan James
Bo Lagerqvist

Signed by author;

Name:	Signature:	Date:
Ollie Östlund		

Reviewed and approved by Biostatistician (UCR);

Name:	Signature:	Date:
Maria Bertilsson		

Approved by chairman of the executive steering committee;

Name:	Signature:	Date:
Stefan James		

Table of Contents

1. Introduction

The purpose of this statistical analysis plan is to elaborate on the pre-defined statistical analysis in the TASTE trial, and other analyses that were decided before clean file. All analyses are performed in accordance with the protocol. Some changes and elaborations on the analyses were made in Amendment 5 and 6, but no changes are introduced in the SAP. However, this SAP clarifies the secondary outcome definitions and analysis populations and introduces a few supplementary analyses. The secondary outcome acute coronary occlusion is removed, since it is no longer considered to add clinically interesting information to the analysis of stent thrombosis. The pre-defined analyses of 1 to 10 years follow-up are not included in the primary report and may not be fully covered in this SAP. Text in UPPERCASE ARIAL denotes variable names.

2. Study Objectives

2.1. Primary Objective

The primary objective is to test the hypothesis that PCI and thrombus aspiration is superior to PCI alone in reducing death in patients with STEMI.

2.2. Secondary Objectives

Secondary objectives are to compare PCI and thrombus aspiration to PCI alone with respect to TIMI flow grade, time to re-hospitalisation with nonfatal reinfarction, heart failure, target vessel revascularisation, all-cause death or new myocardial infarction, acute coronary occlusion, stent thrombosis and restenosis, complications of PCI during index hospitalisation and length of hospital stay, in patients with STEMI.

3. Endpoints and background variables

3.1. Endpoints

3.1.1. Primary Endpoint

The primary endpoint is time to all-cause death at 30 days. After termination of enrolment the necessary data for the primary variable will be collected for all patients. For Swedish patients, data on death is updated from the population registry at monthly scheduled time points, and the final analysis data set for the primary report and publication will be based on the mid-june 2013 update (about 80 days after the last included index PCI) to ensure sufficient reporting of 30-day mortality. For non-Swedish patients, data on deaths, death times, and censoring times, will be collected with similar quality. Time will be counted from the date of PCI, taken as INTERDAT in SCAAR, which is time 0. Surviving patients will be censored at 30

days. Patients that withdrew their consent will be censored at the date consent was withdrawn.

3.1.2. Pre-defined Secondary Endpoints

3.1.2.1. Time to all-cause death after 1year, 2 years, 5 years and 10 years.

These will not be reported in the primary report but in later follow-up publications. Outcomes at 1, 2, 5 and 10 years will be defined in a corresponding way to 30-day outcomes.

3.1.2.2. Time to re-hospitalization with reinfarction, heart failure and target vessel revascularization after 30 days and 1 year, 2 years, 5 years and 10 years.

Only 30-day outcomes will be included in the primary report. This item comprises the three outcomes described below. All times are counted from date of PCI (time 0, defined by INTERDAT) using dates only, even if time points should be available in some case. Patients without events will be censored at 30 days. Patients that withdrew their consent will be censored at the date consent was withdrawn. Patients that died without event will be censored at the day of death. Outcomes at 1, 2, 5 and 10 years will be defined in a corresponding way and reported in future publications.

- Time from date of PCI to reinfarction as recorded in the SWEDEHEART registry. Reinfarction is defined as presence of a diagnosis with ICD code I21 or I22 (including subcategories), and time of reinfarction is defined as the admittance date. To give easily interpreted results, reinfarctions that might have resulted in death will not be removed from the analysis. In future publications reinfarctions identified from the Swedish inpatient registry may also be analysed.
- Time from date of PCI to heart failure as recorded in SWEDEHEART. Heart failure is defined as presence of a diagnosis in ICD code I50 (including subcategories), and time of heart failure is defined as the admittance date.
- Time from date of PCI to target vessel revascularisation. Will be obtained by matching SCAAR records on SSN and treated vessel as defined below, for vessels with PROCTYP 2 or 3 (stent), disregarding new records with PROCTYP 9 (diagnostic).

3.1.2.3. Time to all-cause death or new myocardial infarction (first occurring) after 30 days, 1 year, 2 years, 5 years and 10 years.

