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VIEWPOINT AND COMMENTARY

ST-Segment Elevation Myocardial Infarction: Recommendations on Triage of Patients to Heart Attack Centers

Is it Time for a National Policy for the Treatment of ST-Segment Elevation Myocardial Infarction?

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Despite substantial progress in the diagnosis and treatment of acute ST-segment elevation myocardial infarction (STEMI), implementation of this knowledge into routine clinical practice has been variable. It has become increasing clear that primary percutaneous coronary intervention (PCI) is the preferred method of reperfusion if it can be performed in a timely manner. Recent European data suggest that transfer for direct PCI may also be preferable to fibrinolytic therapy. We believe it is time to establish a national policy for treatment of patients with STEMI to develop a coordinated system of care similar to that of the level 1 trauma system. (J Am Coll Cardiol 2006;47:1339–45) © 2006 by the American College of Cardiology Foundation

Knowing is not enough, we must apply. Willing is not enough, we must do.

—Goethe (1)

In the past 20 years, substantial progress has been made in the diagnosis and treatment of acute ST-segment elevation myocardial infarction (STEMI) (2). The results from randomized clinical trials indicate that the 30-day mortality has decreased from 25% to 30% to 4% to 6%. Advances in reperfusion therapy, in particular both primary and postlytic percutaneous coronary intervention (PCI), have contributed to a decrease in mortality and reinfarction rates. The integration of these data into routine clinical practice, however, has been variable (3). Both fibrinolytic therapy and PCI may result in successful reperfusion of the infarct-related artery and lead to a decrease in morbidity and mortality. It has become increasingly clear, however, that primary PCI is a superior treatment strategy if it can be performed in a timely manner by an experienced team (4–6). Data also indicate that outcomes of patients with STEMI are superior when they are managed by a cardiovascular specialist and in high-volume cardiac centers (7–11). In this regard, treatment of STEMI has many similarities to trauma. Definitive treatment of trauma victims in the U.S. has been concentrated in trauma centers with clear triage and treatment guidelines, leading to improved outcomes (12,13). With this in mind, is it time to establish national or state policies with a coordinated system for the treatment of STEMI? Should we adopt a policy of primary PCI in centers with cardiac catheterization laboratories as well as in centers within easy transfer distance? What criteria should these heart attack centers possess? Who should play a leadership role in developing the criteria?

THE IDEAL METHOD OF REPERFUSION

The advantage of fibrinolytic therapy is its widespread availability, ease of use, and rapid administration. The disadvantages include failure to open the infarct-related artery in 20% of patients and to provide complete reperfusion (Thrombolysis In Myocardial Infarction [TIMI] flow grade 2) in an additional 30%. Re-occlusion of the infarct-related artery occurs in up to 20% of patients when not followed by PCI, and the risk of intracranial hemorrhage is 1% to 2%, and substantially higher in the elderly. A wealth of data suggest that fibrinolytic therapy is underutilized in

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Abbreviations and Acronyms

NRMI-2 = Second National Registry of Myocardial Infarction
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction

the U.S. and relative contraindications are present in up to 40% of patients, which may temper its use (14).

The advantages of primary PCI are the high rate of reperfusion success, its limited contraindications, and the early risk stratification made possible by angiography. The primary PCI strategy also results in improved clinical outcomes, including reduced rates of recurrent ischemia and infarction, stroke, length of stay, and mortality (Fig. 1) (15). The disadvantages are the lack of ready availability and resources. Of the hospitals in the U.S., <25% have facilities to perform primary PCI, and even fewer have 24-h availability. The best outcomes are likely obtained in high-volume centers with high-volume operators. Approximately two-thirds of STEMI patients in the U.S. present to hospitals without catheterization laboratories, but the vast majority are within reasonable transfer times to a hospital with PCI available. In Minnesota, for example, 70% of hospitals without cardiac catheterization laboratories are located within a 90-min transfer time to a high-volume PCI center (16).

