INTRODUCTION

At the most severe end of the spectrum of acute coronary syndromes is ST-segment elevation myocardial infarction (STEMI), which usually occurs when a fibrin-rich thrombus completely occludes an epicardial coronary artery. The diagnosis of STEMI is based on clinical characteristics and persistent ST-segment elevation as demonstrated by 12-lead electrocardiography. Patients with STEMI should undergo rapid assessment for reperfusion therapy, and a reperfusion strategy should be implemented promptly after the patient's contact with the health care system. Two methods are currently available for establishing timely coronary reperfusion: primary percutaneous coronary intervention and fibrinolytic therapy. Percutaneous coronary intervention is the preferred method but is not always available. Antiplatelet agents and anticoagulants are critical adjuncts to reperfusion. This article summarizes the current evidence-based guidelines for the diagnosis and management of STEMI. This summary is followed by a brief discussion of the role of noninvasive stress testing in the assessment of patients with acute coronary syndrome and their selection for coronary revascularization.

Unlike unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI), ST-segment elevation myocardial infarction (STEMI) is characterized by total occlusion of the infarct-related artery. Evidence from several randomized clinical trials during the past 2 decades has established the importance of the open artery theory, which states that prompt and complete restoration of flow in the occluded artery decreases infarct size, preserves left ventricular (LV) function, and improves survival rates. Two types of strategies are currently available for the judicious establishment of coronary reperfusion: pharmacological (fibrinolysis) and mechanical (primary percutaneous coronary intervention [PCI]). Regardless of the mode of reperfusion, the overarching concept is to minimize total ischemic time, which is defined as the time from the onset of symptoms of STEMI to the initiation of reperfusion therapy.

REPERFUSION THERAPY

Fibrinolysis

An overview of the results of 9 trials by the Fibrinolytic Therapy Trialists’ Collaborative Group comparing the outcomes of patients undergoing fibrinolytic therapy and those of controls demonstrated statistically significant absolute reductions in 35-day mortality rates of approximately 30 per 1000 for patients who arrived at the hospital within 6 hours of the onset of symptoms and of approximately 20 per 1000 for patients who arrived 7 to 12 hours after the onset of symptoms. Benefit was observed among patients with ST-segment elevation or left bundle branch block (LBBB) at the time of presentation, irrespective of age, sex, blood pressure, heart rate, or a history of myocardial infarction (MI) or diabetes. The greatest benefit was observed among patients with LBBB or anterior STEMI.

Fibrinolytic therapy is currently indicated, in the absence of contraindications (for patients with STEMI who have experienced symptom onset within the previous 12 hours and in whom electrocardiography (ECG) demonstrates ST-segment elevation of more than 0.1 mV in at least 2 contiguous precordial leads or at least 2 adjacent limb leads, or new or presumably new LBBB). The fibrinolytic agents currently approved for treating patients with STEMI include streptokinase, alteplase, reteplase, and tenecteplase. The TIMI (Thrombolysis in Myocardial Infarction), phase 1 trial randomly assigned 290 patients with evolving acute MI to alteplase (the first tissue plasminogen activator to be produced through recombinant DNA technology) or to streptokinase. Alteplase was far superior in achieving coronary reperfusion; twice as many occluded infarct-related arteries opened after 90 minutes with alteplase than with streptokinase. The Tenecteplase therapy was assessed in the ASSENT (Assessment of the Safety of a New Thrombolytic)-2 trial, which randomly assigned 16,949 patients to weight-based single-bolus tenecteplase or to accelerated alteplase infusion. The 30-day mortality rates were virtually identical; this outcome met the predefined criteria for equivalence. As a single-bolus agent, tenecteplase has become the most widely used fibrin-specific agent.

