

Pharmacoinvasive Strategies for ST-Elevation MI

Is the “drip-and-ship” strategy a viable option for patients without immediate access to primary PCI?

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Cardiologists are well aware of the superiority of primary percutaneous coronary intervention (PCI) when compared with fibrinolytic therapy (FT). Primary PCI is the preferred reperfusion strategy for ST-elevation myocardial infarction (STEMI) if it can be performed in a timely fashion by skilled staff. Because many patients first arrive at hospitals that lack the capability to perform primary PCI, there has been considerable interest in strategies to increase access to timely reperfusion therapy for STEMI. These include proliferation of facilities that can provide primary PCI services (both with and without cardiac surgical backup) and therapies that involve administration of pharmacologic agents combined with use of cardiac catheterization. However, there is significant confusion regarding the use of these various strategies and the benefits associated with each.

STRATEGIES TO IMPROVE OUTCOMES FOR THOSE WITHOUT ACCESS

It has been shown that primary PCI can be performed safely and rapidly at hospitals without cardiac surgery back-up.¹ However, building new catheterization laboratories is only cost effective if these facilities increase the number of patients who have access to primary PCI, as it is more expensive than regionalization strategies. For example, there were 1,176 centers providing primary PCI

in 2001 and 1,695 in 2006, a 44% increase. One analysis showed that in 2001, for 79% of patients, there was a facility that could provide PCI within 60 minutes of their home. When the number of catheterization laboratories increased, the proportion of patients undergoing PCI increased to only 79.9%.^{2,3} In other words, facilities were built that did not increase access for patients and instead were built to compete with one another. Obviously, when not implemented in a coherent fashion, access to timely reperfusion does not improve with the proliferation of cardiac catheterization facilities and represents a missed opportunity in improving access to primary PCI for STEMI patients.

Another strategy is combining FT and primary PCI. Initial evaluation of a combined approach demonstrated unacceptable bleeding complications and was abandoned for some time.⁴ Combination therapy was revisited with the advent of contemporary anticoagulant and access site management. Several clinical trials were undertaken to investigate combination therapy, with differing clinical trial designs that bear clarification. Facilitated PCI trials served to improve primary PCI outcomes by adding pharmacologic agents. In these trials, all patients received PCI with a goal door-to-balloon (D2B) time of 90 to 120 minutes. Patients in these trials were randomized to additional pharmacotherapy with FT, glycoprotein IIb/IIIa receptor inhibition, or a combination

TABLE 1. PHARMACOINVASIVE TRIALS

Trial	Number of Patients	Study Arms	Medication	Primary Outcome Measure	Results
SIAM III (2003)	163	• FT with early PCI (< 6 h) • FT with delayed PCI (14 d)	Reteplase	Death, reinfarction, ischemic events, target lesion revascularization	FT with early PCI = 25.6% FT with delayed PCI = 50.6% $P = .001$
CAPTIAL-AMI (2005)	170	• FT • FT with facilitated PCI	Tenecteplase	Death, reinfarction, recurrent unstable ischemia, stroke	FT = 24.4% FT with facilitated PCI = 11.6% $P = .04$
CARESS-IN-AMI (2008)	600	• FT with early PCI • FT with medical management (rescue PCI if necessary)	Half-dose reteplase + abciximab	Death, reinfarction, refractory ischemia	FT with early PCI = 4.4% FT with medical management/rescue PCI = 10.7% $P = .004$
TRANSFER-AMI (2009)	1,059	• FT with early PCI • FT with delayed PCI (emergent rescue PCI if necessary)	Tenecteplase	Death, reinfarction, recurrent ischemia, new or worsening heart failure, cardiogenic shock	FT with early PCI = 11% FT with delayed PCI = 17.2% $P = .004$ Delayed PCI median time = 32.5
NORDISTEMI (2010)	268	• FT with early PCI • FT with medical management (rescue PCI if necessary)	Tenecteplase	Death, reinfarction, stroke, new ischemia	FT with early PCI = 21% FT with medical management/rescue PCI = 27% $P = .19$
STREAM (2013)	1,892	• Primary PCI • FT with delayed PCI (emergent rescue PCI if necessary)	Tenecteplase ^a	Death, shock, congestive heart failure, reinfarction	Primary PCI = 14.3% FT with delayed PCI = 12.4% $P = .21$ Delayed PCI median time = 17 h
^a Early in the trial, the tenecteplase dose was reduced by half among those ≥ 75 years due to an increased rate of intracranial hemorrhage.					

of the two. These trials were mainly performed at primary PCI centers, and the times from administration of medications to primary PCI were short. These trials were largely unsuccessful.^{5,6}

Despite increased rates of arterial patency at the time of catheterization, there was no significant benefit in final angiographic outcomes and increase in the rates of bleeding. In the FINESSE trial,⁵ patients were randomized to primary PCI or facilitated PCI with abciximab or facilitated PCI with half-dose reteplase and full-dose abciximab. The median D2B time was 132 minutes, and there were similar rates of death, heart failure, and ischemic outcome at 90 days for all three groups. More

major bleeding events occurred with the facilitated strategies.

