The Strategic Reperfusion Early After Myocardial Infarction (STREAM) study

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Background Primary percutaneous coronary intervention (PCI) has emerged as the preferred therapy for acute ST-elevation myocardial infarction (STEMI) provided it is performed in a timely fashion at an expert 24/7 facility. Fibrinolysis is a well-accepted alternative, especially in patients presenting early after symptom onset. The STREAM study will provide novel information on whether prompt fibrinolysis at first medical contact, followed by timely catheterization or rescue coronary intervention in STEMI patients presenting within 3 hours of symptom onset, represents an appropriate alternative strategy to primary PCI.

Methods Acute STEMI patients presenting early after symptom onset are eligible if PCI is not feasible within 60 minutes of first medical contact. This is an open-label, prospective, randomized, parallel, comparative, international multicenter trial. Patients are randomized to fibrinolysis combined with enoxaparin, clopidogrel, and aspirin, and cardiac catheterization within 6 to 24 hours or rescue coronary intervention if reperfusion fails within 90 minutes of fibrinolysis versus PCI performed according to local guidelines. Composite efficacy end points at 30 days include death, shock, heart failure, and reinfarction. Safety end points include ischemic stroke, intracranial hemorrhage, and major nonintracranial bleeding. Follow-up is extended to 1 year and includes all-cause mortality.

Discussion Continuing delays in achieving timely PCI remain a difficult issue. Many patients fail to achieve the desired reperfusion times of 90 to 120 minutes after first medical contact. The STREAM results will provide useful additional data on which to base informed therapeutic decisions. (Am Heart J 2010;160:30-35.e1.)

Based on class IA evidence, primary percutaneous coronary intervention (PCI) has emerged as the preferred therapy for acute ST-elevation myocardial infarction (STEMI).[1,2] This has resulted in a steady increase in its uptake into the therapeutic armamentarium of physicians. To achieve its potential, however, PCI must be performed in a timely fashion at an expert 24/7 facility; this is not easily or equally attainable for all STEMI patients in all circumstances. Moreover, the frequency with which primary PCI is applied differs between countries and even across regions in the same country. The alternative approach to reperfusion with fibrinolytic therapy is traditionally well accepted, evidence based, and guideline supported, especially in patients presenting early after symptom onset, that is, within 3 hours.[1,2] Moreover, when administered very early, for example, in the prehospital setting, it extends the mortality benefit over that achieved with in-hospital administration.[3] This approach to fibrinolysis has proven feasible in various countries and effective in increasing the proportion of patients treated earlier in their course with resultant improved outcomes.[4,5] Further advances in this approach have emerged from the CAPTIM, WEST, and NORDISTEMI trials (all of which randomized patients within 6 hours of symptom onset) as well as the French FAST-MI registries, indicating that prehospital fibrinolysis followed by mechanical cointervention (a pharmacoinvasive strategy) and/or appropriate rescue PCI results in comparable outcomes to those undergoing primary PCI.[6-9] The benefits provided by rescue PCI after fibrinolysis are also supported by the REACT trial and subsequent meta-analyses of this approach.[10,11]

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Table I. Inclusion and exclusion criteria

Inclusion criteria

1. Age ≥18 y
2. Onset of symptoms <3 h before randomization
3. 12-Lead ECG indicative of an acute STEMI (ST elevation will be measured from the J point; scale: 1 mm per 0.1 mV:
   ≥2-mm ST elevation across 2 contiguous precordial leads (V_1-V_6) or leads I and aVL for a minimum combined total of ≥4-mm ST elevation
   Or
   ≥3-mm ST elevation in 2 contiguous inferior leads (II, III, aVF) for a minimum combined total of ≥6-mm ST elevation
4. Informed consent received