Primary PCI

A meta-analysis of 23 randomized clinical trials that compared primary PCI with fibrinolytic therapy demonstrated that PCI was better than fibrinolysis in reducing the incidence of short-term and long-term adverse outcomes, including death. Although the clinical superiority of primary PCI is clear, the main challenge lies in the ability to implement such a strategy promptly (maintaining
2 hours of symptom onset, 30-day mortality was higher in the
patients randomised within rescue PCI if necessary, with PPCI in patients with STEMI (In followed by transfer to a centre with interventional facilities and fibrinolysis with primary PCI (PPCI). The trial compared PhT, CAPTIM is the only randomised trial comparing pre-hospital transfer patients
Comparing fibrinolysis and primary PCI: specific focus on PHT and IIa recommendation).

Time Since Onset of Symptoms. The effectiveness of both fibrinolytic therapy and primary PCI diminishes with the passage of time however, the ability of PCI to produce a patent infarct-related artery is much less time-dependent. Thus, PCI is generally preferred for patients who arrive at the hospital late after the onset of symptoms (>3 hours). In contrast, clinical trials have shown that early initiation of fibrinolytic therapy (within the first 2-3 hours after the onset of symptoms) may lead to outcomes that are similar to or better than those achieved with PCI.

Prehospital Fibrinolytic Therapy
A meta-analysis of 6 randomized trials comparing prehospital and in-hospital fibrinolytic therapy for acute MI showed that prehospital fibrinolysis significantly decreased all-cause hospital mortality rates (odds ratio, 0.83; 95% confidence interval, 0.70-0.98) The estimated time to fibrinolysis was 104 minutes for the prehospital group and 162 minutes for the in-hospital fibrinolysis group (P=.007).

The CAPTIM (Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction) trial directly compared the outcomes of 840 patients treated with prehospital fibrinolysis or primary PCI within 6 hours of the onset of STEMI. The results showed no significant difference in the incidence of the primary end point (a composite of death, nonfatal reinfarction, and nonfatal disabling stroke) at 30 days between the group treated with prehospital fibrinolysis (8.2%) and those treated with primary PCI (6.2%).

The ACC/AHA guidelines state that it is reasonable to initiate prehospital fibrinolytic therapy if a physician is present in the ambulance or if the emergency medical services system provides full-time paramedics who have the equipment necessary for performing and transmitting the results of 12-lead ECG (class Ilb recommendation).

Comparing fibrinolysis and primary PCI: specific focus on PHT and transfer patients

CAPTIM
CAPTIM is the only randomised trial comparing pre-hospital fibrinolysis with primary PCI (PPCI). The trial compared PHT, followed by transfer to a centre with interventional facilities and rescue PCI if necessary, with PPCI in patients with STEMI (In patients randomised within 2 hours of symptom onset, 30-day mortality was higher in the
PPCI group compared to the PHT group (5.7% vs. 2.2%, 95% CI 0.95 to 7.24; P=0.058); but this trend was reversed in the patients randomised after 2 hours of symptom onset (3.7% vs. 5.9%, 95% CI 0.25 to 1.61; P=0.47; P=0.039 for heterogeneity between early and late randomisation) (2). In the 5-year analysis, the results were similar, with a lower mortality in the group treated within 2 hours of symptom onset with fibrinolysis compared to primary angioplasty (5.8% vs. 11.1%, 95% CI 0.25 to 0.97; P=0.04). This benefit was not seen in the cohort treated after 2 hours (14.5% vs. 14.4%, 95% CI 0.59-1.75; P=0.92) (3).

DANAMI-2 and PRAGUE-2
Several trials addressed the question of the best option for reperfusion therapy in patients presenting at non-PCI hospitals, comparing immediate fibrinolysis with immediate angioplasty requiring transfer at a tertiary centre. The investigators concluded that transfer to a PCI centre is superior to fibrinolysis, providing that the transfer can be carried out in less than 2 hours (4).

