JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 2, NO. 10, 2009

ISSN 1936-8798/09/$36.00
PUBLISHED BY ELSEVIER INC.
DOI: 10.1016/j.jcin.2009.05.025

MINI-FOCUS ISSUE: SYSTEMS OF CARE FOR AMI
State-of-the-Art Paper

Systems of Care for ST-Segment Elevation Myocardial Infarction

Impact of Different Models on Clinical Outcomes

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ST-segment elevation myocardial infarction (STEMI) is one of the greatest medical emergencies, for which organization of care has a determinant impact on patient outcomes. The purpose of this paper is to review systems of care for STEMI patients. Although primary percutaneous coronary intervention (PCI) is the preferred option for patients with STEMI, offering easy and emergent access to this procedure often remains difficult because of geographic and diverse structural difficulties. intravenous fibrinolysis, especially when administered early after symptom onset and as part of a pharmacoinvasive strategy (i.e., followed by rapid coronary angiography with PCI when necessary), offers a reasonable therapeutic option in selected cases and has yielded satisfactory clinical results. Network organization is central for optimizing patient care at the acute stage of myocardial infarction. This review describes different clinical experiences with network implementation both in Europe and in North America. In all instances, early recognition of STEMI and, particularly in the pre-hospital setting, shortening time delays is central for the achievement of optimal clinical results. Overall, the encouraging results described in the models presented here, as diverse as they might be, should be an encouragement to promote and implement regional protocols according to the specific local constraints and to monitor their effectiveness by recording simple quality indicators in ongoing registries. (J Am Coll Cardiol Intv 2009; 2:901–8) © 2009 by the American College of Cardiology Foundation

Historical Perspective

Considerable progress has been made in the management of patients with ST-segment elevation myocardial infarction (STEMI) over the past 20 years. One major step forward has been the recognition of the pathogenic role of thrombus leading to prolonged occlusion of a coronary artery as the trigger of myocardial infarction (MI) (1). Hence, much emphasis has been put on reperfusion therapy, the role of which is to restore early coronary artery patency. The first methods of reperfusion were based on an invasive approach, and in the late 1970s, K. P. Rentrop was the first to perform an invasive reperfusion therapy with mechanical recanalization during a complication of coronary angiography; he subsequently added intracoronary fibrinolysis to mechanical recanalization, forming the basis for the intracoronary thrombolytic treatment of STEMI (2,3). The first trials of intracoronary streptokinase use in the 1980s showed a reduction in infarct size as well as a decrease in mortality (4). These trials led to the subsequent intravenous fibrinolysis trials, which were set up because emergency coronary angiography seemed highly impractical at that time (5,6). Later on, there was a first set of trials attempting to combine the best of both worlds by using intravenous fibrinolytics first, to gain time, followed by rapid coronary angioplasty;

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Manuscript received March 23, 2009; revised manuscript received May 18, 2009, accepted May 29, 2009.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 2, NO. 10, 2009
OCTOBER 2009:901–8

unfortunately, these attempts at a combined pharmacoinvasive strategy yielded poorer clinical results than intravenous fibrinolysis as a stand-alone treatment and were rapidly abandoned (7). In the 1990s, the concept of primary angioplasty (i.e., coronary angioplasty not preceded by intravenous fibrinolytic treatment) was developed, and randomized clinical trials consistently showed that this reperfusion technique was superior to intravenous fibrinolysis, making it the reference method of reperfusion at the acute stage of MI (8,9). Practical considerations remain, however, and we are still confronted with the necessity of finding a tailored approach for each patient and defining systems of care appropriate for all. The goal of the present article is to describe where we currently stand in that regard and what future directions might be taken to improve things further.

A Summary of Recent Randomized Controlled Trials Comparing Primary PCI and Intravenous Fibrinolysis

Abbreviations and Acronyms

DB = door-to-balloon
ECG = electrocardiogram
MICU = mobile intensive care unit
PCI = percutaneous coronary intervention
PPCI = primary PCI
SAMU = Service d'Aide Médicale Urgente
STEMI = ST-segment elevation myocardial infarction

Fibrinolytic therapy versus primary PCI. The results from randomized clinical trials have formed the basis of the current reperfusion practices and of international and national guidelines (10,11). Keeley et al. (8) performed a quantitative analysis of 23 trials and demonstrated that primary percutaneous coronary intervention (PPCI) compared with thrombolytic therapy in STEMI patients resulted in reduced mortality (7% vs. 9%, $p = 0.0002$), reinfarction (3% vs. 7%, $p < 0.0001$), stroke (1% vs. 2%, $p = 0.0004$), and the combined end point of death, reinfarction, and stroke (8% vs. 14%, $p < 0.0001$). Among these trials, the CAPTIM (Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction) trial was the only one to compare PPCI and pre-hospital thrombolytic therapy, and it was also the only one to find a trend toward reduced mortality at 30 days and 1 year with pre-hospital fibrinolysis compared with PPCI (12). Conversely, comparing PPCI with thrombolytic treatment in patients admitted to hospitals without PCI capability showed a clear advantage of the interventional technique (9). In particular, the DANAMI-2 (Danish Trial in Acute Myocardial Infarction-2) indicated that transferring a patient for PPCI (provided that the transfer took <2 h) was beneficial, particularly in terms of reinfarction, compared with treating with intravenous thrombolytic therapy in the primary hospital (13,14).

