Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE trial). A multicenter, prospective, randomized, controlled clinical registry trial based on the Swedish angiography and angioplasty registry (SCAAR) platform. Study design and rationale

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Background In ST-elevation myocardial infarction (STEMI), distal embolization of thrombus material often precludes restoration of normal coronary artery flow. Small-scaled studies have demonstrated that intracoronary thrombus aspiration improves flow and myocardial perfusion, but only one larger randomized single-center study has suggested a survival benefit. Thrombus aspiration is widely used in clinical practice and is recommended by international guidelines despite limited evidence.

Methods/design The Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia is a multicenter, prospective, randomized, controlled, clinical open-label trial based on the Swedish angiography and angioplasty registry (SCAAR) platform with blinded evaluation of end points. A total of 5,000 patients with STEMI undergoing primary percutaneous coronary intervention (PCI) will randomly be assigned either to conventional PCI or to thrombus aspiration followed by PCI. SCAAR will be used as the platform for randomization, allowing a broad population of all-comers in the registry network to be enrolled. All follow-up will also be done in SCAAR and other national registries. The primary end point is time to all-cause death at 30 days.

Discussion The Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia trial is the largest trial to date to evaluate the effect of thrombus aspiration on death following PCI in patients with STEMI. We propose the term randomized clinical registry trial to describe the novel entity of using an online national registry as platform for case records, randomization, and follow-up. (Am Heart J 2010;160:1042-8.)

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Thrombolysis was a major step forward in the treatment of STEMI,1,2 and further progress was done when primary percutaneous coronary intervention (PCI) was established as a golden therapeutic standard.3 Treatment has been further optimized with pre-, peri-, and postprocedure platelet inhibition, statins, angiotensin-converting enzyme inhibition, and β-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.4,5 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.6,7 In reperfusion injury, restoration of coronary flow results in arrhythmias, contractile dysfunction, microvascular impairment, and irreversible myocardial damage through apoptosis and necrosis.8
Thrombus aspiration may contribute to improve coronary artery flow post-PCI.\textsuperscript{14-16} Although this is not a universal finding,\textsuperscript{14-16} however, most previous studies on thrombus aspiration have not been powered for hard clinical end points, such as mortality. To date, the only large-scale randomized trial of thrombus aspiration for STEMI to demonstrate a survival benefit is the 1,071-patient single-center Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) trial in which death was a secondary end point.\textsuperscript{10,17} In TAPAS, after 1 year, cardiac death was 3.6\% in the thrombus aspiration group and 6.7\% in the conventional PCI group; and this difference was statistically significant ($P = .020$). 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.\textsuperscript{18-20} Thrombus aspiration is not necessarily a risk-free procedure; systemic embolization may occur,\textsuperscript{21} and some mechanical thrombectomy devices could worsen outcome.\textsuperscript{22} Recently, we reported data on all patients in Sweden undergoing PCI for STEMI from January 1, 2005, to December 31, 2009. Contrary to our expectations, following adjustment for sex, age, diabetes, tobacco use, hypertension, type of platelet inhibition, and hospital where the PCI was performed, patients undergoing thrombus aspiration before PCI (4,212 patients) had an increased risk of death compared with patients treated by routine PCI (18,420 patients, relative risk 1.16, 95\% CI 1.05-1.28).\textsuperscript{23}

Thrombus aspiration is easy, quickly performed, and a relatively cheap adjunct to PCI. Perhaps because of the low-tech nature and the limited possibilities of future patents and economic revenue of thrombus aspiration devices, the interest from the medical technology 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 are left to the scientific community. 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 (ie, it is reasonable to perform the procedure) with a level of evidence B (ie limited populations evaluated).\textsuperscript{24} In our view, additional evidence needs to be established before thrombus aspiration becomes routine for some and is discarded by others because of the uncertainty related to verification.

**Methodology**

**Hypothesis, and primary and secondary end points**

The Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE) trial is a multicenter, prospective, randomized, controlled, clinical open-label trial in patients with STEMI undergoing primary PCI.

