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Balancing the Benefits of Primary Angioplasty against the Benefits of Thrombolytic Therapy for Acute Myocardial Infarction: The Importance of Timing

CONTEXT. A meta-analysis found that primary percutaneous transluminal coronary angioplasty (PTCA) was more effective than thrombolytic therapy in reducing mortality from acute myocardial infarction. However, fewer than 20% of U.S. hospitals have facilities to perform PTCA and many clinicians must choose between immediate thrombolytic therapy and delayed PTCA.

COUNT. The number of minutes of PTCA-related delay that would nullify its benefits.

CALCULATION. For 10 published randomized trials, we calculated the following:

PTCA-related delay = median "door-to-balloon" time – median "door-to-needle" time

Survival benefit = 30-day mortality after thrombolytic therapy – 30-day mortality after PTCA

The relationship between delay and benefit was assessed with linear regression.

RESULTS. The reported PTCA-related delay ranged from 7 to 59 minutes, while the absolute survival benefit ranged from –2.2% (favoring thrombolytic therapy) to 7.4% (favoring PTCA). Across trials, the survival benefit decreased as the PTCA-related delay increased: For each additional 10-minute delay, the benefit was predicted to decrease 1.7% ($P < 0.001$). Linear regression showed that at a PTCA-related delay of 50 minutes, PTCA and thrombolytic therapy yielded equivalent reductions in mortality .

CONCLUSIONS. In clinical trials with short PTCA-related delays, PTCA produced better outcomes, while trials with longer delays favored thrombolytic therapy. A more precise estimate of the time interval to equipoise between the two therapies needs to be modeled with patient-level data. At experienced cardiac centers, PTCA is probably still preferable, even with delays longer than 50 minutes.

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In the treatment of acute myocardial infarction (AMI),[1–3] restoring coronary perfusion at the earliest possible time is critical. There are two general modes of coronary reperfusion therapy: 1) pharmacologic thrombolytic therapy and 2) mechanical, catheter-based, emergency "primary" percutaneous transluminal coronary angioplasty (PTCA).

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In 1997, a meta-analysis of 10 randomized trials demonstrated the superiority of PTCA over thrombolytic therapy in preventing death and other adverse clinical outcomes.[4] Patients with AMI who received thrombolytic therapy had a mortality rate of 6.5%, while those who had primary PTCA had a mortality rate of 4.4%, a 34% reduction ($P = 0.02$). Primary PTCA also reduced the risk for other outcomes: The composite outcome of death or nonfatal AMI was 11.9% versus 7.2% ($P < 0.001$), all stroke was 2.0% versus 0.7% ($P = 0.007$), and hemorrhagic stroke was 1.1% versus 0.1% ($P < 0.001$).[4]

Despite these findings, thrombolytic therapy has some practical advantages over PTCA. It can be given in any emergency department, and potentially in the field, while PTCA must be done by a trained interventional cardiologist in a specialized center. Because primary PTCA is unavailable in most hospitals, thrombolytic therapy remains the standard of care and accounts for roughly 80% of all reperfusion therapy for AMI in the United States.

Regardless of the method of reperfusion used, time to treatment remains a critical determinant of outcome. Thus, when patients are brought to hospitals that lack catheterization laboratories or cannot offer immediate PTCA, physicians are faced with a choice between immediate thrombolytic therapy or delayed PTCA (resulting from the need to prepare a catheterization laboratory or transport to a cardiac center). The purpose of our study was to explore the relationship between PTCA-related delay and the benefits of PTCA, using the results of published clinical trials. We sought to determine the length of PTCA-related delay that would be likely to nullify its expected incremental benefit over immediately available thrombolytic therapy.

Methods

Table 1 shows the results of 10 randomized trials comparing primary angioplasty with thrombolytic therapy.[5–14] **Figure 1** shows our approach. We calculated PTCA-related delay as the difference between the median "door-to-balloon" time with PTCA and the median "door-to-needle" time with thrombolytic therapy. We calculated benefit as the difference between mortality rates observed with thrombolytic therapy and mortality rates observed with PTCA.

