Primary Percutaneous Coronary Intervention for Every Patient With ST Elevation MI: What Stands in the Way?

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Clinical and research interests:

As an interventional cardiologist, my clinical interest is in percutaneous revascularization treatments of acute coronary syndromes, particularly catheter-based reperfusion strategies for the treatment of ST elevation myocardial infarction. My research interests include studying the role of inflammation in acute coronary syndromes, and the genetic predispositions that result in these syndromes.

Introduction

According to data from randomized controlled trials, primary percutaneous coronary intervention (PCI) is the unambiguous treatment of choice for ST elevation myocardial infarction (STEMI): in these trials, one life was saved and two other complications were prevented for every 50 patients with STEMI treated with primary PCI rather than with thrombolytic therapy. How can these superior results be realized in the real world, outside the context of randomized trials? I anticipate five obstacles to the institution of primary PCI as the universal treatment for STEMI (Table): 1) lack of ready availability, 2) technical expertise of center and operator, 3) addressing patient subgroups not studied in randomized trials, 4) cost, and 5) comparisons of primary PCI to newer pharmacologic regimens. In this presentation, I propose 3 strategies to increase the availability of this procedure: A) perform primary PCI in qualified community hospitals without surgical back-up, B) transfer patients from community hospitals without primary PCI capability to hospitals with primary PCI capability, and C) develop a universal system where ambulances directly transfer patients to a regional primary PCI center, not necessarily to the closest hospital, similar to that used for trauma patients. I contend that in light of the superior clinical outcomes seen with primary PCI for the treatment of STEMI, this procedure should be made available to all patients with STEMI, and efforts should be made to institute these measures.

Summary Of Results From Randomized Controlled Trials Of Primary PCI

For every 50 patients with STEMI treated with primary PCI rather than thrombolytic therapy in randomized trials, one life was saved and another two complications were prevented (1). According to these data, treatment with primary PCI reduces overall short-term death (7% vs 9%, $p = 0.0002$), non-fatal reinfarction (3% vs 7%, $p < 0.0001$), stroke (1% vs 2%, $p < 0.0004$), and the combined endpoint of death, non-fatal reinfarction, and stroke (8% vs 14%, $p < 0.0001$); it nearly obliterates the devastating complication of hemorrhagic stroke (0.05% vs 1%, $p < 0.0001$) (1). These superior outcomes are attained regardless of the type of thrombolytic agent used or the delay between symptom onset and treatment (2). Primary PCI decreases mortality in patients with cardiogenic shock who are < 75 years old (3) and in patients with contra-indications to thrombolysis (4). Patients treated with primary PCI have a lower incidence of free-wall rupture and ventricular septal defect (5-7), a lower risk of reinfarction, and improved long-term survival (8-11). Primary PCI restores epicardial blood flow in >90% of patients as compared to 30-55% with thrombolytic therapy (12, 13) and results in greater myocardial salvage (14). Recently, primary PCI has been shown to be better than thrombolytic therapy even when performed in community hospitals without on-site surgical back-up (15), and when the patient is transferred for primary PCI instead of receiving on-site thrombolytic therapy (16). Perhaps as a result of these findings, the use of primary PCI for STEMI has increased three-fold in the past decade (2.4% to 7.3%, $p=0.0001$), while the use of thrombolytic therapy has decreased (34.3% to 20.8%, $p=0.0001$) (17).

1. Availability

Lack of availability is the most important obstacle preventing the use of primary PCI in all patients with STEMI: fewer than 1 in 5 hospitals in the United States and 1 in 10 in Europe have cardiac catheterization facilities, and even fewer have the capability to perform primary PCI on a full-time emergency basis (18). Three strategies can

improve access to primary PCI: A) developing primary PCI programs in community hospitals regardless of availability of on-site surgical back-up, B) transferring patients with STEMI from hospitals without primary PCI capability to specialized regional primary PCI centers, and C) coordinating an Emergency Medical System (EMS) network similar to that used for trauma and burn patients, to transport STEMI patients directly to specialized primary PCI centers and not necessarily to the nearest emergency department (Figure).

