

## REVIEW ARTICLE

## CURRENT CONCEPTS

# Time to Treatment in Primary Percutaneous Coronary Intervention

Brahmajee K. Nallamothu, M.D., M.P.H., Elizabeth H. Bradley, Ph.D.,  
and Harlan M. Krumholz, M.D., S.M.

**E**ARLY ADMINISTRATION OF REPERFUSION THERAPY IMPROVES SURVIVAL in patients with ST-elevation myocardial infarction by reestablishing coronary blood flow within the occluded infarct-related artery.<sup>1</sup> Primary percutaneous coronary intervention (PCI) is superior to fibrinolytic therapy when performed rapidly by expert teams,<sup>2</sup> but its effectiveness may be limited by delays in delivery.<sup>3</sup>

Recent national efforts are drawing attention to the importance of door-to-balloon time as a key indicator of quality of care for patients with ST-elevation myocardial infarction who are treated with primary PCI.<sup>4</sup> The American College of Cardiology (ACC), in collaboration with the American Heart Association (AHA), the American College of Emergency Physicians (ACEP), the National Heart, Lung, and Blood Institute (NHLBI), and other partners, has implemented a national quality-improvement campaign to decrease door-to-balloon time in primary PCI.<sup>5</sup> The convergence of clinical and policy interest in door-to-balloon time makes this an opportune occasion to review current knowledge on this topic.

## PATHOPHYSIOLOGY OF MYOCARDIAL NECROSIS

Animal models demonstrate a direct relationship between the duration of coronary-artery occlusion and the extent of myocardial necrosis.<sup>6</sup> Myocardial cell death begins as early as 20 minutes after coronary-artery occlusion and is usually complete within 6 hours. This period may be extended considerably, however, depending on several clinical factors, including the presence or absence of intermittent episodes of transient reperfusion, the extent of collateral circulation, and the presence or absence of a history of ischemic preconditioning.<sup>7,8</sup> Prompt reperfusion therapy can limit myocardial necrosis, although delayed treatment may still provide some benefit by improving left ventricular remodeling and electrical stability.<sup>9</sup> Nevertheless, timely treatment produces the most pronounced benefit.

## FIBRINOLYTIC THERAPY

Patients with ST-elevation myocardial infarction who receive fibrinolytic therapy have better short- and long-term survival when treatment is instituted rapidly, with early reestablishment of flow.<sup>10</sup> This relationship between time to treatment and outcomes of fibrinolytic therapy appears to be nonlinear, with the best chance of survival when fibrinolytic therapy is administered within 2 to 3 hours after the onset of symptoms.<sup>11</sup> Little benefit is seen with fibrinolytic therapy after 12 hours, probably because of lost

From the Health Services Research and Development Center of Excellence, Ann Arbor Veterans Affairs Medical Center, and the Department of Internal Medicine, Division of Cardiovascular Disease, University of Michigan Medical School — both in Ann Arbor (B.K.N.); the Section of Health Policy and Administration, Department of Epidemiology and Public Health and the Robert Wood Johnson Clinical Scholars Program, Department of Medicine, Yale University School of Medicine, New Haven, CT (E.H.B., H.M.K.); and the Section of Cardiovascular Medicine, Department of Medicine, Yale University School of Medicine, and the Center for Outcomes Research and Evaluation, Yale–New Haven Hospital — both in New Haven, CT (H.M.K.). Address reprint requests to Dr. Krumholz at 333 Cedar St., Rm. I-456 SHM, P.O. Box 208088, New Haven, CT 06520-8088, or at harlan.krumholz@yale.edu.

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opportunities for both myocardial salvage<sup>12</sup> and restoration of blood flow, as the thrombus organizes within the coronary artery over time.<sup>13</sup>

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PRIMARY PCI

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Longer intervals between the onset of symptoms and balloon time have been correlated with poorer outcomes in several,<sup>14-17</sup> but not all, studies of primary PCI.<sup>18-20</sup> Some studies have also suggested that delays in the delivery of primary PCI are important only within the first 2 or 3 hours after the onset of symptoms (since this is the time when myocardial salvage is greatest)<sup>21</sup> or in high-risk patients, such as those with cardiogenic shock.<sup>22</sup> In general, studies that have not shown a relationship between the time from the onset of symptoms to treatment and outcome have had smaller samples, involved special subpopulations of patients, or included narrower ranges of time than studies that have shown such a relationship. However, it is also possible that even though the extent of myocardial salvage may be similar for fibrinolytic therapy and primary PCI in the early period after the onset of symptoms, PCI is more effective in restoring flow and improving outcomes during later periods. Accordingly, some investigators have hypothesized that there is a longer treatment window for primary PCI than has been suggested in studies of fibrinolytic therapy.<sup>23</sup> Data supporting this theory are sparse at this time and are not incorporated into current guideline recommendations.