The study hypothesis is that thrombus aspiration, as an adjunct to standard PCI, confers a better outcome compared with PCI alone in patients with STEMI. All baseline information will be obtained from the Swedish Coronary Angiography and angioplasty registry (SCAAR) database in which a number of variables (from 47 variables in the simplest PCI up to \( \geq 100 \) variables in complex PCIs) are routinely registered directly in the catheterization laboratory via a Web-based interface on all patients undergoing coronary arteriography and PCI. Thus, in the TASTE trial, the extra work associated with inclusion of each patient is minimal and restricted to activating a minute randomization module within the database. Clinical end point parameters will be obtained from continuous national health registries. No study-specific clinical follow-up is therefore needed. The primary end point is time to all-cause death at 30 days. The secondary end points are as follows: time to all-cause death after 1, 2, 5, and 10 years; time to rehospitalization with nonfatal reinfarction, heart failure, and target vessel revascularization after 30 days, 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 the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART\textsuperscript{25}); length of hospital stay as reported in SWEDEHEART; and Thrombolysis in Myocardial Infarction (TIMI) flow grade assessed by the treating physician immediately after the index procedure.

The TIMI flow grade after PCI is defined as follows: grade 0, 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.\textsuperscript{2,26} Merging SCAAR with other national registries collects information about coronary artery bypass surgery after randomization and rehospitalization after the index procedure. Myocardial infarction is defined as International Classification of Diseases codes I21 and I22; and heart failure, as I50. Any new PCI performed in the SCAAR network area is recorded 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.

**Patient population**

Individuals for inclusion will be recruited among the patients referred to the participating centers for PCI because of STEMI. The patients or participating centers will not receive any honorarium. ST-elevation myocardial infarction is defined by chest pain suggestive for myocardial ischemia for at least 30 minutes before hospital admission, time from onset of symptoms of \( \geq 24 \) hours, and an electrocardiogram with new ST-segment elevation in \( \geq 2 \) contiguous leads of \( \geq 0.2 \) mV in leads V\textsubscript{2} through V\textsubscript{4} and/or \( \geq 0.1 \) mV in other leads or a probable new-onset left bundle-branch block. In patients considered for inclusion, correspondence between electrocardiographic findings and culprit artery pathoanatomy is a requirement; there
must be a minimum of 50% stenosis in the culprit artery by visual estimate, and the operator must consider it possible to perform thrombus aspiration. The exclusion criteria are need for emergency coronary artery bypass grafting, inability to provide informed consent, age <18 years, or previous randomization in the TASTE trial.

Randomization and ethics

After a study coordinator has confirmed patient eligibility, the patient will receive standardized oral information about the TASTE study. If a patient accepts to participate, randomization will be performed online in the SCAAR database. The patient will receive study information on paper within 24 hours and will be asked to confirm participation by signature. If the patient wishes not to sign the informed consent, he or she will be actively withdrawn from the TASTE study cohort. He or she will be followed up in the national health databases but consequently not be part of scientific reports related to the TASTE study. A maximum of 3 months following inclusion of the first 1,500 patients and again following 3,000 patients, an independent end point committee will monitor study end points. 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. The concept of a trial design using a national registry as the basis for continuous enrolment and randomization of all-comers is potentially limited by the lack of formal central adjudication of clinical events. Therefore, we have chosen all-cause mortality from the national complete mortality registry as the primary end point of the trial. Secondary end points will be investigator reported and collected from the SCAAR/SWEDEHEART registry. These events may suffer from a lower overall quality. The trial is conducted in accordance with the Declaration of Helsinki and has been approved by the regional ethical review board of Uppsala, Sweden. The trial is registered under www.clinicaltrials.gov: NCT01093404. Recruitment and study flow is illustrated in Figure 1. It is expected that all PCI centers in Sweden and Iceland and selected centers in Denmark will participate in TASTE using the SCAAR registry for entry of baseline variables and for randomization. Follow-up in these countries will be done using Icelandic and Danish national health registries, respectively.

