Perspective

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Time to Treatment in Patients with STEMI

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ST-segment elevation myocardial infarction (STEMI) usually results from acute thrombotic occlusion of a coronary artery and is a leading cause of death. Although myocardial cell injury can occur after
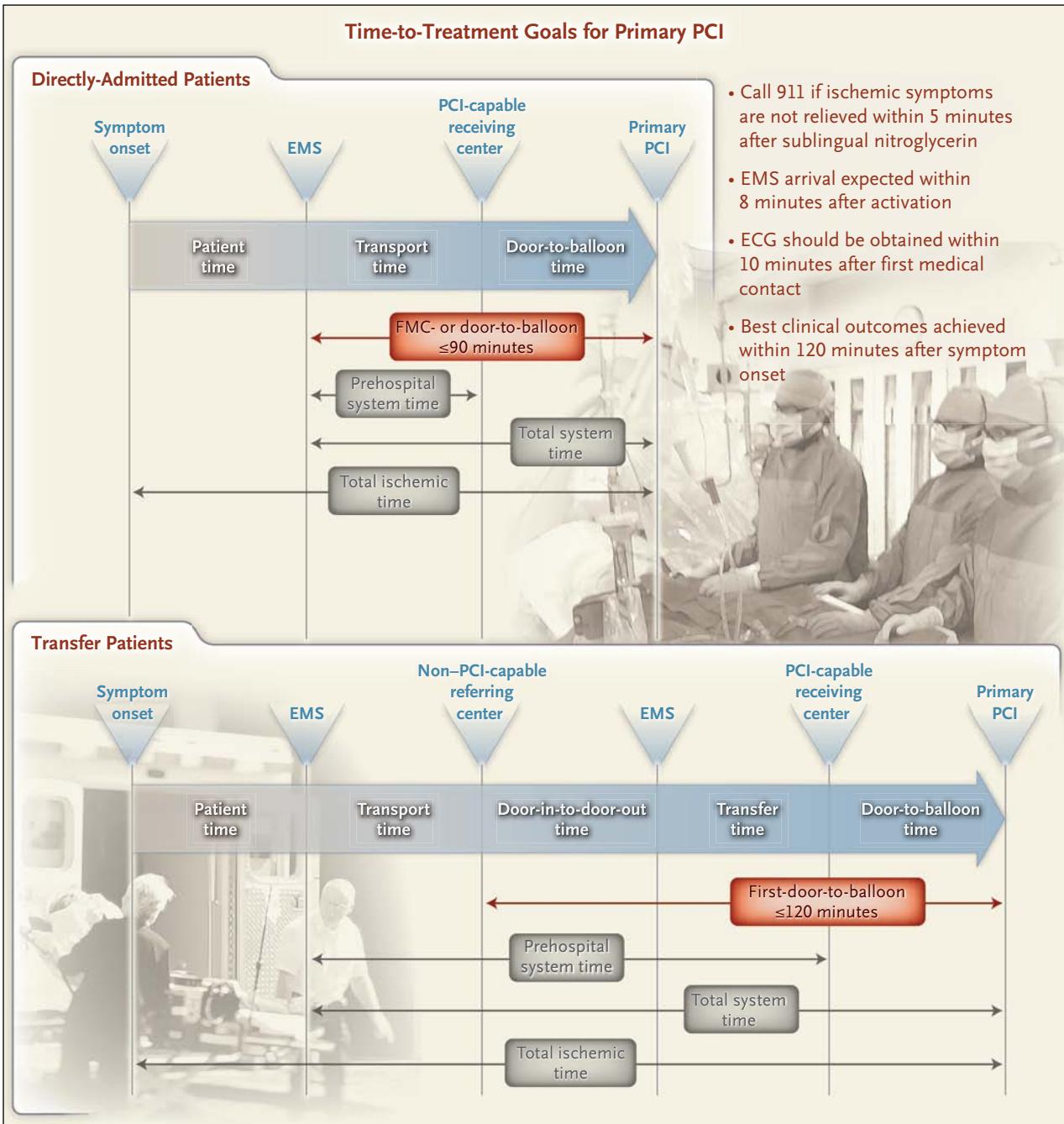
20 to 30 minutes of ischemia, it takes several hours for transmural myocardial necrosis to develop. The goal of reperfusion therapy with fibrinolytic drugs or primary percutaneous coronary intervention (PCI) is to restore blood flow to ischemic, but still viable, myocardium and reduce infarct size. Reducing the time to treatment and maximizing myocardial salvage — in keeping with the mantra that "time is muscle" — present a logistic challenge.