The PRAGUE-2 trial enrolled 850 patients admitted to non-PCI centres. Mortality was not significantly different between patients who received fibrinolysis on site, compared with those transferred for PPCI, although there was a trend favouring PPCI (30-day mortality 6.8% vs. 10.0%, P=0.12). In patients randomised within 3 hours of symptom onset, mortality was comparable in the two groups (PPCI: 7.2%, fibrinolysis: 7.4%) (5).

PCI after fibrinolytic treatment
In spite of the disappointing results achieved in the late 1980s with angioplasty immediately following intravenous fibrinolysis, new attempts were made in the 2000s, because considerable progress had been made in both angioplasty techniques and in adjunctive antithrombotic therapy, and in particular the combined use of aspirin, thienopyridine therapy and intravenous glycoprotein IIb/IIIa inhibitors. These attempts were made in two directions: improving the efficacy of primary PCI by administering fibrinolytic treatment or GP IIb/IIIa inhibitors upfront of the interventional procedure (so-called “facilitated” PCI); or improving the result of fibrinolysis by performing subsequent PCI in all or selected patients.

Facilitated PCI
A number of randomised trials have compared primary PCI with PCI “facilitated” by either fibrinolytic treatment, GP IIb/IIIa inhibitors, or both. A meta-analysis published in 2006 showed that, though more patients assigned to facilitated PCI had initial TIMI 3 flow, there was no clinical benefit, compared with primary PCI (7). Recently, facilitated PCI was evaluated in two large randomised trials. The ASSENT-4 PCI trial (8) compared primary PCI with PCI immediately preceded by tenecteplase and was stopped prematurely because an excess of events was observed in the facilitated arm, and this despite the fact that more patients had an open infarct-related artery before the angioplasty procedure. Two factors may have explained these findings: first, concomitant antithrombotic therapy may have been insufficient.
in the tenecteplase arm of the trial, with the use of a low dose of heparin and minimal use of GP Ib/IIa inhibitors; second, PCI was performed soon after administration of fibrinolytic treatment (median time 104 minutes), at a time when platelet reactivity was still increased. Both factors may have played a role in the excess reinfarction rate observed in the facilitated arm. In the FINESSE trial, patients were randomised in a 1:1:1 fashion to primary PCI with in-lab abciximab, upfront abciximab-facilitated primary PCI, or half-dose reteplase/abciximab-facilitated PCI (9). The trial was stopped prematurely because of difficulties in recruiting patients. Median time from first bolus to balloon inflation was 90 minutes.

Although ST-segment resolution was more frequently observed in the combination facilitated PCI, no difference was found in the primary outcome of the trial (death, late ventricular fibrillation, cardiogenic shock or congestive heart failure at 90 days).

**RESCUE PCI**

Because intravenous fibrinolysis fails to restore arterial patency in a substantial proportion of patients, the potential benefit of early angioplasty in patients showing no signs of early reperfusion needed to be assessed. The REACT trial involved 427 patients treated with fibrinolysis in whom there was no sign of reperfusion (>50% resolution of ST segment elevation) at 90 minutes after the administration of fibrinolytic treatment. The patients were randomised to conservative management, repeat fibrinolysis, or emergency PCI. The primary endpoint (death, re-MI, stroke, hospitalisation for heart failure) was observed in 29.8% of the conservative arm, 31.0% of the repeated thrombolysis arm, and 15.3% of the rescue PCI arm (P<0.01). Death occurred in 6.2% of the rescue PCI patients, compared with 12.8% of the conservative management patients (P=0.12) (10).

**ROUTINE PCI AFTER LYSIS**

Moving one step further, several trials have addressed the potential benefit of routine (systematic) coronary angiography, with PCI when needed, following intravenous fibrinolysis. GRACIA-I included 500 patients, who were randomised to either “delayed” PCI (6-24 hours after fibrinolysis, mean 17 hours) or to an ischaemia-guided conservative approach (11). The systematic approach was associated with a reduction in mortality, reinfarction and revascularisation rates at one year (risk ratio 0.44; 95% confidence interval: 0.28-0.70), including favourable trends for mortality (P=0.07) and reinfarction. Similar results were achieved in the CAPITAL-AMI and SIAM-III trials (12,13).