Exclusion criteria

1. Expected performance of PCI <60 min from diagnosis (qualifying ECG) or inability to arrive at the catheterization laboratory within 3 h
2. Previous CABG
3. Left bundle-branch block or ventricular pacing
4. Patients with cardiogenic shock—Killip Class 4
5. Patients with a body weight <55 kg (known or estimated)
6. *Uncontrolled hypertension*, defined as a single BP measurement ≥180/110 mm Hg (systolic BP ≥180 mm Hg and/or diastolic BP ≥110 mm Hg) before randomization
7. Hospitalization for cardiac reason within past 48 h
8. Recent administration of any IV or SC anticoagulation within 12 h, including unfractionated heparin, enoxaparin, and/or bivalirudin or current use of oral anticoagulation (ie, warfarin or Coumadin)
9. Active bleeding or known bleeding disorder/diathesis or the clinical diagnosis known to be associated with increased bleeding risk
10. Any history of central nervous system damage (ie, neoplasm, aneurysm, intracranial or spinal surgery) or recent trauma to the head or cranium (ie, <3 m)
11. Major surgery, biopsy of a parenchymal organ, or significant trauma within the past 2 m (this includes any trauma associated with the current myocardial infarction)
12. Any known history of hemorrhagic stroke, ischemic stroke, TIA, or stroke of unknown origin
13. Prolonged or traumatic cardiopulmonary resuscitation (>10 min) within the past 2 wk
14. Known acute pericarditis and/or subacute bacterial endocarditis
15. Known acute pancreatitis or known severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (esophageal varices), and active hepatitis
16. Long-term dialysis or known renal insufficiency
17. Arterial aneurysm and known arterial/venous malformation
18. Pregnancy or lactation or parturition within the previous 30 d; women of childbearing potential must have a negative urine pregnancy test result or use a medically accepted method of birth control
19. Previous enrolment in this study or treatment with an investigational drug or device under another study protocol in the past 7 d
20. Known hypersensitivity to tenecteplase, alteplase, acetylsalicylic acid, clopidogrel, enoxaparin, or any of the excipients or the contrast media used in angiography
21. Inability to follow the protocol and comply with follow-up requirements or any other reason that the investigator feels would place the patient at increased risk if the investigational therapy is initiated

CABG, Coronary artery bypass graft surgery; *SC*, subcutaneous; *BP*, blood pressure; *TIA*, transient ischemic attack.

Given the continuing challenge in delivering timely and effective primary PCI for STEMI and compelling evidence that delay to PCI is associated with lesser myocardial salvage and worse outcomes, we designed the current trial to evaluate whether a strategy of prompt fibrinolysis coupled with contemporary antiplatelet and antithrombotic therapy at the time of first medical contact followed by timely catheterization or rescue coronary intervention in STEMI patients presenting within 3 hours of symptom onset represents an appropriate alternative strategy to primary PCI.[12,13]

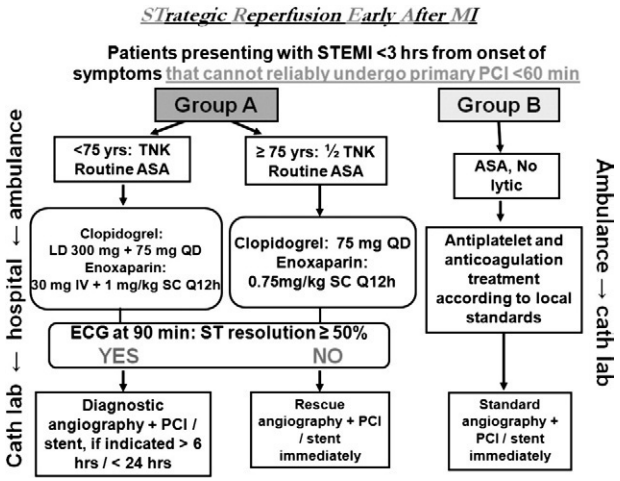
Methods

Trial methods

The trial was designed to enroll patients presenting within 3 hours of symptom onset who demonstrate acute STEMI and in whom primary PCI is not feasible within 60 minutes of a qualifying diagnostic electrocardiogram (ECG) (first medical contact).

The trial is an open-label, prospective, randomized, parallel, comparative, international multicenter trial. The inclusion and exclusion criteria are depicted in Table I. Patients are randomized to a strategy of fibrinolysis with tenecteplase coupled with additional antiplatelet and antithrombin therapy followed by cardiac catheterization within 6 to 24 hours, or rescue coronary intervention in the event that ECG (failure to achieve at least 50% ST resolution in the single lead with maximal elevation) or clinical evidence of failed reperfusion within 90 minutes of commencement of fibrinolytic therapy is present. This strategy will be compared with a strategy of primary PCI administered according to local standards (Figure 1). Tenecteplase will be administered in a dose based upon weight combined with antithrombotic therapy, that is, low–molecular weight enoxaparin (30 mg intravenous [IV] bolus followed by 1 mg/kg every 12 hours) except for patients >75 years old in whom the IV bolus will be omitted.[14] Antiplatelet therapy will consist of clopidogrel administered as a 300-mg loading dose followed by 75 mg daily, except that the loading dose will be again omitted for patients >75 years old,[15] as well as aspirin (150-325 mg) administered immediately followed by 75 to 325 mg daily.

Figure 1



Final Ammended STREAM Protocol.

In the primary PCI arm, treatment will be performed according to accepted practice with preceding and concomitant medication, including additional discretionary glycoprotein IIb/IIIa antagonists, given according to local standards and in compliance with international guidelines. All patients will be transferred to a hospital with PCI facilities; for non-PCI community hospitals to participate, a well-developed hub-and-spoke relationship with a PCI facility must be demonstrable to ensure timely urgent rescue coronary intervention if required. Adjudication will be undertaken for all patients deemed to require rescue in the fibrinolytic arm in a core ECG laboratory with analysis of baseline and 90-minute ST segment elevation. All strokes will be centrally adjudicated by a stroke review panel.