Early randomized trials of fibrinolytic therapy established the direct relationship between symptom duration, myocardial infarct size, and mortality. At the time, however, treatment delays were prolonged because of the lack of prehospital and in-hospital sys-

tems of care to facilitate timely STEMI therapy. To address this problem, the National Heart, Lung, and Blood Institute launched the National Heart Attack Alert Program in 1991. Four critical time points in the emergency department (ED) were identified and dubbed the "4Ds": "door," the time of arrival in the ED; "data," the time of acquisition of an electrocardiogram (ECG); "decision," the time of ordering of fibrinolytic therapy; and "drug," the time of initiation of fibrinolytic drug infusion. Within 3 years, by reducing ED delays, participating hospitals had doubled the percentage of patients treated within the door-to-needle goal of 30 minutes. The treatment goal is the same today, but less than half of

patients in the United States are treated within 30 minutes, perhaps because fibrinolytic therapy is used so infrequently.

Primary PCI has replaced fibrinolytic therapy as the preferred reperfusion strategy, despite the delays inherent in transferring the patient from the ED to the cardiac catheterization laboratory and then performing the procedure (see the figure). The Centers for Medicare and Medicaid Services and the Joint Commission began using door-to-balloon time as a performance measure for public reporting in 2002. In 2006, the American College of Cardiology (ACC) launched the Door-to-Balloon Alliance with a goal of providing treatment within 90 minutes after arrival for at least 75% of patients with STEMI who present directly to a PCI-capable hospital.[1] Several strategies were promoted, including activation of the cardiac catheterization laboratory with a single call by the

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Time-to-Treatment Goals for Primary PCI

Directly-Admitted Patients

Symptom onset — EMS — PCI-capable receiving center — Primary PCI

Patient time — Transport time — Door-to-balloon time

FMC- or door-to-balloon ≤90 minutes

Prehospital system time

Total system time

Total ischemic time

- Call 911 if ischemic symptoms are not relieved within 5 minutes after sublingual nitroglycerin
- EMS arrival expected within 8 minutes after activation
- ECG should be obtained within 10 minutes after first medical contact
- Best clinical outcomes achieved within 120 minutes after symptom onset

Transfer Patients

Symptom onset — EMS — Non–PCI-capable referring center — EMS — PCI-capable receiving center — Primary PCI

Patient time — Transport time — Door-in-to-door-out time — Transfer time — Door-to-balloon time

First-door-to-balloon ≤120 minutes

Prehospital system time

Total system time

Total ischemic time

Time-to-Treatment Goals for Primary PCI.

ECG denotes electrocardiogram, EMS emergency medical services, FMC first medical contact, PCI percutaneous coronary intervention, and STEMI ST-segment–elevation myocardial infarction.

ED physician, ensuring readiness of the catheterization laboratory team within 30 minutes, prompt provision of data feedback to the ED and the catheterization labora- tory, commitment from senior management, and a team-based approach spanning multiple de- partments. The most recent data suggest that more than 90% of patients who present directly to PCI-capable hospitals (and who are not excluded from reporting because of extenuating clinical circumstances) have door-to-bal-

loon times of 90 minutes or less, with a median time of approximately 60 minutes — a major improvement from only a few years ago.

Recognizing that major delays can occur before patients arrive at the hospital, practice guidelines now recommend that the time from first medical contact to PCI be 90 minutes or less.[2] For patients who transport themselves to the hospital, the time from first medical contact to balloon is the same as door-to-balloon time, but for patients transported by emergency medical services (EMS), the clock starts when the first provider comes in direct contact with the patient. Prehospital ECG diagnosis, EMS bypass of hospitals without PCI capability, prehospital activation of the cardiac catheterization laboratory, and transport from the field directly to the catheterization laboratory reduce treatment delays. Aware that the majority of patients with STEMI present to hospitals without PCI capability, the American Heart Association (AHA) in 2007 launched Mission: Lifeline, a community-based, comprehensive national initiative for developing systems and processes of care for patients with STEMI, with a major focus on reducing prehospital delays by engaging patients and EMS.[3]

For patients requiring interhospital transfer for primary PCI, additional delays include the door-in–door-out time in the ED of the referring center and the transport time to the receiving center (see the figure). An ACC–AHA performance measure sets a door-in–door-out goal of 30 minutes for internal quality-improvement purposes,[4] but the metric is not used for public reporting, and the best regional STEMI systems are

averaging 45 minutes. Transfer time from the door of the referring center to the door of the receiving center presents another logistic challenge. In urban centers, traffic and competition among EMS or hospital services can be problematic. In rural centers, access to transport units, geographic distances, and weather can cause time delays. The guideline recommendation for first-door-to-balloon time for transfer patients has been increased from 90 minutes to 120 minutes to encourage more transfers for primary PCI.[2]