The European Society of Cardiology has recently indicated primary PCI (class I-A) as the recommended treatment for STEMI if performed by an experienced team <90 min after first medical contact (17). The current American College of Cardiology/American Heart Association (ACC/AHA) guidelines on STEMI recommend primary PCI as an alternative to fibrinolytic therapy if done in a timely fashion (90 min) by experienced providers (18). For patients in cardiogenic shock or with contraindications to fibrinolytic agents, both guidelines recommend primary PCI as the optimal reperfusion strategy (class I-B).

IMPLEMENTATION OF CLINICAL TRIAL RESULTS

Despite the large quantity of data in STEMI (~120,000 patients enrolled in randomized clinical trials), the widespread and consistent implementation of these randomized clinical trial results has been disappointing (19). A quote from The Institute of Medicine report *Crossing the Quality Chasm* summarizes the problem:

> Research on the quality of care reveals a health system that frequently falls short in its ability to translate knowledge into practice . . . care must be delivered by systems that are carefully and consciously designed to provide care that is safe, effective, patient centered, timely, efficient, and equitable . . . such systems must facilitate the applications of scientific knowledge to practice and provide clinicians with the tools and supports necessary to deliver evidence based care consistently and safely (20).

A number of studies have documented the delay in the adoption of therapies (for example, beta-blocker and aspirin) clearly shown to improve the outcome in STEMI (21,22). Likewise, data from the Second National Registry of Myocardial Infarction (NRMI-2) have shown that reperfusion therapy continues to be underutilized in the U.S., in particular in high-risk groups such as women and the elderly (14). There is substantial geographic variation in the treatment of STEMI that occurs within the same state and region, and the treatment of this life-threatening condition instead seems to be relegated to local clinical practice (23). In particular, it seems that treatment in rural settings is less likely to adhere to clinical guidelines than that in urban settings (16,24).

OUTCOMES IN SPECIALTY CENTERS

Data are available indicating that the outcome of STEMI patients is better when treated by cardiovascular specialists. For example, in-hospital, 30-day, and 1-year morality were significantly reduced in patients treated by cardiologists when compared with other physicians. Cardiologist-treated patients had higher utilization of cardiac procedures and medications associated with survival (7). Admission to

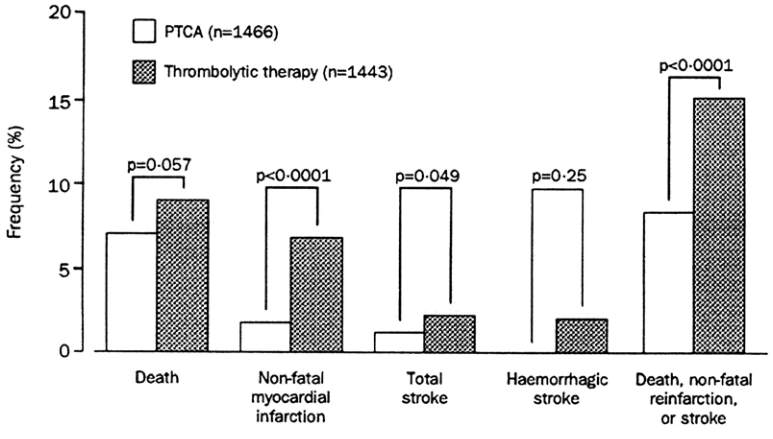

Figure 1. Trials comparing direct percutaneous coronary intervention with thrombolytic therapy show a significant reduction in events with primary percutaneous coronary intervention. PTCA = percutaneous transluminal coronary angioplasty. Reprinted, with permission, from Keeley et al. (15).