Urgent coronary intervention in the strategic fibrinolytic arm may be undertaken at any time should hemodynamic instability, refractory ventricular arrhythmias, worsening ischemia, or progressive or sustained ST elevation occur that, in the judgment of the investigator, requires immediate coronary intervention. Follow-up will be extended to 1 year and include all-cause mortality. The study end points are listed in Table II. Subgroups as previously defined in ASSENT-2 and ASSENT-3 and 3+ will be analyzed descriptively.[16-18] These include age >75 years, sex, Killip class, diabetes, infarct location, and time from symptom onset. Further definitions of efficacy and safety end points are provided in Table III.

Statistical methods

All statistical tests are of an exploratory nature and will be completed by presenting confidence limits and descriptive *P* values. The primary analysis is an intent to treat of all randomized patients according to treatment group. Single and composite end points will be expressed with 95% confidence limits and between-group comparisons done by presenting the confidence limits of the corresponding difference and/or odds ratio for each clinical end point.

The sample size of 1,000 patients per group is derived from the accuracy of the estimation of the 95% confidence limits for each end point within the 2 treatment groups as well as for between-group comparisons. To exclude the possibility of 1% worsening for a difference in proportions, the point estimate in the experimental lytic arm would have to be at least 1.3% better than in the reference group if there was a 4% event rate in the reference group. In the event that death, shock, heart failure, and reinfarction occur in 15% of the primary PCI group, a necessary advantage of the point estimate in the strategic fibrinolytic group would be 2.8% to exclude minimally important difference of, for example, 1.5%.

Table II. End point data

Composite efficacy end points within 30 d
Death and shock
Death and shock and CHF
Death and shock and reinfarction
Death and shock and CHF and reinfarction
Single efficacy end points within 30 d
All-cause mortality
Cardiogenic shock
CHF
Recurrent myocardial infarction (reinfarction)
Rehospitalization for cardiac reasons*
Rehospitalization for noncardiac reasons
Composite safety end points within 30 d
Total stroke (fatal, disabling, nondisabling)
Disabling stroke
Single safety end points within 30 d
Ischemic stroke
ICH
Nonintracranial bleeds (total, major, minor, and blood transfusions)
Serious clinical events (resuscitated ventricular fibrillation, repeat target vessel recanalization)
Mixed (efficacy and safety) composite end points within 30 d
Death and nonfatal stroke
Death and shock and CHF and reinfarction and disabling stroke

CHF, Congestive heart failure.
*Cardiogenic shock, congestive heart failure, reinfarction, recurrent ischemia, and revascularization.

Study organization

Before commencement of the trial, composition of ambulance/emergency staff involved in prehospital trial procedures will be clearly established; and study medication, logistics, and associated procedures as well as ambulance transfers will be documented. Patients are randomized early after symptom onset with an emphasis on the prehospital setting according to an interactive voice response system and assessments in-hospital performed up to and including the day of discharge or day 4, whichever occurs first. An Executive and Steering Committee is responsible for the overall conduct of the trial and will have full access to the database after concluding the trial. The results will be analyzed independently by the Executive Committee in a manner consistent with prior ASSENT studies and VIGOUR group procedures.[19] The study will be monitored by an independent Data and Safety Monitoring Board (DSMB) who will review safety data regularly provided by the Leuven safety group. An Operations Committee responsible for all operational issues on a daily basis and including clinical monitors and data management staff will interact closely with the study Chairman and Executive Committee. The study is international in scope and includes the

Table III. Definitions

Term	Definition
Cardiogenic shock	Defined as one of the following: - Systolic blood pressure <90 mm Hg for at least 30 min (or the need for supportive measures to maintain a systolic blood pressure of >90 mm Hg) in the presence of a heart rate of >60 beat/min in association with signs of end-organ hypoperfusion (cold extremities, low urinary output <30 mL/h and/or mental confusion). - A cardiac index <2.21 L/(min m^2) in the presence of a PWCP of >15 mm Hg.

