Primary angioplasty offers benefits as compared with fibrinolysis for many patients with acute ST-elevation myocardial infarction (STEMI). This superiority of percutaneous coronary intervention (PCI) in trials has led to the investigation of transfer strategies that would make PCI more widely available. Such a strategy would regionalize care and divert patients with STEMI to centers with PCI capability. The clinical cost of such a strategy in terms of time and divert patients with STEMI to centers with PCI capability. The clinical cost of such a strategy in terms of time requires investigation.

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Time to reperfusion after fibrinolysis is a critical determinant of outcome. In some reports of primary angioplasty, the time to reperfusion has had little effect on mortality. In most other studies, however, a longer door-to-balloon time worsened outcome as assessed by myocardial infarct size as well as mortality. In one recent analysis of 1791 patients with STEMI treated by primary angioplasty, each 30-minute delay in reperfusion was associated with a relative risk for 1-year mortality of 1.075. In a retrospective analysis of randomized trials that compared fibrinolysis to primary angioplasty, the mortality benefit associated with PCI was lost when the door-to-balloon time was delayed by >1 hour as compared with the door-to-needle time. Some of the difference in the comparison of fibrinolysis and primary angioplasty may reflect a relative decrease in the efficacy of fibrinolysis with time after symptom onset or the relatively good outcome that occurs in the lowest-risk STEMI patients. On the basis of the benefit associated with primary angioplasty over fibrinolysis in randomized trials, new trials were designed and carried out that involved transferring patients from hospitals without cardiac catheterization capability to PCI centers. The proper interpretation of the results of these trials requires a careful analysis of the importance of time.

Trials of Transfer for PCI

Five randomized trials compare fibrinolysis with transfer to another hospital for primary angioplasty. The results of these trials (shown in the Table) summarized in 2 meta-analyses have been interpreted to demonstrate that transfer for primary angioplasty is a better treatment than thrombolysis at the presenting hospital. Before the results of these trials can be generalized to routine practice, however, a number of caveats need to be considered.

First, the overall door-to-balloon time in these 5 trials was short and minimized by protocols that involved calling ahead to the transfer hospital and bypassing the emergency department and coronary care unit in the transfer hospital on the way to the cardiac catheterization laboratory. Thus, the transfer time could be considered “parallel” rather than additive to the usual door-to-balloon time. As summarized in the Table, the delay in transfer resulted in a total door- (or symptom-) to-balloon time that was only 69 minutes longer than the corresponding door- (or symptom-) to-lysis time. This time was only 30 minutes longer than the door-to-balloon time in the randomized trials of primary angioplasty. Unfortunately, as shown by the Second National Registry of Myocardial Infarction database, <30% of US patients can actually achieve door-to-balloon times <90 minutes even in the presenting hospital.

Several biases also favored PCI in these transfer trials. First, there is a selection bias, in that most of the studies excluded patients who were believed to be unsafe for transfer. In the largest trial, patients with a previous cerebral vascular accident were not excluded from fibrinolysis. Similarly, the patients with recurrent myocardial infarction (MI) after fibrinolysis in this largest transfer trial were treated with repeat lysis rather than rescue angioplasty, the latter treatment being one that was recently demonstrated to reduce mortality by 50%. Furthermore, procedural MIs, which occur in 5% to 10% of patients with acute coronary syndromes undergoing PCI, were not included in the primary PCI endpoint.

The low rate of both rescue PCI and subsequent catheterization, which can limit the rate of recurrent MI included in the 30-day composite end point, also may have influenced the results of several of these trials. In the DANAMI-2 (Danish Acute Myocardial Infarction-2) trial, only 21% of fibrinolytic-treated patients received revascularization within 30 days, and these patients had a recurrent MI rate of 6.3%, the major determinant of the difference in the composite end point. In the AIR-PAMI (A Randomized Trial of Thrombolysis Compared to Transfer For Air Primary Angioplasty in Myocardial Infarction) trial, 52% of patients were revascularized within 30 days and had a repeat MI rate of 0%. In the meta-analysis of these trials, a statistically significant reduction in mortality alone could not be demonstrated. Finally, the benefit of primary PCI was greatest in patients who presented >3 hours after the onset of symptoms, consistent...
with the relatively greater benefit of fibrinolysis in early presenters.4,12

What does the study by Nallamothu et al22 in this issue of Circulation add to our consideration of the importance of time in patients transferred for primary angioplasty? Their study demonstrates from a large registry of MI in the United States that the “total” door-to-balloon time in 4278 transfer patients was a median of 180 minutes, with only 4% of patients having a door-to-balloon time of <90 minutes and 15% ≤120 minutes.22 These values contrast with the current American College of Cardiology/American Heart Association guidelines, which recommend a goal of <90 minutes for total door-to-balloon time.23 The longest delay occurred in patients with comorbid conditions, a delayed presentation after symptom onset, nonspecific ECG findings, and presentation during off hours and to nonteaching hospitals in rural areas.

