

Prehospital management of acute ST-elevation myocardial infarction: A time for reappraisal in North America

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Although the medical and technologic revolution in the last 3 decades has improved clinical outcome in patients sustaining acute ST-elevation myocardial infarction (STEMI), residual morbidity and mortality remain major health concerns. The critical roles of temporal delay and optimal sustained patency as modulators of successful reperfusion have been repeatedly demonstrated, and investigation into the ideal interface between pharmacologic and mechanical reperfusion continues. Despite physician awareness and patient education programs, time from symptom onset to treatment in STEMI remains stalled at approximately 3 hours for pharmacologic reperfusion, as documented in major clinical trials. Multifaceted improvements with advanced paramedic training, transmittable 12-lead electrocardiograms, and bolus fibrinolytics facilitate potential prehospital diagnosis and treatment. Thus, as we proceed into the 21st century, it is essential to reexamine strategies for addressing these and other issues relating to the process of delivering optimal care to most patients with STEMI. Especially notable are the opportunities provided through prehospital management with initiation of therapy, triage to appropriate hospitals, or both as major potential avenues to further enhance patient outcomes. We review past research in prehospital therapy for STEMI and practical impediments to implementation to establish a framework for interpretation of future developments. (*Am Heart J* 2003;145:1-8.)

Although the medical and technologic revolution in the last 3 decades has improved clinical outcome in patients sustaining acute ST-elevation myocardial infarction (STEMI), residual morbidity and mortality remain major health concerns. Pharmacologic development with the advent of agents capable of treating the putative thrombotic lesion with fibrinolysis and parallel advances in interventional cardiology ushered in the contemporary era of reperfusion. The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) trial established the "gold standard" pharmacologic reperfusion therapy, with accelerated tissue-type plasminogen activator (tPA) achieving a 1% mortality advantage compared with streptokinase at 30 days.¹ However, concerns with suboptimal patency, reocclusion, and failure of consistent myocardial perfusion at the tissue level remain.² The quest for an ideal fibrinolytic regimen has fueled the last decade of research into combinations of novel fibrinolytic, antithrombotic, and anti-

platelet agents, with >85,000 patients enrolled in 6 large-scale trials.³⁻⁸ Although some progress has been achieved, including ease of administration with bolus fibrinolytic agents (rPA [reteplase] and TNK-tPA [tenecteplase]^{3,4}) and improved safety profile (TNK-tPA⁴), none of the trials have demonstrated a reduction in mortality more than the "gold standard" therapy with rtPA (alteplase).

The critical role of temporal delay and optimal sustained patency as modulators of successful reperfusion have been repeatedly demonstrated, and investigation into the ideal interface between pharmacologic and mechanical reperfusion continues. Unfortunately, a growing body of evidence suggests that approximately one third of patients who are eligible for reperfusion therapies are inappropriately denied its life-saving benefits.⁹ Therefore, as we proceed into the 21st century, it is essential to reexamine strategies to address these and other issues relating to the process of delivering care to most patients with STEMI. Especially notable are the opportunities provided through prehospital management, with the initiation of therapy, triage to appropriate hospitals, or both as major potential mechanisms for further enhancing patient outcomes.

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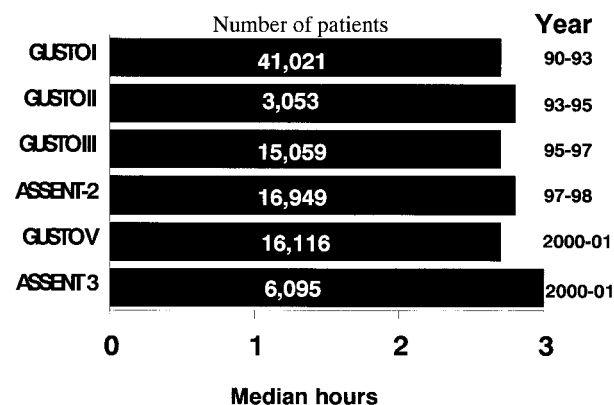
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The importance of time-to-treatment