Strategy A: Primary PCI In Community Hospitals Regardless Of Availability Of On-Site Surgical Back-Up. The ability to perform primary PCI in hospitals without on-site cardiac surgery is logistically important: the Society for Coronary Angiography and Intervention directory indicates that there are approximately 850 community hospitals in the United States with cardiac catheterization laboratories without on-site cardiac surgery, and at least 97 of these hospitals in 30 states are performing primary PCI (Wharton TP. Personal communication). In addition, of the 1,506 hospitals in the National Registry of Myocardial Infarction-2 most had the capability to perform on-site primary PCI (19): 39.2% had on-site surgical back-up, 25.2% had the capability to perform coronary angiography, and 7.4% had the capability to perform PCI, only 28.1% did not have a cardiac catheterization laboratory. Increasing the proportion of community hospitals that do not have on-site cardiac surgery but are qualified to perform primary PCI would increase access to this procedure.

The obvious question is whether primary PCI in such a setting is safe and effective. With the routine availability of stents, emergency coronary artery bypass surgery (CABG) due to failed PCI has become extremely rare. In the Myocardial Infarction, Triage, and Intervention registry of STEMI, 441 (12%) of 3750 patients underwent primary PCI, and 233 were performed in hospitals without on-site surgical back-up (20). Only 1.4% required emergency CABG, and clinical outcomes were dependent on hemodynamic stability and infarct location, but not on the presence of on-site surgery. In another observational study of primary PCI performed in two community hospitals without on-site surgical back-up, 506 primary PCI procedures were performed, and no patient died or required emergent CABG (21). The infrequent need for emergent CABG during PCI has also been shown in prospective trials: In the Primary Angioplasty in Myocardial Infarction-2 trial, primary PCI was performed in 982 patients, and only 4 patients (0.4%) required emergency CABG (22). In a review of 6 major randomized trials comparing balloon angioplasty to coronary stenting in STEMI (23-28) only 6 of 1,953 patients (0.31%) required emergency CABG for a failed PCI (29).

The efficacy and safety of primary PCI in hospitals without on-site surgical back-up has been examined directly in a prospective controlled trial which randomized 453 patients to thrombolytic therapy or primary PCI in this setting (15). Patients treated with primary PCI in hospitals without on-site surgical back-up had 42% lower incidence of the combined endpoint of death, recurrent infarction, and stroke at 6 months as compared to patients treated with thrombolytic therapy. No patient in the primary PCI group required emergency CABG for a PCI-related complication or failure, and the median length of stay was significantly shorter in patients treated with primary PCI compared to those treated with thrombolytic therapy (4.5 days versus 6 days, $p=0.02$). I contend, therefore, that "on-site surgical back-up" is no longer a requirement for primary PCI centers.

Strategy B: Emergent Transfer For Primary PCI. It is generally accepted that high-risk patients such as those in cardiogenic shock (3), or with contra-indications to thrombolytic therapy (4) presenting to hospitals without primary PCI capability should be rapidly transferred to hospitals that can provide this therapy. Recently, it has been suggested that all patients with STEMI, including those without these high-risk features, could be safely transferred for primary PCI rather than receive on-site thrombolytic therapy. This approach stemmed from the observation that survival following STEMI is influenced not only by the time to presentation but also the choice of reperfusion therapy: while the efficacy of thrombolytic therapy decreases with increasing age of the occlusive coronary thrombus (30-34), the efficacy of primary PCI remains stable over time and clinical outcomes are less dependent on the time to treatment compared to thrombolytic therapy (35) -- this phenomenon is referred to as the time-to-treatment paradox.

