CHAPTER

3

Can New Thrombolytics Replace Primary Angioplasty?

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The relationship between normal coronary artery blood flow and mortality after myocardial infarction is well documented, so the primary target in MI, caused by acute coronary occlusion, is rapid, early, complete, and sustained myocardial reperfusion. Pharmacological treatment with thrombolytic therapy and primary angioplasty are two different modes of reperfusion treatment for ST elevation myocardial infarction (STEMI).

There are several clinical trials which have been conducted comparing the risks and benefits of percutaneous coronary intervention (PCI) and thrombolysis in the treatment of patients of STEMI. Meta-analyses of the various randomised trials comparing thrombolysis and primary angioplasty have shown improvements in mortality, non-fatal reinfarction and stroke from the use of angioplasty;[1-4] and they have also shown that angioplasty has lower recurrence rates and less residual stenosis.[5,6]

A meta-analysis of 22 clinical studies conducted comparing the efficacy of thrombolysis and PCI was published in the *Heart* 2007[7] in which 3760 and 3758 patients were randomized to primary angioplasty and thrombolysis respectively. The authors concluded that the benefit of primary angioplasty, over thrombolysis, depends on the former's additional time delay. For delays of 30–90 minutes, angioplasty is superior for 1 month fatal and non-fatal outcomes. For delays of around 90 minutes thrombolysis may be the preferred option as assessed by 6-month mortality; there is considerable uncertainty for longer time delays. Hence , if there is a delay to do PCI, thrombolysis is preferred. Another meta-analysis[8] of the clinical trials conducted in the elderly comparing thrombolysis to PCI suggests a survival benefit of thrombolytic therapy in the elderly with STEMI.

The studies which have been included in these meta-analyses have also used "contemporary" thrombolytic agents as streptokinase, which are not as efficacious as newer thrombolytic agents such as Tenecteplase in revascularization of the occluded arteries. When the 11 trials from the meta-analysis that used accelerated administration of fibrin-specific agents are considered separately, the advantage for angioplasty decreases to 13 lives saved/1000 patients treated (excess mortality of 4 deaths/1000 persons treated to 27 lives saved/1000 persons treated) and is not statistically significant. In other words, even when angioplasty is performed in high-volume centers of excellence and compared with nonbolus fibrin-specific thrombolytic regimens (which have relatively longer door-to-treatment times), the "compelling" evidence for primary angioplasty is also compatible with a small survival advantage for thrombolysis. This smaller degree of benefit is to be expected because accelerated

protocols of fibrin-specific thrombolytics reduce mortality compared with streptokinase.[9]

The 'first generation' thrombolytics had clinical disadvantages such as low specificity for fibrin, increased risk of allergic reactions (in particular with streptokinase) and short half-life. Newer thrombolytic agents such as reteplase and Tenecteplase have been developed with potential advantages that include: prolonged half-life, increased fibrin specificity and increased resistance to inhibition by plasminogen activators.

The Keeley et al[1] review shows only a trend in mortality reduction when primary PTCA is compared with accelerated recombinant tissue-type plasminogen activator (rt-PA), if the "Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock" (SHOCK) trial[10] is excluded (5.5% versus 6.7%; odds ratio 0.81; 95% CI 0.64 to 1.03; $P = 0.081$). It is not clinically or statistically significant. The absolute benefit is only 1.2% (the number needed to treat is 82; 95% CI 40 to infinite).

In the SHOCK trial, thrombolysis was given in 63% of medical patients and 49% of those patients treated aggressively. So this is a trial of some thrombolysis against some thrombolysis plus revascularization and cannot be included in the final analysis. Including in the "fibrin-specific" group studies in which rt-PA was infused in 3 hours and duteplase in 4 hours is incorrect in the times of modern thrombolysis. The correct comparison is with accelerated rt-PA (5012 of the original 7739 patients).

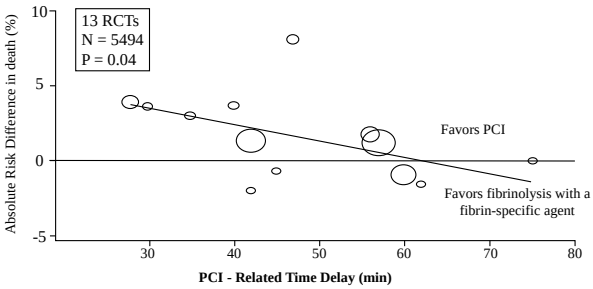
Reinfarction in the first 24 hours after thrombolysis is diagnosed mainly by the recurrence of ST elevation with chest pain.[11] Most of these episodes occur during the first hour after thrombolysis,[12] a time at which approximately the same rate of patients undergoing primary PTCA show signs of no re-flow, side-branch occlusion, dissection, spasm, and distal embolization in the catheterization laboratory.[13] Thus, it appears as if many reinfarctions counted after thrombolysis were hidden in the catheterization laboratory in the primary PTCA group. Moreover, there are no data showing that preventing such reinfarctions will ultimately improve short-term and long-term prognosis.

