Rationale and Strategies for Implementing Community-Based Transfer Protocols for Primary Percutaneous Coronary Intervention for Acute ST-Segment Elevation Myocardial Infarction

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The focus for the initial approach to the treatment of acute ST-segment elevation myocardial infarction (STEMI) has shifted toward extending the benefits of mechanical reperfusion with primary percutaneous coronary intervention (PCI) to patients who present to community hospitals that have no interventional capabilities. Several randomized clinical trials have shown that transferring STEMI patients to tertiary centers for primary PCI leads to better outcomes than when fibrinolytic therapy is administered at community hospitals. Furthermore, potent pharmacologic reperfusion regimens that enhance early reperfusion of the infarct vessel before primary PCI may enhance the positive result of the transfer approach.

Despite these promising findings, several obstacles have hindered the adoption of patient-transfer strategies in the U.S., including greater distances between community and tertiary hospitals, a lack of integrated emergency medical services, and the medical community’s limited experience with centralized acute myocardial infarction (AMI) care networks. Nonetheless, the implementation of system-wide changes in the care of STEMI patients analogous to the creation of trauma networks could facilitate the creation and ongoing evaluation of dedicated patient transfer strategies and better early invasive care in the U.S.

Within this context, a systematic, stepwise approach to the creation of AMI care networks and to the development of standard nomenclature and performance indicators is necessary to guide quality assurance monitoring and future research efforts as the care of STEMI patients is redefined. Consequently, this current evolution of reperfusion strategies has the potential to further reduce morbidity and mortality for patients presenting with STEMI.

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BENEFITS OF PRIMARY PCI

Primary PCI has emerged as the preferred reperfusion strategy for patients with STEMI at institutions with appropriate interventional capabilities and experience. When accomplished quickly by skilled operators, primary PCI leads to decreased rates of mortality, reinfarction, stroke, and hemorrhagic complications compared with full-dose fibrinolysis (1). In a recent systematic overview of data from 11 fibrinolysis versus primary PCI trials, patients in the primary PCI arm had lower rates of mortality, nonfatal reinfarction, and stroke compared with patients given full-dose fibrinolytic therapy (Fig. 1) (1). The results of another meta-analysis comparing 23 fibrinolysis versus primary PCI comparison trials for STEMI revealed similar findings (5).
Although these overviews likely overestimate the benefit of primary PCI in "real-world" clinical practice, they nevertheless provide strong evidence that mechanical reperfusion is the preferred therapeutic approach for STEMI.

**GEOGRAPHIC DISPARITIES IN THE AVAILABILITY OF PRIMARY PCI**

The widespread use of primary PCI is restricted by a lack of properly equipped hospitals and experienced staff. Clustering of interventional hospitals in cities and suburban areas has left vast regions of the U.S. without timely access to primary PCI. In a recent STEMI registry, only 39% of the 1,506 participating U.S. hospitals had the recommended primary PCI capabilities with back-up cardiac surgical coverage (6,7). Accurate and comprehensive data for all primary PCI-capable hospitals in the U.S. do not exist, but it is likely that most primary PCI centers are in moderate-to-large-size communities with greater populations.

**PRIMARY PCI AT COMMUNITY HOSPITALS**

New treatment strategies and changes in health care systems are needed to extend the benefits of primary PCI to more patients with STEMI. One approach is to offer onsite primary PCI in community hospitals with cardiac catheterization laboratories but without cardiac surgical back-up coverage. The Atlantic Cardiovascular Patient Outcomes Research Team examined the feasibility of this approach when they introduced primary PCI at 11 community hospitals equipped with catheterization laboratories but without PCI or cardiac surgery programs (8). After initial training in performing PCI, doctors at participating sites randomly assigned STEMI patients to primary PCI or full-dose fibrinolysis. Despite early termination of this study (funding limitations and poor enrollment), the incidence of recurrent myocardial infarction (MI), stroke, or death at six months was reduced in the primary PCI arm (12.4% vs. 19.9%; p = 0.03). However, these findings were confounded by insufficient power to show definitive results and early study termination.