The CARESS-in-AMI trial (14) included 600 patients and demonstrated that a strategy of immediate PCI was better than the standard of rescue-only angioplasty after fibrinolysis. In the non-systematic arm of the trial, 30% underwent rescue angioplasty, while 86% of the systematic arm received PCI. There was a significant and marked reduction in the primary endpoint of death, reinfarction, or refractory ischaemia at 30 days (10.7% vs. 4.4%, P=0.005). Favourable trends were observed for all individual endpoints. In this trial, the time delay from fibrinolysis to PCI was 135 minutes in the immediate angiography arm of the trial.

More recently, the Trial of Routine ANgioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI) trial enrolled 1,039 patients less than 12 hours after acute myocardial infarction who received fibrinolytic treatment and were randomly assigned to transfer for angioplasty within 6 hours or to a strategy limiting emergency angiography to rescue angioplasty, associated with elective angiography in those not needing rescue angioplasty. The results showed there was no difference in mortality between standard and pharmaco-invasive treatment (3.4% vs. 4.5%, 95% CI 0.71 to 2.36; P=0.39), but the composite primary endpoint of death, MI, or recurrent ischaemia, new or worsening congestive heart failure, or cardiogenic shock within 30 days, was strongly in favour of the pharmaco-invasive strategy (11.0% vs. 17.2%, 95% CI 0.47 to 0.87; P=0.004). At 6 months, there was no significant difference between the groups with regard to reinfarction and death or reinfarction (15).

The WEST study further strengthens the concept of a pharmaco-invasive approach, by suggesting that rapidly applied pharmacological reperfusion with follow-up (rescue and routine) PCI within 24 hours produces results equivalent to PPCI (14). The WEST study compared contemporary pharmacological therapy with or without routine or rescue PCI with primary PCI. All patients (n=304) with STEMI were given ASA and subcutaneous enoxaparin on study entry and then randomised to: group A – tenecteplase with conventional care; group B – tenecteplase followed by routine or rescue PCI within 24 hours; or group C – primary PCI with a 300 mg loading dose of clopidogrel.Abciximab was also recommended for patients undergoing any kind of PCI, providing it was not given within 3 hours of fibrinolysis. The primary endpoint, a composite of 30-day mortality, re-infarction, refractory ischaemia, congestive heart failure, cardiogenic shock and major ventricular arrhythmia, was similar in all three groups (25% vs. 24% vs. 23%, all non-significant). However, the rate of death and recurrent MI was 13% in group A vs. 4% in group C (P=0.021), and 6.7% in group B (P=0.378 when compared with group C). Death rates were 1% in both the B and C arms, versus 4% in group A (P=NS). The time from symptom onset to treatment was also calculated for patients randomised before hospital admission and in hospital, and was approximately one hour less for group C patients randomised before admission, indicating that coordinated networks, with pre-hospital diagnosis result in faster randomisation and ultimately earlier treatment and reperfusion (16).

Overall, these trials show that rapid coronary angiography after fibrinolysis results in improved clinical outcomes compared with fibrinolysis in isolation.

The REACT trial documented the benefit of rescue PCI in the absence of signs of reperfusion after fibrinolysis; the GRACIA-I, CAPITAL-AMI, SIAM-III, CARESS and TRANSFER-AMI trials showed that routine PCI was superior to rescue-only PCI, and the WEST trial showed that fibrinolysis foiled (16) owed by routine PCI within 24 hours yielded clinical results similar to those of
PPCI (11-16).