hospitals ranked high on a list of "America's Best Hospitals" was also associated with lower 30-day mortality in elderly patients with STEMI than admission to unranked hospitals (25). It has become increasingly clear as well that the results of PCI (both primary and elective procedures) are better in the hands of high-volume operators in high-volume centers. For example, mortality was lower in patients treated with primary PCI versus fibrinolytic agents at hospitals with intermediate (4.5% vs. 5.9%, $p < 0.001$) and high volumes (3.4% vs. 5.4%, $p < 0.001$). In contrast, in low-volume centers, mortality with primary PCI was similar to that with fibrinolytic agents (6.2% vs. 5.9%) (8). A retrospective study using data from the Cooperative Cardiovascular Project found that patients admitted to low-volume hospitals had a 17% higher mortality rate at 30 days than patients admitted directly to hospitals with more experience treating STEMI (9). Delays in door-to-balloon times are also more common in low-volume centers (<49 primary PCIs per year) (26). Although these studies are not randomized or of the best scientific methods, the results are overwhelmingly consistent showing that high-volume systematic approaches with these procedures yield the best outcome results.

SAFETY OF TRANSFER

Initial reports suggested excellent safety and potential benefits of transferring patients with STEMI for primary or rescue PCI from hospitals without the availability of a catheterization laboratory (27–29). Several recent randomized controlled trials further support the safety and effectiveness of transferring acute STEMI patients for primary PCI from community hospitals that do not have PCI capabilities.

RECENT CLINICAL TRIALS REGARDING TRANSFER

The first of these was the PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis (PRAGUE) study, a multicenter, randomized controlled trial designed to find the best reperfusion strategy in 300 patients with STEMI presenting to community hospitals without cardiac catheterization laboratories (30). The lowest rate of death, myocardial infarction, or stroke at 30 days occurred in patients transferred for primary PCI (8%) versus 15% in patients receiving streptokinase during transfer for facilitated PCI and 23% for patients treated with streptokinase without transfer. There were no deaths during transfers. The mean door-to-balloon (from the community hospital) time was 95 min in the primary PCI group versus 108 min in the fibrinolysis and transfer group. The PRAGUE-2 study was a larger nationwide trial in the Czech Republic comparing intravenous streptokinase versus transfer for primary PCI in patients ($n = 850$) with STEMI presenting to hospitals without PCI capabilities. The primary end point, 30-day mortality (intention to treat), was 10% in the streptokinase group compared with 6.8% in the PCI group ($p = 0.12$), and death/reinfarction/stroke at 30 days was 15.2% in the streptokinase group versus 8.4% in the PCI group ($p < 0.003$) (31). In particular, patients who presented >3 h after the onset of chest pain had significantly decreased mortality if transferred for primary PCI (15.3% streptokinase vs. 6.0% PCI; $p < 0.02$). There were five complications (1.2%) during transfer, including two deaths. Ventricular fibrillation developed in three patients, and they were successfully resuscitated.

The Danish Multicenter Randomized Study on Fibrinolytic Therapy versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI-2) was a Danish national, multicenter, randomized controlled trial comparing primary PCI with fibrinolysis for the treatment of STEMI (32). Participating in this trial were 24 referral hospitals (without angioplasty capability) and 5 invasive centers. The distance from the referral hospitals to the invasive centers ranged from 35 to 95 miles. The results showed an overall statistically significant reduction of the primary end point of death, reinfarction, and stroke at 30 days for patients treated with primary PCI (8.0% for primary PCI vs. 13.7% for fibrinolysis, $p < 0.001$). Most of the difference was the rate of reinfarction, which was much higher when patients received only thrombolytic agents, and few underwent subsequent angiography. Of the 1,572 patients enrolled, 1,129 (72%) presented initially to the referral hospitals and were randomized to fibrinolysis with front-loaded tissue plasminogen activator versus transfer for primary PCI without the fibrinolytic agent. The results favoring primary PCI were also evident in patients who presented initially to the referral hospitals (8.5% for transfer for primary PCI vs. 14.2% for fibrinolysis, $p = 0.002$). There were no deaths during transfer from the referral hospitals to the invasive centers.