Early fibrinolytic research identified a series of "lessons" that contemporary and future trials continue to

Figure 1

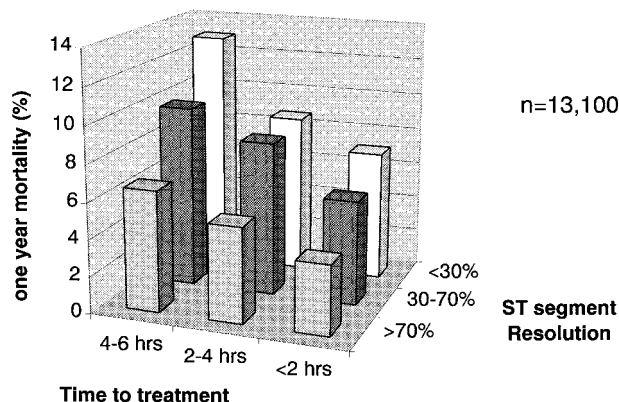


Median time to treatment in contemporary fibrinolytic trials.

replicate and refine. Of these, the importance of time-to-treatment in maximizing the benefit of reperfusion therapy is the most consistent. By means of the analysis of the 58,600 patients in the Fibrinolytic Therapy Trial, it was demonstrated that maximal effectiveness of fibrinolytic therapy is achieved when treatment was initiated within the first hour of symptom onset (65 lives saved/1000 treated patients), whereas the benefit is reduced by nearly 50% in the subsequent hour (37 lives saved/1000 treated patients).¹⁰ By means of retrospective analysis of the Seattle prehospital fibrinolysis trial (MITD),¹¹ further suggestion of the benefit of early reperfusion was provided when patients treated before 70 minutes had a 7-fold reduction in mortality rate compared with patients treated later (30-day unadjusted mortality rate, >70 minutes 8.7% vs <70 minutes 1.2%). Although these data have been recognized and communicated for more than a decade, time-to-treatment in major clinical STEMI trials remains stalled at approximately 3 hours after symptom onset (Figure 1).

A prospective electrocardiogram (ECG) substudy of 13,100 patients enrolled in the second Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT 2) trial has provided further insight into the interaction of temporal factors and effective reperfusion.¹² This trial clarified the independent relationship between 1-year mortality rate and ST-segment resolution on a 24- to 36-hour ECG (>70%, 30%-70%, and <30% ST-resolution results in mortality rates of 5.1%, 8.0%, and 9.7%, respectively) and also demonstrated the additional prognostic interaction of time-to-treatment and ST-segment resolution. Of patients treated in <2 hours after symptom onset, 55.6% had complete ST-segment resolution, compared with 52.1% of patients treated between 2 and 4 hours and 43% of pa-

Figure 2



Interaction of time, ST segment resolution, and mortality. Reproduced with permission from: Fu Y, Goodman S, Chang WC, et al. Time to treatment influences the impact of ST-segment resolution on one-year prognosis: insights from the assessment of the safety and efficacy of a new thrombolytic (ASSENT-2) trial. *Circulation* 2001;104:2653-9.

tients treated between 4 and 6 hours. Earlier therapy increased the chance of aborting STEMI (peak creatine kinase <2 \times upper limit of normal), thereby improving clinical outcomes, with subsequent mortality rates of 2.2% and 5.4% at 30 days and 1 year, respectively.¹³ Furthermore, the impact of time was consistent, regardless of the extent of ST-segment resolution, with the lowest mortality rate achieved in all subgroups with earlier treatment (Figure 2).¹²