Setting the door-to-balloon goal at 90 or 120 minutes has sparked controversy for a decade. More controversy has been generated by several studies suggesting that recent additional reductions in door-to-balloon time have not been associated with parallel reductions in in-hospital mortality.[5] Possible explanations include initiation of treatment that is too late or reductions in door-to-balloon time that are too small to reduce infarct size or follow-up that is too short (examining only in-hospital mortality) to show a survival benefit. It's possible that patients at low risk for death from STEMI are being treated more quickly and that patients with more complications who are at higher risk for death take longer to treat, which dilutes the association between improvement in door-to-balloon time and reduced mortality. It's also possible that previous time-to-treatment interventions and widespread implementation of evidence-based, guideline-recommended therapies have reduced in-hospital mortality as much as possible. Because of selection bias and confounding, observational registries that may reveal an association between

treatment times and mortality cannot prove causality; they were developed to promote evidence-based treatments and to encourage hospitals to improve quality by focusing on processes of care.

There have been some unintended consequences of trying to reduce door-to-balloon time by a few more minutes after the initial interventions were successfully implemented. As many as one third of activations of STEMI teams are now false alarms. Efforts at initial patient triage, diagnosis and treatment of coexisting conditions, and obtaining of informed consent can be truncated in the rush to perform primary PCI more quickly, potentially compromising patient safety. Public reporting of door-to-balloon times and mortality can create a disincentive for cardiologists and hospitals to perform primary PCI in the highest-risk patients, among whom the greatest mortality reductions might be achieved. Recently granted permission to exclude patients with nonsystem delays from the reports of door-to-balloon times offers the opportunity for gaming the reportable performance measure.

Door-to-balloon time has been an excellent process-of-care metric for expediting patients' arrival in the cardiac catheterization laboratory. It's unlikely that reducing in-hospital delays by another few minutes will affect clinical outcomes, given the small portion of total ischemic time those minutes would represent and the success that's been achieved in the system of in-hospital STEMI care. The primary opportunity for reducing total ischemic time and time to treatment, and for improving outcomes, now lies in the prehospital STEMI system of care, where logistic chal-

lenges remain. For patients requiring interhospital transfer, first-door-to-balloon time is 90 minutes or less in only 33% of cases, and 120 minutes or less in only 66%. Most difficult to achieve has been a reduction in the delay from symptom onset to first medical contact. Although it is shorter than it was several years ago, mean symptom duration is still 2 hours before first medical contact, and 40% of patients do not contact EMS. Continued efforts are needed to educate patients about STEMI symptoms and about calling 911 to permit EMS triage, treatment, and transport, as STEMI teams shift their focus from in-hospital to prehospital treatment delays. Although door-to-balloon time remains important, it's time to turn our attention to the further development of systems that address the continuum of STEMI care, from symptom onset through return to the community.

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Risks (and Benefits) in Comparative Effectiveness Research Trials

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Comparative effectiveness research (CER) aims to provide high-quality evidence to help patients and clinicians make informed clinical decisions and to assist health systems in improving the quality and cost-effectiveness of clinical care.[1] Recently, the Department of Health and Human Services indicated that the regulatory framework for protecting human subjects is inadequate to evaluate the multifaceted risks of CER randomized, controlled trials (RCTs).[2] As the federal Common Rule states, risks to subjects must be "reasonable in relation to anticipated benefit." Institutional review boards (IRBs) are directed to "consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research)." Furthermore, unless the requirement for informed consent is waived by the IRB, subjects must be informed of "any reasonably foreseeable risks or discomforts" associated with participation. The enmeshment of research and standard clinical care makes evaluation of the risks posed by a CER RCT complex. In order to provide ethically appropriate oversight and informed consent, investigators should consider, manage, and communicate with potential participants about at least nine different types of potential risk — some unique to CER RCTs, some common to all RCTs.

1. Risks associated with the standard of care. All patients, when receiving the standard of care, are at risk for both the ills of the underlying disease processes and iatrogenic harm. Patients should be informed about undesired events or outcomes that are likely to occur with some frequency or that would be severe. Patients who are not participating in research studies may not be as thoroughly informed about the absolute risks associated with the proposed treatment or the relative risks of alternative treatments. A collateral benefit of trial participation is access to better information.

2. Risks (and benefits) of intervention A as compared with intervention B. CER studies are warranted when, within the range of the standard of care, more than one intervention is in common use for the same diagnostic, therapeutic, or other core clinical purpose, when there is debate among clinicians about which intervention is superior, and when evidence from a clinical trial could resolve the dispute and improve outcomes. In such situations, the relative risks associated with interventions A and B may be unknown, or one intervention may be known to be