In all these trials, however, the use of coronary angiography and angioplasty in fibrinolytic-treated patients was limited to a minority, although there were large differences between trials: in CAPTIM, rescue PCI was performed in 26% of the patients receiving pre-hospital fibrinolysis, whereas in DANAMI-2, only 1.9% of patients had a rescue procedure; for any subsequent PCI during the hospital stay, the respective figures in the 2 trials were 34.5% and 16.4% (12,13).

PCI after fibrinolytic treatment. In spite of the disappointing results achieved with angioplasty after intravenous fibrinolysis in the late 1980s, new attempts were made in the 2000s, because considerable progress had been made with adjunctive antithrombotic therapy and, in particular, the combined use of aspirin and thienopyridine therapy and intravenous glycoprotein IIb/IIIa inhibitors. Those attempts were made in 2 directions: improving the efficacy of PPCI by administering fibrinolytic treatment or GP IIb/IIIa inhibitors en route to 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 randomized trials have compared PPCI with PCI "facilitated" by either fibrinolytic treatment or GP IIb/IIIa inhibitors or both. A meta-analysis published in 2006 showed that, although more patients assigned to facilitated PCI had initial Thrombolysis In Myocardial Infarction flow grade 3, there was no clinical benefit, compared with PPCI (15). Recently, facilitated PCI was evaluated in 2 large randomized trials. The ASSENT-4 (Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction) PCI trial compared PPCI with PCI immediately preceded by tenecteplase and was interrupted 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 (16). Two factors might have explained these findings: first, concomitant antithrombotic therapy might have been insufficient in the tenecteplase arm of the trial, with the use of a low dose of heparin and minimal use of GP IIb/IIIa inhibitors; and second, PCI was performed very soon after administration of fibrinolytic treatment, at a time when platelet reactivity was still increased. Both factors might have played a role in the excess reinfarction rate observed in the facilitated arm. In the FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial, patients were randomized in a 1:1:1 fashion to PPCI with in-lab abciximab, upfront abciximab-facilitated PPCI, or half-dose reteplase/abciximab-facilitated PCI (17). 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. Several trials addressed the question of the benefit of coronary angiography and PCI after fibrinolytic treatment. The REACT (Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis) trial showed that, in patients who had failed fibrinolytic therapy, rescue PCI was better than a conservative approach or repeated fibrinolysis (18).

Systematic PCI and timing of PCI after fibrinolysis. Furthermore, the role of systematic PCI within 24 h of fibrinolysis was investigated in the GRACIA-1 (Grupo de Analisis de la Cardiopatia Isquemica Aguda) trial (19), the CAPITAL-AMI (Combined Angioplasty and Pharmacological Intervention versus Thrombolysis Alone in Acute Myocardial Infarction) trial (20), the SIAM-III (Southwest German Interventional Study in Acute Myocardial Infarction) (21), and in the larger CARESS-in-AMI (Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction) trial (22). In all instances, a strategy of systematic PCI after intravenous fibrinolytic treatment yielded better results than conservative management. The CARESS-in-AMI trial (22) demonstrated that a strategy of immediate PCI was better than the standard of rescue-only angioplasty after fibrinolysis, with a significant and marked reduction in the primary end point of death, reinfarction, or refractory ischemia at 30 days (10.7% vs. 4.4%, $p = 0.005$). More recently, the TRANSFER-AMI (Trial of Routine ANgioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction) enrolled 1,030 patients <12 h after acute MI who received fibrinolytic treatment and were randomly assigned to transfer for angioplasty within 6 h or to a strategy limiting emergency angiography to rescue angioplasty, associated with elective angiography in those not needing rescue angioplasty. The primary results (23) showed there was no difference in mortality between the standard and pharmacoinvasive treatment (3.4% vs. 4.5%, $p = 0.39$), but the composite end point of death, MI, recurrent ischemia, new or worsening heart failure, or cardiogenic shock was strongly in favor of the pharmacoinvasive strategy (11.0% vs. 17.2%, $p = 0.004$).

The WEST (Which Early ST-segment elevation myocardial infarction Therapy) study (24) further strengthens this concept by suggesting that rapidly applied pharmacological reperfusion with follow-up (rescue and routine) PCI within 24 h produces results equivalent to PPCI.