Several possible mechanisms may explain the time-to-treatment paradox. In thrombolytic therapy, there is an inverse relationship between the rate of achieving normal blood flow and the interval between symptom onset and administration of therapy (time-to-treatment). This is important, since failure to achieve normal blood flow in the infarct-related artery is a major determinant of short and long-term survival. In primary PCI, however, the rate of achieving normal blood flow remains high (> 90%) regardless of the time-to-treatment interval (35, 36). With progressive increases in time-to-treatment, patients treated with thrombolytic therapy have an increased risk of mechanical complications (5-7), including myocardial rupture. Mechanical complications, however, are rare in patients treated with primary PCI (37, 38). Patients treated with thrombolytic therapy also have an increased incidence of re-occlusion of the infarct-related artery, reinfarction, and worse long-term survival as compared to patients treated with primary PCI (8). Finally, in patients treated with thrombolytic therapy, the extent of myocardial salvage is inversely proportional to the time-to-treatment, but in patients treated with primary PCI, particularly with adjunctive stenting, myocardial salvage remains stable and independent of time-to-treatment (14).

Following early reports suggesting that the routine transfer of STEMI patients to hospitals that perform primary PCI is safe and feasible (39, 40), investigators prospectively compared the safety and efficacy of immediate transfer of patients with STEMI to hospitals capable of performing primary PCI to the on-site administration of thrombolytic therapy (41-46). A meta-analysis of these 6 trials (3750 patients; 1887 randomized to emergent transfer for primary PCI, and 1863 to on-site thrombolytic therapy) showed that emergent transfer is both safe and technically feasible and is associated with improved clinical outcomes compared to on-site thrombolytic therapy, including a 68% ($p < 0.001$) reduction in the combined endpoint of death, reinfarction or stroke (16). A potential limitation of this strategy is that the transfer time was < 3 hours in all these studies. Whether transfer for primary PCI is superior to on-site thrombolysis when transfer delays exceed 3 hours is unknown and awaits further studies. In addition, since care of patients with STEMI is one of the most profitable hospital services, there might be a financial disincentive to transfer these patients to another hospital.

Strategy C: Direct EMS Transport To Centers That Perform Primary PCI. Patients with STEMI are usually transported by EMS to the nearest acute-care hospital regardless of whether or not the hospital is capable of performing primary PCI. Since the clinical outcomes with primary PCI are less time dependent than those seen with thrombolytic

therapy, a strategy of obtaining electrocardiograms in the field followed by EMS transport of STEMI patients directly to a hospital capable of performing primary PCI has been proposed (47, 48). This proposal parallels the trauma center model, in which patients are triaged not to the nearest emergency department but to a regional trauma center. Since trials show that transfer times up to 3 hours are associated with better clinical outcomes than on-site thrombolytic therapy, direct EMS transport to a regional primary PCI center may be the most efficient and effective treatment for STEMI. This approach will require substantial regional coordination and administrative oversight.

2. Technical Expertise Of Center And Operator

As noted above, primary PCI can be performed safely and effectively in qualified community hospitals without on-site surgical back-up provided that specific criteria are fulfilled as delineated by the American College of Cardiology/American Heart Association (49). These guidelines include recommendations regarding hospital and operator procedural volume and the presence of a dedicated primary PCI program. The results of primary PCI are, in large part, dependent on the experience of the operators and volume of cases performed at the center: In a study of STEMI patients from the National Registry of Myocardial Infarction treated in hospitals with varying levels of experience with primary PCI, patients were stratified into groups representing low- (<16 primary PCI's/year), intermediate- (17-48 primary PCI's/year), and high-volume centers (>49 primary PCI's/year) (50). There was an inverse relationship between institutional volume of primary PCI performed per year and mortality. Mortality was lower among patients who received primary PCI compared to those who received thrombolytic therapy if performed in intermediate- (4.5% versus 5.9%) and high-volume hospitals (3.4% versus 5.4%). In contrast, the risk of death among patients treated with primary PCI and thrombolysis at low-volume hospitals was similar (approximately 6%). Interestingly, even patients treated with primary PCI in low-volume centers were less likely to have strokes (0.4% versus 1.1%) or to undergo subsequent revascularization procedures compared with those treated with thrombolytic therapy. Similar results were seen in a separate analysis of the same registry that included a larger numbers of patients (51).