Further studies evaluating primary PCI in community hospitals are needed.

### Abbreviations and Acronyms

- **AMI** = acute myocardial infarction
- **AIR-PAMI** = Air Primary Angioplasty in Myocardial Infarction
- **DANAMI** = Danish Multicenter Randomized Trial on Thrombolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction
- **MI** = myocardial infarction
- **PCI** = percutaneous coronary intervention
- **PRAGUE** = Primary Angioplasty After Transport of Patients from General Community Hospitals to Catheterization Units With/Without Emergency Thrombolysis Infusion
- **SK** = streptokinase
- **STEMI** = ST-segment elevation myocardial infarction

### Table

<table>
<thead>
<tr>
<th>Trial</th>
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<th>PTCA (%)</th>
<th>Lytic (%)</th>
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<td></td>
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<tr>
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<td>4.3</td>
<td>6.9</td>
<td>0.62 (0.44–0.86)</td>
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</table>

Figure 1. Mortality to 30 days for ST-segment elevation myocardial infarction patients treated with primary percutaneous transluminal coronary angioplasty (PTCA) versus fibrinolytic therapy (lytic). Reproduced with permission from the Primary Coronary Angioplasty Trialists’ (PCAT) Collaborators (1). CI = confidence interval; SK = streptokinase; tPA = tissue plasminogen activator.
hospitals are needed to determine the efficacy or feasibility of implementing such a strategy. Additionally, the financial and institutional commitment required to create a primary PCI program in a hospital that has only a diagnostic catheterization laboratory needs to be more fully defined. Current guidelines recommend that when no on-site surgery program exists, primary PCI should be performed only at institutions with a proven plan for rapid access (within 60 min) to a nearby facility with capability for performing at least 36 primary PCI procedures per year by skilled operators (who perform at least 75 PCI procedures per year) (7). Given these limitations, a strategy for the interhospital transfer of STEMI patients from community hospitals to tertiary hospitals equipped to perform primary PCI may be more feasible and may capitalize on the resources already present at tertiary hospitals.

TRANSFER FOR PRIMARY PCI

In the largest experience of transfer for primary PCI, the Danish Multicenter Randomized Trial on Thrombolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI-2), 1,572 patients with STEMI were randomly assigned to on-site accelerated tissue plasminogen activator or primary PCI at 24 hospitals in Denmark (9). Patients who were randomized to primary PCI at referral centers were transferred to one of five invasive centers, provided that transfer would likely take <3 h. Transfer for primary PCI was well tolerated, with no deaths or serious adverse events. The median transfer distance was 50 km (range, 3 to 150 km), and the median transfer time was 67 min (interquartile range, 50 to 85 min). The DANAMI-2 trial was stopped early because of an approximately 40% lower incidence of the primary end point of recurrent MI, disabling stroke, or death at 30 days with primary PCI compared with fibrinolysis (8.5% vs. 14.2%; p = 0.002). However, the significance of these findings has been questioned because: 1) recurrent MI was the only end point that was significantly reduced with primary PCI; 2) different definitions of MI were used in the two treatment groups; and 3) early-rescue PCI was prohibited for reperfusion failures in the fibrinolytic group. Nonetheless, the Danish experience reveals that a cohesive network of centers could rapidly and safely transfer STEMI patients for primary PCI.

In the Primary Angioplasty After Transport of Patients from General Community Hospitals to Catheterization Units With/Without Emergency Thrombolysis Infusion (PRAGUE-1) study, the safety and feasibility of interhospital transfer of patients with STEMI in the Czech Republic was evaluated (10). Patients were randomly assigned to three groups: group A received intravenous streptokinase (SK); group B received SK with immediate transfer to an invasive center for subsequent PCI; and group C was transported to an invasive center without receiving fibrinolytic therapy. Transfer was tolerated well, with rare nonfatal complications and no deaths. The primary composite end point (reinfarction, stroke, or death at 30 days) was reduced across groups A, B, and C (23%, 15%, and 8%, respectively; p < 0.02).