The Importance of Time Delays

The success of reperfusion in STEMI is dependent on the time of administration. For all recent guidelines, including the American College of Cardiology/American Heart Association guidelines (25), time delays are central in the decision-making process. However, registry data show that the 30-min door-to-needle and 90-min door-to-balloon (DB) time goals are extremely difficult to achieve. In particular, DB times are often much longer in clinical practice than in randomized controlled trials, because transfer of patients for PCI, local factors (weather conditions, geographic location, staff initially involved, and so forth), or poor management strategies can lead to long delays (26). An analysis of the NRMI (National Registry of Myocardial Infarction) 3/4 data demonstrated that only 4.2% of patients undergoing PPCI achieve a DB time <90 min (27). Despite continued efforts, the most recent data from the GRACE (Global Registry of Acute Coronary Events) failed to document any meaningful improvement in time delays for reperfusion therapy between 2000 and 2005: the prehospital delay time was slightly longer in the latest time period (133 min during July 2005 to June 2006) compared with the earliest one (120 min during April 1999 to June 2000); times from admission to the hospital to PPCI or fibrinolysis decreased, however (from 99 to 80 min for PPCI and from 40 to 34 min for fibrinolysis) (26).

Time delays are also crucial to determine the best reperfusion strategy: the superiority of PPCI over fibrinolysis exists only as far as the time to reperfusion is not exceedingly increased by opting for PCI rather than the simpler approach of intravenous fibrinolysis.

From their review of the NRMI database, Pinto et al. (28) found that the equipoise between the 2 reperfusion techniques varied according to time from symptom onset, location of MI, and age of the patient. Primary PCI yielded better results than fibrinolysis when the excess time delay for delivering reperfusion therapy (PCI-related delay) did not exceed 114 min on average; however, the benefit of PCI was lost when the PCI-related delay was longer than 40 min for patients younger than 65 years of age with an anterior MI presenting within 2 h of symptom onset, whereas a PCI-related delay of 179 min still yielded equivalent results for both reperfusion techniques in patients over 65 years of age, with a nonanterior MI seen more than 2 h from symptom onset.

Organization of Care: Bringing Treatment to the Patient or Bringing the Patient to Treatment

The current challenge is therefore to organize care in order to optimize the implementation of early reperfusion therapy in patients developing STEMI, with a tailored approach for each patient. Two main directions can be used, depending on the local environment: either bringing the patient to treatment (i.e., bringing the patient in a timely manner to a catheterization laboratory where primary angiography will be performed), or bringing the treatment to the patient (i.e., administering intravenous fibrinolytic treatment in the prehospital setting). Both methods can be jointly used, as concomitant antithrombotic medications can be administered in the pre-hospital setting, en route to the catheterization laboratory. In the past few years, the results achieved

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 2, NO. 10, 2009
OCTOBER 2009:901–8

with several types of networks have been reported with satisfactory clinical results and emphasize that there is no unique way to deliver reperfusion therapy for STEMI patients.

The Vienna experience. In March 2003, an initiative with the goal of optimizing the organization of reperfusion strategies was started in the city of Vienna (29). The system organized a network of catheterization laboratories, with a central triage organization via the Viennese Ambulance System. An algorithm derived from the 2003 European guidelines recommended bringing the patient to a PCI-capable hospital as soon as possible, in conjunction with recommendations to initiate thrombolytic therapy, preferably before arrival at the hospital if PPCI could not be offered in a timely fashion, particularly in the case of patients with a duration of symptoms of <2 h. Concurrently, a prospective registry was established for control and quality assurance purposes. Results of the Vienna STEMI registry indicate that there was a shift in terms of the types of reperfusion therapy used from 2002 to 2004, with a decline in the use of fibrinolysis, and an increase in the use of PPCI. Importantly, the new organization resulted in a marked decrease in the proportion of patients who received no reperfusion therapy. However, even in this well-organized network system, a minority of patients who underwent PPCI had the procedure within 2 h from symptom onset; in contrast, 50% of those treated with fibrinolysis had treatment within 2 h. After thrombolytic therapy, 91% of patients overall underwent coronary angiography, 50% immediately, and 41% within 1 to 5 days of fibrinolysis. Overall, mortality rates for patients who did not receive reperfusion therapy were strikingly higher than in those patients who received PPCI or thrombolytic therapy (18.4% vs. 8.1% and 8.2%, respectively). In patients who were treated early (0 to 2 h from onset of pain), there was a slight advantage for thrombolytic therapy over PPCI (5.1% vs. 7.8%), whereas the mortality advantage favored PPCI if the delay was between 2 and 6 h (6.7% vs. 10.6%) or 6 and 12 h (12.5% vs. 28.6%).

The French experience with the Service d'Aide Médicale Urgente (SAMU) system. The SAMU is a nationwide system implemented slightly more than 20 years ago, with a unique nationwide call number. There is 1 SAMU medical response center for each French administrative region, which dispatches 1 of several mobile intensive care units (MICUs) that can provide critical care in the field and during transport. By French law, each MICU team must include a physician, usually an anesthesiologist or emergency physician, a nurse, and a driver trained as an emergency medical technician. Management on scene by the MICU team and precise notification to the medical center of the patient status allow direct admission to the most appropriate setting.