There is also an inverse relationship between operator volume and clinical outcomes. An analysis from the Coronary Angioplasty Reporting System of the New York State Department of Health showed that, in addition to hospital volume, operator volume also effected the clinical outcomes of primary PCI and that there was an interaction between hospital and operator volume (52). Primary PCI performed by an operator who performed > 10 procedures annually resulted in 33 lives saved per 1000 patients treated, and if performed in a high-volume center (defined as ≥ 57 procedures/year), 18 lives saved per 1000 patients treated. Patients treated in high-volume centers by high-volume operators had a 49% decrease in death compared to patients treated in low-volume centers by low-volume operators.

As a result of these data, the American College of Cardiology/American Heart Association recommends that operators performing primary PCI in hospitals without on-site cardiac surgery must be experienced interventionalists who regularly perform elective interventions at a surgical center (≥ 75 cases/year), and that the hospital should perform a minimum of 36 primary PCI procedures/year (49).

Development of a formal primary PCI program is critical to the effective and efficient provision of this treatment. Primary PCI requires close coordination of the emergency department and the cardiac catheterization laboratory. The American

College of Cardiology/American Heart Association recommends that hospitals performing primary PCI adhere to the following criteria (49): 1) rapid activation of the cardiac catheterization laboratory on-call team, 2) continuing education of the cardiac catheterization laboratory and coronary care unit staff to the special needs of critically ill and hemodynamically unstable STEMI patients, 3) appropriately stocked cardiac catheterization laboratory, 4) established protocols for immediate and efficient transfer for surgical revascularization to nearby tertiary care centers, and 5) provision of primary PCI as the routine treatment of STEMI 24 hours a day, 7 days a week. When these criteria are fulfilled, the results obtained with primary PCI are superior to thrombolytic therapy, and consistent with the results seen in randomized controlled trials, regardless of availability of on-site surgical back-up (15).

3. Patient Subgroups Not Studied In Randomized Trials

Patients with chronic kidney disease, previous coronary artery bypass surgery, and the elderly have been excluded from most randomized trials for STEMI. Management decisions regarding these patients, therefore, are derived either from data obtained from observational studies or extrapolated results obtained from randomized trials enrolling healthier and younger patient populations. Both of these approaches are problematic, since data from observational studies are skewed by selection bias, and extrapolation of data from other populations may not be valid due to co-morbidities in these groups. Since there is no satisfactory data in these populations, they often do not receive any of the treatments considered to be standard of care – for instance, reperfusion therapy for STEMI is often withheld in patients with chronic kidney disease and the elderly, even though these populations have a higher incidence of complications of STEMI (53, 54).

Clearly, this problem should be addressed by performing randomized trials targeting these specific populations. Two such trials have been performed in elderly patients with STEMI, who were randomized to primary PCI or thrombolytic therapy. Compared with thrombolytic therapy, primary PCI with adjunctive stenting was associated with a significant reduction in the combined endpoint of death, reinfarction and revascularization for recurrent ischemia (29% vs 93%, $p < 0.01$), and a reduction in major bleeding complications (0% vs 17%, $p= 0.03$) in patients > 70 years of age (55). In patients > 75 years of age randomized to PCI or thrombolytic therapy, primary PCI was associated with a significant reduction in the combined endpoint of death, reinfarction or stroke (9% vs 29%, $p=0.01$) (56).

I contend that the overall lack of data should stimulate randomized controlled trials to specifically study these patient subgroups, and should not be used as an argument against universal availability of primary PCI to STEMI patients.

