Is duration of symptoms the key modulator of the choice of reperfusion for ST-elevation myocardial infarction?

Duration of Symptoms Is Not Always the Key Modulator of the Choice of Reperfusion for ST-Elevation Myocardial Infarction

Peter Bogaty, MD

Fibrinolytic therapy (FT) and primary percutaneous coronary intervention (PCI) are both well-accepted reperfusion therapies in ST-segment elevation myocardial infarction (STEMI). The evidence of randomized clinical trials indicates a relatively modest difference in 30-day mortality (≈1%) in favor of primary PCI over fibrin-specific FT and was based on very timely primary PCI (ie, a primary PCI-related delay of 40 minutes [door-to-balloon less door-to-needle time]). Longer delays to primary PCI, which are far more frequent in clinical practice, are associated with attenuated benefit or no benefit at all, particularly when compared with fibrin-specific FT. The benefit of timely primary PCI over FT is likely to especially apply to higher-risk patients. Irrespective of the method of reperfusion, the potential for myocardial salvage and better clinical outcome is inversely proportional to ischemic time or its only available clinical surrogate, symptom duration. These considerations underpin the notion expressed in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the treatment of STEMI that timely reperfusion therapy is likely more important in determining outcome than whether FT or primary PCI is the chosen reperfusion method.

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The ACC/AHA STEMI guidelines highlight the time point of 3 hours of symptom duration in guiding the choice of reperfusion therapy. They state that if symptom duration is <3 hours, no preference exists between FT and primary PCI provided that treatment is timely (for FT, door-to-needle time <30 minutes; for primary PCI, door-to-balloon time <90 minutes and ≤60 minutes between estimated needle time and estimated balloon time). However, if symptom duration exceeds 3 hours, these guidelines favor primary PCI over FT, again provided that primary PCI can be performed in a timely fashion. This article reexamines the evidence that may or may not be the basis for orienting the choice of reperfusion therapy in patients with STEMI according to symptom duration. It is emphasized that this work is not intended to reopen a primary PCI versus FT, “1 size fits all” debate. It rather addresses the question of the extent to which the evidence suggests that symptom duration should modulate the choice of reperfusion therapy.

Within the “Golden Hour”

Within the “golden hour” for reperfusion (symptom duration <2 hours, ideally <1 hour), the slope of the relation between ischemic time and outcome is extremely steep. Both experimentally and clinically, in this critical time frame, a small increment (or decrement) of time to treatment may have dramatic consequences on the quantity of irreversibly damaged myocardium and on clinical outcome. A substantial
proportion of patients who receive reperfusion therapy within this period may actually “abort” their impending myocardial infarction.\(^{14}\) This appears to be more likely with prompt FT than with primary PCI because the latter would necessarily prolong ischemic time at least 30 to 60 minutes more (and often orders of magnitude longer in the real world)\(^2\) than the time to FT, substantially augmenting the probability of necrosis and its extent. The better clinical outcomes with FT in the Comparison of Angioplasty and Prehospital Thrombolysis In acute Myocardial infarction (CAPTIM) study in patients with ischemic times \(\leq 2\) hours are consistent with these premises (Figure 1).\(^{15}\) Thus, notwithstanding the notion of equipoise between FT and primary PCI expressed in the ACC/AHA guidelines when symptom duration is \(\leq 3\) hours, data suggest the potential for greater clinical benefit with rapid FT within the first 2 hours of symptom duration, especially in the real world, where door-to-balloon times, particularly for transferred patients, substantially exceed those in the randomized clinical trials.\(^2\) The proportion of patients affected by this consideration is substantial; in the National Registry of Myocardial Infarction of nearly 200,000 patients with STEMI, 65% presented within 2 hours of symptom onset.\(^{16}\)

**Beyond 3 Hours**

The notion that primary PCI should be favored when symptom duration exceeds 3 hours has had the important consequence of leading clinicians, particularly in centers that must transfer patients for primary PCI, to integrate this recommendation into their decisional algorithm. The proportion of patients implicated by an application of this principle is not negligible; in large series of patients receiving reperfusion therapy for STEMI, it has varied from 34% to 66%.\(^{17,18}\)

It is postulated that longer symptom duration results in older, firmer occlusive fibrin clots more resistant to FT, whereas this would not be a limitation for occlusive clots submitted to the mechanical intervention of angioplasty. What is the strength of the evidence that older clots are more resistant to fibrinolysis?