The FAST-MI (French registry of Acute ST-segment elevation or non–ST-segment elevation Myocardial Infarction) evaluated all patients hospitalized for acute MI in an intensive care unit in France; approximately 60% of all French hospitals participated (30). For patients seen within 12 h of symptom onset, first medical contact was through SAMU in approximately 40% of the cases, whereas 30% of the patients initially called their general practitioner, and 15% of patients went directly to the emergency room. However, the proportion of patients transported by the SAMU was nearly two-thirds, because in many instances the SAMU was called by the first medical party involved. In terms of reperfusion strategies, 21% of patients received pre-hospital fibrinolysis, 11% received in-hospital fibrinolysis, 38% underwent PPCI, and 30% received no reperfusion therapy. The use and type of reperfusion therapy were dependent on the use of the SAMU system. All patients receiving pre-hospital thrombolytic therapy had been transported by the SAMU. Of patients having called the SAMU initially, 18% had no reperfusion therapy; in contrast, when the first medical contact was not the SAMU, 36% received no reperfusion therapy (The FAST-MI Registry, unpublished data, July 2009) (Fig. 1). Median time from first call to reperfusion was 45 min for pre-hospital lysis and 166 min for PPCI; even in patients who called the SAMU directly, median time from call to PPCI was 130 min. Because the average time for the SAMU to reach the patients after being called is on the order of 20 to 25 min, median time to PPCI after the first electrocardiogram (ECG) is still long (100 to 110 min), whereas time to initiation of fibrinolytic treatment is much shorter (20 to 25 min), thanks to the use of pre-hospital fibrinolysis.

It was also observed that the number of parties involved before hospital admission was a determinant of both time to

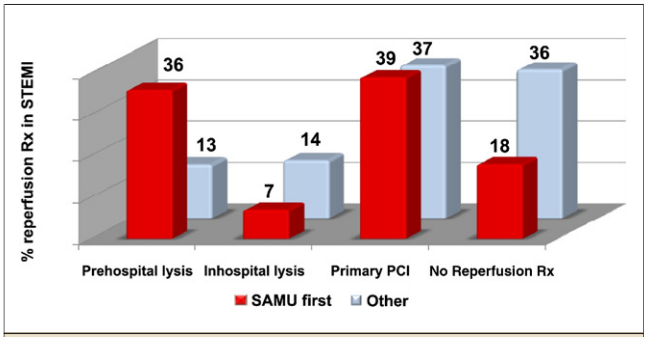

Figure 1. Use of Reperfusion Therapy According to Initial Pathway in the FAST-MI Registry

Patients having called the Service d'Aide Médicale Urgente (SAMU) directly had a higher rate of pre-hospital fibrinolysis, and fewer had no reperfusion therapy. FAST-MI = French registry of Acute ST-segment elevation or non–ST-segment elevation Myocardial Infarction; PCI = percutaneous coronary intervention; Rx = therapy; STEMI = ST-segment elevation myocardial infarction.

Table 1. Impact on Time Delays and 30-Day Mortality of the Number of Medical Parties Involved Before Hospital Admission in the French FAST-MI Registry

	0 or 1 Party	2 Parties	≥3 Parties
Median time from first call to reperfusion (range)	100 (50–170)	122 (60–201)	155 (80–270)
30-day mortality	5.5%	7.1%	12.1%

FAST-MI = French registry of Acute ST-segment elevation or non–ST-segment elevation Myocardial Infarction.

reperfusion and clinical outcomes (Table 1) (The FAST-MI Registry, unpublished data, July 2009).

When PPCI is not performed, the most widely used strategy in France is a pharmaco-invasive approach, with 96% of patients undergoing coronary angiography after intravenous fibrinolysis (31). Approximately 85% of patients undergo subsequent PCI (87% after pre-hospital fibrinolysis), and 58% of these patients undergo PCI within 24 h of the administration of fibrinolysis. In-hospital mortality was 4.3% for fibrinolysis and 5.0% for PPCI. In patients receiving fibrinolysis, 30-day mortality was 9.2% when PCI was not used and 3.9% when PCI was subsequently performed. Overall, no difference was observed according to the time lag between administration of fibrinolysis and PCI; however, these seemingly uniform outcomes result from opposite trends: in patients in whom PCI is performed as a systematic policy, mortality is lower when PCI is performed after the first hours, whereas in patients in whom PCI is indicated because of persisting or recurring symptoms (rescue PCI), mortality is higher when PCI is performed after a longer time lag.

One-year survival was 94% for fibrinolysis and 92% for PPCI ($p = 0.31$); after propensity score matching, 1-year survival was 94% and 93%, respectively. These results confirm that, in selected patients presenting early after symptom onset, fibrinolytic treatment followed by systematic angiography and—when needed—PCI is a true alternative to PPCI.