Only 30-day outcomes will be included in the primary report. The time is counted from date of PCI (time 0, defined by INTERDAT) using dates only, even if time points should be available in some case, to the first occurrence of all-cause death (the primary end point) or reinfarction (secondary end point defined above). Patients without events will be censored at 30 days. Patients that withdrew their consent will be censored at the date consent was withdrawn. Outcomes at 1, 2, 5 and 10 years will be defined in a corresponding way and reported in future publications.

3.1.2.4. Time to acute coronary occlusion, stent thrombosis and restenosis in treated lesions as reported in SCAAR.

This point comprises three outcomes described below. All times are counted from date of PCI (time 0, defined by INTERDAT) using dates only, even if time points should be available in some cases. Patients without events will be censored at the time of last follow-up. Patients that withdrew their consent will be censored at the date consent was withdrawn. Patients that died without event will be censored at the day of death.

- Time from date of PCI to stent thrombosis. Time of stent thrombosis is obtained from D_SAT_DATUM, using the first occurrence in any segment.
- Time from date of PCI to restenosis of treated lesions. Time of restenosis is obtained from D_RESTENOS_DATUM, using the first occurrence in any segment.

Acute coronary occlusion will not be analysed, since this subgroup of stent thrombosis is not considered to add clinically interesting information.

3.1.2.5. Reported heart failure and complications of PCI during index hospitalization as reported in SWEDEHEART.

- Heart failure during index hospitalisation will be derived from SWEDEHEART as ICD code I50 (including subcategories) as diagnosis for the index event.
- Stroke during index hospitalisation will be derived from SWEDEHEART as ICD codes I60-I64 (including subcategories) as diagnosis for the index event.
- Other complications that will be reported are defined by the following SCAAR variables: AVDALLERGISK, AVDBLODMAJOR, AVDBLODMINOR, AVDBLODMINI, AVDBEHPSEUDO, AVDANNANVASK, AVDNEURO, AVDNJURINSUFF, AVDTAMP, AVDREPCI, AVDCABG, AVDHJARTINFARKT, AVDANNANALLV, AVDDODSFALL, AVDPROCEDURDOD, AVDBLODNING, AVDHEMATOM, AVDHBFALL, AVDFORLANGDKOMPTID, AVDVARDTID, AVDULTRALJUD, AVDBLODTRANSFUSION, AVDKIRURGISKATGARD, AVDANNANBEHUTOVERKOMP, AVDFORTIDAUTSATTNING, LABALLERGILATT, LABALLERGIALLV, LABBEHARYTMI, LABHEMO, LABBESTSIDO, LABAKUTCABG, LABANNANALLV, LABNEURO, LABVASK, LABTAPPAT, LABPERF, LABTAMP, LABPROCEDURDOD.

3.1.2.6. Length of hospital stay as reported in SWEDEHEART.

Length of hospital stay for the index event will be computed as DISCHARGE_DATE-ADMISSION_DATE+1 using SWEDEHEART data for the index event.

3.1.2.7. TIMI-flow grade.

TIMI flow grade after PCI is collected as the TASTE variable TASTETIMIFLOWAFTER in SCAAR.

3.1.2.8. Stroke as reported in the Swedish national patient registry

This outcome was introduced in a note to file dated November 2011. The outcome will not be included in the primary report, since data from the patient registry will not be available. Time of stroke will be counted from date of PCI (time 0, defined by INTERDAT) using dates only, even if time points should be available in some case, to the first occurrence of stroke, defined as ICD code I60-I64 (including subcategories). Patients without events will be censored at 30 days. Patients that died will be censored at the day of death. Patients that withdrew their consent will be censored at the date consent was withdrawn.

3.1.3. Other secondary end points

3.1.3.1. Time to all-cause death during the entire follow-up time

This is the same as the primary variable, but patients are censored at the day of the last update from the population registry. For Danish and Icelandic patients, the censoring date will be the date when data was sent to UCR.

3.1.3.2. Left ventricular function during index hospitalisation

Obtained in the categories <30%, 30-39%, 40-49% and ≥50% from D_LEFT_VENTRICULAR_FUNCTION in SWEDEHEART.