In the Thrombolysis in Myocardial Infarction (TIMI)-1 clinical trial, although patients treated with streptokinase showed a decrease in coronary artery patency (TIMI 2 or 3 flow) from 44% in the 41 patients treated before 4 hours to 24% in the 78 patients treated after 4 hours, no difference was found in coronary artery patency in patients treated with tissue-type plasminogen activator (tPA) within (41 patients) or after 4 hours (72 patients).\(^{19}\) Similarly, in a retrospective analysis of 2 French studies of coronary artery patency in patients receiving FT, Steg et al\(^{20}\) found that when streptokinase was used (244 patients), the achievement of normal flow (TIMI 3) and TIMI 2/3 flow decreased with longer symptom duration (<3 versus \(\geq 3\) hours), whereas with tPA (237 patients), coronary artery TIMI flows 3 and 2/3 remained stable regardless of symptom duration.\(^{20}\) This distinction was reinforced by Zeymer et al\(^{21}\) in a retrospective analysis of 6 other angiographic trials in 1111 patients with STEMI treated with FT that examined TIMI flow relative to symptom duration that was dichotomized between 0 to 180 minutes and 181 to 360 minutes (Table). They found that the non–fibrin-specific agents streptokinase, urokinase, and anisoylated plasminogen-streptokinase activator complex achieved significantly less TIMI 3 and TIMI 2/3 flow with longer symptom duration. However, the fibrin-specific agent tPA administered over 3 hours or in accelerated mode and the bolus fibrin-specific agent reteplase did not show a decrease in TIMI 2/3 and TIMI 3 flow when symptom duration was 181 to 360 minutes compared with 0 to 180 minutes.\(^{21}\) Thus, the data strongly suggest that at up to 6 hours of symptom duration, although nonspecific fibrinolytics like streptokinase are less effective in achieving coronary artery patency and normal flow with increasing ischemic time, this limitation does not extend to the fibrin-specific fibrinolytics. Some in vitro data exist consistent with these observations that could be explained by less effective penetration of older clots by non–fibrin-specific fibrinolytic drugs.\(^{21,22}\)

A mechanistic study examined the relationship between myocardial salvage and symptom time with the use of
Tc-99m sestamibi scintigraphy in patients with STEMI treated with stenting versus FT with tPA.23 It found that although infarct size expectedly increased in the cohort treated with FT with each increasing tertile of symptom duration, infarct size appeared unaffected by symptom duration in the cohort treated with stenting. Thus, the relative benefit of stenting versus FT in terms of myocardial salvage widened with increasing symptom duration before treatment. On intuitive grounds, it is difficult to understand why the experimentally well-established time dependence of the wavefront of necrosis would apply in the FT cohort but would be suspended in an ischemic myocardium faced with an impending stenting intervention.24,25 The apparent constancy of infarct size independent of ischemic time when stenting was used suggests that other factors, such as clinical differences of the patients in the tertiles of symptom duration examined or limitations of the measuring technique (lack of adequate spatial resolution with single-photon emission computed tomography for degree of transmurality),26 may have intervened in the determination of infarct size in the stenting cohort. In support of this, clinical studies have confirmed that, just as with FT, mortality with primary PCI is indeed ischemic time dependent.9,18 Therefore, this mechanistic study appears to be too slender a rationale for triaging patients with longer symptom duration to primary PCI on the assumption that ischemic time does not affect infarct size in patients to be treated with primary PCI.