In contrast, delays in door-to-balloon time have been consistently associated with poorer outcomes in many studies.<sup>15,18-20,24</sup> Using data from the National Registry of Myocardial Infarction, McNamara and colleagues recently noted a strong relationship between door-to-balloon time and in-hospital mortality among 29,222 patients with ST-elevation myocardial infarction.<sup>20</sup> When treatment was started within 90 minutes after arrival, in-hospital mortality was 3.0%, but it increased to 4.2%, 5.7%, and 7.4% when delays were 91 to 120 minutes, 121 to 150 minutes, and more than 150 minutes, respectively. When adjusted for differences in patient characteristics, each 15-minute reduction in door-to-balloon time from 150 to less than 90 minutes was associated with 6.3 fewer deaths per 1000 patients treated (Fig. 1). This relationship was particularly apparent in patients who arrived at the hospital within 1 hour after the onset of symptoms and had high-risk features, a finding

consistent with that in other reports.<sup>14,21,24</sup> Other researchers have noted similar findings, with evidence of smaller infarct sizes, fewer major adverse cardiovascular events, and better long-term survival with door-to-balloon times of 90 minutes or less.<sup>24,25</sup>

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PERFORMANCE WITH RESPECT  
TO DOOR-TO-BALLOON TIME

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Guidelines from the ACC–AHA and the European Society of Cardiology recommend a treatment goal of 90 minutes or less for door-to-balloon time (or the time from initial medical contact to treatment),<sup>26,27</sup> and this measure is incorporated into national, publicly reported quality indicators for hospital performance. The Health Quality Alliance program, which is a combined effort of the Centers for Medicare and Medicaid Services and the Joint Commission, includes door-to-balloon time among its core measures of quality of care for acute myocardial infarction.<sup>4</sup>

Door-to-balloon time, as currently measured by the Health Quality Alliance, addresses several practical concerns. First (despite its terminology), the measure permits the use of devices other than angioplasty balloons that are occasionally used to initially reestablish reperfusion. Second, reporting on the measure changed substantially in July 2006, shifting from a treatment goal of 120 minutes or less to one of 90 minutes or less, reporting hospital median as opposed to mean door-to-balloon time, and allowing for clinicians to exclude from the calculation patients for whom delays are considered unavoidable. These modifications encourage a treatment goal that is consistent with the guidelines, reduce the influence of outlier times, and acknowledge that delays may be due to extenuating circumstances in which time is spent on other necessary clinical activities, such as ruling out an aortic dissection. Despite these improvements, the current measure still has some limitations. For example, patients in whom ST-elevation myocardial infarction develops after admission to the hospital or who are transferred from another hospital for primary PCI are not currently included. These issues deserve more attention in future iterations of the measure.

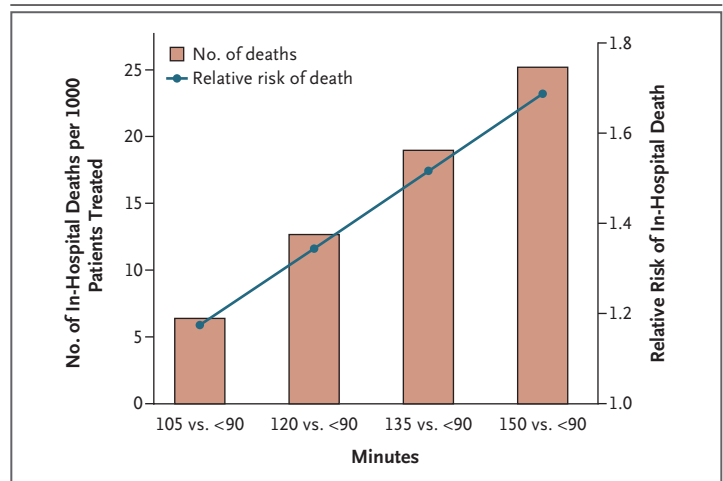
Currently available data suggest that there has been little improvement in door-to-balloon times in the recent past, and performance on this indicator lags behind performance on other quality

