

Primary Angioplasty and Thrombolysis Are Both Reasonable Options in Acute Myocardial Infarction

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Primary angioplasty is increasingly being advocated as the preferred approach for treating acute ST-segment elevation myocardial infarction regardless of whether interinstitutional transfer is required. This review critically analyzes the evidence comparing primary angioplasty with thrombolytic therapy and concludes that reasonable health care professionals may still find considerable uncertainty about the superiority of primary angioplasty for all situations. The magnitude of benefit for primary angioplasty over thrombolysis is probably less than 1 to 2 lives saved/100 patients treated and largely depends on the choice of thrombolytic agent, time to treatment, place of treatment, and adjunctive therapy.

There is little evidence that systematically transferring patients for primary angioplasty in routine practice will provide any health benefits over thrombolysis. Consequently, it may be most useful to view these treatments as complementary rather than competitive. Thrombolysis remains a clinically and economically attractive option for the treatment of acute myocardial infarction that does not require the radical restructuring of our health care systems.

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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 (1-5). A clarion call is being heard to expand the capabilities for percutaneous coronary intervention and to make its use universally available around the clock, as well as to develop "centers of excellence" for the treatment of acute myocardial infarction (1, 2, 6-8). It is declared that the best method of reperfusion is no longer in any doubt and that as a result there is an urgency to radically restructure health care. This paradigm shift, which would render the routine first-line treatment of acute myocardial infarction at once both tertiary and invasive, has enormous implications. In this review, we propose that reasonable health care professionals may still find considerable uncertainty about the underlying premise of the superiority of primary angioplasty.

Recently a plea has been made for a more rigorous examination of the medical literature on the treatment of acute coronary syndromes (9), and we believe that a critical evaluation of the evidence for the superiority of primary angioplasty will benefit patients, doctors, and health care planners. We limit our remarks and arguments to mortality differences, although stroke and intracranial hemorrhages in particular are also important outcomes. Thrombolysis increases the risk for intracranial hemorrhage by approximately 1% (10), but many cases are fatal and therefore are included with deaths. Myocardial infarction and repeat revascularization are also important end points, but less so than death; in addition, ascertainment bias remains a possibility in unblinded trials (9). Moreover, the definition of a repeat myocardial infarction may vary according to whether a coronary revascularization procedure is performed or not. Finally, repeat revascularizations are often driven more by clinical preferences than clinical need (11).

TIME IS MUSCLE (EVEN IN 2004)

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. There is no doubt that primary angioplasty can reestablish coronary flow in more cases than can thrombolysis, all things being equal. The question is, are all other things always equal? It is also implicitly assumed that reestablished epicardial coronary flow is synonymous with effective and timely myocardial reperfusion, but this is not necessarily the case. 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 (12-14). 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.

More than 25 years ago, Reimer and colleagues (15) described the wavefront phenomenon of ischemic cell death in dogs. They demonstrated increasing myocardial necrosis with increasing times of coronary occlusion and suggested a window of myocardial salvage that extended at least partially to 6 hours. These findings, coupled with DeWood and colleagues' seminal observation that most patients with acute myocardial infarction had intracoronary thrombosis (16), provided the impetus for large-scale randomized clinical trials of intravenous thrombolysis. An early meta-analysis (17) from 9 trials of 58 000 patients with ST-segment elevation or left bundle-branch block unequivocally demonstrated that in patients receiving thrombolytic therapy, earlier treatment was associated with improved survival. These authors suggested a roughly linear decline in benefit (mean \pm SD, 35 \pm 11 lives saved/1000 treated in the first hour, 25 \pm 5 lives saved in hours 1 to 3, and 19 \pm 5 lives saved in hours 3 to 6). Subsequently, Boersma and colleagues (18) used an extended database

from 22 trials (50 246 patients) to propose the concept of the “golden hour,” with increased (exponential) survival benefits in the first 2 hours (65 ± 14 lives saved/1000 patients treated in the first hour and 37 ± 9 lives saved in the second hour).

More evidence of the importance of time to treatment came from a meta-analysis (19) of 6 randomized trials comparing prehospital to in-hospital thrombolysis. The pooled results ($n = 6434$ patients; 604 total deaths) showed decreased all-cause hospital mortality among patients treated with prehospital thrombolysis compared with in-hospital thrombolysis (odds ratio, 0.83 [95% CI, 0.70 to 0.98]). Prehospital care was associated with a 60-minute reduction in treatment time and a 1.6–percentage point absolute reduction in mortality consistent with that predicted by the in-hospital thrombolytic trials mentioned earlier. Finally, a recent regression analysis of all randomized clinical trials has suggested that the mortality benefit observed with primary angioplasty may be lost if the door-to-balloon time exceeds door-to-needle time by 60 minutes (20).