3.2. Treatment administration variables

3.2.1. Actual treatment

Obtained from the SCAAR variable ADJTROMB.

3.2.2. Thrombus aspiration device

Obtained from TASTEDEVICE.

3.2.3. Number of treated coronary segments

Obtained from D_SEGMENTANT.

3.2.4. Number of treated vessels

Obtained from SEGMENT.

3.2.5. Stent diameter and stent length

Obtained from DIAM and STENTLANGD. If more than one stent is used, mean diameter and cumulative stentlength will be obtained from all used stents in the individual procedures.

3.2.6. Post-dilatation

Obtained from EFTERDILATATION. Will be reported as Yes if Yes for any segment in the patient.

3.2.7. Direct stenting

Obtained from PROCTYP. Will be reported as Yes if Yes for any segment in the patient.

3.2.8. Drug-eluting stent implantation and bare metal stent implantation

Obtained from D_DES_PROC and D_STENT_PROC, procedures with D_STENT_PROC=Yes and D_DES_PROC=No will be regarded as bare metal stent implantation.

3.2.9. Numbers of used stents

Obtained from D_STENTANT.

3.2.10. Drug-eluting balloons

Obtained from PROCTYP.

3.2.11. Complete revascularisation

Obtained from KOMPREV.

3.2.12. General success

Obtained from SUCCESS.

3.3. Demographic and background variables

3.3.1. Diabetes yes/no

Obtained from SCAAR variable DIABETES. Diabetes with insulin treatment obtained from SCAAR variable DIABETESINSULIN.

3.3.2. Thrombus burden

Obtained from TASTE variable EV_TASTEVISIBLETROMB in SCAAR.

3.3.3. TIMI flow before PCI

Obtained from the TASTE variable TASTETIMIFLOWBEFORE in SCAAR.

3.3.4. Time from symptom onset to PCI

Time points are defined by the variables SYMPTOM_ONSET_DATE and SYMPTOM_ONSET_TIME, and STICKDAT and STICKTID, respectively.

3.3.5. Time from reperfusion ECG to PCI

Time points are defined by the variables D_REPERF_ECG_DATE and D_REPERF_ECG_TIME, and STICKDAT and STICKTID, respectively. If D_REPERF_ECG_DATE or D_REPERF_ECG_TIME are missing, PREHOSPITAL_ECG_DATE and PREHOSPITAL_ECG_TIME will be used.

3.3.6. Previous myocardial infarction

Obtained from TIDINF.

3.3.7. Previous PCI

Obtained from TIDPCI.

3.3.8. Previous CABG

Obtained from TIDCABG.

3.3.9. Treated vessel

Obtained from SEGMENT (RCA, LM, LAD or LCx), or arterial or venous graft according to GRAFT. This will be further summarised over treated vessels by patient.

3.3.10. ACC/AHA lesion class

Obtained from STENOSKLASS. This will be further summarised over treated vessels by patient.

3.3.11. Other background variables

- Hospital: CENTREID
- Sex: D_GENDER
- Killip class: KILLIPKLASS
- Finding (Inconclusive, Normal/Atheromatosis, 1-, 2- or 3-vessel disease, or Main stem stenosis): FYND
- Age: D_AGE_ANGIOPCI
- BMI: D_BMI. Note that this variable is missing for a substantial number of patients.
- Smoking status: SMOKING_STATUS.
- Lipid lowering drugs: HYPERLIP.
- Hypertension treatment: HYPERTON.
- Previous myocardial infarction: TIDINF
- Previous coronary by-pass grafting: TIDCABG
- Medications prior to procedure:
    - ASA: ASAFORE
    - Clopidogrel/ticlopidin: CLOFORE
    - Ticagrelor: TICFORE
    - Prasugrel: PRAFORE

- Warfarin: WARFORE

If the variables are missing or unknown in SCAAR, corresponding information may be obtained from SWEDEHEART records.

4. Study design

TASTE is a controlled, randomised, open label trial to investigate the effect of PCI with manual thrombus aspiration versus PCI alone, in patients with STEMI. Treatment allocation and data collection was performed using the SCAAR platform, and the primary outcome of death was obtained from national registries. Patients were randomised in a 1:1 ratio using block randomisation stratified on hospital. Although the study was not blinded, investigators and steering committee did not have access to treatment allocation data or data summaries by treatment during the study.