A small, predominately U.S. multicenter randomized study, the Air Primary Angioplasty in Myocardial Infarction (Air-PAMI) study, also compared fibrinolysis with transfer for primary PCI (33). The mean distance from the referral hospitals to the PCI center was 32 ± 36 miles. There were no deaths or complications in any of the transferred patients. The mean door-to-balloon time in the group transferred for primary PCI was 174 ± 80 min, which is considerably longer than in the European trials. Despite these delays, there was a trend toward fewer major adverse cardiac events (death, reinfarction, or stoke) in the primary PCI group at 30 days (8.4% vs. 13.6%, $p = 0.33$).

A recent meta-analysis involving six randomized trials (3,750 patients) compared the strategy of transfer for primary PCI versus on-site thrombolysis. Transfer time was always <3 h. The combined end point of death, reinfarction, or stroke was reduced by 42% favoring the transfer for PCI strategy ($p < 0.001$) (Fig. 2) (34). In metropolitan areas, the expanded use of pre-hospital electrocardiograms may allow direct transfer to designated PCI hospitals and further decrease door-to-balloon times and improve outcomes (35,36).

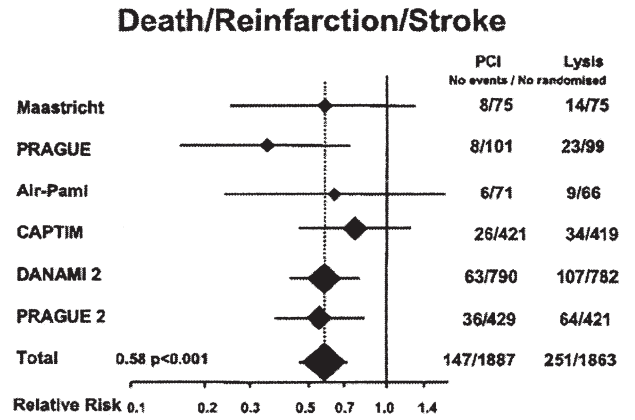

Figure 2. Meta-analysis of six randomized trials comparing transfer for primary percutaneous coronary intervention (PCI) versus on-site thrombolysis shows a significant reduction in the combined end point of death, reinfarction, or stroke favoring transfer for PCI. Reprinted, with permission, from Dalby et al. (34).

INFLUENCE OF TIME TO TREATMENT FOR PCI

Although the correlation of time to treatment and outcome with fibrinolytic therapy is clear, there are less consistent data regarding the importance of time to treatment with PCI (37). The largest observational study from the NRMI-2 showed that the in-hospital mortality did not increase significantly with increasing delay from symptom onset to PCI. However, mortality did increase if door-to-balloon times were >120 min (38). In an analysis from the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO-IIb) study, 30-day mortality rates of patients who underwent balloon inflation <60 min after study enrollment was 1%; 61 to 75 min, 3.7%; 76 to 90 min, 4.0%; and >91 min, 6.4% (39). In an analysis of the Zwolle PCI trials, there was a strong relationship between delay to PCI and outcomes in high-risk patients, whereas time had little influence on those at low risk (40). In a recent review of 10 randomized trials of PCI versus fibrinolysis (2,635 patients), there was an increase in major cardiac events associated with increased time to presentation after fibrinolysis but not with PCI (41). In this same review, the mortality benefit of PCI was especially apparent in those who presented >4 h after onset of symptoms (fibrinolysis, 12.1% vs. PCI, 4.7%). Currently, the bulk of data support that time delays, in particular 2 h and longer, affect outcomes in high-risk patients and that patients who present after 4 h do better with primary PCI.

ANALOGIES TO THE TRAUMA SYSTEM

To optimize treatment and meet the recommended door-to-balloon times of 90 min or less, there needs to be an efficient, coordinated system of regionalized cardiac care similar to the trauma system model. Such a system would encourage pre-arranged transfer agreements and protocols between the referring hospital and the PCI center.