Invasive procedures

The use of glycoprotein 2b/3a inhibitor treatment or other platelet inhibitors or anticoagulants is left to the discretion of the treating physician.

Specific guidelines for the performance of the procedures are provided and are compliant with European Society of Cardiology
guidelines and the instructions of the TAPAS study protocol. Following coronary arteriography, in all patients, initially a guidewire will be passed through the culprit lesion. For patients randomized to conventional PCI, guidewire advancement will be followed by balloon dilatation, balloon dilatation and stenting, or direct stenting to achieve antegrade flow. In all patients, after the restoration of antegrade flow, intracoronary nitrates will be administered to ensure maximal epicardial vasodilation to determine the size and length of the stent and to facilitate stent placement. Postdilatation of stents is optional.

For patients randomized to thrombus aspiration, guidewire passing will be followed by thrombus aspiration with a 6F compatible aspiration catheter. Continuous manual suction will be 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 the smallest possible 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. Passage of the culprit lesion with suction should preferably be performed 4 times. After thrombus aspiration, PCI will be done as described above. To qualify for use in the TASTE trial, a thrombus aspiration catheter must be 6F compatible, simple and low profile in design, and meant for manual aspiration. At the time of writing, the following catheters have been approved: Eliminate (Terumo Medical Corporation, Tokyo, Japan, crossing profile 0.068 in), Export Aspiration Catheter (Medtronic, Minneapolis, MN, crossing profile 0.067 in), OXT (Vascular Solutions, Minneapolis, MN, crossing profile 0.067 in), and Pronto (Vascular Solution, crossing profile 0.065 in).27

Direct stenting or stenting after initial balloon dilatation and choice of stent (bare metal or drug eluting) are per physician discretion. After the index PCI, lifelong acetylsalicylic acid in a dose of 75 to 160 mg/d will be prescribed. Duration of clopidogrel or other P2Y12 inhibitor treatment is also left to the discretion of the treating physician.

Crossover from one group to the other is discouraged but is allowed on the operator's discretion. Crossovers will be recorded and followed up in the national registries in line with all other patients.

Substudies

In selected centers, the amount of salvaged myocardium will be measured using cardiac magnetic resonance.28 T2-weighted short tau inversion recovery cardiac magnetic resonance will be done in 150 patients (75 patients randomized to thrombus aspiration and 75 patients randomized to conventional PCI) on day 4 ± 2 following PCI.

A substantial number of patients with STEMI have a patent infarct-related artery at arrival in the catheterization laboratory.29 Using venous blood samples and aspirated coronary artery blood and thrombus, a substudy will investigate factors related to platelets and the coagulation cascade associated with spontaneous repersusion. Any possible impact of thrombus aspiration on coagulation cascade activation will also be studied.

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The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Statistical considerations

Sample size was calculated on the basis of 2 sources. We used cardiac death at 1 year in TAPAS that demonstrated a hazard ratio of 1.93 for conventional PCI compared with the thrombus aspiration group.17 In addition, we used available data from 2005-2007 in the SCAAR, which showed an overall 1-year mortality of 9.0% in PCI-treated STEMI patients (~6,500 PCIs in STEMI per 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 2,334 conventional PCI patients and 2,334 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 .80. The type I error probability associated with testing of this null hypothesis is 0.05.30 To control for crossing from one group to the other and aspiration device failure, 5,000 patients will be included.

The results will be analyzed according to the intention-to-treat principle, that is, patients randomized to a certain group will be followed and assessed irrespective of the actual treatment. Differences between groups in time-to-event end points will be assessed with the log-rank test. 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 2-tailed Student t test. The χ² analysis or Fisher exact test will be used to test differences between proportions. A 2-tailed P value < .05 is considered statistically significant.