The trial was originally planned to randomise 5000 patients. Due to a lower than expected rate of death, the maximum number of patients was increased to 7200 in Amendment 6, together with the adoption of a group-sequential plan that would allow early termination after about 4800 patients. The study design changes and sample size update were decided by study team members with access to data on overall mortality rate, but without access to any data that allowed treatment comparisons.

The trial was monitored by an independent data safety monitoring board (DSMB) that received unblinded summaries of data at two interim analyses, originally planned at 1500 and 3000 patients. The mandates for the DSMB were clarified in Amendment 5 prior to the first interim analysis, to only evaluate specific safety concerns and not differences in efficacy in a single interim analysis after 2500 patients. The mandates were expanded in Amendment 6, to evaluate efficacy in a second interim analysis including at least 4800 patients, with the option to either declare statistical significance, recommend early termination of the study because of a low probability to obtain a statistically significant result at the end of the study, or to recommend that the study is continued until 7200 patients have been enrolled.

5. Interim analysis plan

The interim analysis for efficacy was performed after 30 days follow-up on all-cause death has been obtained for 4798 patients, which was deemed sufficiently close to the 4800 specified in the interim analysis plan. The DSMB was entrusted to either declare that a statistically significant treatment difference has been detected for the primary variable and that enrolment will stop, recommend that the study is terminated due to a low confidence in the possibility to detect a meaningful treatment difference after 7200 patients have been included (futility), or recommend that the study continues until 7200 patients have been included. The recommendation of the DSMB (2012-08-29) was to continue the study.

Statistical significance at the interim analysis was defined by p<0.01 (two-sided). If significance is not obtained, the DSMB had the opportunity to recommend stopping the study due to a low confidence in the possibility to detect a meaningful treatment difference. The recommended, non-binding, criterion for futility stopping was that the interim analysis gives p>0.49, based on a spending of beta=0.05. To aid the decision, the conditional probability of obtaining a significant result at 7200 patients, and the estimated hazard ratio with 95% confidence interval, was calculated.

If the study was not discontinued after the interim analysis, statistical significance at the final analysis, even if the goal of 7200 patients was not reached, is defined by p<0.0471 (two-sided), to ensure that the total type I error rate is below 5%. The p-value boundaries were calculated based on interpolated alpha- and beta-spending methodology, using East version 5.4.2.0 (Cytel, Inc., Cambridge, MA, USA), for a comparison of the proportion patients that die within 30 days. By estimating the expected accumulated information fraction by the number of patients, these boundaries are valid for the primary analysis, time to death within 30 days. In the event that more than 7300 patients are included in the final analysis, the p-value for declaring statistical significance was to be recalculated using Haybittle-Peto alpha-spending, based on 4800 patients in the interim analysis and the actual number of patients in the final analysis, with expected information fractions estimated using the number of patients. Since the study was continued and the final number of patients is below 7300, statistical significance for the primary variable will be defined by a two-sided p<0.0471.

6. Definition of Analysis Populations

All analyses will be performed on the full analysis set (FAS), comprising all randomised patients with the following exceptions:

- Patients where the date of index PCI (INTERDAT) is unknown. These patients lack a SWEDEHEART record relating to the index event. For two patients, patient number 110022 and 129065, a matching SWEDEHEART record could be found although the initial record matching the randomisation had been removed, leaving 14 patients without date of index PCI.
- Patients that did not give initial informed consent or withdrew consent within a short time span. In total, four patients (118068, 118001, 128016, and 133150) are excluded from the FAS for this reason.

The analysis population was determined at a meeting 2013-03-26 using a document prepared by Bo Lagerqvist. Some changes may occur up to the formal clean file meeting, and the patients excluded from the FAS will be described in the data base closure document.

The eligible patient set (EPS) consists of all patients in Sweden with STEMI referred to PCI during the enrolment period, according to SWEDEHEART. The EPS will be used to compare background variables and primary outcome in the selected TASTE

population to the non-included population, as an aid to assess the external validity of the randomised comparison.