The American College of Surgeons (ACS) has developed an organized system of regionalized trauma care to standardize and improve the care of critically injured trauma patients (42). This system is organized on a state level with oversight and standards developed by the ACS. Hospitals are accredited to level of service by the ACS. The level 1 centers are usually tertiary care centers with a commitment to research. The level 2 trauma hospital may be a community hospital that meets the standards of providing availability of appropriate physician specialties as well as diagnostic and other therapeutic resources. The level 3 facility may be a rural or suburban hospital where trauma patients will be initially stabilized and transferred to a level 1 or 2 trauma hospital using standardized transfer protocols and guidelines. An important component of the trauma system is the collection of outcome data in the form of a trauma registry (43). Such a system-wide approach has reduced preventable trauma-related deaths (13,44,45). Seventy percent of trauma deaths attributable to motor vehicle crashes occur in rural areas. One of the key components of the trauma system is to train and assist rural practitioners in the initial treatment and stabilization of injured patients with appropriate triage guidelines that facilitate rapid transfer to level 1 and 2 trauma centers.

Because more than 70% of U.S. hospitals do not have PCI capability, an analogous, integrated, organized system could be developed for the treatment of STEMI. The concept of the "golden hour" in trauma care is analogous to the "golden hour" and "time is muscle" concept of acute cardiac care.

Table 1. Criteria for Level 1 Heart Attack Center

24-h cardiac catheterization laboratory availability
24-h cardiovascular surgery availability
Comprehensive interventional cardiology and cardiovascular surgery services
>200 patients/yr (>36 STEMI) per hospital
>75 patients/yr per interventional cardiologist
Standardized protocols at referral and receiving hospitals
Transfer agreements in place
Education and training programs for transport, referral, and receiving hospital personnel
Quality assurance program

STEMI = ST-segment elevation myocardial infarction.

ACCREDITATION AND QUALITY ASSURANCE

Tables 1 and 2 outline the possible attributes of a STEMI center and consideration for transfer. Organizations such as the ACC and the AHA could help in the development of policies and standards of excellence. Although national standards would be established, state or regional bodies

Table 2. Criteria for Transfer of STEMI Patients

Expected door-to-balloon time ≤90 min for patients <3 h after onset of symptoms
Patients >3 h after onset of symptoms
Patients with cardiogenic shock or severe congestive heart failure
Patients with contraindications for thrombolytic therapy

STEMI = ST-segment elevation myocardial infarction.

would be responsible to ensure that they are implemented on a local level. This system should be inclusive rather than exclusive. All hospitals in a region would be encouraged to participate. Pre-hospital electrocardiograms obtained in the ambulance now allow a strategy of triage and transporting patients directly to hospitals with PCI capability. Unfortunately, only 50% of myocardial infarction patients are transported to the hospital by ambulance (46). Therefore, hospitals without PCI availability will also play a key role and will need to be part of the system as well. The activities of the regional cardiac system might include the following: 1) accreditation of hospitals, 2) development of triage and transfer guidelines, 3) facilitation of quality review, 4) promotion of educational activities.

Although this system is particularly important for STEMI, it may also be applied to other acute cardiovascular events such as stroke, aortic dissection, out-of-hospital cardiac arrest, and high-risk non-STEMI patients, in whom an early invasive approach seems warranted.

HIGH-RISK PATIENTS

At the present time, a number of high-risk patient groups already require transfer to hospitals with PCI or cardiovascular surgical capabilities. Patients in cardiogenic shock or those with contraindications to fibrinolytic agents would likely benefit from a more standardized approach than the patient-specific emergency transfer that occurs now.