4. Cost

Ultimately, whether the benefits of primary PCI over thrombolytic therapy in terms of lives saved justifies the expense of universal access is a matter of public policy. The cost of primary PCI as compared to thrombolytic therapy is likely to vary in different health delivery systems. Available data (57-60) indicate that primary PCI is no more expensive than thrombolysis, since patients treated with thrombolysis have longer hospital stays, more subsequent hospitalizations, and increased need for subsequent coronary revascularization procedures. If instituted, the cost of providing pre-hospital thrombolytic therapy would include the cost of having a physician on board each

ambulance and the cost of providing subsequent PCI in 70% of patients, 26% of which are on an emergent basis (46).

5. Comparisons Of Primary PCI To Newer Pharmacologic Regimens

Comparison with pre-hospital thrombolytic therapy. Pre-hospital thrombolytic therapy (administration of thrombolytic therapy in the ambulance) has been proposed as a method of reducing the delay between symptom onset and re-establishment of coronary blood flow. A meta-analysis of 6 trials comparing in-hospital to pre-hospital thrombolytic therapy found a 1% improvement in survival with pre-hospital treatment (61). These studies, however, excluded patients with symptoms > 4-6 hours, thus selecting a population more likely to achieve reperfusion with thrombolytic therapy. Whether similar results would be seen with longer time-to-treatment intervals has not been studied.

Pre-hospital thrombolytic therapy has been directly compared to primary PCI in only one randomized trial (46). This trial enrolled patients with symptoms for < 6 hours and was stopped prematurely due to poor recruitment; it found no difference in outcome between the two study groups. While promising, these results await confirmation in other trials. In addition, pre-hospital thrombolytic therapy will only be available to a minority of patients with STEMI, since only half of the patients with STEMI are transported to the hospital by ambulance and only 4% of all chest pain calls to EMS are eligible for thrombolytic therapy (62). Patients treated with pre-hospital thrombolytic therapy usually also require PCI: 26% of patients randomized to pre-hospital thrombolytics in the above study required urgent rescue PCI and 70% eventually underwent PCI in the ensuing 30 days. It is therefore essential that any patient treated with this modality is immediately transferred to a primary PCI center.

Comparison with facilitated PCI. Facilitated PCI is the treatment with low-dose thrombolytic therapy, platelet glycoprotein IIb/IIIa inhibitors, or both, prior to PCI. The rationale for this approach is to provide the earliest possible pharmacologic reperfusion before attempting definitive mechanical revascularization of the infarct-related artery. Randomized controlled trials comparing facilitated PCI to primary PCI have shown no benefit and possible harm associated with the facilitated approach, primarily due to increased bleeding complications (41, 44, 63, 64). Additional trials enrolling larger numbers of patients will be needed to evaluate the efficacy and safety of this approach using various doses and combinations of thrombolytic therapy and platelet glycoprotein IIb/IIIa inhibition, and studying transfer delays of > 3 hours.

In summary, new treatment regimens will continue to be developed and compared to primary PCI. While these studies are certainly appropriate, I contend that to date, they do not provide a rationale to limit universal access to primary PCI.

Conclusions

Primary PCI is the reperfusion strategy of choice in patients with STEMI, and should be made universally available to most, if not all, of these patients. The major obstacle to achieving this goal is the lack of ready availability of primary PCI. Primary PCI can be made more accessible by three strategies: 1) performing primary PCI in qualified community hospitals without on-site surgical back-up, 2) transferring patients from community hospitals without primary PCI capability to primary PCI centers, and 3) directly transporting STEMI patients by EMS to regional primary PCI centers, not necessarily to the nearest emergency department. If adopted, these strategies should

increase the availability of primary PCI for STEMI and significantly improve clinical outcomes in this disease.