TABLE 1
Ten Randomized Trials of Primary Angioplasty vs Thrombolytic Therapy in Acute Myocardial Infarction*

TRIAL LOCATION	PATIENTS, *n*	THROMBOLYTIC AGENT	TIME (min)			30-DAY MORTALITY		
			DOOR TO BALLOON	DOOR TO NEEDLE	PTCA DELAY	PTCA	THROMBOLYSIS	PTCA BENEFIT
Italy[5]	83	t-PA	40	33	7	0%	2.4%	2.4%
Spain[6]	189	t-PA	84	69	15	3.2%	10.6%	7.4%
United States[7]	105	DUT	45	20	25	4.3%	3.4%	–0.9%
Multicenter, United States and France[8]	395	t-PA	60	32	28	2.6%	6.5%	3.9%
The Netherlands[9]	301	SK	62	30	32	2.0%	7.4%	5.4%
The Netherlands[10]	95	SK	68	30	38	2.2%	0%	–2.2%
United States[11]	90	DUT	126	84	42	6.5%	4.5%	–2%
Multicenter, GUSTO IIb[12]	1158	t-PA	114	72	42	5.5%	7.0%	1.5%
Argentina[13]	112	SK	63	18	45	9.3%	10.3%	1.0%
Brazil[14]	100	SK	238	179	59	6.0%	2.0%	–4%

**DUT = duteplase; GUSTO = Global Use of Strategies To Open Occluded Coronary Arteries in Acute Coronary Syndromes; SK = streptokinase; t-PA = tissue plasminogen activator.*

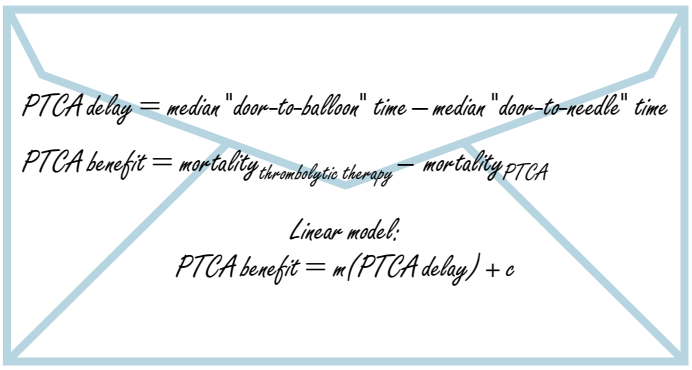

FIGURE 1. Back-of-the-envelope calculation for the benefit of PTCA and PTCA-related delay.

Linear regression was used to assess the relationship between PTCA-related delay and treatment benefit. The magnitude and statistical significance of the relationship were estimated by using weighted least-squares regression, weighting each trial's results by the square root of the number of patients in that trial. Using linear regression, we estimated 1) the decrease in benefit for each additional minute of delay in receipt of PTCA therapy and 2) the delay expected to lead to equipoise between PTCA and thrombolytic therapy (after which the mortality for the former would exceed that for the latter). Sensitivity analyses were performed to test the stability of these estimates by excluding trials at either extreme of PTCA-related delay.

Results

The reported PTCA-related delay ranged from 7 to 59 minutes. Our regression analysis showed that the treatment benefit of PTCA decreased substantially across trials as PTCA-related delay increased. **Figures 2** and **3** plot the absolute risk reduction and relative risk for death with PTCA compared with thrombolytic therapy for the 10 trials, according to PTCA-related delay. The absolute survival benefit of PTCA compared with thrombolytic therapy decreased by 1.7% for every additional 10-minute delay ($P < 0.001$). The regression showed that when PTCA-related delay reached 50 minutes, the mortality rates for PTCA and thrombolytic therapy were likely to be equivalent (i.e., a state of