The limited number of patients with STEMI in randomized trials of primary percutaneous coronary intervention (PCI) has hampered the assessment of time-to-treatment by means of this method of reperfusion. Available trial data demonstrate that both delayed symptom onset to randomization and randomization to first balloon inflation are associated with detrimental patient outcomes (Figure 3). Delayed time from symptom onset until randomization in the DANAMI trial (present European Society of Cardiology, 2002, www.danami-2.dk) was associated with an increased incidence of the composite primary end point (death, re-myocardial infarction, stroke) consistent with the more robust clinical experience with fibrinolytic therapy. Randomization 4 hours after symptom onset was associated with a >2-fold increased risk of adverse outcomes compared with randomization before 1.5 hours. Although potentially limited by confounding factors, adjusted analysis of the National Registry of Myocardial Infarction-2 (NRM-2) trial in >27,000 patients has bolstered this data, demonstrating a 41% to 62% increased mortality rate with delayed door-to-balloon time (121-

150 minutes, odds ratio [OR] 1.41, $P = .01$; 151-180 minutes, OR 1.62, $P < .001$; >180 minutes, OR 1.61, $P < .001$).¹⁴ Furthermore, the clinical benefit of PCI demonstrated in randomized trials has not been consistently replicated in real world settings, possibly because of the lack of operator experience and excessive delay in treatment, with a mean door-to-balloon time of 111 minutes compared with a door-to-drug time of 42 minutes with fibrinolysis.¹⁵ Although it has been a topic of considerable debate, the pathophysiologic evidence of an expanding wave of myocardial necrosis with time, coupled with available trial and registry data, consistently underscores the detrimental impact of treatment delay, regardless of whether pharmacologic or mechanical reperfusion is used.

Barriers for timely reperfusion therapy

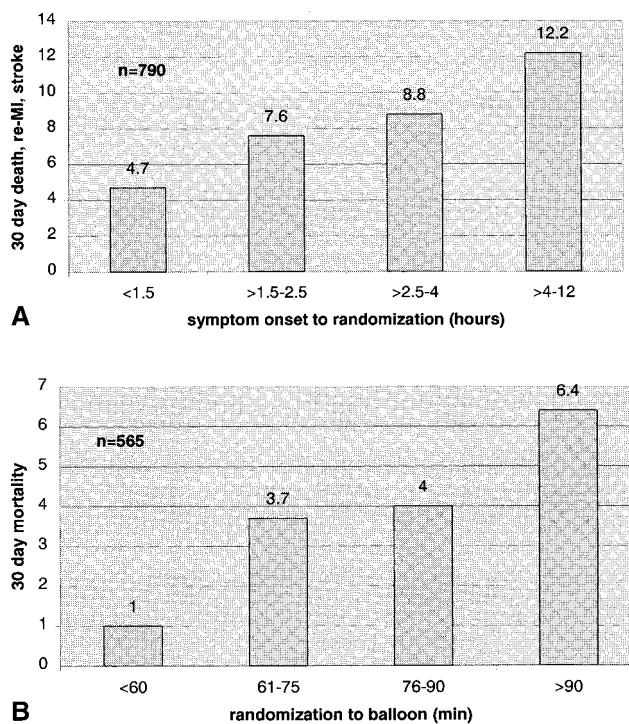
Patient delay in presentation

Recognizing that presentation delay remains a key impediment to timely therapy, it has been argued that community education programs would be effective in minimizing patient delay in seeking medical assistance. Such programs in Europe and the United States have demonstrated the capacity to reduce patient delay; however, the benefit was not sustained, and the cost effectiveness was questioned.^{16,17} As a means of further assessing this concept, a randomized trial matched control and intervention communities in the United States to a comprehensive education campaign using radio, television, print media, and seminars in an attempt to shorten patient time-to-presentation. At the end of 18 months, the intervention communities had a 20% increase in usage of Emergency Medical Services, but there was no reduction in the presentation delay in those patients suspected of sustaining an acute coronary syndrome.¹⁸ These disappointing results should not discourage ongoing patient and public education programs such as the recently developed National Heart Lung and Blood Institute and American Heart Association initiative “Act in Time to Heart Attack Signs” (www.nhlbi.nih.gov/actintime); however, the impact of such efforts on the time-to-treatment appears minimal to date, and they may require a different strategic intervention. An area deserving of further investigation relates to the choices patients make about the use of emergency medical services (EMS) versus self-presentation (walk ins) to the emergency department (ED). In particular, patients who self-present may be subject to delayed reperfusion.