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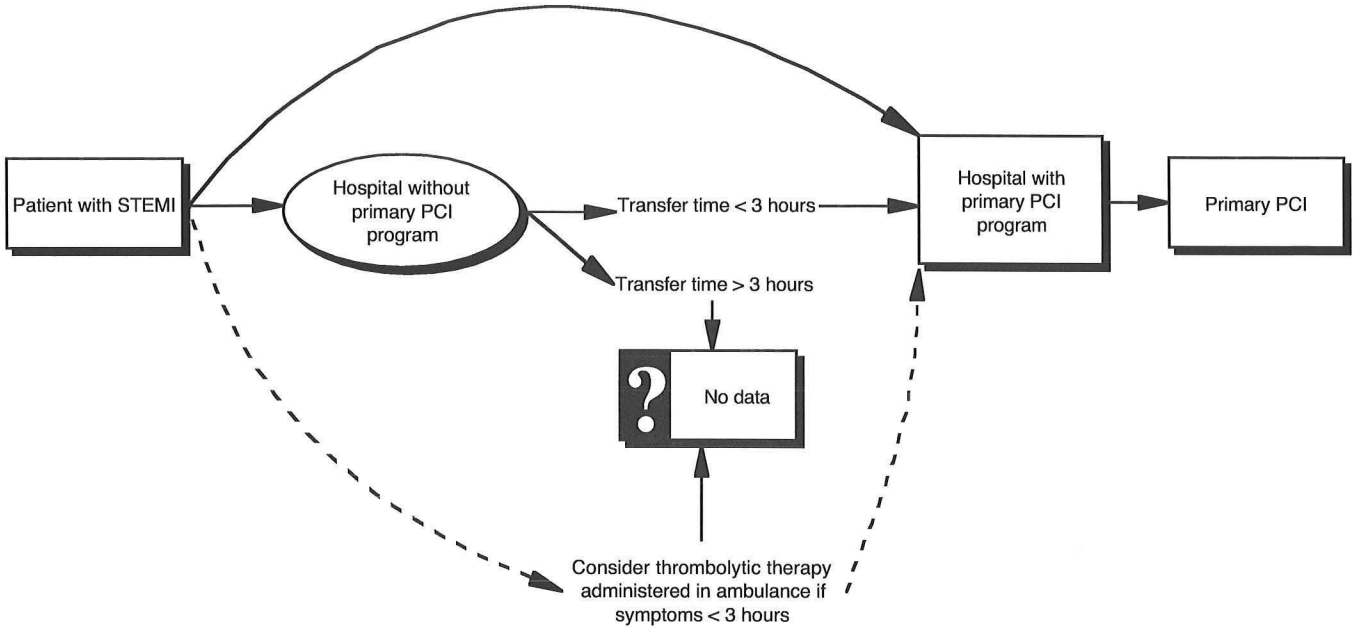
Table. Obstacles To Institution of Primary PCI As the Universal Treatment for STEMI

1.	Availability
2.	Technical expertise of center and operator
3.	Patient subgroups not studied in randomized trials
4.	Cost
5.	Comparisons of primary PCI to newer pharmacologic regimens



Proposed algorithm to increase the availability of primary percutaneous coronary intervention for patients with ST elevation myocardial infarction.
Primary percutaneous coronary intervention (PCI) is the treatment of choice for ST elevation myocardial infarction. Three strategies are proposed to increase the availability of this procedure: A) perform primary PCI in community hospitals without on-site surgical back-up, B) transfer patients from hospitals without primary PCI capability to primary PCI centers, provided the transfer time is < 3 hours, and C) develop a triage system, similar to that seen with trauma, where the patient is directly transferred by the Emergency Medical System to a primary PCI center not necessarily the closest emergency department. There is limited data on "pre-hospital" thrombolytic therapy, administered in the ambulance, as compared to primary PCI (dotted line). If adopted, this approach would require eligibility for thrombolytic therapy, presence of a physician in the ambulance, and immediate transfer to a primary PCI center, since rescue PCI was required in a quarter of patients.