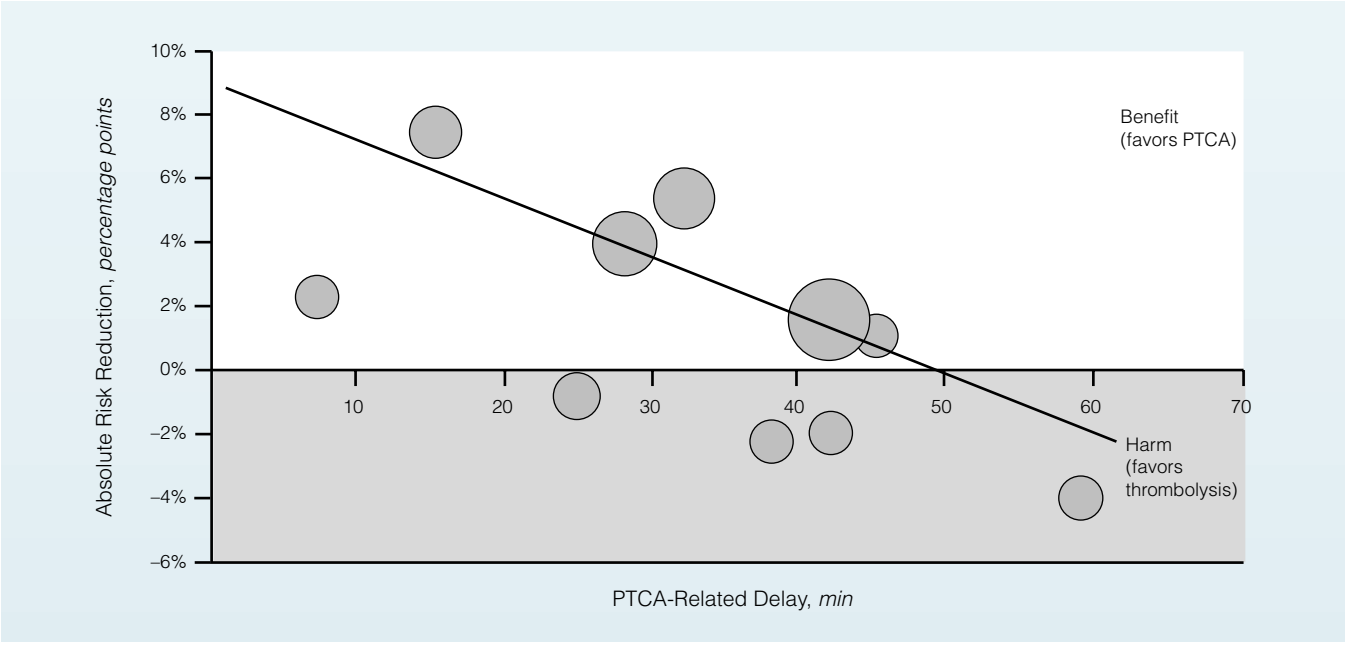

FIGURE 2. Absolute risk reduction in 30-day mortality rate, with PTCA as a function of PTCA-related delay. The size of the circle reflects the study sample size. Values above zero represent benefit, and values below zero represent harm. Line = weighted regression.