Reinfarction	In the first 18 h after randomization, *reinfarction* is defined as recurrent signs and symptoms of ischemia at rest, accompanied by new or recurrent ST-segment elevations of ≥ 0.1 mV in at least 2 contiguous leads lasting ≥30 min
	After 18 h, reinfarction is defined as follows:
	- New Q waves (by Minnesota Code Criteria) in 2 or more leads and/or enzyme/biochemical evidence of reinfarction: reelevation of CK-MB or troponin to greater than the upper limit of normal and increased by ≥50% over the previous value
	- If CK-MB or troponin is not available, the total CK will be evaluated
	  - The total CK must either be reevaluated to ≥2 times the upper limit of normal and increased by ≥25% or be reelevated to ≥200 U/mL over the previous value
	  - If reelevated to <2 times the upper limit of normal, the total CK must exceed the upper limit of normal by ≥50% and exceed the previous value by 2-fold or be reelevated to ≥200 U/mL
	Reinfarction after PCI is defined as:
	- CK-MB or (CK, if MB is not available) >3 times the upper limit of normal and ≥50% greater than the previous value and/or new Q waves (Minnesota Code) in 2 or more contiguous leads
	Reinfarction after CABG surgery is defined as:
	- CK-MB (or CK, if MB is not available) >5 times the upper limit of normal and ≥50% greater than the previous value and/or new Q waves (Minnesota Code) in 2 or more contiguous leads

Aborted MI	Combination of chest pain and transient ECG changes (≥50% ST resolution) suggesting transmural ischemia, and CK/CK-MB levels ≤2 times the upper limit of normal and/or troponin I/T levels corresponding to this CK/CK-MB metric within 24 h after randomization
Major bleeds	*Severe bleed*—a bleed that leads to a hemodynamic compromise requiring intervention (eg, blood or fluid replacement, inotropic support, ventricular assist device, surgical repair), or life-threatening or fatal bleeds. *Moderate bleed*—bleeding requiring transfusion of blood but that does not lead to hemodynamic compromise requiring intervention.

PWCP, Pulmonary capillary wedge pressure; *CK*, creatine kinase.

following countries: Austria, Belgium, Brazil, Canada, France, Germany, Italy, Norway, Poland, Russia, Spain, and the United Kingdom. Additional countries are expected to join the trial.

Discussion

Since the Strategic Reperfusion Early After Myocardial Infarction (STREAM) protocol was designed in 2007 and commenced in 2008, the care of patients with STEMI has continued to evolve. Despite multiple attempts at facilitation with full-dose fibrinolysis or combination therapy, this approach to reperfusion has not proven to be successful.[20,21] What has proven to be useful however is strategic cointervention with timely rescue of patients receiving fibrinolysis and coronary revascularization in appropriate candidates within the first 24 to 48 hours after therapy.[13,22] Despite concerted efforts in the United States and elsewhere, continuing delays in achieving timely primary PCI, especially among patients presenting outside of the minority of hospitals that have PCI capability, remain a difficult issue, with most patients failing to achieve the desired reperfusion times of 90 to 120 minutes after first medical contact.[23] Whereas, undoubtedly, patient risk and time from symptom onset play an important role in outcome, there is increasing evidence that early reperfusion with fibrinolysis in patients presenting within 3 hours of symptom onset is an attractive alternative to primary PCI.[13] Because current guidelines continue to reflect these therapies as alternative approaches and that "given the current literature it is not possible to say definitively that a particular reperfusion approach is superior for all patients in all clinical settings at all times of the day," the results when STREAM is complete should provide useful additional data on which to base informed therapeutic decisions.[1]

The trial entered its first patient on March 19, 2008, in France; and 3 amendments have been incorporated:

1) As compared with other clinical trials of STEMI, the initial STREAM ECG criteria were recognized as overly restrictive especially relating to inferior myocardial infarction. Hence, in consideration of the ECG entry criteria of CAPTIM, ASSENT-3/3+, EXTRACT, and TRANSFER-AMI, the Executive/Steering Committee decided to reduce the required ST elevation for inferior myocardial infarctions to at least 2 mm in 2 contiguous inferior leads and/or a maximum combined total of ≥ 4-mm ST elevation.[24]
2) The second amendment relates to a reduction in the dose of tenecteplase in patients ≥75 years of age randomized to treatment group A. This modification was recommended by the Executive Committee in conjunction with the Chair of the DSMB because the initial rate of intracranial hemorrhage (ICH) observed in elderly patients was higher than expected. Because this represented a very small number of cases and the overall number of elderly patients was modest, coupled with the fact that one or more entry criteria and/or trial procedures were violated in some of these cases, the Executive Committee nonetheless decided to reduce the dose of tenecteplase to half the usual dose for these patients for whom there was already provision for omission of the 30-mg IV bolus and a lower dose of clopidogrel (75 vs 300 mg). This dose

reduction is supported by a treatment paradigm developed by Henry et al[25] and Larson et al[26] who have studied >100 patients who were >75 years old and confirmed a low rate of ICH and good clinical outcomes';

3) Because approximately one half of STEMI patients are self transported and the majority present to community hospitals, thereby requiring transfer for PCI, the contemporary delays to reperfusion therapy cannot all be addressed in the prehospital setting.[27] Accordingly, randomization was extended to patients presenting to community hospitals provided there is access to PCI facilities in a developed hub-and-spoke relationship to ensure timely urgent rescue coronary intervention if required.

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Disclosures

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Appendix

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