7. Description of statistical analyses

7.1. Study conduct and Subject/Patient disposition

Patients that withdrew their informed consent are described in the data base closure document. The number of patients that are excluded from the FAS due to missing index date and due to missing informed consent will be described by randomised treatment. FAS patients missing or having no in either EV_TASTEPATIENTSUITABLE or EV_TASTECONCENT, and patients without a PCI, will be tabulated by randomised treatment. The patient numbers will be taken from the data base closure document.

7.2. Baseline Characteristics and Treatment Group Comparability

Background characteristics will be tabulated using descriptive statistics such as absolute and relative frequencies, mean and standard deviation, and quartiles, as appropriate.

7.3. Treatment Administration/Compliance

Actual treatment and data for the index PCI will be described using descriptive statistics such as absolute and relative frequencies.

7.4. Efficacy analyses

7.4.1. General considerations

All efficacy analyses will be performed as described in the protocol, Amendment 6, using the FAS, for observed cases only.

Differences between groups in time-to-event endpoints will be assessed with the log-rank test. For the primary endpoint, patients will be censored at 30 days (where the day of PCI is day 0); analyses at other time points will be handled in a similar way. Survival probabilities will be displayed and calculated using Kaplan-Meier methodology. Hazard ratios between groups will be calculated using Cox proportional hazard model. Differences between group means will be assessed with the two-tailed Student's t-test. Chi-square analysis or Fisher's exact test will be used to test differences between proportions. Estimates will be presented with nominal 95% confidence limits and nominal 2-tailed p-values.

7.4.2. Primary efficacy analysis

Time to death within 30 days, and within the study up to 30 days after the inclusion of the last patient, will be presented by randomised treatment using Kaplan-Meier curves.

The treatment hazard ratio of death within 30 days, from a Cox proportional hazards model with treatment as the only factor, will be presented with its nominal 95% confidence interval and the nominal p-value from the log-rank test. Surviving patients will be censored on day 30, where the day of PCI is day 0. Statistical significance will be determined by $p<0.0471$ as by the interim analysis plan.

As a supplementary analysis, the proportion patients that died before or on day 30 after PCI will be tabulated and analysed using logistic regression with randomized treatment as a factor, and the odds ratio presented with its 95% confidence interval and p-value from the Pearson chi-square test.

To assess possible impact of the design changes on the interpretation of the results, a comparison of treatment hazard ratios based on the primary variable will be presented, comparing patients enrolled up to the date that the interim analysis data was extracted from the registry, to patients enrolled after that date. This analysis will be based on a Cox model with factors randomized treatment, study period, and interaction. A sensitivity analysis using a Cox model with factors randomized treatment and center will be performed.

7.5. Secondary efficacy analyses

7.5.1. Time to re-hospitalization with reinfarction, heart failure, target vessel revascularization, composite of all-cause death and re-hospitalisation with reinfarction, stent thrombosis, restenosis in treated lesions, and stroke, within 30 days

These variables will be described and analysed in the same manner as the primary variable, including a supplemental analysis of proportions. No sensitivity analyses will be performed.

7.5.2. Reported heart failure and complications of PCI during index hospitalisation

The outcomes will be presented as number and frequency of patients with each complication, the related estimated odds ratio with 95% confidence interval from a logistic regression model with factor randomised treatment, and the p-value from a Pearson's chi-2 test. Due to the multiplicity of tests, the p-values for complications should be interpreted as a descriptive signalling device.

7.5.3. Length of hospital stay

Length of hospital stay will be presented using descriptive statistics, the Hodges-Lehmann estimate of distribution shift between the treatments with 95% confidence

interval, and the p-value from a Wilcoxon's rank sum test. An additional confidence interval for the difference in means may be computed using bootstrap.

7.5.4. TIMI flow

TIMI flow will be tabulated by randomised treatment and in a shift table by randomised treatment and TIMI flow before PCI. The p-value from a Pearson's chi-2-test will be presented. A supplementary exact Wilcoxon's rank sum test will be performed as a test for trend.

7.5.5. Left ventricular function

Left ventricular function will be tabulated by randomised treatment. The p-value from a Pearson's chi-2-test will be presented. A supplementary exact Wilcoxon's rank sum test will be performed.

7.6. Imputation of Missing Data

No imputation of missing data will be performed. For the primary variable, death time within 30 days, follow-up is complete for the patients in the FAS, and the number of randomised patients not included in the FAS is considered too small to substantially alter any conclusions.