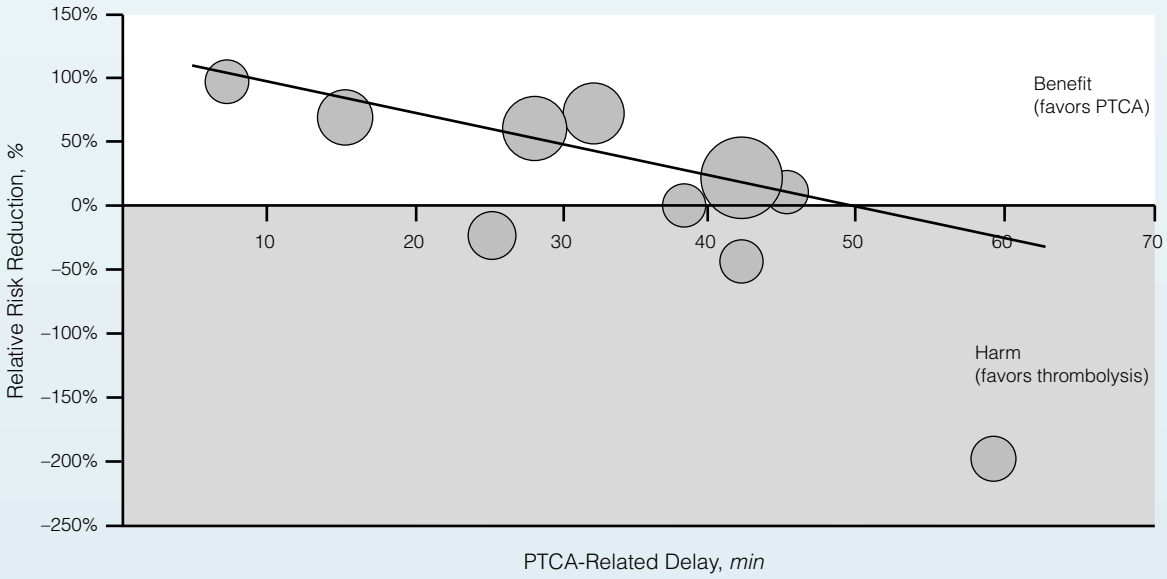

FIGURE 3. Relative risk reduction in 30-day mortality rate, with PTCA as a function of PTCA-related delay. The size of the circle reflects the study sample size. Values above zero represent benefit, and values below zero represent harm. Line = weighted regression.

"equipoise"); in trials with longer delays, PTCA was likely to have less benefit than thrombolysis.

Table 2 shows the change in absolute survival benefit for each 10 minutes of PTCA-related delay. It also shows the delay leading to equipoise in the base case (including all 10 trials), when trials with the longest or shortest delay were excluded. The estimates of the effect of PTCA-related delay were not significantly altered by the exclusion of these "outlier" trials.

Discussion

A meta-analysis of extant trials comparing primary PTCA with thrombolytic therapy for AMI showed that PTCA yielded an average absolute risk reduction for death of approximately 2%.[4] In contrast to meta-analysis, which seeks to arrive at a single summed result from often heterogeneous clinical trials, our regression analysis seeks to explore the relationship between the variation in the results of trials and the variation in their designs and study samples. This technique has been called meta-regression.[15] Our analysis suggests that the benefits of PTCA decrease substantially with increasing PTCA-related delay and, on average, are nullified when this delay reaches approximately 50 minutes. While previous studies have demonstrated that increasing door-to-balloon time is associated with poorer PTCA outcomes,[16,17] they have not specifically estimated how the benefit of primary PTCA compared with thrombolytic therapy diminishes with increasing PTCA-related delay.

Use of conventional analysis to estimate the change in treatment effect seen with increasing PTCA-related delay is problematic because both treatment benefit and procedure-related delay are derived from groups of

TABLE 2
Sensitivity of the Regression to Outliers*

DATA	SLOPE (CHANGE IN BENEFIT PER 10-MINUTE DELAY)	DELAY LEADING TO EQUIPOISE BETWEEN PTCA AND THROMBOLYTIC THERAPY
Base case (10 trials)	1.7%	50.1 min
Long-delay outlier excluded (9 trials)	1.6%	51.0 min
Short-delay outlier excluded (9 trials)	1.9%	49.4 min
Both outliers excluded (8 trials)	1.8%	50.1 min

**Outliers are the trials that had the longest or shortest delay.*

patients rather than individuals. In other words, although individual patients can be stratified by door-to-needle or door-to-balloon time, they cannot be stratified by "PTCA-related delay" (the difference between these terms) because any individual patient received one method of reperfusion, but not both. For the same reason, marginal benefit related to PTCA cannot be measured in individual patients. In this study, we addressed this issue by using meta-regression, in which the unit of analysis is not individual patients, but individual clinical trials.

Nonetheless, readers should be cautious in making inferences from our results. Increasing PTCA-related delay is likely to be a marker for poorer-quality PTCA overall. It is well established that high-volume hospitals have shorter door-to-balloon times, higher rates of successful reperfusion, and lower mortality rates.[18, 19] Thus, the diminishing benefit in trials with increasing delays may be related not only to the delay itself but also to a constellation of factors associated with slower, less experienced centers, such as lower rates of successful reperfusion. Some trials performed at high-volume cardiac centers with relatively short door-to-balloon times reported normal coronary blood flow after angioplasty in more than 90% of patients.[8, 9] However, the Global Use of Strategies To Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO) IIb trial, which included a large variety of hospitals (e.g., low-volume community hospitals), reported normal flow in only 73% of angioplasty-treated patients and had a relatively long median door-to-balloon time.[12] Because increasing PTCA-related delay is confounded by decreasing overall PTCA quality, it is likely that the downward slope of our study's meta-regression line (i.e., the impact of delay on treatment effect) is exaggerated. Thus, we may have underestimated the time to equipoise between the treatments.