The encouraging findings from the PRAGUE-1 trial spurred the subsequent nationwide PRAGUE-2 trial (11). In PRAGUE-2, 850 STEMI patients from community hospitals in the Czech Republic were randomly assigned to on-site fibrinolysis with SK or transfer to invasive centers for primary PCI. There was a modest trend toward reduction in the primary end point of 30-day mortality with primary PCI versus SK (6.8% vs. 10.0%; p = 0.12). Analysis of a prespecified subgroup of patients who presented within 3 h of symptom onset showed no mortality benefit with transfer for PCI (7.3% vs. 7.4%), whereas patients who presented within 3 to 12 h of symptom onset had a significant reduction in mortality (6.0% vs. 15.3%; p < 0.02). Therefore, the PRAGUE-2 results confirm the feasibility of transferring STEMI patients for primary PCI but also suggest that transfer for primary PCI may primarily benefit patients who do not present soon after symptom onset.

The only clinical trial in the U.S. with transfer for primary PCI was the Air Primary Angioplasty in Myocardial Infarction (AIR-PAMI) study, which included nine U.S. hospitals and three non-U.S. hospitals. High-risk patients with STEMI who presented to community hospitals without interventional capabilities were assigned randomly to fibrinolysis or immediate transfer to a nearby tertiary center for primary PCI (12). The mean distance between community and invasive hospitals was 32 miles; mean transport time was 33 min. After 39 months, the AIR-PAMI trial was terminated early because of slow enrollment; only 138 patients (32% of the anticipated sample size) were randomized. Despite early termination, the study revealed that patients transferred for primary PCI had a nonsignificant lower risk of reinfarction, disabling stroke, or death at 30 days (8.4% vs. 13.6%; p = 0.33). The disappointing enrollment in the AIR-PAMI trial suggests that significant obstacles may impede studies of transferring patients with STEMI for primary PCI in the U.S.

A recently published meta-analysis of results from fibrinolysis versus primary PCI trials included data from five trials (DANAMI-2, PRAGUE-1 and -2, AIR-PAMI, and the Limburg Intervention/MI trial) that compared on-site fibrinolysis with immediate transfer for primary PCI (5,13). Combined data from these trials showed that transfer for primary PCI was associated with a significant decrease in the composite end point of nonfatal MI, stroke, or death compared with fibrinolysis (Figs. 2 and 3). Two other reviews had similar conclusions (14,15). These cumulative results underscore the concept that transferring STEMI patients for primary PCI appears to be a superior reperfusion strategy compared with on-site fibrinolysis at a community hospital, but time delays associated with transferring patients for PCI in routine clinical practice may be a major
hindrance to the more widespread adoption of transfer strategies for community hospitals (2,6).

**TIME TO REPERFUSION WITH PRIMARY PCI**

Data indicate that the earlier administration of fibrinolytics after the onset of symptoms improves myocardial salvage and preserves left ventricular function, resulting in a significant, time-dependent survival benefit (16). Although a time-to-treatment relation with primary PCI has not been proven, a similar relation persists in data from observational registries. In data from more than 27,000 patients treated with primary PCI for STEMI in the National Registry of Myocardial Infarction-2, a direct relation was shown between shorter “door-to-balloon” times and lower adjusted risks of mortality, although the time from onset of symptoms to balloon inflation actually showed little relation to outcomes (17). Current guidelines for primary PCI recommend that balloon inflation be performed within 90 (± 30) min of hospital arrival (7,18). However, the average “door-to-balloon” in the recent National Registry of Myocardial Infarction-3 registry was slightly more than 2 h at primary PCI centers and more than 3 h for patients transferred from a community hospital to a tertiary hospital for primary PCI (6). Therefore, the administration of potent adjunctive pharmacologic agents at the time of initial presentation may be synergistic and overcome the delays inherent in reperfusion when transferring patients for primary PCI.