Adverse clinical outcomes were noted, and the ASSENT-IV PCI trial was halted early because of an increased mortality associated with facilitated PCI.⁶ A variety of theories have been suggested to explain these findings, such as inadequate antiplatelet or antithrombin therapy among patients receiving FT. Nevertheless, the marriage of primary PCI and FT to improve primary PCI outcomes was not a successful one, and immediate primary PCI after FT should not be a routine strategy for STEMI patients when primary PCI can be performed in a timely fashion.

The facilitated approach, however, does not apply to STEMI patients at facilities without primary PCI capability or where there will be a substantial delay to primary PCI, making patients ineligible for primary PCI. In these cases, options include PCI performed in transfer, regardless of the delay, or a strategy of FT followed by routine or selective angiography 3 to 24 hours after FT. In considering these approaches, it is known that the benefit of primary PCI over FT is time dependent and varies according to patient risk. In clinical trials comparing FT to primary PCI, the mortality benefit of primary PCI over FT was nullified at approximately 110 minutes.⁷ Various other analyses have shown a similar time-dependent loss of the benefit of primary PCI over FT.

Furthermore, the time course of this decline varies based on patient risk.⁸ In other words, the clinician should consider the relative benefit of primary PCI over FT as time dependent, and if the delay to implementation of primary PCI is substantial, PCI may not confer substantial benefit over FT. The benefit of primary PCI over FT is lost more quickly when the patient has a greater ischemic risk or if there is greater relative efficacy with FT, as in those who present very early after symptom onset.^{8,9} The benefit is extended somewhat among patients with an increased risk of bleeding, especially intracranial hemorrhage.⁹

Although some medical systems have been successful in providing timely access to primary PCI by regionalizing it^{10,11} and focusing on an integrated system of care, most STEMI patients are subject to unacceptable delays to reperfusion with PCI. In the United States, many patients are not treated with primary PCI within the recommended D2B time or within a window of time when primary PCI is thought to be superior to FT. In the National Cardiovascular Data Registry from 2005 to 2006, the median transfer time for STEMI was 109 minutes, resulting in a median D2B time of 152 minutes. Only 27.7% of D2B times were < 120 minutes, the metric recommended by both the European and American guidelines for STEMI patients transferred for treatment.¹² As such, pharmacoinvasive strategies have been evaluated to address this gap in care (Table 1).

THE “DRIP-AND-SHIP” STRATEGY

A pharmacoinvasive approach, or the so-called drip-and-ship strategy, differs from a facilitated PCI approach and is intended to improve outcomes for patients receiving FT who are ineligible for primary PCI due to a time delay and should not be confused with facilitated PCI. Among trials evaluating the pharmacoinvasive approach, FT is administered to all, and patients are randomized to routine angiography and

revascularization at 3 to 24 hours or a more conservative approach to revascularization after FT. The first question is, what do you do when FT does not work in a STEMI patient? The term for PCI after failed FT is “rescue PCI,” which has been evaluated in a variety of trials. These trials have shown the superiority of PCI for failed FT compared with repeat FT or continued medical management.^{13,14}

Due to the difficulty in predicting whether FT will be effective and the time delays inherent in awaiting the maximal effect of FT and arranging transfer for primary PCI, the obvious question arises as to whether patients should be routinely transferred after FT to a primary PCI center for angiography, regardless of whether they are reperfused or not. The TRANSFER-AMI trial evaluated 1,059 patients and showed that routine catheterization after FT was associated with reduced rates of the composite endpoint of death, reinfarction, recurrent ischemia, new or worsening heart failure, and cardiogenic shock (11% vs 17.2%; $P = .004$).¹⁵

Most recently, the STREAM trial¹⁶ randomized STEMI patients in whom primary PCI could not be performed within 60 minutes of first medical contact and compared transfer for primary PCI versus the use of urgent PCI after FT only if there was evidence that reperfusion had not occurred. Urgent catheterization was avoided in two-thirds of FT patients. The patients who did not undergo urgent angiography subsequently underwent elective angiography at an average of 17 hours after arrival and, based on the results, received PCI or coronary artery bypass graft surgery (CABG) under nonurgent circumstances. PCI was performed (at some point) in 90% of the PCI group versus 80% of the FT group. CABG was performed in more patients in the FT group (4.7% vs 2.1%). The primary endpoint, a composite of all-cause mortality, shock, congestive heart failure, and subsequent heart attack at 30 days, was similar between the PCI and pharmacoinvasive groups (12.4% vs 14.3%; $P = .21$), validating this strategy as an alternative for patients in whom there will be a delay to primary PCI and providing the clinician with more time to determine the optimal reperfusion strategy, such as CABG or medical therapy. These findings have led to the recommendation in the European STEMI guidelines to perform rescue PCI in patients who do not respond to FT and to transfer all patients after FT to a PCI center.¹⁷

CONCLUSION

Primary PCI remains the best therapy for STEMI patients, and there have been substantial gains in reducing the time to primary PCI for many patients. There remains a gap in care for those who require transfer to a

primary PCI facility due to extensive time delays related to transport. Regionalization strategies have been successful in some areas; however, many patients still do not have the necessary rapid access to this technology. Until systems of care can be organized and developed, pharmacoinvasive or drip-and-ship strategies represent the next best option to extend the benefit of timely reperfusion therapy to STEMI patients who have the misfortune of arriving at hospitals without primary PCI capability and within health care systems that cannot provide timely access to primary PCI. ■

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