Mechanisms to reduced in-hospital delay in reperfusion

Recognition of the importance of time-to-treatment in the management of STEMI has led to multiple initiatives to minimize in-hospital delay and maximize pa-

Figure 3



A, Temporal interaction of percutaneous coronary intervention and composite clinical events: relationship of symptom onset until randomization (modified from: DANAMI; www.danami-2.dk). **B**, Temporal interaction of percutaneous coronary intervention and mortality: relationship of randomization until angioplasty (GUSTO IIb). Reproduced with permission from: Berger PB, Ellis SG, Holmes DR Jr, et al. Relationship between delay in performing direct coronary angioplasty and early clinical outcome in patients with acute myocardial infarction: results from the global use of strategies to open occluded arteries in Acute Coronary Syndromes (GUSTO-IIb) trial. *Circulation* 1999;100:14-20.

tient benefit from reperfusion therapy. Focusing on the process of care delivery has the potential of achieving significant reductions in adverse events in a cost-effective manner, because it does not require elaborate, expensive technologies and resources. The pivotal first step was to empower emergency physicians with the capacity to administer fibrinolytic therapy, as opposed to awaiting assessment by a cardiologist or a transfer to a cardiac intensive care unit (CCU). Although this concept is taken for granted in the current era, it required a paradigm shift in management, with physician and nurse education and the capacity to appropriately monitor patients, treat complications of the disease, and use fibrinolytic therapy. The dissemination of chest pain centers that focus on protocol implementation with performance tracking to maximize appro-

ropriate therapy while minimizing inappropriate delays in treatment of STEMI has facilitated further advances. Attempts to minimize in-hospital delays have been partially effective, but crowded EDs, constrained resources, and a multitude of other practical issues have limited the consistency and sustainability of this intervention. Similar to the paradigm shift of reperfusion therapy from the CCU to the ED; in the 21st century, the concept of time-to-treatment on the basis of hospital arrival and traditional institutional boundaries needs to be redefined. This should embrace the opportunity for appropriate triage and effective therapy initiated before arrival at the hospital.

Overcoming the barriers: Revisiting prehospital management of ST-elevation myocardial infarction

Advances in the network of prehospital care in North America in the last 2 decades has been multifaceted, with improved technology, pharmaceuticals, paramedic training, and implementation of evidence-based care and investigation. Ambulance services initially provided transportation with minimal medical assistance, but as EMS providers matured, so did their capability to enhance patient care. Standard prehospital therapy of STEMI includes aggressive stabilization, management of potentially fatal complications, and timely transportation to a medical center capable of reperfusion therapy. The true potential of prehospital EMS care to the full spectrum of patients with acute coronary syndrome has not yet been fully realized.

Prehospital 12-lead electrocardiogram

Through improved mobile electrocardiographic equipment, the capability to obtain and transmit 12-lead ECGs allows for the potential prehospital diagnosis in patients who are reperfusion eligible. A number of studies have demonstrated the feasibility of paramedics acquiring 12-lead ECGs; this development has had minimal effect (ie, 1- to 7-minute delay) on scene-evaluation time.^{19,20} Small studies have shown that paramedics with or without computer assistance are capable of preliminary 12-lead ECG interpretation, with excellent sensitivity and specificity rates.^{21,22} Although limited by design and confounding variables, observational data from NRMI-2 demonstrated that prehospital ECG transmission reduces the time-to-treatment (door-to-fibrinolysis and door-to-balloon, 10 and 23 minutes, respectively) with an associated mortality benefit (adjusted OR 0.83).²³ To significantly enhance patient outcomes, this capability must be linked to a prehospital fibrinolysis program or a dedicated in-hospital response system so that the earlier diagnosis is associated with faster initiation of definitive therapy. Para-

