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Time Is Muscle

Translation Into Practice

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In the future, advances in the care of patients with ST-segment elevation myocardial infarction (STEMI) will not come from the analysis of trials that do not reflect current practice in an effort to rationalize extending the percutaneous coronary intervention (PCI)-related delay time. We must move beyond such arguments and find ways to shorten total ischemic time. With the launching of the American College of Cardiology's D2B Alliance and the American Heart Association's Mission: Lifeline programs, the focus is now on systems improvement for reperfusion in patients with STEMI. The D2B Alliance was developed to focus on improvement in door-to-balloon times for patients with STEMI who are undergoing primary PCI. The American Heart Association Mission: Lifeline program is a broad, comprehensive national initiative to improve the quality of care and outcomes of patients with STEMI by improving health care system readiness and response to STEMI. Improvements in access to timely care for patients with STEMI will require a multifaceted approach involving patient education, improvements in the Emergency Medical Services and emergency department components of care, the establishment of networks of STEMI-referral hospitals (not PCI capable) and STEMI-receiving hospitals (PCI capable), as well as coordinated advocacy efforts to work with payers and policy makers to implement a much-needed health care system redesign. By focusing now on system efforts for improvements in timely care for STEMI, we will complete the cycle of research initiated by Reimer and Jennings 30 years ago. Time is muscle . . . we must translate that into practice. (J Am Coll Cardiol 2008;52:1216–21) © 2008 by the American College of Cardiology Foundation

Given the urgency of reperfusion of the occluded infarct artery in patients with ST-segment elevation myocardial infarction (STEMI), it is not unexpected that the most frequently discussed aspects of management are the selection and implementation of a reperfusion strategy. Despite the importance of these topics, when attempting to write guidelines for management of STEMI, clinicians should realize that the "evidence" on which to base such recommendations is derived from databases that do not completely answer all of our questions.

For example, a frequently quoted overview by Keeley et al. (1) in which they compare fibrinolytic reperfusion with catheter-based reperfusion summarizes the experience from a total of only 7,739 patients enrolled collectively in 23 randomized trials. These 23 trials have publication dates ranging from 1990 to 2002, raising questions about their contemporary relevance because of shifts in the use of other effective therapies besides the exact mode of reperfusion for STEMI.

Furthermore, the largest difference in absolute event rates between pharmacologic and catheter-based reperfusion was in recurrent infarction (something that is difficult to diagnose accurately in the setting of primary percutaneous coronary intervention [PCI] for STEMI); the differences in mortality and hemorrhagic stroke, although still favoring those patients undergoing primary PCI, were much more modest. Contemporary attempts by researchers to merge the 2 reperfusion strategies in the form of facilitated PCI (a preparatory pharmacologic regimen followed at varying times by PCI) have not shown this approach to be an attractive one—there is no clear reduction in mortality or reinfarction with facilitated PCI, and concerns exist about a definite increase in the risk of bleeding (2–4).

Despite the deficiencies in the evidence base, it is generally accepted that primary PCI is the preferred mode of reperfusion, provided it can be delivered in a timely fashion by an experienced operator (>75 PCI procedures/year) and team (at least 200 PCI procedures per year, including at least 36 primary PCI procedures/year) (5). The issue centers on what is meant by a "timely fashion." Because in virtually all cases there is an inherent delay in implementation of a primary PCI strategy, many analyses have been performed to provide guidance on the acceptable delays to primary PCI—the metric "door-to-balloon" (D2B) time arose and was initially proposed to be 120 min.

By 2004, several pieces of evidence had emerged that led to a shortening of the recommended D2B time to 90 min. Concern arose that long delays to primary PCI run counter to the guiding principle that "time is muscle," as shown by

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Reimer and Jennings nearly 30 years ago (6). Investigators understood that the amount of myocardial salvage per unit time from the moment of coronary occlusion is not linear but rather curvilinear with the maximum amount of salvage in the first few hours after the onset of infarction, with sharp reductions in the amount of salvage thereafter as each hour passes (7).