The 1% absolute stroke reduction with primary PTCA, compared with thrombolysis, results in 3 fewer patients per 1000 treated surviving the index infarction with disabling stroke. This advantage is at least partially counterbalanced by an excess in major hemorrhage in the primary PTCA group (20 more major bleeds per 1000 treated with primary PTCA). Thus, based on the available evidence, clinical advantages of primary PTCA, if any, are apparently small. They should be confirmed in a large mortality trial comparing primary PTCA with the quick infusion of a modern lytic drug, possibly including its prehospital administration, a setting in which the absolute benefit is a 1.6% mortality reduction, as compared with inhospital thrombolysis.

The choice of appropriate management needs to consider the possible time delay in initiating reperfusion with primary angioplasty compared with thrombolysis. In spite of the apparent clinical superiority of primary angioplasty, thrombolytic treatment is the default treatment option in many countries because of practical limitations on the use of percutaneous interventions, including a shortage of cardiac catheter facilities and appropriately skilled staff.

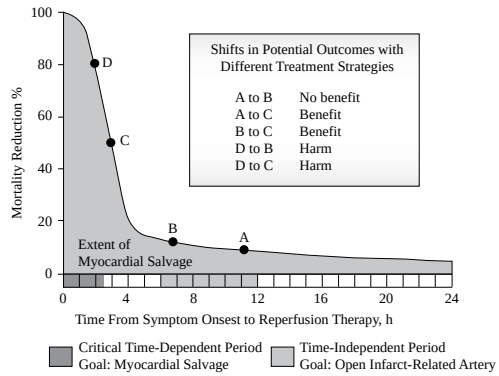
Animal models of coronary occlusion have demonstrated myocardial necrosis after 30 minutes, with 50% myocardial salvage, if reperfusion is accomplished within 90 minutes.[14] The highest number of lives saved is within the first hour after symptom onset: the "golden hour." The exponential form of the curve relating mortality to time-to-reperfusion has major implications for the timing of treatment. Reperfusion in STEMI limits myocardial damage and decreases mortality by about 25%.[15] The American College of Cardiology (ACC)/American Heart Association (AHA), 2004 guidelines suggest

Figure 1 : For every 10 min delay to PCI: 1% reduction in mortality difference towards lytics



Source: Nallamothu BK, Bates ER. *Am J Cardiol.* 2003;92:824-6

Figure 2 : Hypothetical Construct of the Relationship Among the Duration of Symptoms of Acute MI Before Reperfusion Therapy, Mortality Reduction, and Extent of Myocardial Salvage



Source: JAMA 2005

a maximum time from initial medical contact to initiation of thrombolytic therapy of 30 minutes and to balloon inflation of no more than 90 minutes if percutaneous coronary intervention (PCI) is chosen.[16] Some studies suggest that primary PCI loses its advantages over fibrinolytic therapy when door-to-balloon times exceed door-to-drug times by 60 to 90 minutes.[17,18] So, a realistic assessment of time required to initiate therapy must be a factor in the choice of reperfusion strategy.

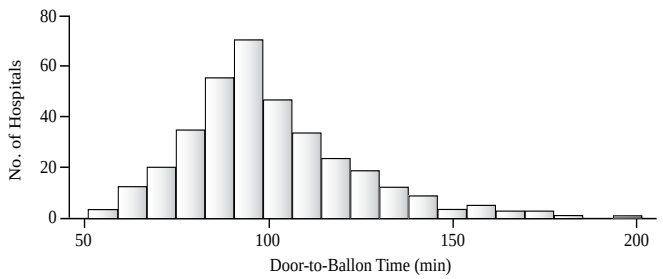
Thrombolytic therapy with streptokinase was first attempted in 1958[19] and since then various drugs with improved pharmacological characteristics have been developed and used in myocardial infarction. The beneficial effect of fibrinolytic therapy is substantially higher in patients presenting within 2 hours after symptom onset than in those presenting later.[20] Administration of thrombolytics primarily occurs upon patient presentation to the hospital, but prehospital thrombolysis reduces time to treatment by up to 1 hour and reduces mortality by 7%.[21]

The GRACIA-1[22] trial was designed to reassess the benefits of an early post-thrombolysis interventional approach in the era of stents and new antiplatelet agents. 500 patients with thrombolysed STEMI (with recombinant tissue plasminogen activator) were randomly assigned to angiography and intervention if indicated within 24 h of thrombolysis, or to an ischemia-guided conservative approach. The primary endpoint was the combined rate of death, reinfarction, or revascularisation at 12 months. The interpretation was that in patients with STEMI, early post-thrombolysis catheterisation and appropriate intervention is safe and might be preferable to a conservative strategy since it reduces the need for unplanned in-hospital revascularisation, and improves 1-year clinical outcome.