measures for the treatment of acute myocardial infarction.<sup>28,29</sup> In recently reported data from hospitals participating in the National Registry of Myocardial Infarction between 1999 and 2002, only 35% of all patients were treated within 90 minutes after arrival at the hospital, and less than 15% of hospitals had a median time of less than 90 minutes.<sup>30</sup> Two particular patient subgroups appear to be at highest risk for long delays in door-to-balloon time: patients who present during off-hours (nights and weekends) and those who are transferred from other acute-care facilities. Patients with ST-elevation myocardial infarction frequently present during off-hours, and many health care facilities are challenged to maintain the availability of primary PCI around the clock. Outcomes with primary PCI are also poorer during off-hours in part because of longer delays in activating cardiac-catheterization laboratories.<sup>31</sup> For patients who are transferred from other hospitals, there is the additional challenge of coordinating efforts between facilities on an emergency basis. Unlike trauma care systems in many states, for example, care for patients with ST-elevation myocardial infarction is frequently disjointed. In the United States, data on the time from arrival at the initial hospital to PCI at the receiving hospital suggest that median delays are as long as 180 minutes and that less than 5% of patients are treated within 90 minutes.<sup>32</sup>

Although several clinical trials have shown promising results of emergency transfer for primary PCI as compared with on-site fibrinolytic therapy,<sup>33</sup> only one of these studies involved hospitals in the United States.<sup>34</sup> European health care systems have been more successful at rapidly transferring and coordinating care for patients with ST-elevation myocardial infarction because of better integration of emergency medical systems and hospital networks.<sup>35</sup> In limited areas of the United States, the emergency transfer of such patients between referral and tertiary care hospitals has also been successfully demonstrated.<sup>36-38</sup>

#### SELECTING A REPERFUSION THERAPY

Given the substantial resources required, many hospitals in the United States and Europe lack PCI capabilities, and even fewer provide around-the-clock staffing for these procedures. The decision to use primary PCI could substantially delay access



**Figure 1. Relative Risk of In-Hospital Death with Each Additional 15-Minute Interval and Number of Deaths Associated with Increases in Door-to-Balloon Time as Compared with Treatment within 90 Minutes.**

The bars represent the number of in-hospital deaths per 1000 patients treated, and the line represents the relative risk associated with longer door-to-balloon times with primary PCI as compared with treatment within 90 minutes. Adapted from McNamara et al.<sup>20</sup>

to reperfusion for some patients with ST-elevation myocardial infarction who otherwise could immediately be given fibrinolytic therapy. When both reperfusion strategies can be rapidly performed, current evidence from clinical trials and registries strongly supports the use of primary PCI, based on its superiority in reestablishing coronary blood flow and the lower risks of reinfarction and intracerebral hemorrhage.<sup>2,39</sup> PCI is also the best option for patients with cardiogenic shock<sup>40</sup> and the only option for those with contraindications to fibrinolytic therapy. However, fibrinolytic therapy remains a practical option for a large number of patients when there is no immediate access to a catheterization laboratory, particularly since the reduced risk of death associated with primary PCI may be restricted to high-risk patients.<sup>41</sup>

The relevant question for clinicians is how long a delay in access to primary PCI would make fibrinolytic therapy the preferred reperfusion therapy. Unfortunately, there is no clear answer. Several meta-regression analyses and a recent pooled analysis of patient-level data have examined this issue.<sup>42-45</sup> Although results vary substantially among these studies, all suggest that differences between reperfusion therapies with respect to mortality favor primary PCI but diminish as PCI-related delays increase, potentially reaching equipoise between 60 and 120 minutes. A recent observational study

from the National Registry of Myocardial Infarction<sup>46</sup> showed a similar association, but the report noted that the effect of PCI-related delays may depend on the patient's age, location of the infarct, and duration of symptoms. Patients who are younger, have anterior infarction, and present with a shorter duration of symptoms — all factors related to the efficacy and safety of fibrinolytic therapy as well as the dangers of delaying treatment — may have worse outcomes with delays in primary PCI as compared with rapid fibrinolytic therapy. This study, however, does not provide strong enough evidence that there are subgroups for which PCI-related delays are unimportant.