Thus, total ischemic time is of paramount importance and often is overlooked in discussions about time to reperfusion. The importance of total ischemic time holds true regardless of whether reperfusion is attempted with a fibrinolytic or by PCI (8,9). Clinical trials in Europe testing the strategy of transfer of STEMI patients from community hospitals to PCI centers (10,11) consistently showed lower mortality in the transfer patients but also showed that it was possible to implement the PCI strategy within 90 min from randomization—giving birth to the recommendations in 2004 on both sides of the Atlantic that the system goal should be to perform primary PCI within 90 min of the first medical contact (preferably the Emergency Medical Services [EMS] team in patients who call 911 [EMS-to-balloon = 90 min], but D2B should comprise 90 min in those patients whose first medical contact is the door of the hospital) (5,12).

Several authors have argued that the benefits of primary PCI compared with fibrinolytic therapy extend well beyond the 90-min window noted previously (13). Claims have been published that the benefit of primary PCI is still observed even if there is a 3-h delay compared with the time when a fibrinolytic could be administered (14). In a patient-level analysis from 22 trials (total sample size = 6,763) that largely overlaps with the Keeley et al. (1) overview noted previously in this commentary, Boersma (15) concluded that primary PCI was associated with a lower 30-day mortality compared with fibrinolytic therapy regardless of the PCI-related delay time (a hospital-level factor).

It is hard to accept the argument that PCI-related delay time does not matter at all both on a biologic basis and also on a statistical basis. A particularly concerning observation in the Boersma meta-analysis (15) is the finding of an unusual relationship between the 30-day mortality and PCI-related delay time. Although there is the expected increase in mortality with longer delays to PCI in patients allocated to PCI, a biologically implausible pattern was observed in those allocated to fibrinolysis. The 30-day mortality in the fibrinolytic group was 8.2% when the PCI-related delay compared with fibrinolysis was 0 to 35 min, decreased to 6.8% when it was >35 to 50 min, decreased further to 5.4% when it was >50 to 62 min, increased abruptly to 9.5% when it was >62 to 79 min, and then remained at 9.6% when it was >79 to 120 min. Why should the efficiency with which a hospital can implement a primary PCI strategy have any bearing on the mortality rate when patients receive a fibrinolytic (16)?

Another difficulty with the Boersma meta-analysis (15) is the under-representation of patients with a relatively short presentation delay. Pre-hospital fibrinolysis, which helps reduce total ischemic time, is an important treatment consideration in such patients, given the much shorter time to initiation of a reperfusion strategy compared with the time delay to implement primary PCI (17,18). When pre-hospital lysis is combined with the aggressive use of rescue PCI, 1-year mortality appears comparable with that achieved with primary PCI (19,20).

Abbreviations and Acronyms

ACC = American College of Cardiology

AHA = American Heart Association

D2B = door-to-balloon

EMS = Emergency Medical Services

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

Other attempts to estimate the time tradeoff between fibrinolysis and primary PCI suggest that the mortality benefit of primary PCI is lost if it is delayed by more than 60 min compared with a fibrin-specific lytic; when one adds the door-to-needle time of 30 min for a lytic, further support is found for the recommendation of a D2B time of 90 min (21,22). Indeed, as suggested by Pinto et al. (23), the situation is much more complex than can be represented by a single number. Using a large dataset from NRMI (National Registry of Myocardial Infarction), Pinto et al. (23) showed that the equipoise point between primary PCI and a fibrinolytic may be as little as 40 min in a high-risk situation with much myocardium to salvage when one factors in the time from onset of symptoms, age of the patient, and location of the infarction (e.g., early presentation after the onset of infarction in a young patient with an anterior infarction); it may extend to 179 min in other situations (late presentation in an elderly patient with a nonanterior infarction) (23). These points emphasize, as stated in the preamble to STEMI clinical practice guidelines, that the recommendations put forward by writing committees are system goals but are not meant to supersede clinician judgment in individual cases.

The latest discussion about the 90-min system goal for implementing primary PCI is in this issue of the *Journal* by Terkelsen et al. (24), who ask, "Is there any time left for primary PCI according to the 2007 Updated American College of Cardiology (ACC)/American Heart Association (AHA) STEMI Guidelines and the D2B Alliance?" (24). Their interpretation of the 2007 ACC/AHA STEMI Guidelines is that the Writing Committee advocates what amounts to a PCI-related delay of only 40 min, and they ask that consideration be given to extending the D2B time back to 120 min.