**MERGING PHARMACOLOGIC AND MECHANICAL REPERFUSION**

Improved pharmacologic reperfusion regimens enhance reperfusion before definitive mechanical recanalization and may be useful adjunctive therapies when combined with a transfer strategy for primary PCI (19–23). The PRAGUE-1 trial included a “fibrinolysis-before-transfer” arm, and a recent report from the largest PRAGUE-1 contributing center (49% of total patients) described lower mortality rates in this group of patients compared with both “fibrinolysis-only” and “transfer-only” patients (19). Because similar findings were not observed in the overall trial, these results should be interpreted cautiously; further studies are underway to investigate the potential benefits of full-dose fibrinolysis before transfer for PCI. The administration of the glycoprotein IIb/IIIa inhibitor abciximab before primary PCI improves reperfusion before PCI and has improved clinical outcomes in small studies and a systematic overview (20,21). An alternative approach that combines reduced-dose fibrinolytic therapy + glycoprotein IIb/IIIa inhibitors before PCI also has shown favorable procedural and clinical outcomes in small studies (22–24). Although these combinations of adjunctive therapies before planned primary PCI must still be validated in large-scale randomized trials, pharmacologic reperfusion for patients initially presenting to community hospitals may become the preferred initial treatment strategy used before transferring patients to tertiary hospitals.

**ADOPTING TRANSFER STRATEGIES IN THE U.S.**

Because more than one-half of STEMI patients in the U.S. present to hospitals without on-site primary PCI and back-up coronary artery bypass grafting capabilities, the opportunity exists for implementing a widespread transfer strategy (6). However, in a recent study, patients transferred for primary PCI between 6:00 PM and 8:00 AM had a greater frequency of failed PCI procedures; in another study, prehospital fibrinolysis <2 h after symptom onset was associated with improved survival compared with primary PCI, as in the PRAGUE-2 findings (11,25,26). Rapid risk stratification protocols may help identify patients likely to benefit from transfer for primary PCI compared with those who may benefit more from onsite fibrinolysis, for example, patients who present early after the onset of symptoms or those not expected to receive significant benefit from pri-
mary PCI. Large-scale randomized studies are clearly needed to precisely define the “ideal” transfer population and delineate appropriate triage strategies.

To successfully implement transfer strategies for primary PCI in the U.S., obstacles must be overcome: delays due to large distances between hospitals in certain regions, highly variable skills and training of emergency medicine personnel, and liability issues regarding complications that could stem from the transfer. Additionally, current reimbursement policies for acute myocardial infarction (AMI) care may be a major deterrent to transferring patients for primary PCI; such patients represent potential financial losses to community hospitals and financial gains for tertiary hospitals. Nonetheless, transfer strategies could be implemented in the U.S. if the current structure of STEMI care were changed (2).

Integrated and coordinated acute STEMI systems similar to trauma systems/networks should be established, with the goals of improving the process of early care and the outcomes of patients with STEMI (2). Acute STEMI systems could facilitate the immediate transfer of patients with STEMI to high-volume tertiary hospitals that have primary PCI capabilities because these hospitals have lower mortality rates and improved procedural outcomes with primary PCI (27,28). However, the distribution of primary PCI-capable centers in the U.S. remains difficult to characterize; therefore, accurate data regarding local population densities, distances between hospitals, and transportation capabilities are needed before STEMI transfer networks can be established. Nonetheless, we propose the following steps to implement dedicated transfer strategies in local communities:

1. The designation of centralized AMI centers located within a reasonable distance from all referral community hospitals; centers should have proven expertise in performing primary PCI.
2. The development of AMI teams at community hospitals that can accurately identify STEMI patients eligible for primary PCI, correctly administer preferred initial medications, and rapidly transfer patients directly to the AMI center.
3. The central coordination and management of care at community and tertiary hospitals.
4. The implementation of quality monitoring to continually assess processes of care and outcomes for patients transferred for primary PCI.
5. The creation of clinical research networks to extend AMI research into community hospitals and provide a structure to prospectively evaluate transfer strategies and adjunctive pharmacologic regimens.

INITIAL EXPERIENCES WITH TRANSFER STRATEGIES FOR PRIMARY PCI IN THE U.S.