The satisfactory results of pre-hospital fibrinolysis when used in a timely fashion in physician-staffed ambulances are confirmed by the German data from the PREMIR (Prehospital Myocardial Infarction Registry), showing that in-hospital mortality was not different from that of PPCI (32). Likewise, the Israeli experience from the city of Haifa showed very favorable results with wide use of intravenous fibrinolysis followed by an aggressive policy of rescue PCI and early intervention (33): in this registry, 25% of the patients treated with fibrinolysis had rescue PCI, and 92% underwent coronary angiography during the same hospital stay, with 79% undergoing PCI. The 30-day mortality was 4.7%, and 1-year mortality was 6.7%. Of note, mortality was lower in the patients receiving fibrinolysis within 150 min of symptom onset and in those undergoing subsequent PCI. The same findings are reported from the Polish Wielkopolska registry, in which thrombolytic treatment with tissue plasminogen activator followed by PCI in 26% of the patients provided results that compared to those of PPCI in patients with onset of chest pain <4 h (34).

Overall, the European experience suggests that a pharmacoinvasive strategy combining fibrinolysis followed by early coronary angiography (with PCI when deemed necessary) yields excellent clinical results and that, in selected patients, it can constitute an alternative to PPCI.

Recent experiences from North America. The organization of care in North America is confronted with the difficulty of dealing with the long distance that separates many patients from tertiary centers capable of providing "24/7" emergency interventions. Therefore transfer must be envisaged in such cases, and very encouraging results have been recently reported from regional systems set up to provide optimal care for STEMI patients, wherever the MI occurred. The Minnesota regional system of care (35) designed specific therapeutic protocols for patients with STEMI presenting to hospitals far from the main PCI center; patients presenting at hospitals within 60 miles of the tertiary center (zone 1) were directly transferred to the catheterization laboratory of the tertiary center; patients presenting at hospitals 60 to 210 miles from the tertiary center (zone 2) received one-half-dose tenecteplase en route to the PCI center. Personnel at the primary care hospitals were specially trained, and ECGs were faxed to the PCI center before transfer. In the case of inclement weather or other anticipated delays, patients from zone 1 received one-half-dose tenecteplase, and those from zone 2 received full-dose lytics. Thirty-day mortality was similar in patients presenting directly at the tertiary center (4.4%) and in those from zone 1 (4.7%) and zone 2 (5.2%).

A similar experience was reported with the Mayo Clinic STEMI protocol (36). A network was organized between a tertiary hospital with 24/7 PCI capability and primary care institutions located in a radius for which the maximum transfer time did not exceed 90 min. The primary reperfusion strategy at local hospitals was fibrinolysis (full dose) in patients presenting <3 h of symptom onset and PPCI in those presenting >3 h. For PPCI, the emergency department at the tertiary hospital was bypassed to avoid losing time; patients with fibrinolysis were evaluated by a cardiologist upon arrival, those without signs of reperfusion underwent immediate rescue PCI, and coronary angiography was performed on a systematic basis in all other patients 24 to 48 h later. In-hospital mortality was 6.6% in patients admitted directly to the tertiary center, 5.7% in those admitted to regional centers and treated with PPCI, and 3.1% in those admitted to regional centers and treated with fibrinolysis.

Similar efforts have been made in North Carolina and have led to marked reductions in times to reperfusion in

patients initially admitted to primary care hospitals; in spite of these improvements, however, no further reduction in early mortality, compared with historic control subjects, was observed in a recently reported series of 1,164 patients (37).

A recent review of 10 organizations of 72 hospitals geographically spread across the U.S. but sharing a common use of pre-hospital triage methods showed that DB times ≤90 min could be achieved in 86% of the patients with a pre-hospital STEMI diagnosis and that ECG-to-balloon times were ≤90 min in 68% of the patients (38).

Table 2. Specificities of 4 Different Systems of Care With Both PPCI and Pharmacoinvasive Strategies for STEMI Patients

Location (Ref. #)	Specificities
Vienna (29)	Citywide system of care. Unique call number. Physician-staffed ambulances sent on site. Direct dispatching to PCI hospital if estimated time to PCI <90 min or if time from symptom onset >2–3 h or if contraindication to fibrinolysis. Otherwise, fibrinolysis pre-hospital or at emergency room. Network of 1 academic and 4 other institutions with rotation during off-hours on weekdays (1 institution on-call/day); the system permits that only experienced interventional cardiologists operate while the institution is on-call.
France (SAMU) (31)	Nationwide system of care. Unique call number. One call-center/administrative region. Physician-staffed ambulance sent on site. Dispatching to nearest PCI-capable institution if expected time from contact to PCI <90 min or if contraindications. Otherwise, pre-hospital fibrinolysis (tenecteplase or reteplase) and admission to either nearest hospital or nearest hospital with PCI capability: 96% of patients treated with fibrinolysis undergo coronary angiography (75% within 24 h of administration of fibrinolysis).
Minneapolis (35)	Regional system of care (30 institutions, 1 PCI center; 210-mile radius). Diagnosis made at the emergency department of any of the participating hospitals. Single phone call to PCI hospital. 1. 11 hospitals <60 miles from PCI center: one-half-dose tenecteplase (if no contraindication). Direct transfer to cath lab (bypassing PCI center emergency department). 2. 19 hospitals 60–210 miles from PCI center: full-dose tenecteplase (if no contraindication). Direct transfer to cath lab (bypassing PCI center emergency department). 70% transported by helicopter; cardiac arrest in 2% during transfer.
Mayo Clinic (36)	Regional system of care (28 institutions, 1 PCI center; 150-mile radius). Diagnosis made at regional center. Single phone call to PCI hospital. 1. If symptoms <3 h: full-dose fibrinolysis, if no contraindication (reteplase or tenecteplase). Evaluation on admission at PCI center; if no reperfusion: rescue PCI, otherwise, systematic coronary angiography 24–48 h after admission. 2. If symptoms >3 h: PPCI. Direct transfer to cath lab (bypassing PCI center emergency department).