To buttress their argument, Terkelsen et al. (24) cite much of the information discussed previously in this commentary and place emphasis on the Boersma meta-analysis (15) without commenting on the problems noted in a key figure, which they reproduced. In their Figure 1, Terkelsen et al. (24) also use unrealistically short transfer times that are not representative of experience in large parts of the U.S. (5,24,25). The D2B time of 30 min proposed by Terkelsen

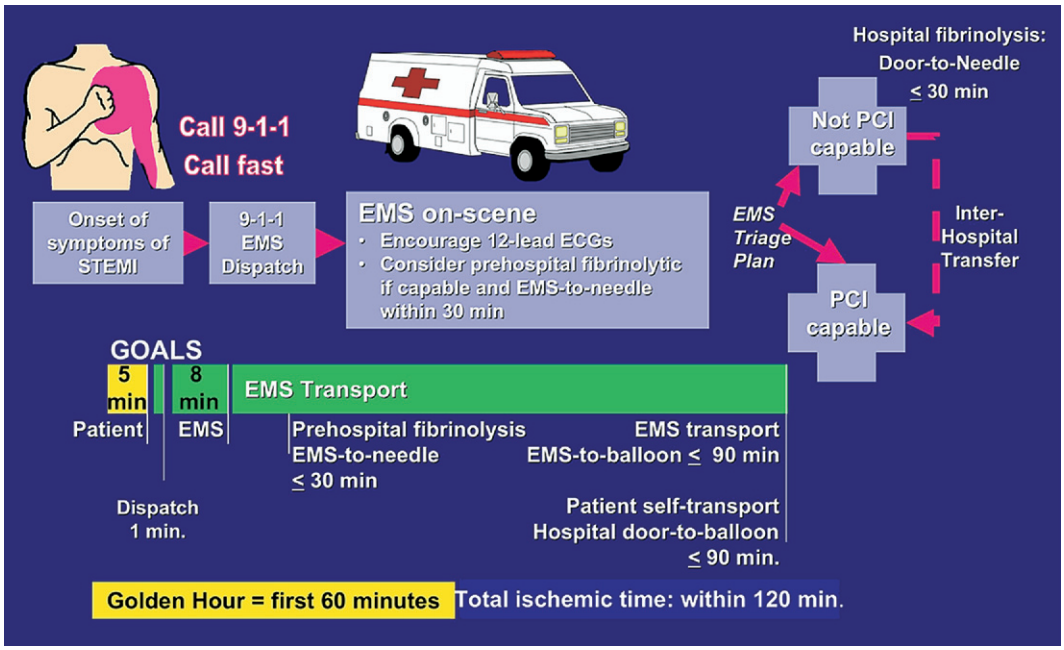

Figure 1 **Options for Transportation of STEMI Patients and Initial Reperfusion Treatment Goals**

Reperfusion in patients with STEMI can be accomplished by pharmacological (fibrinolysis) or catheter-based (primary PCI) approaches. The overarching goal is to keep total ischemic time within 120 min (ideally within 60 min) from symptom onset to initiation of reperfusion treatment. Within this context, the following are goals for the medical system based on the mode of patient transportation and the capabilities of the receiving hospital. The medical system goal is to facilitate rapid recognition and treatment of patients with STEMI so that door-to-needle (or medical contact-to-needle) for initiation of fibrinolytic therapy can be achieved within 30 min or door-to-balloon (or medical contact-to-balloon) for PCI can be achieved within 90 min. These goals should not be understood as "ideal" times but rather the longest times that should be considered acceptable for a given system. Systems that are able to achieve even more rapid times for treatment of patients with STEMI should be encouraged. Medical system goals: EMS transport (recommended): 1. If EMS has fibrinolytic capability and the patient qualifies for therapy, pre-hospital fibrinolysis should be started within 30 min of arrival of EMS on the scene; 2. If EMS is not capable of administering pre-hospital fibrinolysis and the patient is transported to a non–PCI-capable hospital, the door-to-needle time should be within 30 min for patients for whom fibrinolysis is indicated; 3. If EMS is not capable of administering pre-hospital fibrinolysis and the patient is transported to a PCI-capable hospital, the EMS arrival-to-balloon time should be within 90 min; 4. If EMS takes the patient to a non–PCI-capable hospital, it is appropriate to consider emergency interhospital transfer of the patient to a PCI-capable hospital for mechanical revascularization if: there is a contraindication to fibrinolysis; PCI can be initiated promptly within 90 min from EMS arrival-to-balloon time at the PCI-capable hospital*; or fibrinolysis is administered and is unsuccessful (i.e., "rescue PCI"). Patient self-transport (discouraged): 1. If the patient arrives at a non–PCI-capable hospital, the door-to-needle time should be within 30 min of arrival at the emergency department; 2. If the patient arrives at a PCI-capable hospital, the door-to-balloon time should be within 90 min; 3. If the patient presents to a non–PCI-capable hospital, it is appropriate to consider emergency interhospital transfer of the patient to a PCI-capable hospital if: there is a contraindication to fibrinolysis; PCI can be initiated within 90 min after the patient presented to the initial receiving hospital or within 60 min compared with when fibrinolysis with a fibrin-specific agent could be initiated at the initial receiving hospital; or fibrinolysis is administered and is unsuccessful (i.e., "rescue PCI"). Note that "medical contact" is defined as "time of EMS arrival on scene" after the patient calls EMS/911 or "time of arrival at the emergency department door" (whether PCI-capable or non–PCI-capable hospital) when the patient transports himself/herself to the hospital. Source: Figure 1 in Antman et al. (26). *EMS Arrival→Transport to non–PCI-capable hospital→Arrival at non–PCI-capable hospital to transfer to PCI-capable hospital→Arrival at PCI-capable hospital-to-balloon time = 90 min. EMS = emergency medical system; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