The GRACIA-2 study was conducted to determine the safety and efficacy of the facilitated strategy versus a strategy of immediate primary PCI alone (< 3 hours). The primary end points were infarct size, as assessed by CK-MB mass curve and cardiac troponin, myocardial reperfusion (percentage of patients with complete ST resolution at 1, 3, and 6 hours) and left ventricular evolution (volume, ejection fraction, and wall motion index). The secondary endpoints were combined incidence of death, nonfatal myocardial infarction, and ischemia-driven revascularization at 6 weeks and at 6 months and the incidence of bleeding complications and noncardiac events at 6 weeks and at 6 months.

Normal coronary artery blood flow in the infarct-related artery was more frequently achieved in patients randomized to the facilitated arm (14% vs 59%, $P = .005$). There was no difference with respect to ST-segment resolution at 1 or 3 hours, but at 6 hours, a higher percentage of patients from the facilitated PCI arm had ST-segment resolution (43% vs 61%, $P = .03$). Infarct size, as determined

Figure 3 : Frequency Distribution for Median Door-to-Balloon Times among Study Hospitals



The Median door-to-balloon time was calculated for each hospital in the study. The mean (± SD) of these median times was 100.4 ± 23.5 minutes, which is considerably longer than the 90 minute interval recommended in the 2004 guidelines of the American Heart Association and the American College of Cardiology.[4]

Source: *N Engl J Med* 2006;355

by enzyme levels and left ventricular function, were similar in both groups. There was no significant difference in the combined incidence of cardiac events, such as death, reinfarction, and ischemia-driven PCI, between the primary PCI and facilitated PCI groups (12% vs 9%, respectively). Investigators reported that the rate of death was lower in the facilitated group (3% vs 6%, respectively), but the rates of reinfarction (2% vs 1%) and readmission (11% vs 9%) were higher in the facilitated PCI group compared with the primary PCI group (*P* = NS for all comparisons). Bleeding and vascular complications were similar in both groups, although a favorable trend toward a lower rate of major bleeding (non-significant) was noted in the facilitated PCI group.

GRACIA-2 investigators concluded that catheterization plus adequate revascularization within 12 hours after the administration of facilitated fibrinolytic tenecteplase seems to be as safe and as effective as primary PCI. These results suggest that both strategies are similarly effective in restoring myocardial perfusion and preserving left ventricular function, and both are associated with a beneficial clinical outcome.

Two concepts key to improving outcomes after acute myocardial infarction are 1) the reestablishment of coronary flow and 2) the speed with which this may be accomplished. After these trials it can be safely concluded that thrombolysis with new thrombolytic agents such as Tenecteplase is effective as well as safe in the management of acute STEMI. Primary angioplasty is increasingly being advocated by clinical investigators and editorialists as an approach that should supersede thrombolysis for the treatment of acute ST-segment elevation myocardial infarction. It is highly effective, but, due to a number of geographic and other constraints, the therapy is available for less than 20% of all patients with STEMI in Europe, and an even smaller number of patients are treated within the optimal therapeutic window of 2 hours following symptom onset (6% in the PAMI trial). A Canadian study[23] also showed that in 2003, many patients with STEMI in Quebec were not treated within the recommended times.

The availability of cardiac centers with a cathlab facility round the clock is a major hurdle even in the developed nations and in a country like India, this problem is even larger. For conductance of technically demanding procedure such as a primary PCI, the centers should have experienced staff, a reasonably good turnover of patients and a surgical backup facility. All catheterization centers may not fulfill these criteria. With immense traffic congestion in major cities where functional cathlab facilities are available, the time taken by the ambulances to reach the hospitals drastically brings down the advantage that primary angioplasty offers to the patients with STEMI. The window period of 90 minutes for the catheterization is possible only in a miniscule of patients after development of symptoms. Thrombolytic therapy on the other hand can be administered within a few minutes of patients entering the emergency room and even in centers where availability of catheterization facility is questionable.

Ideally, the optimal site for initiation of reperfusion strategies is the patient's home or place where the infarction occurs. Prehospital treatment and prompt transfer to tertiary care hospitals require an elaborate system of well trained ambulance personnel and

regional collaboration of cardiology hospitals. This is of particular importance because in many parts of the world early primary PCI is still an illusion, whereas ambulances can reach patients quickly and start reperfusion therapy with fibrinolysis followed by transfer to a tertiary care facility where PCI can be performed. The average Pain-to-Door time in India ranges between 5.2 (North India) to 10.8 hours (South India).[24,25] As the saying goes in acute coronary syndrome "time is muscle", early thrombolytic therapy, even in the ambulance after the correct diagnosis can go a long way in reducing the morbidity and mortality due to this widespread medical problem. In 1999 Boersma in *Heart* gave an editorial "Acute Myocardial Infarction – Bring the Treatment to the Patient" which is very relevant in this scenario of unavoidable delays in the initiation of therapy.