Because of the lack of definitive data, there is no consensus on the selection of reperfusion therapy in situations in which primary PCI is not readily available. Triage protocols to determine which patients are better candidates for primary PCI than for immediate fibrinolytic therapy have been proposed, but they have not gained widespread support in the United States. As discussions of improved coordination of care for patients with ST-elevation myocardial infarction across hospitals moves forward, matching individual patients with the most appropriate treatment will be an important goal for health care systems. In most situations, rapid administration of fibrinolytic therapy — within 30 minutes after arrival at the hospital for patients without contraindications to its use — is recommended when door-to-balloon times of more than 90 minutes are anticipated with primary PCI. As noted earlier, however, some experts have suggested that equipoise between the strategies may occur with delays in access to primary PCI of as much as 120 minutes or more, depending on the clinical scenario.<sup>47</sup>

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#### REDUCING DOOR-TO-BALLOON TIME

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Evidence is emerging about the best approaches to improving the timeliness of treatment. Establishing hospital-based strategies to reduce door-to-balloon time in primary PCI requires fundamental changes within complex clinical systems. Bradley and colleagues performed in-depth site visits at 11 top-performing hospitals within the National Registry of Myocardial Infarction that had dramatically shortened their median door-to-balloon time over recent years.<sup>48</sup> Several critical innovations at the organizational level were noted at

these facilities, including the support of senior management, innovative and flexible protocols, individual clinical leaders and collaborative teams, use of data feedback to monitor progress and identify problems and successes, and an organizational culture that fostered improvement efforts.

More recent work has quantified the effects of different specific strategies associated with shorter door-to-balloon times, with the use of data from a national survey of 365 hospitals.<sup>49</sup> Strategies identified as beneficial in this study ranged from approaches with minimal resource requirements, such as activation of the catheterization laboratory by emergency medicine physicians rather than cardiologists and single-call activation by a central page operator, to more complex practices, such as the use of prehospital electrocardiography and 24-hour availability of an on-site cardiologist. Others have reported similar findings, with available data particularly supporting the use of prehospital electrocardiography,<sup>50,51</sup> activation of the catheterization laboratory by emergency medicine physicians,<sup>52,53</sup> and data-monitoring systems with prompt feedback on door-to-balloon time.<sup>54</sup> Only a minority of the hospitals surveyed used many of these strategies.<sup>49</sup>

In an effort to help hospitals improve door-to-balloon time and translate research into practice, the ACC, in partnership with the AHA, the ACEP, the NHLBI, and others, initiated the Door-to-Balloon (D2B) Alliance, a national quality-improvement effort.<sup>5</sup> A tool kit and an implementation package for the D2B Alliance have been created on the basis of an expert review of the literature on strategies for improving door-to-balloon time (Table 1).

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#### COMBINATION STRATEGIES

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Given that there is a limit to how much door-to-balloon time can be shortened, attempts have been made to minimize the impact of delays on outcomes by combining the two reperfusion strategies. In one strategy, commonly referred to as facilitated PCI, pharmacologic reperfusion with fibrinolytic therapy and glycoprotein IIb/IIIa receptor blockers is used to reestablish flow early on and is followed by emergency PCI. Clinical trials have failed to demonstrate that facilitated PCI improves outcomes as compared with primary PCI, and it may actually result in higher mortality.<sup>55,56</sup>

**Table 1. Hospital-Based Strategies Associated with Shorter Door-to-Balloon Time and Potential Tools to Implement Them.\***