In-hospital mortality increased significantly with increasing door-to-balloon time, regardless of subgroup or the presence of risk factors. Overall, mortality increased from 3.0%, when door-to-balloon time was ≤90 minutes, to 7.4%, when door-to-balloon time was >150 minutes. Interestingly, mortality increased with increasing door-to-balloon times, whatever the symptom-onset-to-door times. A more recent analysis confirmed these findings and showed that any increase in door-to-balloon times will result in increased mortality, although the relation is not linear: for instance, reducing door-to-balloon time from 90 to 60 minutes will result in a 0.8% reduction in mortality, whereas a reduction in time from 60 to 30 minutes will result in a 0.5% reduction in mortality (20).

The influence of time to treatment was specifically assessed in 4,278 patients who were transferred for PPCI (18). Median total (first) door-to-balloon time was 180 minutes. Only 4.2% were treated within 90 minutes, and approximately 15% within 120 minutes.

Patients with longer door-to-balloon times were older, more often female, nonwhite and with more complex medical conditions. They also often presented much later after symptom onset or during weekends or off-hours. Finally, door-to-balloon times were longer when the annual case load of PPCI at the “receiving” hospital was less than 20.

Finally, a detailed analysis of the survival benefit associated with PPCI, compared with intravenous fibrinolysis was made in a population of 192,509 STEMI patients (19). The difference in time between use of fibrinolysis and PPCI was calculated by subtracting door-to-needle (DN) time from door-to-balloon (DB) time at a given hospital. Longer door-to-balloon minus door-to-needle times were associated with increased mortality and the time equipoise (i.e. the time beyond which the survival advantage of PPCI over fibrinolysis was lost) was calculated for the whole population and for different subgroups of patients (Fig. 2). Overall, the time equipoise was 114 minutes.

For every 30-minute increase in DB-DN time, in-hospital mortality increased by approximately 10% (OR 1.095; 95% CI 1.065 to 1.126, P<0.001). Patients <65 years lost the advantage of PPCI over fibrinolysis after just 71 minutes; ≥65-year-olds had an advantage up to 155 minutes. PPCI had a survival advantage up to 94 minutes in those presenting within 120 minutes of symptom onset, but this increased to 190 minutes in patients presenting after 120 minutes of symptom onset. In contrast, infarct location had less influence (time equipoise for anterior MI: 112 minutes, non-anterior MI: 115 minutes), but the importance of infarct location was greater in patients over 65 years of age (19).

USIC AND FAST-MI

Three registries were carried out in France, each 5 years apart, from 1995 to 2005. All three were based upon the same principle: a consecutive collection of data on all AMI patients admitted to ICUs within 48 hours of symptom onset, over a one-month period. 60% to 75% of all French ICUs participated.

In 1995, only 21% of STEMI patients getting reperfusion therapy were treated with primary PCI; 5-day mortality was 5.5% in the fibrinolysis group, versus 6.6% in the primary angioplasty group (21). Multivariate analyses showed that the type of reperfusion therapy was not correlated with early and one-year mortality. The percentage of patients treated with pre-hospital fibrinolysis was not known, and was probably low, because the use of pre-hospital fibrinolysis was not widespread in France at that time.

The USIC 2000 registry included 1,922 STEMI patients, of whom 49% received no reperfusion therapy. Of those with reperfusion therapy, 18% had pre-hospital fibrinolysis, 37% in-hospital fibrinolysis, and 44% primary PCI.

Patients without reperfusion therapy were older, and had a higher prevalence of cardiovascular history and most risk factors. Median time from symptom onset to hospital admission was 3.6 hours for PHT, 3.5 hours for IHT, 3.2 hours for PPCI, and 12 hours for no reperfusion therapy. In-hospital mortality was 3.3% for PHT, 8.0% for IHT, 6.7% for PPCI and 12.2% for no reperfusion therapy. At one year; survival was 94% for PHT, 89% for IHT and PPCI, and 70% for no reperfusion therapy. In a multivariate analysis of all patients, the relative risk of death with PHT was 0.49 (95% CI 0.24-1.00; P=0.05). When the patients without reperfusion therapy were excluded from the analysis, the RR of death was 0.52 for PHT (95% CI 0.25-1.08; P=0.08), compared with other modes of reperfusion therapy (either IHT or primary PCI) (22).