et al. (24) in the "rerouting" strategy for STEMI (option C in their Fig. 1), although potentially achievable, requires a highly integrated pre-hospital notification system to alert the catheterization team while the patient is being transported—a laudable goal but not yet achieved in most parts of the U.S.

It appears that Terkelsen et al. (24) only focused on selective sentences in the text of Section 6.3.1.6: Reperfusion of the 2007 Update to the STEMI Guideline (26). They argue, without providing data, that the typical pre-hospital delay includes 10 min at the scene and 10 min for transportation. By subtracting these 20 min from the difference in the recommendation of EMS-to-balloon of 90 min and door-to-needle time of 30 min, they conclude that the Writing Committee was only allowing a PCI-related delay of 40 min. Their conclusion is not correct and does not reflect the spirit and intent of the Writing Committee, nor is it consistent with the wording of the recommendations or the algorithm that is clearly described in Figure 1, summarizing the options for transportation of STEMI patients and initial reperfusion treatment goals.

Most EMS systems in the U.S. do not have teams trained in the administration of pre-hospital fibrinolysis for STEMI. Recognizing this fact, the Writing Committee emphasized that the system goal is to deliver the drug within 30 min of the time the patient presents to the door of the hospital. Also noting that a critical component of efforts to shorten the time to primary PCI is prompt

activation of the catheterization lab (including from the ambulance en route to the PCI center), the Writing Committee emphasized a system goal of primary PCI within 90 min of first medical contact.

The system goal for hospitals without PCI capability was kept at a door-to-needle time for fibrinolysis to reflect current practice. However, as clearly stated in the text, "This committee continues to endorse the concept that faster times to reperfusion and better systems of care are associated with important reductions in morbidity and mortality rates in patients with STEMI. An underused but effective strategy for improving systems of care for STEMI patients is to expand the use of pre-hospital 12-lead electrocardiography programs by emergency medical systems (EMS) that provide advanced life support" (33,34). In addition, "The writing group does believe that every effort should be made to reduce the time from first medical contact to fibrinolytic therapy when that is considered the appropriate reperfusion strategy." The exact wording of the current recommendations is shown in Table 1. The Writing Committee reiterated in Figure 1 that EMS transport is the recommended method of transport and clearly stated in the legend to Figure 1 (26) that 1) If EMS has fibrinolytic capability and the patient qualifies for therapy, pre-hospital fibrinolysis should be started within 30 min of arrival of EMS on the scene; 2) if EMS is not capable of administering pre-hospital fibrinolysis and the patient is transported to a non–PCI-capable hospital, the door-to-needle time should be within 30 min for patients for whom fibrinolysis is indicated; and 3) if EMS is not capable of administering pre-hospital fibrinolysis and the patient is transported to a PCI-capable hospital, the EMS arrival-to-balloon time should be within 90 min.