PPCI = primary percutaneous coronary intervention; SAMU = Service d'Aide Médicale Urgente; STEMI = ST-segment elevation myocardial infarction.

All systems of care had in common the fact that the catheterization laboratory could be activated by a single call from the initial emergency physicians in charge of the patients. In addition, all continuously monitored the clinical results achieved (Table 2).

Other organizational issues: place of admission, time of admission, time delays. Beyond the choice of the reperfusion strategy, STEMI networks allow better organization of the initial management of patients. Important factors leading to improved delivery of reperfusion therapy have been evidenced from a large survey of 365 institutions from the U.S. (39). These included direct activation of the catheterization laboratory by the emergency physicians, with a single call number to activate the catheterization laboratory; having staff arriving at the catheterization laboratory within 20 min after being paged; or having an attending cardiologist on site.

Pre-hospital diagnosis of STEMI leads to shortened times to reperfusion (40–42). Pre-hospital triage can be made either by physicians, as is the case in France with the SAMU physician-staffed emergency medical system, or with specially trained paramedics (42). Teletransmission of the ECG recorded in the field can be helpful to achieve a faster initial diagnosis and has been shown to reduce time to initiation of reperfusion therapy (43).

Protocols can be implemented to reduce the time between hospital admission and recording and interpretation of the first ECG (if that has not been done before hospital admission). Once the diagnosis is made, it is also essential to facilitate admission to the catheterization laboratory and to have staff at the catheterization laboratory available as quickly as possible. In the French experience, bypassing the emergency room was associated with higher rates of reperfusion therapy, reductions in time delays before initiation of reperfusion therapy, and improved survival (44).

Finally, special efforts are warranted for the organization of care for patients admitted "off-hours." The Get with the Guidelines Committee observed that there were fewer PPCI procedures and overall revascularizations and longer DB times in patients presenting off-hours (45). However, there was no difference in mortality in patients admitted on- versus off-hours, a finding that was confirmed in a large Swiss registry including 12,480 patients, one-half of whom were admitted off-hours (in-hospital mortality was 8.5% in patients admitted during routine working hours, and 8.8% in those admitted off-hours) (46).

Conclusions

PCI is central in the management of acute STEMI. Although, in optimal conditions, PPCI is the undisputed preferred therapeutic approach, organizational difficulties are numerous and have led to alternative reperfusion strat-

egies, among which the pharmacoinvasive approach is the most attractive.

Therefore, one of the key questions for policymakers is to decide whether to push for more local hospitals with PCI capability or to promote tertiary (quaternary?) centers with the use of a more pharmacoinvasive approach for those patients at a distance. Beyond cost issues (installation of catheterization laboratories in smaller hospitals supposes additional costs for both equipment and the medical/paramedical environment to run the laboratory), "spreading" 24/7 catheterization laboratories all over the country—many of which will have to treat only a few STEMI patients—is likely to result in less-than-optimal care for patients treated with PPCI overall. A recent analysis from the New York State PCI registry shows that early mortality (adjusted for the registry risk score) increased from 3.32% in hospitals with an annual volume ≥75 cases to 5.37% in institutions with an annual volume <25 cases, representing a 61% relative risk increase, potentially offsetting any possible benefit compared with an initial pharmacologic strategy (47). In the same analysis, individual physician volume was also an important determinant of outcome; in this respect, the organization of care in Vienna, with hospitals on-call during off-hours only 1 day/week, ensures that only senior, experienced operators will manage STEMI patients. The question of hospital and physician volumes of activity will be all the more crucial with the current decline in the incidence of STEMI (48).

Organization of networks on the basis of the use of both PPCI and pharmacoinvasive approaches should be the most efficacious strategy; most patients will be treated with PPCI in large institutions within reasonable time limits, whereas others—living farther away from PCI centers—will be treated with fibrinolysis first. In France, the pre-hospital, state-run system of care (SAMU) is the only structured system available, and the patients initially managed by the SAMU are dispatched to the most readily available facilities, whether state-run hospitals or private clinics; a regional health agency is in charge of the organization of the network for cardiac emergencies. In countries such as the U.S., the existence of competing hospital systems might constitute a barrier to the implementation of optimal systems of care for the population, because there might be more financial incentive within a hospital system to have institutions providing more costly technology—such as PCI—even if these do not constitute the best medical option. Ideally, public health agencies might be the solution for designing networks, harmonizing the activities of the existing hospital systems to provide the population the best possible system, making the best of the 2 options for reperfusion therapy (PPCI or pharmacoinvasive strategy) according to the time required for the patient to get to a (free and operational) catheterization laboratory. This would probably represent a major cultural change in the country of free enterprise.