How compelling is the clinical evidence favoring primary PCI over FT when symptom duration exceeds 3 hours? Registry data suggest that with increasing symptom duration, survival outcomes are better with primary PCI than with FT.16,27 Such data may be problematic, however, not only because of the nonrandomized nature of the data but also because either only primary PCI actually performed was considered16,28 or it was unspecified whether it was or not.27 Thus, patients who had long ischemic times and were directed to primary PCI but either did not survive until primary PCI or did not have a completed, generally successful procedure might not have been tallied in the primary PCI arm as they would otherwise have been in the “intention-to-treat” approach that is used in properly conducted randomized clinical trials. Thus, the finding of a gradient of increasing relative benefit of primary PCI over FT with

<table>
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<th>Substance and Flow</th>
<th>0–180 Minutes</th>
<th>181–360 Minutes</th>
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<td>Patients, n</td>
<td>156</td>
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APSAC indicates anisoylated plasminogen-streptokinase activator complex.

Figure 2. Thirty-day mortality in the PRAGUE-2 study of patients (Pts) with STEMI treated with thrombolysis with streptokinase compared with primary PCI. Adapted from Widimsky et al29 with permission of the publisher. Copyright © 2003, Oxford University Press.
increasing symptom duration would be compatible with a greater relative efficacy of primary PCI over FT with increasing ischemic time. The largest single randomized trial that evaluated streptokinase versus primary PCI was the PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis–2 (PRAGUE-2) trial (850 patients). For patients randomized <3 hours from symptom onset, mortality was similar between streptokinase and primary PCI (7.4% and 7.3%, respectively); however, for patients randomized after 3 hours, mortality was 15.3% with streptokinase versus 6.0% for primary angioplasty (P<0.02) (Figure 2). These findings are consistent with a relative loss of fibrinolytic efficacy for streptokinase with longer ischemic time and are supported by the in vitro and angiographic data discussed previously. However, when the large randomized trials that compared accelerated tPA with primary PCI are examined, a different picture is suggested. There appears to be no gradient of increasing relative benefit in terms of mortality reduction for primary PCI over tPA as symptom duration increased in the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) study or for the primary composite end point of death, reinfarction, or disabling stroke in the Danish Multicenter Randomized Study on Fibrinolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction–2 (DANAMI-2) study (Figure 3). In the latter study, the benefit of primary PCI over FT at all strata of symptom duration was essentially driven by the reinfarction end point; however, this should be tempered by the fact that <2% of patients treated with FT in DANAMI-2 had rescue angioplasty, that different definitions of reinfarction were applied in the 2 reperfusion arms, and that thienopyridines, known to reduce reinfarction and recurrent ischemia, were systematically given to patients who had primary PCI and not to those treated with FT. In the CAPTIM study, although the data are compatible with a mortality benefit of tPA over primary PCI for symptom duration <2 hours, no conclusion can be drawn for ischemic time exceeding 2 hours (Figure 1). Thus, these data from the 3 largest trials comparing tPA with primary PCI are consistent...
with the in vitro and angiographic TIMI flow data suggesting that fibrin-specific agents are as effective within the 3- to 6-hour symptom duration window as within the 0- to 3-hour window.

On the other hand, in a subgroup overview of the randomized trials that compared accelerated tPA with primary PCI and that dichotomized between presentation delays (ie, time from symptom onset to randomization) of >2 versus <2 hours, Boersma et al. found that the mortality benefit of primary PCI was confined to the subgroup with >2 hours of presentation delay (odds ratio, 0.72; 95% confidence interval, 0.54 to 0.95). However, an examination of the data from this same publication, showing odds ratios (and 95% confidence intervals) by strata of presentation delay adjusted for patient, hospital, and study level covariates suggests no gradient of increasing relative benefit in favor of primary PCI over tPA, with increasing presentation delay out to 12 hours (Figure 4). A limitation of the latter data is that it excludes the robust contingent of the CAPTIM study, a majority of whose patients had <2 hours of symptom duration until treatment. It must also be emphasized that in all of these subgroup analyses, although a time-dependent treatment effect is not suggested, it cannot be excluded, given the width of the confidence intervals.