The hypothesis that we overestimated the effect of PTCA-related delay (by underestimating the time to equipoise) is supported by a recent analysis of the largest registry of outcomes in AMI. In this study, primary PTCA was found to have a beneficial effect at high-volume hospitals, despite having a mean (not median) door-to-balloon time that was roughly 70 minutes longer than the mean door-to-needle time.[19] (No benefit was found in low-volume hospitals.) In addition, a time to equipoise of 50 minutes is difficult to reconcile with angiographic studies demonstrating that thrombolysis (with tissue plasminogen activator) achieves reperfusion in only 12% to 24% of patients 30 minutes after therapy initiation and in only approximately 50% of patients at 60 minutes, while PTCA administered by experienced physicians achieves reperfusion immediately after balloon inflation in more than 90% of patients.[20] Although a PTCA-related delay of 50 minutes may nullify the benefits of PTCA at low-volume hospitals, where normal coronary flow might be achieved in only 50% of patients,[21] it is biologically implausible for such a delay to nullify the benefits of PTCA at high-volume centers, where normal coronary flow is achieved in more than 90% of patients. Thus, the characteristics and experience of the hospital at which PTCA is performed probably have a considerable role in determining the delay to equipoise.

Several other details are not reflected in our analysis. In particular, as with thrombolytic therapy, the change in the benefit of PTCA over time from symptom onset is likely to be nonlinear.[22, 23] A given period of delay is likely to be of greater import earlier rather than later in the course of AMI. Accordingly, a shorter time to equipoise may be expected for patients who present very early, especially because the coronary thrombus is much more vulnerable to thrombolytic therapy at this time.[24, 25] Later, the passage of time is likely to be less critical, and PTCA may have particular advantages in achieving reperfusion as the clot stabilizes. For example, 6 hours after symptom onset, normal coronary flow is achieved in only 28% of patients treated with tissue plasminogen activator, whereas PTCA still achieves reperfusion in more than 90% of those treated.

The time to equipoise is also affected by the specific characteristics of the individual and the AMI. The patient's baseline risk for death, as determined by his or her age, vital signs, and AMI size and location, may be an important determinant of the time to equipoise. It has been suggested that patients at greater risk for death[26] are more likely to benefit from PTCA; therefore, a longer delay might be justified for high-risk patients, although the risks associated with delay may be commensurately higher.

In summary, our meta-regression suggests that PTCA-related delays have a substantial effect on the benefits of primary PTCA relative to thrombolytic therapy. In clinical trials in which the average PTCA-related delay was less than 50 minutes, primary PTCA has been shown to provide substantially better survival benefit. Studies with longer delays demonstrate a trend toward less benefit than that seen with thrombolytic therapy. These findings should be of some assistance to the clinician deciding between immediate thrombolytic therapy and delayed PTCA. However, estimating the justifiable PTCA-related delay in individual patients will ultimately require sophisticated modeling techniques at the individual case level.[27]

Take-Home Points

- **A recent meta-analysis of 10 randomized trials of therapy for acute myocardial infarction concluded that percutaneous transluminal coronary angioplasty (PTCA) offered a survival benefit over thrombolytic therapy.**
- **Many clinicians, however, must choose between immediate thrombolysis and delayed PTCA.**
- **Using the same 10 trials, we investigated the relationship between PTCA-related delay and its survival benefit.**
- **Trials with shorter delays generally reported larger PTCA survival benefits. Longer delays favored thrombolytic therapy.**
- **The choice of therapy for acute myocardial infarction is sensitive to delay. This relationship warrants further investigation with patient-level data.**

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