Strengths of this study include the large number of patients analyzed, which is ≈3 times the total previously studied in all of the randomized trials (Table). In addition, the patients were unselected from a wide cross-section of hospital types, and in this regard represent a real-world study population. A weakness of the study, as noted by the authors, is the fact that the data were voluntarily reported. The lack of outcome data to provide a context for both the baseline characteristics and the effects of transfer times is an additional shortcoming.

Finally, although the door-to-balloon times in the transfer hospital were relatively short, with a median of 53 minutes, there were still 12% of patients who had a door-to-balloon time of >2 hours in the transfer hospital. Furthermore, a longer door-to-door time for transfer was not associated with a shorter door-to-balloon time in the transfer hospital. This finding contrasts directly with the planning and execution of the randomized transfer trials described above and suggests a clear opportunity for improvement.

Clinical Implications

Currently, real-world hospital transfer greatly increases door-to-balloon time.6,22 Furthermore, the total door-to-balloon time is substantially (2-fold) longer than in the randomized trials of transfer for primary PCI. For this reason, we must exercise caution in applying the conclusions from the randomized trials to general practice.

To make a transfer strategy successful, it is essential to reduce the door-to-balloon time by improving systems and processes of care. To minimize the effect of the transfer on the time to reperfusion, communication should be optimized to include early mobilization of the cardiac catheterization laboratory team in the transfer hospital. Efforts must be made to minimize delays on arrival at the transfer hospital on the way to the catheterization laboratory. The randomized trials, as well as treatment networks now established in Poland, the Czech Republic, and isolated networks in the United States, demonstrate that this can indeed be accomplished. This study demonstrates that in the United States many patients are being transferred for primary PCI, with remarkably long door-to-balloon times averaging ≈3 hours. For most patients in whom the total door-to-balloon time (including the transfer time) is expected to exceed 120 minutes and without contraindications, a fibrinolytic agent administered at the first hospital is the better treatment choice.23

If organized systems can be implemented to optimize transfer for primary angioplasty, then there may be a synergistic benefit with technologically advanced therapies that may be available only in specialized centers. Several authors have called for the development of regional and national strategies to create such centers of excellence.24 Therapies that may be expensive but beneficial, including advanced support mechanisms for cardiogenic shock, for myocardial reperfusion, and potentially for myocardial preservation, could be centralized at such sites.25 In this regard, it would be important to identify those patients who benefit most from transfer.

The long time to transfer also suggests that a strategy of treatment on the way to primary angioplasty may be necessary. This approach of “facilitated PCI” has the potential benefit of opening the artery on the way to the transfer hospital, thereby resulting in earlier reperfusion and a more successful intervention with more complete patency and better perfusion.26 This idea is being tested in the ongoing FINESSE (Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events) and ASSENT-4 (Assessment of the Safety and Efficacy of a New Treatment Strategy for

<table>
<thead>
<tr>
<th>Study/Reference</th>
<th>No./Arm</th>
<th>Total Symptom or Door-to-Lysis, min*</th>
<th>Total Symptom or Door-to-PCI, min*</th>
<th>Difference (Transfer Delay), min</th>
<th>Door-to-Balloon in Transfer Hospital, min</th>
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</tr>
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</table>

‡Data provided by H. Krumholz, MD, written communication, 2004.
*Symptom-to-therapy in Vermeer et al, PRAGUE-2, and DANAMI-2 trials; door-to-therapy in AIR-PAMI and DANAMI trials.
†Data available in 82% of patients.
Acute Myocardial Infarction-4) trials. Finally, regardless of whether patients are transferred for primary PCI, undergo primary PCI at the presenting hospital, or have fibrinolysis with or without subsequent catheterization, it is imperative that clinicians not ignore postinfarction care to minimize adverse remodeling, the risk of sudden death, and to provide secondary prevention.

Conclusion

The study by Nallamothu et al. demonstrates that in a real-world US population, transfer for primary angioplasty markedly delays door-to-balloon time and must be carefully balanced against any potential benefit of primary PCI over fibrinolysis. For this reason, it is too early to recommend routine transfer for primary angioplasty for all patients with STEMI. It may be most appropriate for patients with large MIs, cardiogenic shock, Killip class ≥3, failed fibrinolysis, a long symptom-to-presentation time, or a short transfer delay. This study also suggests major areas for improvement that can result in better outcomes for patients that are in need of transfer therapy. In the debate of fibrinolysis versus primary PCI with or without transfer, we should not lose sight of the importance of time.

References


Key Words: Editorials ■ angioplasty ■ fibrinolysis ■ myocardial infarction ■ catheterization
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Howard C. Herrmann

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