Clinical Implications

Therefore, if the fibrinolytic agent used is accelerated tPA or 1 of the fibrin-specific bolus agents, available evidence does not appear compelling in favor of an approach triaging to primary PCI based on symptom duration. The ACC/AHA STEMI guidelines that recommend favoring primary PCI over FT if symptom duration exceeds 3 hours do not appear supported by the available data if fibrin-specific FT is to be used. In the latter context, longer symptom duration should not be grounds for selecting one reperfusion option over another. Factors that should affect the choice of therapy are the timeliness of the 2 options (with, for example, more consideration in favor of primary PCI if delay to balloon time relative to immediate FT is more toward 30 minutes rather than 60 minutes), the relative risk of bleeding with both options, and the level of risk of the STEMI with a preference for timely primary PCI in very-high-risk patients such as those in Killip class 3/4.

Importantly, beyond consideration of the relative efficacies of FT and primary PCI in “opening up” acutely occluded coronary arteries, studies also suggest that longer ischemic times lessen the chances for successful myocardial reperfusion, as evaluated by ST-segment resolution or myocardial blush grade, whether the method of reperfusion is FT or primary PCI. Thus, late reperfusion therapy, whatever the reperfusion method, adds, to the irreversible injury of an expanded wave front of myocardial necrosis, the insult of an increased likelihood of less successful myocardial reperfusion, even if coronary artery opening and TIMI 3 flow are achieved. This “double jeopardy” of longer ischemic time reinforces the need for ischemic time to be as short as possible.

Conclusion

Should symptom duration intervene in the choice of which reperfusion therapy to give to patients with STEMI? In the golden hour, when symptom duration is within 1 to 2 hours, prompt FT may provide clinical benefit compared with primary PCI and should be considered as a potentially preferable option. Beyond this critical time window, provided that the fibrinolytic drug considered for use is fibrin specific, the available data suggest that symptom duration need not guide the choice of reperfusion therapy.

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Disclosures

None.

References


Response to Bogaty

Paul W. Armstrong, MD; Cynthia M. Westerhout, PhD; Robert C. Welsh, MD

We are pleased Bogaty concurs that little difference exists between the choices of fibrinolysis and percutaneous coronary intervention (PCI) early after the onset of ST-elevation myocardial infarction symptoms. The lack of prospective randomized data underscores the need for additional data; hence, we and others have begun a trial (STREAM [STRategic Reperfusion Early After Myocardial infarction]) in patients within 3 hours of symptom onset randomized to a strategy of direct PCI or strategic pharmacological therapy with tenecteplase and age- and weight-adjusted concomitant therapy, including enoxaparin and clopidogrel. Rescue PCI is mandatory, and the remainder of the patients will undergo angiography and (where appropriate) revascularization within the subsequent 6 to 24 hours.

Although delay attenuates benefit, whatever reperfusion strategy is chosen, the persisting excess hazard posed by fibrinolysis contributes to the narrower margin between benefit and risk, unlike direct PCI. Moreover, PCI-induced late opening of coronary arteries obstructed by clot that is more resistant to fibrinolysis may be beneficial through alternative mechanisms (ie, enhanced left ventricular remodeling, lesser electrical instability, and more potential coronary collateral formation). Although the use of prehospital fibrinolysis–enhanced outcomes compared with primary PCI within the 2-hour window from symptom onset in the Comparison of Angioplasty and Prehospital Thrombolysis In acute Myocardial infarction (CAPTIM) study, patients treated later did less well with fibrinolysis, which attests to the importance of elapsed time when reperfusion therapy is selected.

Finally, we would reemphasize the deleterious impact on mortality of each 10-minute reperfusion delay within the Global Registry of Acute Coronary Events (GRACE) for ST-elevation myocardial infarction. For fibrin-specific fibrinolysis, this excess was 0.30% (95% confidence interval 0.22 to 0.40) versus 0.18% (95% confidence interval 0.08 to 0.35%) for PCI.
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