Hospital-Based Strategy	Description	Potential Tools
Prehospital ECG and activation	Greater use of prehospital ECGs by emergency medical services, with early activation of catheterization laboratory en route	Prehospital ECG policy Clinical pathway (ECG in emergency department) Guidelines for rapid assessment Protocol for obtaining prompt ECG
Emergency department bypass	Direct transfer to the catheterization laboratory by emergency medical services using pre-hospital ECGs	Prehospital ECG policy Guidelines for direct activation of catheterization laboratory
Process for triaging patients and rapidly obtaining ECG in the emergency department	Establishment of physical space and guidelines in the emergency department for obtaining ECGs during triage evaluations	Dedicated personnel and private area for obtaining ECG in triage
Emergency department activation of the catheterization laboratory	Activation of the catheterization laboratory team by emergency medicine physicians without routine cardiology consultation	Activation policy
Single-call activation	Establishment of a single-call system for activating the entire catheterization laboratory team	Alert system
Rapid arrival of PCI team at hospital	Establishment of the expectation that team members will be available to receive the patient 20–30 min after being paged	Staff policy
Process of performing PCI	Clearance of elective cases during routine work hours; preparation of angioplasty tables during off-hours; clear demarcation of roles for technical and nursing staff	Guidelines for work flow during the day and maintaining availability of standardized equipment during off-hours Protocol for typical diagnostic and PCI approaches
Prompt data feedback	Routine data monitoring of performance with provision of prompt feedback	Time-entry form E-mail team members door-to-balloon times after procedure
Senior management commitment	Organizational environment with strong support by senior management as well as a culture that fosters and sustains organizational change directed at improving door-to-balloon time	Leadership development program
Team-based approach	Emphasis on a team-based approach that provides seamless care from arrival of ambulance to balloon inflation before reperfusion — limit handoffs, one team; organizational support for continuous quality improvement	Tutorial on continuous quality improvement Team training program

\* ECG denotes electrocardiogram, and PCI percutaneous coronary intervention. Adapted from the D2B Alliance.<sup>5</sup>

However, many of these trials included patients at hospitals where primary PCI was already rapidly available, and the approach has yet to be evaluated in a large number of patients at high risk for prolonged delays to mechanical reperfusion, such as transfer patients. Another widely discussed strategy is the pharmacoinvasive approach,<sup>57</sup> in which emergency PCI is not routinely performed after fibrinolytic therapy but is reserved for failed reperfusion based on evidence of improved clinical outcomes in this setting (i.e., rescue PCI).<sup>58</sup> After successful reperfusion, routine (nonemergency)

catheterization with the pharmacoinvasive approach is performed at a later time (e.g., the next day) as opposed to noninvasive risk stratification.

Although anecdotal reports indicate that clinicians are increasingly using facilitated PCI and the pharmacoinvasive approach, neither can be recommended at this time. This is especially true when full-dose fibrinolytic therapy is combined with emergency PCI. This practice, one form of facilitated PCI, should be strongly discouraged, given its potential harm.

FUTURE CHALLENGES  
IN IMPROVING TIME  
TO TREATMENT IN PRIMARY PCI

Targeting improvement of door-to-balloon time at hospitals that already provide primary PCI is the aim of current efforts such as the D2B Alliance. If successful, this work will enhance quality at these facilities. Future challenges will be to optimize primary PCI as its use extends to larger populations of patients by shortening the overall time from the onset of symptoms to treatment. This focus will include strategies for reducing the time from symptom onset to initial contact by patients with the health care system and improving the use of emergency medical systems, both of which have been largely unresponsive to traditional public education campaigns.<sup>59</sup>

In an effort to expand the availability of PCI, some regions are now permitting primary PCI at hospitals with catheterization laboratories but no on-site cardiac surgery or elective PCI. Early studies suggest improved clinical outcomes with this approach, as compared with fibrinolytic therapy, when it is associated with a dedicated, primary PCI development program.<sup>60</sup> As compared with transfer for primary PCI, primary PCI at hospitals without on-site cardiac surgery has been associated with shorter times to treatment, with some data suggesting similar short-term mortality.<sup>61,62</sup> The evidence in this area, however, is very limited. More recently, there has been great interest in

using “bypass” protocols that are similar to the trauma model. This would allow patients with ST-elevation myocardial infarction to be triaged directly to hospitals with PCI capabilities by emergency medical services rather than to the nearest hospital. However, this approach would be best implemented with the use of prehospital electrocardiography, which is still uncommon in the United States.<sup>63</sup>

Systems of care that integrate many of these approaches are being developed in some regions of the United States and are the focus of the AHA program Mission Lifeline.<sup>64</sup> Although there is early evidence of success in limited areas, broad generalizability of these systems has yet to be demonstrated. Any improvements in access to primary PCI with these strategies also must be balanced against the use of immediate fibrinolytic therapy, which remains a reasonable alternative for reperfusion therapy in selected instances. Matching patients with the most appropriate treatment and location will entail developing a level of coordination and collaboration among hospitals beyond what is currently available in the U.S. health care system but is achievable.

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