Advances in the care of patients with STEMI in the future will not come from analysis of trials that do not reflect current practice in an effort to rationalize extending the PCI-related delay time (24). We must move beyond such arguments and find ways to shorten total ischemic time. We need to focus on translational research in the sense described by Woolf (27)—". . . ensuring that new treatments and research knowledge actually reach the patients or populations for whom they are intended and are implemented correctly." The way forward for transformation of reperfusion for STEMI will come from the kind of thinking described by Dougherty and Conway (28), who outlined the "3 T's" road map to improve U.S. health care (Table 2).

Table 1 2007 STEMI Focused Update Recommendation: Class I

1. STEMI patients presenting to a hospital with PCI capability should be treated with primary PCI within 90 min of first medical contact (Fig. 1) as a systems goal. (Level of Evidence: A)
2. STEMI patients presenting to a hospital without PCI capability and who cannot be transferred to a PCI center and undergo PCI within 90 min of first medical contact (Fig. 1) should be treated with fibrinolytic therapy within 30 min of hospital presentation as a systems goal unless fibrinolytic therapy is contraindicated. (Level of Evidence: B)

Modified from Antman et al. (26).
PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Table 2 Road Map for Transformation of Reperfusion Therapy for STEMI

Translational Step	Key Aspects of Translational Step	Reperfusion for STEMI
1	Activity to test what care works: • Clinical efficacy research	Randomized clinical trials of fibrinolysis and catheter-based therapies
2	Activities to test who benefits from providing care: • Outcomes research • Comparative effectiveness research • Health services research	Registries such as the joint ACC/AHA ACTION-GWTG Registry
3	Activities to test how to deliver high-quality care reliably and in all settings: • Measurement and accountability of health care quality and cost • Implementation of interventions and health care system redesign • Scaling and spread of effective interventions • Research in above domains	ACC D2B Alliance AHA Mission: Lifeline

Adapted from information in Dougherty and Conway (28).
ACC = American College of Cardiology; ACTION = Acute Coronary Treatment and Intervention Outcomes Network; AHA = American Heart Association; D2B = door-to-balloon; GWTG = Get With the Guidelines; other abbreviation as in Table 1.

We have acquired a rich database of clinical trials that frame our understanding of the clinical efficacy of fibrinolysis and primary PCI for reperfusion in STEMI (T1 phase of the road map in Table 2). Cardiologists have been leaders in internal medicine by participation in registries such as NRMI, NCDR (National Cardiovascular Data Registry), GAP (Guidelines Applied in Practice), and GWTG (Get With the Guidelines). The latest of these is the newly formed ACTION (Acute Coronary Treatment and Intervention Outcomes Network)-GWTG Registry as a joint effort of the ACC and AHA. Registry efforts form the T2 phase of the road map and provide much-needed information regarding outcomes and clinical effectiveness (Table 2). We have now entered the T3 phase of the road map with major efforts at systems improvement for reperfusion in STEMI by the launching of the ACC's D2B Alliance and the AHA's Mission: Lifeline programs (Table 2) (29,30). The Danish core strategies proposed by Terkelsen et al. (24) to reduce system delay in all STEMI patients are a highly commendable effort in this regard and are already being addressed in the AHA's Mission: Lifeline program.

The D2B Alliance was developed to focus on improvement in D2B times for patients with STEMI undergoing primary PCI. It is based on 6 core principles that have been shown to shorten D2B (30). Approximately 1,000 hospitals are participating in the D2B Alliance, the goal of which is to achieve the recommended system goal D2B time of ≤90 min for at least 75% of nontransferred patients (30).

The AHA Mission: Lifeline program is a broad, comprehensive national initiative to improve the quality of care and outcomes of patients with STEMI by improving health care system readiness and response to STEMI (29). The Mission: Lifeline program will incorporate lessons learned from successful vanguard systems of care efforts in the U.S. as well as Europe on citywide, regional, and national levels (19,31–36). Improvements in access to timely care for patients with STEMI will require a multifaceted approach involving patient education, improvements in the EMS and emergency department components of care, the establishment of networks of STEMI-referral hospitals (not PCI capable) and STEMI-receiving hospitals (PCI capable), as well as coordinated advocacy efforts to work with payers and policy makers to implement much needed health care system redesign (29). Clinicians caring for patients with STEMI are encouraged to visit the new AHA Mission: Lifeline website and register their system—a vital step in this T3 phase effort.

By focusing now on system efforts for improvements in timely care for STEMI, we will complete the cycle of research initiated by Reimer and Jennings (6) 30 years ago. Time is muscle . . . we must translate that into practice.

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