As previously discussed the primary aim in the management of STEMI is reperfusion of the coronary myocardium. This can be achieved by thrombolysis at the earliest. It leads to symptomatic improvement, normalization of blood investigations such as cardiac enzymes and ST elevation on the ECG. This can be followed by a coronary angiogram after 3 – 24 hours and intervention be done if so required. This widens the window of opportunity of a percutaneous intervention and it can be done in a much more planned manner rather than in a great hurry as in the case of a primary angioplasty.

Regardless of the method of reperfusion, the fact that the arterial conduit is opened does not guarantee that the downstream myocardial cells are receiving adequate nourishment. Indeed, mechanical intervention may favor the potential for atherothrombotic embolization into myocardial tissue, and in theory this could attenuate angioplasty's more consistent ability to reestablish large coronary artery flow.

The proponents of primary angioplasty claim that it is the superior treatment even when it requires hospital transfers. The trials conducted in this regard show that there is no conclusive evidence for the superiority of transferring patients for primary angioplasty over performing immediate on-site thrombolysis.

Both treatments are continuously evolving, making comparisons difficult ("moving targets"), but the lag seems more important in the thrombolytic arms of the trials because recent angioplasty arms have used coronary stents and modern adjunctive therapy. Many institutions are now using tissue plasminogen activator or its analogs, at least for high-risk patients. Moreover, current practice is to use better adjunctive therapy with thrombolysis, a method that improves clinical outcomes. Physicians also regularly use rescue and delayed angioplasty in patients with refractory and recurrent ischemia, an option that was infrequently used in the trials and that may improve prognosis.

It has been suggested that the mortality benefits for primary angioplasty over thrombolysis are likely to be small and perhaps not achievable in routine clinical practice. Nevertheless, accepting for the moment that there may be an initial 30-day 1% to 2% mortality benefit, one may ask whether this benefit can be sustained. Long-term results are difficult to find. The largest published results come from the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) trial (26), which showed an advantage at 30 days in reduction of the composite end point (death, nonfatal myocardial infarction, or stroke) with primary angioplasty; however, this finding becomes statistically nonsignificant at 6 months. This raises questions about the durability of any short-term differences.

Conclusion

There are 3 possible attitudes toward coronary reperfusion for acute myocardial infarction (ignoring so-called facilitated angioplasty, which combines thrombolysis with subsequent angioplasty and is of yet unproven benefit). The first attitude is primary angioplasty for all. The second is primary angioplasty as the preferred option if it can be performed quickly. The third is thrombolysis

with judicious use of timely angioplasty. This last attitude would favor angioplasty in patients who have contraindications to thrombolysis, are at high risk for bleeding, have hemodynamic compromise, or have a large infarction with the possibility of rapid angioplasty. This approach would also include rescue angioplasty for patients who appear not to have responded to thrombolysis and in whom the anticipated gain in terms of amount of salvageable myocardium justifies this incremental treatment.

Although both primary angioplasty and thrombolysis are effective treatments for acute myocardial infarction, it is felt that the evidence does not support the case for primary angioplasty as the sole or even main treatment option. The other two choices are well founded, and their selection will depend on the clinical setting. Definitive studies favoring one option over the other have yet to be performed. It may be more useful to view these approaches as complementary rather than competitive. It is erroneous to assume that primary angioplasty is always the preferred policy and that our limited resources should be committed solely to advancing this option. Appropriately, smaller hospitals, patients, and health care planners look to university hospitals and specialists for guidance in the interpretation of new scientific evidence. We must be vigilant about providing unbiased interpretations that may be realistically extrapolated to the real world. Health policy planners should be made aware that the implantation of effective systems of prehospital thrombolysis is a clinically and economically attractive alternative to the uncontrolled expansion of tertiary cardiac infrastructures.

In the meantime, clinicians without facile access to primary angioplasty have no reason to feel that they are administering inferior therapy. They should be encouraged to apply thrombolytic therapy promptly and with confidence. It would be unfortunate, even deleterious, if the current infatuation with primary angioplasty generates insecurity, undue hesitations, and delays in treatment and precipitates unnecessary transfers when a universally accessible treatment alternative, thrombolysis, can and should be punctually provided. Unbridled enthusiasm for any approach should not trump firm scientific evidence; otherwise, unsupported conviction risks becoming the basis for new orthodoxy, if not dogma. While undoubtedly more progress in treating acute myocardial infarction will be forthcoming, it is essential that currently proven therapies such as thrombolysis be administered in a timely and universal manner.

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