Discussion

The TASTE trial investigates the effect on clinical outcome of thrombus aspiration in STEMI, an area in which conflicting evidence exists today. Manual thrombus aspiration catheters are relatively low-tech products with limited possibilities for new patents. Because large-scale randomized clinical trials are expensive to undertake and because economic revenue typically is the primary incentive to inaugurate large trials, it cannot be expected that commercial interests will make such an initiative. Furthermore, the requirements for documentation in
randomized clinical trials, installed to shield patients, ensure reproducibility, and avoid fraud, impede realization of simple yet relevant trials because of economic barriers. A catch 22 is this: to protect patient interests, several relevant clinical problems are not addressed and evidence is not established. It is our conviction that introduction of the "randomized clinical registry trial" concept is a way forward. This concept has several advantages: a database platform that must be filled in for other documentation purposes serves as clinical report form; the responsible physician has very little additional work; all follow-up is done via databases; and many patients can be included during a short period, enabling evaluation of hard clinical end points. Thus, in TASTE, we intend to include 5 times more patients compared with the largest randomized thrombus aspiration trial hitherto, the TAPAS trial. The disadvantages of the "randomized clinical registry trial" concept in a study of the clinical effect of thrombus aspiration include no follow-up information on clinical status, quality of life, biochemical parameters, ejection fraction, or myocardial salvage. By addressing the hardest of end points, death, and additional relevant variables including in-hospital complications, time to rehospitalization with nonfatal reinfarction, heart failure and target vessel revascularization, time to acute coronary occlusion, stent thrombosis, and restenosis, in our opinion, this outweighs the drawbacks.

In TASTE, inclusion is broad; and there are very few and limited exclusion criteria. The intent of this design is to ensure clinical applicability and aspire toward an all-comers study but also to simplify inclusion to maximize commitment and compliance among staffs in the partaking hospitals. We assume a much more conservative estimate of hazard ratio compared with what was found in the TAPAS study. It is our opinion that the outcome in hazard ratio found in TAPAS was remarkable; and when compared with other clinical trials of different treatment modalities within cardiology, it is reasonable to aim lower in order not to miss a clinical effect (Figure 2), although this is at the expense of a much higher requirement in patient number.

Several advanced thrombus aspiration designs have been investigated in previous small-scale studies.

Illustration of hazard ratios in major previous randomized trials within the field of cardiology. The hazard ratio is a ratio of the risk (or hazard) of an event in one group compared with the risk in a comparison group. TAPAS: cardiac death (top) and total death.17 The 3,991-patient MERIT-HF trial31 investigated the effects of the β1-blocker controlled-release/extended-release metoprolol succinate on mortality, hospitalization, symptoms, and quality of life in patients with heart failure. MERIT-HF demonstrated a hazard ratio of 1.52 for total mortality after 1 year. 4S: Simvastatin for coronary heart disease and elevated cholesterol (5.5-8.0 mmol/L).32 A total of 4,444 patients were randomized to treatment with simvastatin or placebo. The simvastatin group demonstrated a hazard ratio of 1.43 for total mortality after 5.4 years. Cure: 12,562 patients with non–ST-elevation acute coronary syndrome were randomly assigned to receive clopidogrel or placebo in addition to aspirin for 3 to 12 months.33 The hazard ratio for the composite end point of death from cardiovascular causes, nonfatal myocardial infarction, or stroke was 1.25. In the TASTE trial, we have estimated a hazard ratio of 1.3 for the primary end point of total death. In order not to miss a clinically significant effect of thrombus aspiration, this hazard ratio is more in line with findings with other cardiovascular treatment modalities than with the TAPAS trial.
However, when merging data from such trials and from trials using simpler-design catheters, such catheters seem to be clinically superior with better clinical outcomes. We therefore decided to allow only low-profile manual aspiration catheters.

In conclusion, in the TASTE trial, we introduce the “randomized clinical registry trial” concept to test the hypothesis that manual thrombus aspiration and PCI are clinically superior to PCI alone in patients with STEMI. This new trial concept enables inclusion of many patients in a relatively short time with limited additional effort and expenses. The “randomized clinical registry trial” concept offers new ways to test medical hypotheses and challenges prior trial designs.

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