doxically, the failure to achieve the expected primary benefit of prehospital fibrinolysis in the MITI trial may have related to the short in-hospital time-to-treatment (ie, time-to-treatment 20 minutes) facilitated by means of the prehospital acquisition and transmission of the 12-lead ECG in the control arm. The rapid in-hospital treatment in the MITI trial represents the best available data on the benefit of transmitted ECGs to a medical system geared to rapidly initiate therapy on patient arrival to hospital. Although acquisition of 12-lead ECGs is recommended as a standard of care (class I indication American Heart Association) and prehospital transmission appears to decrease the in-hospital time-to-treatment, the benefit of prehospital 12-lead ECGs without prehospital fibrinolysis has not been, but deserves to be rigorously studied.

Prehospital fibrinolysis

Before 1993, prehospital fibrinolysis was tested in numerous randomized trials, largely outside of North America, and it has been the standard of care in a number of European countries for as long as 17 years. A meta-analysis of the 6 randomized studies involving 6434 patients randomized to prehospital fibrinolysis versus in-hospital fibrinolysis demonstrated that the time-to-treatment was reduced by 58 minutes.²⁴ The reduction varied from 33 minutes in urban Seattle with transmitted 12-lead ECGs and aggressive in-hospital management to 130 minutes in a rural region in Scotland with limited prehospital care in the control arm.^{11,25} The overall 58-minute reduction in time was associated with a 17% relative risk reduction in mortality rate (1.7% absolute risk reduction) and was not associated with an increased risk of inappropriate therapy or compromise of patient safety.²⁴ These impressive results and the magnitude of incremental benefit are larger than those achieved for some therapies that have been widely accepted and implemented, such as the GUSTO-1 results evaluating tPA versus streptokinase. Despite this reality, the concept has not received significant acceptance or widespread implementation in North America.

Lack of North American implementation

Multiple factors have been cited in explaining the lack of widespread dissemination of prehospital fibrinolysis, including issues raised on the basis of earlier research design and applicability to North America. The largest study (5469 patients) was completed during a time when fibrinolysis was administered to patients with both ST elevation and ST depression, and therefore, the validity of these results has been questioned.²⁶ The remainder of the studies were modest in size, and all studies except 1 were completed outside

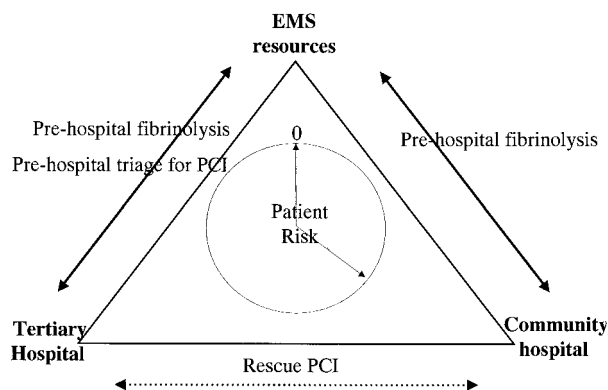
of North America, where a trained physician on scene interpreted the ECG and initiated fibrinolysis. Physicians and nurses do not routinely participate in pre-hospital care in North America, and although the ability of paramedics to administer fibrinolysis was successfully demonstrated in the MITI trial, the concept has not been broadly established or accepted. Although the availability of timely access to cardiac catheterization for PCI remains limited for most patients with STEMI, there has been an increasing use of this method of reperfusion in North America, especially in the United States.

The opportunities and potential benefit of prehospital care depend on multiple factors that vary within individual geographic regions depending on population density, distances to centers capable of pharmacologic or catheter-based reperfusion, paramedic training, and prehospital resources. The failure to implement more sophisticated prehospital emergent cardiac care likely relates to many complex factors. These include a lack of interest and clear ownership of these issues and a lack of support of hospital administrators, cardiologists, and ED physicians who generally do not perceive that prehospital treatment of patients is their priority. Furthermore, the EMS services are fragmented, under-resourced, and generally lack appropriate medical direction and guidance. Additionally, significant economic obstacles exist, particularly those relating to the cost of providing such a service, because it is difficult for EMS agencies to stock adequate supplies of novel and often expensive medications in their ambulances. EMS agencies typically receive a flat advanced life support fee for an emergency call and are not reimbursed fee-for-service for drug or supply use, and hospitals are prohibited from charging patients for medications provided by paramedic staff. Such a challenging quagmire needs common sense, good judgment, and advocacy for patient care as the primary focuses before prehospital fibrinolysis can become a reality in such locations.