FUTURE DIRECTIONS

There are a number of unresolved issues that will require further research to establish the optimal reperfusion strategy for some patient subsets. Transfer for direct PCI seems to be the best strategy for those patients who can be transferred within 90 min to a PCI center. The ideal regimen of adjunctive therapy (glycoprotein IIb/IIIa inhibitors, clopidogrel, reduced-dose fibrinolytic agents, and so on) needs to be better defined before any can be recommended. The ideal strategy for patients who present very early (<1 h) or >120 min from a PCI center is still unclear. Fibrinolytic therapy is very effective when used in the first hour of symptoms, and there may be no preferred approach when transfer times are 2 h or longer. Certain subsets of patients, such as those who present >4 h from symptom onset, those in cardiogenic shock, or elderly patients may benefit from transfer regardless, and a standardized system may improve outcomes. Another question to be addressed is whether patients treated with a fibrinolytic should be transferred for cardiac catheterization immediately or only for clinical signs of failed reperfusion for rescue PCI. The Southwest Germany Interventional Study in Acute Myocardial Infarction (SIAM III) has recently shown a significant reduction in a combined end point of death, reinfarction, and target vessel revascularization in STEMI patients receiving thrombolysis followed by immediate stenting compared with a conservative approach with delayed stenting, but this observation need confirmation in additional larger trials (47). There is evidence from many trials showing that early PCI reduces the rate of reinfarction and recurrent ischemia. Is there a role for pre-hospital fibrinolysis? Some of these questions may be answered as data become available from the large facilitated PCI studies that are currently underway.

A coordinated system will allow implementation of treatment guidelines specific for a state or region. In addition, this system would be better equipped to implement new advances in diagnosis and treatment.

SUMMARY

At the present time, the lack of a coordinated system of STEMI care in the U.S. denies patients the benefits of direct PCI, and too many eligible patients do not receive reperfusion therapy at all. Approximately 500,000 patients per year present with STEMI in U.S. hospitals (17). Based on available data, a coordinated system for direct PCI would prevent 6 to 8 events per 100 patients, affecting 35,000 patients per year (15,35). Additionally, a coordinated system may significantly reduce the number of "eligible but untreated" patients. Finally, the potential long-term health and economic benefits of a coordinated system related to preservation of left ventricular function with a subsequent reduction in congestive heart failure, decreased need for defibrillators, and so on, is difficult to quantify. In recent years there have been a number of investigators emphasizing the importance of regionalization of care and centers of excellence for acute coronary syndromes, but we still do not have a coordinated approach to patients with STEMI (48–50).

Clearly there are a number of obstacles to the development of a national STEMI policy that includes critical economic and political issues (51). The current reimbursement policy would penalize community and rural hospitals without cardiac catheterization laboratories when a patient is transferred directly from the emergency department to a PCI center. An adjustment in this reimbursement strategy would need to be addressed on a national level. Theoretically, establishing heart attack centers could make it less attractive for cardiologists to practice at the non-PCI centers. We do not believe this would be the case, and in fact, closer coordination with centers of excellence would enhance the overall cardiovascular care for community and rural hospitals as well as the centers of excellence. The current 911 system for pre-hospital care is well organized. In contrast, there is considerable variation in the inter-hospital transfer system. Current government regulations (Emergency Medical Treatment And Labor Act [EMTALA]) in fact may have the unintended consequence of delays in transfer. A key component of a national policy would be to coordinate the air and ground transport systems on a state-by-state level. Finally, current resources even at tertiary cardiovascular centers may be challenged in dealing with the volume of STEMI

patients. Many tertiary centers intermittently experience shortages of staff and bed capacity, and a national policy of direct PCI would require a significant commitment on the part of interventional cardiologists and technical staff for PCI hospitals. We believe these obstacles are not insurmountable and that care for STEMI patients in the U.S. would improve. Once a standardized system was in place for STEMI, the system could be utilized to handle other cardiac emergencies as well, including high-risk non-STEMI, aortic dissection, and out-of-hospital cardiac arrest.

CONCLUSIONS

We have made a dramatic improvement in reducing mortality in STEMI over the last three decades. Rapid reperfusion of an infarct-related artery leads to a decrease in morbidity and mortality. It is increasingly clear that primary PCI is the preferred approach, if performed in a timely manner by an experienced operator. Implementation of guidelines and improvements in clinical practice have been less than ideal. We believe it is time to establish a national policy with a coordinated system for the treatment of STEMI.

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