Against this body of knowledge, the advocates of primary angioplasty often affirm that the time to reperfusion is less relevant with their technique (3, 4). Think about this suspension of basic pathophysiology for a moment. Somehow the myocardium knows, understands, and is reassured by the prospect of an impending angioplasty and in consequence acts to minimize any accumulating damage, including death, associated with delayed reperfusion. One study (21) frequently quoted to support this implausible view involved 1352 consecutive patients undergoing primary angioplasty. In fact, these authors did report a substantial time–mortality gradient between patients treated earlier (4.3% at <2 hours) and patients treated later (9.2% at ≥ 2 hours) ($P = 0.04$); the magnitude of this difference may correspond to the “golden hour” phenomenon observed in thrombolytic trials. The authors noted a lack of association between time intervals beyond 2 hours, but this was more likely due to a lack of statistical power than to an invalidation of the important time-to-treatment concept. In statistical parlance, absence of proof is not proof of absence.

Another study quoted to support delays in the performance of primary angioplasty is the recently published DANAMI (Danish Multicenter Randomized Study on Thrombolytic Therapy versus Acute Coronary Angioplasty in Acute Myocardial Infarction) trial (22), which compared primary angioplasty (often with between-hospital transfer) to on-site thrombolysis. The absence of any mortality difference (7.8% for thrombolysis, 6.6% for angioplasty; $P > 0.2$) has been used to justify up to 3-hour delays in assuring reperfusion. This is an example of the erroneous conclusions that may be drawn when decision making is based solely on P values. An examination of these mortality data with confidence intervals shows that they are also compatible with 1.5 extra lives saved per 100

patients treated with thrombolysis (mean difference, 1.2 lives [CI, -1.5 to 3.9 lives]) as opposed to waiting for angioplasty.

A national registry in the United States examined more than 250 000 patients hospitalized with acute myocardial infarction from 1994 to 1998 (23). In general, the door-to–primary angioplasty time was 60 to 100 minutes longer than the door-to-thrombolysis time (23, 24). Newer drug protocols, bolus agents, and prehospital care may further accentuate this time differential. Bolus thrombolytic agents may be expected to shorten the time to treatment by at least the 30-minute preparation time of infusion protocols (25), reduce medication errors, facilitate prehospital thrombolysis, and possibly reduce mortality further.

Even in recipients of primary angioplasty, shorter door-to-balloon times are associated with lower mortality rates (26). Therefore, the totality of the evidence based on controlled measurements in more than 100 000 patients suggests that time indeed is muscle, whether waiting for a thrombolytic agent or waiting for primary angioplasty. This remains true today, notwithstanding the conclusions of recent small underpowered trials.

THE EVIDENCE FOR THE SUPERIORITY OF PRIMARY ANGIOPLASTY

A recent meta-analysis of 23 randomized clinical trials has summarized the evidence for the superiority of primary angioplasty over intravenous thrombolytic therapy for acute myocardial infarction (3). However, as acknowledged by the authors, 1 trial (27) was a randomized trial not of thrombolysis versus primary angioplasty but of 2 strategies for the treatment of cardiogenic shock after acute myocardial infarction. Nevertheless, even after exclusion of this trial, survival was still improved with primary angioplasty (5% [199 of 3720 patients] vs. 7% [276 of 3717 patients]; $P < 0.001$).

In interpreting these results, we must be careful not to be unduly influenced by the P value, which is driven more by sample size than effect size. For example, without changing the amount of benefit, if all the preceding numbers were multiplied by 10, the P value would be 0.3×10^{-15} ; dividing by 10 changes the P value to 0.3. However, in all cases the best estimate of difference between the 2 options is still 2%. The 95% CI from the original data suggests a benefit as large as 3% or as little as 1%. The totality of the evidence for the superiority of primary angioplasty is based on a difference of only 77 fewer deaths than with thrombolysis.

From this disparate collection of studies performed over a 10- to 15-year period, inquiring clinicians might well pose several intriguing questions before accepting as dogma that primary angioplasty is the superior treatment.

DOES THE “BENEFIT” OF PRIMARY ANGIOPLASTY DEPEND ON THE COMPARATIVE THROMBOLYTIC AGENT?

Not surprisingly, the answer is yes. 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 (CI, 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 (28).

DOES THE “BENEFIT” OF PRIMARY ANGIOPLASTY DEPEND ON THE PRESENCE OF ON-SITE FACILITIES?

The proponents of primary angioplasty claim that it is the superior treatment even when it requires hospital transfers. Five randomized studies (22, 29–32) have examined this issue. Pooling of the results of these 5 trials suggests a 2% mortality advantage for primary angioplasty. However, the lack of precision about this result should be troublesome for those advocating this strategy because the data are also compatible with a 9% probability of better survival with thrombolysis. Thus, there is no conclusive evidence for the superiority of transferring patients for primary angioplasty over performing immediate on-site thrombolysis.

The generalizability of even these equivocal results may be furthered questioned on several grounds. First, 3 of the studies randomly assigned patients only if rapid transport was available. This does not influence the internal validity of the results but is disquieting for a public health policy proposing that all patients be treated by primary angioplasty. Moreover, when considering that most of these studies used streptokinase (which is not considered the agent of choice for high-risk myocardial infarctions) or that rescue or delayed angioplasty for patients with refractory or recurrent ischemia was rarely performed, the case for routine transfer becomes even more tenuous. The mortality rate in the thrombolytic groups in these studies was unaccountably elevated, varying from 8% to 14%. How relevant, therefore, are these experiences when contemporary registry and trial data of thrombolytic therapy show mortality rates of 5% to 6% (24, 33, 34)?