Contemporary prehospital fibrinolysis research

Two recent projects have complemented earlier prehospital fibrinolysis research. The Early Retavase-Thrombolysis in Myocardial Infarction 19 (ER-TIMI-19) trial planned enrollment of 1000 patients to open label fibrinolysis (rPA 10 mg + 10 mg, double bolus) with a retrospective comparison group.²⁷ This project was stopped after 315 patients were enrolled, and it demonstrated a 31-minute reduction in time-to-treatment compared with a historical control group of patients, who had come to participating hospitals by ambulance in the preceding 6 to 12 months.²⁸ The Comparison of Angioplasty and Pre-hospital Thrombolysis in AMI trial

Figure 4



Prehospital ST-elevation myocardial infarction management.

(CAPTIM) was a French project that planned randomization of 1200 patients to prehospital fibrinolysis (accelerated rtPA) or prehospital triage for PCI.²⁹ This important study was stopped after 840 patients were enrolled because of slow enrollment and competitive trials, and because no difference in the composite end point was demonstrated between these 2 nearly optimal strategies. Advantages for PCI were mediated by reinfarction and reduction in disabling stroke (3.7% vs 1.7% and 1.0% vs 0%, rtPA and PCI, respectively), whereas this benefit was not evident for major hemorrhage or mortality rates (0.5% vs 2.0% and 3.8% vs 4.8%, rtPA and PCI, respectively). Although none of the individual end points were statistically significant, they provide impetus for further comparison of these 2 strategies. Although significant limitations exist in both of these studies, they demonstrated consistent reduction in time-to-treatment with prehospital fibrinolysis (ER-TIMI-19, prehospital vs in-hospital), and in CAPTIM, there were similar clinical outcomes with fibrinolysis and PCI.

The third Assessment of the Safety and Efficacy of New Thrombolytic Regimens Pre-hospital Substudy (ASSENT 3+) is the largest contemporary multicentered international trial that will assess the benefit of prehospital fibrinolysis. In July 2002, this trial completed its target enrollment of >1600 patients from 73 sites across 11 countries, with patients randomized to TNK-tPA and 1 of the 2 antithrombin arms described in ASSENT 3 (TNK-tPA + unfractionated heparin or TNK-tPA + enoxaparin). The impact of prehospital fibrinolysis will be compared with outcomes from an analogous population from the ASSENT 3 parent trial (nonrandomized comparison). This trial will also provide further randomized evaluation of the difference in the unfractionated heparin versus low-molecular-

Table I. Requirements for a prehospital fibrinolysis program in North America

EMS requirements
Advanced cardiac life support
Trained in symptom recognition and management of STEMI and complications
12 lead ECG acquisition
Capable of reliable lead placement
Capable of reliable transmission (cellular phone and land line)
Preliminary interpretation (computer-assisted)
Completion of reperfusion check list
Establish intravenous access and administer IV medications
Regional requirements
Regional acceptance and support of prehospital fibrinolysis program
Centralized method of
Receiving and interpreting prehospital 12 lead ECG
Reviewing prehospital fibrinolysis check sheet and providing intellectual support for EMS staff

Table II. Trials of facilitation in PCI

Trial name	Patients	Trial design
FINESSE	3000	1°PCI vs abciximab FPCI vs rPA (1/2 dose)/abciximab FPCI
ADVANCE MI	6000	1°PCI vs TNK-tPA (1/2 dose)/eptifibatide FPCI
ASSENT 4 PCI	4000	1°PCI vs TNK/enoxaparin FPCI
CARESS IN AMI	1800	rPA + abciximab FPCI vs rPA + abciximab provisional PCI
TIGER	6000	TNK/enoxaparin + provisional PCI vs 1/2 TNK/enoxaparin + eptifibatide + provisional PCI