Of note, a high proportion of patients who received PHT underwent subsequent coronary angiography and angioplasty: 37% within 1 day and 67% during the initial hospital stay. Overall, patients treated with pre-hospital fibrinolysis were those with the best clinical outcomes, particularly when they were admitted within 3.5 hours of symptom onset (22).

A further analysis of the USIC 2000 data, looking at the difference on outcomes for patients who bypassed the emergency room (ER) compared with those who were admitted via the ER to a cardiac unit (CCU), showed that bypassing the ER was associated with more frequent use of any type of reperfusion therapy (61.7% vs. 53.1%; P=0.001) and a shorter time from symptom onset to admission (244 vs. 292 minutes; P<0.001) (22). Five-day mortality rates were lower in patients who were admitted directly to a CCU (4.9% vs. 8.6%; P=0.01), regardless of the type of reperfusion therapy used. After adjustment on the TIMI risk score, admission via the ER was still an independent predictor for mortality (OR 1.67, 95% CI 1.01-2.75). Follow-up at one year also showed that mortality was less in the group who were originally admitted directly to the CCU (11.5% vs. 15.6%; P<0.05), although admission via the ER was not an independent predictor of one-year mortality when adjusted for TIMI risk score (23). These findings emphasise the importance of choosing appropriate pathways in the management of STEMI patients.

The French Registry on Acute ST-Elevation Myocardial Infarction
(FAST-MI) compared the effects of PPCI with thrombolysis followed by routine angiography and PCI on outcomes (20). As with the previous ones, the survey was conducted over 1 month, at the end of 2005, and 223 centres in France included 1,714 STEMI patients. More than 60% of the patients received reperfusion treatment, with 33% getting PPCI, and 29% iv thrombolysis (18% PHT). Time from symptom onset to reperfusion treatment was significantly shorter in the group receiving iv thrombolysis (median time 130 minutes vs. 300 minutes in the PPCI group; 110 minutes for PHT, and 195 minutes for IHT). In patients who had directly called the emergency services (SAMU), the time from the first call to reperfusion therapy was 40 minutes for PHT vs. 130 minutes for PPCI and 85 minutes for IHT; hence, the PPCI-related time delay (onset-to-PPCI minus onset-to-prehospital fibrinolysis) was approximately 90 minutes over the time needed for administration of PHT. GP IIb/IIIa inhibitors were used more frequently within the first 48 hours of symptom onset in patients undergoing PPCI than in those receiving thrombolysis, and LMWH and clopidogrel also tended to be used less in thrombolysis patients. The use of statins, β-blockers and ACE inhibitors was similar in both groups. After thrombolysis, 96% of patients underwent coronary angiography, and 84% had subsequent PCI (58% within 24 hours), which represented a considerable increase, compared with what was observed in 2000. In-hospital mortality was 4.3% for thrombolysis (3.3% PHT; 6.1% IHT) and 5.0% for PPCI compared with 9.5% for those who received no reperfusion therapy. Thirty-day mortality was similar for PPCI and thrombolysis patients (4.5% vs. 4.4%, P=0.92) if therapy was initiated within 6 hours of symptom onset. After 6 hours, mortality increased with thrombolysis more than for PPCI (7.7% vs. 5.7%; P=0.58). One-year survival was 94% for thrombolysis (92% for IHT; 95% for PHT) and 92% for PPCI (P=0.31); after propensity score matching, one-year survival was 94% for thrombolysis and 93% for PPCI.

Overall, the results (in terms of early and one-year survival) of a pharmaco-invasive strategy, using intravenous fibrinolysis, followed by early coronary angiography and PCI compare favourably with those of primary PCI. The results of the FAST-MI registry also underline the importance of time in the selection of procedures (70% of the patients treated with fibrinolysis had treatment initiated within 3 hours of symptom onset) and suggest a benefit for back-up angiography and PCI in STE.