DO THESE TRIALS REFLECT THE CURRENT STATE OF TREATMENT FOR ACUTE MYOCARDIAL INFARCTION?

On the basis of the preceding discussion, any potential advantage for primary angioplasty appears limited to hos-

pitals able to offer on-site treatment. However, even in this situation, time is crucial. The trials had rapid door-to-balloon times, averaging about 60 minutes, and any advantage could be erased if treatment delays were longer. The trials do not detail the number of patients entered after working hours or their results. We are left to assume that the results are the same regardless of the time of day. This assumption may be questioned because a recent study in a high-volume and top-notch primary angioplasty center has reported a twofold increase in mortality in patients with acute myocardial infarction treated with angioplasty outside normal working hours (35).

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 analogues, at least for high-risk patients. Moreover, current practice is to use better adjunctive therapy with thrombolysis, a method that improves clinical outcomes (33). 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.

The difference between current practice and the experience in the reported trials is expected to reduce any contrast between the 2 strategies. Indeed, an examination of the 10 most recent trials published since 2000 (3) shows a smaller, non-statistically significant benefit (18 lives saved/1000 patients treated [CI, excess mortality of 4 deaths/1000 persons treated to 41 lives saved/1000 persons treated]) than that observed in the older studies.

IF BENEFITS OF PRIMARY ANGIOPLASTY EXIST, ARE THEY WORTH THE INVESTMENT?

We have suggested that 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, 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 (36). This raises questions about the durability of any short-term differences.

Before we adopt a national systematic strategy of primary angioplasty, we must address several additional issues. Tertiary cardiac resources are highly centralized in most countries, and most patients with acute myocardial infarction do not present to hospitals that have an on-site cath-

eterization laboratory. To develop the paradigm of primary angioplasty would necessitate either transferring multitudes of patients or opening new catheterization centers. Regarding the first option, the data would suggest that no mortality benefit is associated with even ideal transfer times. Moreover, routine transfer times will probably exceed the typical 30 minutes reported in the trials. Amazingly, in the largest study, the door-to-balloon time for transferred patients was only 27 minutes longer than for those receiving on-site angioplasty (22). While advocates insist that this policy is safe, a 1% to 2% incidence of ventricular fibrillation and death is reported during transfer (29). Would all these patients require medical supervision during transfer? Do community emergency departments have spare physicians for these transfers? Would other noncardiac patients suffer? It cannot be overemphasized that even in the ideal world of clinical trials, the possibility that this strategy could increase mortality has not been eliminated.

The alternative of opening more catheterization laboratories hardly seems more attractive. These centers are likely to have low volumes, and studies have shown increased mortality in patients treated with primary angioplasty in low-volume centers (23, 37). The difference between centers in the highest and lowest quartiles of volume equals or surpasses any theoretical advantage of angioplasty over thrombolysis, about 2 lives saved/100 patients treated. One angioplasty team cannot be on-call for 365 days per year, and the existence of at least 2 teams may further harm the volume–outcome relationship. Outcomes, good and bad, depend on more than the cardiologist performing the intervention. Assuring the competence of complete teams, including postangioplasty care, in low-volume centers would be a daunting challenge. On the other hand, no volume–outcome relation has been shown for thrombolysis (23).

The recent Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) trial (38) compared prehospital thrombolysis with primary angioplasty in 840 patients who presented within 6 hours of acute myocardial infarction and found a nonsignificant mortality difference of 1% (CI, -1.8% to 3.7%) in favor of thrombolysis. The low 3.8% mortality rate in the thrombolytic group of this trial was probably the result of prompt treatment (median time from symptom onset to treatment was 2.2 hours) and judicious recourse to rescue angioplasty (used in 26% of patients). These results are entirely consistent with previous knowledge suggesting that prehospital thrombolysis has a mortality benefit at least as great as that attained with on-site primary angioplasty. Moreover, this equivalence may be obtained with performance of only a fraction of the invasive interventions. Astonishingly, the publication of this “negative” trial was accompanied by an editorial encouraging primary angioplasty, “regardless of whether the nearest catheterization suite is 3 floors or 3 hours away” (4).

Primary angioplasty is reputed to be a cost-effective

procedure in the United States because of shortened hospital stays (39). However, algorithms for safely shortening hospital stays with a noninterventional approach have also been developed (40). The socioeconomic implications of making the treatment of ST-segment elevation myocardial infarction an obligatory act of tertiary care with routine recourse to primary angioplasty are profound. They include a major mobilization of emergency transport systems; the expanded operation of catheterization laboratories, with their qualified medical and technical personnel, at any time of day or night; and the use of expensive pharmaceuticals and devices (platelet glycoprotein receptor inhibitors, balloon catheters, and coronary stents, with even costlier drug-eluting stents waiting in the wings). Does it not seem intuitively disproportionate to commit such enormous energies and investments when simpler, equally effective treatments are available for most cases?

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, we feel 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 supplied in a timely and universal manner. Fortunately, this does not require the radical restructuring of our health care systems.

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