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REFERENCES

1. DeWood MA, Spores J, Notske R, et al. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. N Engl J Med 1980;303:897–902.
2. Rentrop P, De Vivie ER, Karsch KR, Kreuzer H. Acute coronary occlusion with impending infarction as an angiographic complication relieved by a guide-wire recanalization. Clin Cardiol 1978;1:101–6.
3. Rentrop P, Blanke H, Karsch KR, et al. [Reopening of infarct-occluded vessel by transluminal recanalisation and intracoronary streptokinase application (author's transl)]. Dtsch Med Wochenschr 1979;104:1438–40.
4. Danchin N, Juilliere Y, Cherrier F. [Intracoronary thrombolysis and coronary angioplasty in the acute stage of infarction]. Rev Med Interne 1988;9:49–53.
5. Granger CB, White HD, Bates ER, Ohman EM, Califf RM. A pooled analysis of coronary arterial patency and left ventricular function after intravenous thrombolysis for acute myocardial infarction. Am J Cardiol 1994;74:1220–8.
6. Van de Werf F. Thrombolysis for acute myocardial infarction. Haemostasis 1994;24:65–8.
7. de Bono DP. What is the role of invasive intervention after coronary thrombolysis? Eur Heart J 1991;12 Suppl G:43–6.
8. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13–20.
9. Keeley EC, Grines CL. Should patients with acute myocardial infarction be transferred to a tertiary center for primary angioplasty or receive it at qualified hospitals in the community? The case for emergency transfer for primary percutaneous coronary intervention. Circulation 2005;112:3520–32, discussion 3533.
10. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of patients with acute myocardial infarction). J Am Coll Cardiol 2004;44:E1–211.
11. Van de Werf F, Bax J, Betriu A, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 2008;29:2909–45.
12. Bonnefoy E, Lapostolle F, Leizorovicz A, et al. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. Lancet 2002;360:825–9.
13. Andersen HR, Nielsen TT, Rasmussen K, et al. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. N Engl J Med 2003;349:733–42.
14. Busk M, Maeng M, Rasmussen K, et al. The Danish multicentre randomized study of fibrinolytic therapy vs. primary angioplasty in acute myocardial infarction (the DANAMI-2 trial): outcome after 3 years follow-up. Eur Heart J 2008;29:1259–66.
15. Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. Lancet 2006;367:579–88.
16. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) Investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention

in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. Lancet 2006;367:569–78.
17. Ellis SG, Tendera M, de Belder MA, et al. Facilitated PCI in patients with ST-elevation myocardial infarction. N Engl J Med 2008;358: 2205–17.
18. Gershlick AH, Stephens-Lloyd A, Hughes S, et al. Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. N Engl J Med 2005;353:2758–68.
19. Fernandez-Aviles F, Alonso JJ, Castro-Beiras A, et al. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. Lancet 2004; 364:1045–53.
20. Le May MR, Wells GA, Labinaz M, et al. Combined angioplasty and pharmacological intervention versus thrombolysis alone in acute myocardial infarction (CAPITAL AMI study). J Am Coll Cardiol 2005; 46:417–24.
21. Scheller B, Hennen B, Hammer B, et al. Beneficial effects of immediate stenting after thrombolysis in acute myocardial infarction. J Am Coll Cardiol 2003;42:634–41.
22. Di Mario C, Dudek D, Piscione F, et al. Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomised, multicentre trial. Lancet 2008;371:559–68.
23. Cantor WJ, Fitchett D, Borgundvaag B, et al. Routine early angioplasty after fibrinolysis for acute myocardial infarction. N Engl J Med 2009;360:2705–18.
24. Armstrong PW. A comparison of pharmacologic therapy with/without timely coronary intervention vs. primary percutaneous intervention early after ST-elevation myocardial infarction: the WEST (Which Early ST-elevation myocardial infarction Therapy) study. Eur Heart J 2006;27:1530–8.
25. Antman EM, Hand M, Armstrong PW, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2008;51:210–47.
26. Eagle KA, Nallamothu BK, Mehta RH, et al. Trends in acute reperfusion therapy for ST-segment elevation myocardial infarction from 1999 to 2006: we are getting better but we have got a long way to go. Eur Heart J 2008;29:609–17.
27. Nallamothu BK, Bates ER, Herrin J, Wang Y, Bradley EH, Krumholz HM. Times to treatment in transfer patients undergoing primary percutaneous coronary intervention in the United States: National Registry of Myocardial Infarction (NRMI)-3/4 analysis. Circulation 2005;111:761–7.
28. Pinto DS, Kirtane AJ, Nallamothu BK, et al. Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. Circulation 2006;114:2019–25.
29. Kalla K, Christ G, Karnik R, et al. Implementation of guidelines improves the standard of care: the Viennese registry on reperfusion strategies in ST-elevation myocardial infarction (Vienna STEMI registry). Circulation 2006;113:2398–405.
30. Cambou JP, Simon T, Mulak G, Bataille V, Danchin N. The French registry of Acute ST elevation or non-ST-elevation Myocardial Infarction (FAST-MI): study design and baseline characteristics. Arch Mal Coeur Vaiss 2007;100:524–34.
31. Danchin N, Coste P, Ferrieres J, et al. Comparison of thrombolysis followed by broad use of percutaneous coronary intervention with primary percutaneous coronary intervention for ST-segment-elevation acute myocardial infarction: data from the French registry on acute ST-elevation myocardial infarction (FAST-MI). Circulation 2008;118: 268–76.
32. Zeymer U, Arntz HR, Dirks B, et al. Reperfusion rate and inhospital mortality of patients with ST segment elevation myocardial infarction diagnosed already in the prehospital phase: results of the German Prehospital Myocardial Infarction Registry (PREMIR). Resuscitation 2009;80:402–6.
33. Jaffe R, Halon DA, Karkabi B, et al. Thrombolysis followed by early revascularization: an effective reperfusion strategy in real world patients with ST-elevation myocardial infarction. Cardiology 2007;107:329–36.
34. Grajek S, Lesiak M, Araszkiewicz A, et al. Short- and long-term mortality in patients with ST-elevation myocardial infarction treated with different therapeutic strategies. Results from WIelkopolska REgional 2002 Registry (WIRE Registry). Kardiol Pol 2008;66:154–63, discussion 164–5.
35. Henry TD, Sharkey SW, Burke MN, et al. A regional system to provide timely access to percutaneous coronary intervention for ST-elevation myocardial infarction. Circulation 2007;116:721–8.
36. Ting HH, Rihal CS, Gersh BJ, et al. Regional systems of care to optimize timeliness of reperfusion therapy for ST-elevation myocardial infarction: the Mayo Clinic STEMI Protocol. Circulation 2007;116: 729–36.
37. Jollis JG, Roettig ML, Aluko AO, et al. Implementation of a statewide system for coronary reperfusion for ST-segment elevation myocardial infarction. JAMA 2007;298:2371–80.
38. Rokos IC, French WJ, Koenig WJ, et al. Integration of pre-hospital electrocardiograms and ST-elevation myocardial infarction receiving center (SRC) networks: impact on door-to-balloon times across 10 independent regions. J Am Coll Cardiol Intv 2009;2:339–46.
39. Bradley EH, Herrin J, Wang Y, et al. Strategies for reducing the door-to-balloon time in acute myocardial infarction. N Engl J Med 2006;355:2308–20.
40. Terkelsen CJ, Lassen JF, Norgaard BL, et al. Reduction of treatment delay in patients with ST-elevation myocardial infarction: impact of pre-hospital diagnosis and direct referral to primary percutaneous coronary intervention. Eur Heart J 2005;26:770–7.
41. Bang A, Grip L, Herlitz J, et al. Lower mortality after prehospital recognition and treatment followed by fast tracking to coronary care compared with admittance via emergency department in patients with ST-elevation myocardial infarction. Int J Cardiol 2007 Nov 9 [E-pub ahead of print].
42. Le May MR, So DY, Dionne R, et al. A citywide protocol for primary PCI in ST-segment elevation myocardial infarction. N Engl J Med 2008;358:231–40.
43. Sejersten M, Sillesen M, Hansen PR, et al. Effect on treatment delay of prehospital teletransmission of 12-lead electrocardiogram to a cardiologist for immediate triage and direct referral of patients with ST-segment elevation acute myocardial infarction to primary percutaneous coronary intervention. Am J Cardiol 2008;101:941–6.
44. Steg PG, Cambou JP, Goldstein P, et al. Bypassing the emergency room reduces delays and mortality in ST elevation myocardial infarction: the USIC 2000 registry. Heart 2006;92:1378–83.
45. Jneid H, Fonarow GC, Cannon CP, et al. Impact of time of presentation on the care and outcomes of acute myocardial infarction. Circulation 2008;117:2502–9.
46. Berger A, Stauffer JC, Radovanovic D, Urban P, Bertel O, Erne P. Comparison of in-hospital mortality for acute myocardial infarction in Switzerland with admission during routine duty hours versus admission during out of hours (insight into the AMIS plus registry). Am J Cardiol 2008;101:422–7.
47. Srinivas VS, Hailpern SM, Koss E, Monrad ES, Alderman MH. Effect of physician volume on the relationship between hospital volume and mortality during primary angioplasty. J Am Coll Cardiol 2009;53: 574–9.
48. Myerson M, Coady S, Taylor H, Rosamond WD, Goff DC Jr. Declining severity of myocardial infarction from 1987 to 2002: the Atherosclerosis Risk in Communities (ARIC) study. Circulation 2009; 119:503–14.

Key Words: PCI ■ reperfusion ■ STEMI.