7.7. Subgroup and interaction analyses

Subgroup analyses will be performed for the primary variable using Cox regression with factors randomized treatment, subgroup, and randomized treatment-subgroup interaction. The results will be presented as the hazard ratio with 95% confidence interval for each subgroup and the p-value for interaction. Data will be presented descriptively as Kaplan-Meier curves for each treatment in each subgroup. The following subgroups will be analysed:

- Sex, male/female.
- Age, ≤65/>65 years.
- Smoking, current smoker/not current smoker.
- Previous myocardial infarction, yes/no.
- Diabetes, yes/no.
- Thrombus burden, 0/1/2/3/4/5 and 0-3/4-5.
- TIMI flow grade, 0/1/2/3 and 0-1/2-3.
- Time from symptom onset to PCI, below median/above median, and below 2 hours/above 2 hours.
- Time from first ECG to PCI, below median/above median.
- Treated vessel, LM/LAD/LCx/RCA/Graft and LM+LAD+LCx/RCA.
- Proximal culprit lesion, segment 1,2,5,6,7,11/others.

8. Determination of sample size

The original sample size calculation was based on one-year mortality, and the study was planned to include 5000 patients to be able to detect a hazard ratio of at least

1.3, based on time to death within one year, at the 5% confidence level with 80% power. This calculation was updated in a protocol amendment to reflect the pre-defined primary outcome, which is time to death within 30 days. In addition, the updated sample size calculation accounts for a lower overall mortality rate than expected as revealed by a blinded interim analysis, and the introduction of a formal interim analysis with possible stopping for efficacy.

A blinded interim analysis was performed to estimate the overall all-cause death proportion at 30 days after randomization. With blinded is meant that an overall estimate of the all-cause mortality rate for the total group of patients in the study was determined while keeping the treatment group allocation blinded, and no statistics by randomized treatment group was calculated. Actions were taken to ensure personnel involved in the sample size calculation and calculation of the overall mortality rate had no access to treatment group allocation.

The blinded interim analysis, as per January 15, 2012, resulted in an overall rate of 2.9% (the Kaplan-Meier estimate). The all-cause mortality proportion at 30 days was estimated to 3.5% for patients randomized to conventional PCI by assuming a difference at 30 days between patients randomized to conventional PCI and thrombus-aspiration + PC corresponding to an odds ratio of 1.5 (based on previous study TAPAS).

Assuming a 3.5% 30-day mortality rate for conventional PCI, odds ratio at least 1.5 (conventional PCI/ thrombus-aspiration + PCI), overall type I error 0.05, and an interim analysis at 67% of the total sample size, with interim stopping for significance with $p<0.01$, and interim stopping for futility with $p>0.493$ (non-binding), a total of 7138 patients would give 80% power of obtaining a significant result at the 5% level using 2-sided tests for the odds ratio of death within 30 days. The power for the log-rank test of time to death within 30 days is assumed to be similar. 7138 is rounded upwards to 7200 patients. The calculations were done using interpolated alpha- and beta-spending methodology using East version 5.4.2.0 (Cytel, Inc., Cambridge, MA, USA).

9. Changes in the Planned Analysis

No changes were made from the amended protocol in the analysis of the pre-specified outcomes. Changes introduced in the amendments did not affect the statistical methods employed for hypothesis testing. Compared to the initial protocol, the amendments clarified that for the primary analysis, time to death was to be censored at 30 days, and introduced a group-sequential analysis plan. Methods for calculating point estimates and confidence intervals, consistent with the hypothesis tests, have been added in Amendment 6 and the SAP. This SAP clarifies secondary outcome definitions and analysis populations and introduces a few supplementary analyses. The secondary outcome acute coronary occlusion is removed, since it is no longer considered to add clinically interesting information to the analysis of stent

thrombosis. Left ventricular function is added as a secondary outcome, and a number of subgroup analyses are introduced.

10. Description of Derived Variables

See variable descriptions in Section 3.

11. Description of Output

Output shells will be described in a separate document.

12. Statistical software

Statistical analyses will primarily be performed using SAS v. 9.3 or later. In addition, R version 12.15.0 or later or SPSS may be used.