FINESSE, Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events; *ADVANCE MI*, Addressing the Value of Facilitated Angioplasty after Combination Therapy or Eptifibatide Monotherapy in Acute Myocardial Infarction; *ASSENT 4 PCI*, Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction; *CARESS IN AMI*, Combined Abciximab RE-canalization Synergistic Study IN Acute Myocardial Infarction; *1°PCI*, primary percutaneous coronary intervention; *FPCI*, facilitated PCI (PCI with pharmacologic pre-treatment to enhance early patency).

weight heparin arms. Preliminary results demonstrate a reduction of 1 hour in time-to-treatment, similar to that identified by means of the earlier meta-analysis; therefore, this study should be a robust prospective test of the time-to-treatment hypothesis.³⁰ Approximately 30% of study sites are administering prehospital fibrinolysis without a physician in the ambulance, as is the largest single enrolling site based in North America. Therefore, further information on the impact of this paradigm shift in the process of care will be forthcoming. *ASSENT 3+* will also allow assessment of the impact of variation in process of care used to implement prehospital fibrinolysis across national and health care system boundaries.

The future of prehospital care of ST-elevation myocardial infarction in North America

Multiple advancements in prehospital care by EMS in North America have provided a unique opportunity to enhance time-to-treatment in STEMI and, therefore, improve patient outcomes. Twelve-lead ECG capability has become the standard of care in the prehospital setting, and paramedics are routinely trained for pre-

liminary interpretation. Advancements with information technology allow computer-assisted ECG diagnosis, reliable transmission to hospital facilities or triage centers, and computer-assisted patient risk modeling.³¹ As we move forward, it is essential that every attempt be made to use the available resources to maximize patient care.

The ideal prehospital management program for patients with STEMI has to be adaptable to various centers throughout North America, depending on population demographics, distances from hospitals, patient risk assessment, EMS prehospital capabilities, and in-hospital resources (Figure 4). Conceptually, we need to redefine traditional boundaries of patient care from ED arrival to first medical contact, including appropriately trained EMS personnel. Prehospital triage with an on-scene decision to proceed to a medical center capable of PCI directly could be ideal for appropriate patients in regions with the capability of timely, consistent access to an experienced cardiac catheterization laboratory. In many regions, treatment will remain focused on pharmacologic reperfusion, preferably prehospital initiated therapy when EMS resources are adequate and appropriate physician 12-lead ECG over-read and support are available (Table I). If the synergism

between pharmacologic and catheter-based reperfusion being assessed in the next series of trials of STEMI (Table II) shows a significant benefit, prehospital initiation of pharmacologic therapy with subsequent transfer for coronary angiography/angioplasty in appropriate patients may achieve the desired equipoise between early patency and optimal myocardial perfusion. Analogous to dedicated centers that manage trauma, cardiac centers with optimal reperfusion capabilities, including appropriate prehospital EMS support, may allow the next ascension in the treatment of this high-risk patient population.

Exercising the opportunities in prehospital cardiac care in North America could substantially enhance patient outcomes. With the current EMS capabilities, the ideal prehospital system should include prehospital diagnosis with initiation of fibrinolysis or triage to the appropriate medical institution for rapid institution of definitive therapy. At a minimum, we should aim for a dedicated response system to achieve an increase in inhospital state of readiness to reduce time-to-reperfusion. Extension of these advances to other cardiac emergencies, including sudden cardiac death, high-risk non-STEMI acute coronary syndromes, and stroke, will continue to improve the outcomes in these common potentially catastrophic conditions. There are no longer logical reasons to delay response to these calls for action, because time is elapsing, and, with it, needless morbidity and mortality are occurring in our patients.

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