Using the steps described in the previous text, the Duke University Medical Center has recently implemented a regional transfer system for STEMI. Prompt transfer mechanisms have been developed with local emergency medical services systems, and communications have been streamlined via a central network. Immediate transfer is stimulated by a single telephone call from the referring hospital. All measures of care and long-term outcomes are collected for ongoing quality assurance monitoring. Although early in its inception, this transfer strategy at Duke University Medical Center has generated positive responses from all participating clinicians.

Abbott Northwestern Hospital in Minneapolis, Minnesota, has developed a similar STEMI transfer protocol and has reported their initial experiences. By use of this integrated transfer system, 57 patients from eight hospitals were rapidly and safely transferred for primary PCI with the mean time from initial hospital arrival to first balloon inflation of 98 min (29).

STANDARDIZING THE EVALUATION OF TRANSFER STRATEGIES FOR PRIMARY PCI

As transfer approaches are adopted in the U.S., standard terminology is needed to designate common time intervals and outcome variables for evaluating transfer strategies. Analysis of the four large randomized trials comparing on-site fibrinolysis with transfer for primary PCI revealed variable definitions and inconsistent reporting of critical treatment time intervals, making it difficult to interpret and compare results (Table 1) (9–12). Disparities also are evident in the Centers for Medicare and Medicaid Services 2003 report of mean “door-to-balloon” time of 356 min for 690 participating U.S. hospitals (30). The accuracy of the Centers for Medicare and Medicaid Services data is uncertain but points to the difficulties in accurately identifying patients with STEMI who are eligible for reperfusion with primary PCI, data collection, and studying quality measures in patients undergoing primary PCI.

We propose the following standard time intervals and terminology for evaluating transfer strategies for primary PCI: 1) time at referral hospital = time from initial hospital arrival until transfer to PCI hospital; 2) transfer time = time from transfer from referral hospital until arrival at PCI hospital; 3) door-to-balloon time = time from arrival at PCI hospital until first balloon inflation; 4) first medical contact to first balloon inflation at PCI hospital = total time from first contact by medical personnel to reperfusion with PCI; and 5) symptom onset to first balloon inflation at PCI hospital = total time from onset of symptoms to reperfusion with PCI. Such standardization of critical time intervals will help guide the ongoing assessment of transfer strategies for primary PCI in clinical practice and results from prospective clinical trials.

CONCLUSIONS

As the reperfusion era continues to evolve, the focus of STEMI care must change from subtle refinements in care to
Establishing Transfer Protocols for STEMI Patients

Table 1. Median Time Intervals for Patients Randomly Assigned to Transfer for Primary Percutaneous Coronary Intervention

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Door to Randomization (min)</th>
<th>Randomization to Departure (min)</th>
<th>Transfer Time (min)</th>
<th>Door to Balloon* (min)</th>
<th>Symptom Onset to Balloon (min)</th>
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<tr>
<td>PRAGUE-1 (10)</td>
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*Time from arrival at tertiary hospital until first balloon inflation during percutaneous coronary intervention. NR = not reported.

widespread changes in health care systems. Patient access to rapid, high-quality primary PCI should increase, and dedicated transfer strategies offer the greatest potential to accomplish this goal. Multiple studies have documented the potential for improved outcomes with a strategy of transfer for primary PCI compared with the administration of fibrinolytic therapy at community hospitals; however, a definitive, large-scale clinical trial is needed to verify the results of these small studies in the U.S. Potent pharmacologic “transfer regimens” hold promise for improving early reperfusion of the infarct vessel before primary PCI, so these regimens should also be tested further in prospective clinical trials evaluating transfer strategies. However, poor enrollment leading to early termination of the AIR-PAMI and Atlantic Cardiovascular Patient Outcomes Research Team trials suggests that U.S. investigators are unwilling to randomize STEMI patients in trials evaluating new approaches for STEMI care (8, 12). Acute STEMI networks will be needed to improve participation in clinical trials in the U.S., delineate the optimal approach to STEMI care, overcome obstacles that may hinder further study of transfer strategies, and extend the benefits of mechanical reperfusion to more patients with STEMI. (30)

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