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CME CREDIT

Angioplasty or fibrinolysis for acute MI? The GUSTO IIb study

I N ACUTE MYOCARDIAL INFARCTION, primary angioplasty is better than fibrinolytic therapy, but the advantage is not as large as we once thought. This was the principal finding in the largest and most rigorous comparison of the two therapies performed to date: the angiographic substudy of the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb).[1]

The GUSTO IIb findings underscore at least one other important point: it is crucial to reopen the blocked coronary artery quickly and completely, by whatever means is at hand.

■ THE RATIONALE BEHIND GUSTO IIB

Angioplasty is better, but how much better?

Restoration of blood flow is usually measured according to the criteria of the Thrombolysis in Myocardial Infarction (TIMI) trial.[2] TIMI grade 0 flow means there is no blood flowing in the infarct-related artery, whereas TIMI grade 3 means the artery has been completely reopened. TIMI grade 3 flow is the goal in treating an acute MI, because patients with TIMI grade 3 flow have much better odds of surviving.[3] In addition, TIMI grade 3 flow saves myocardium, prevents ischemia-related ventricular arrhythmia and unfavorable remodeling of the left ventricle, and preserves the potential to provide collateral flow to future ischemic sites.[4,5]

Earlier studies suggested that angioplasty, performed within 60 minutes of coming to the

■ ABSTRACT

The angioplasty substudy of the GUSTO IIb trial confirmed that the short-term results of primary angioplasty are better than those of fibrinolytic therapy in patients with acute myocardial infarction (MI). In the largest and most rigorous study of this topic performed to date, 9.6% of patients who underwent primary angioplasty either died or suffered a disabling stroke or another myocardial infarction within 30 days, compared with 13.7% of patients who received fibrinolytic therapy, for an odds ratio of 0.67 ($P = .033$). This difference was less than in previous studies, possibly in part because fibrinolytic therapy has improved. The findings underscore the importance of promptly restoring complete, brisk, antegrade flow in the infarct-related artery, regardless of what treatment is used.
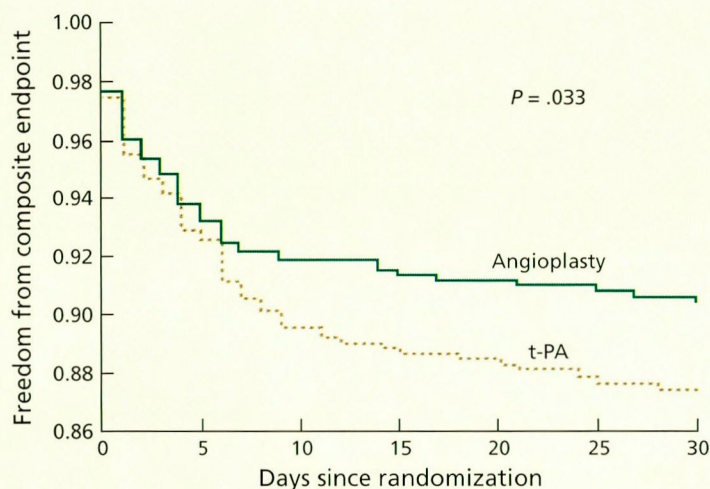
FIGURE 1. Patients who underwent primary angioplasty after an acute MI had a lower incidence of death, reinfarction, or disabling stroke than did patients who received fibrinolytic therapy, but the difference became apparent only after the fifth day after therapy, as shown in this Kaplan-Meier curve.

SOURCE: GUSTO IIB ANGIOGRAPHY SUBSTUDY INVESTIGATORS, REFERENCE 1, WITH PERMISSION.

with an accelerated dosing regimen of tissue-plasminogen activator (t-PA).

GUSTO IIb DESIGN AND PATIENT SELECTION

GUSTO IIb included 1,138 patients, all of whom presented within 12 hours of the onset of an acute myocardial infarction, had ST-segment elevation, and had no contraindications to either t-PA or mechanical reperfusion. As in similar studies, most were men in their 6th or 7th decades. More than 60% were smokers, approximately 39% had hypertension, and approximately 15% had diabetes. The median time from symptom onset to arrival at the hospital was approximately 2 hours.

These patients were randomly assigned to undergo either primary angioplasty or fibrinolytic therapy, after receiving chewable aspirin and a thrombin inhibitor, which, in 1,012 of the patients, consisted of either heparin or hirudin, randomly assigned in a 2 × 2 factorial design.[10] The remainder of the medical regimen was left to the discretion of the attending physicians.

The study was performed at 57 hospitals, all of which met certain requirements for angioplasty experience. At eligible sites, at least 200 angioplasties had to have been performed per year, each investigator had to have performed at least 50 angioplasties per year, and an angioplasty team had to be on call 24 hours per day. At 85% percent of the sites, more than 400 angioplasties per year were performed, and 85% of the operators performed more than 75 procedures per year.

The primary endpoint was the 30-day incidence of death, reinfarction, or disabling stroke. The same endpoints were monitored at 6 months. Unlike previous, smaller randomized trials of primary angioplasty vs fibrinolytic therapy, the GUSTO IIb trial had a central clinical events committee to independently assess all clinical endpoints, and a central angiographic laboratory to independently assess all angiographic endpoints, such as the restoration of complete (TIMI grade 3) blood flow in the infarct-related artery. Strict enzymatic and electrocardiographic criteria were applied to define reinfarction.

hospital, can restore TIMI grade 3 flow in 85% to 90% of patients, and reduce the mortality rate by up to 70% compared with thrombolysis.[6–8] (In contrast, in the GUSTO I trial, even with the best fibrinolytic strategy to date, only about 54% of patients achieved TIMI grade 3 flow.)[9]

However, the earlier studies that compared primary angioplasty and fibrinolytic therapy had several shortcomings. They were small, numbering only approximately 1,500 patients between them, and used less-than-optimal fibrinolytic agents or regimens. They were performed in large university hospitals that had extensive experience in angioplasty, rather than in the "real world" of community hospitals. Importantly, they tended to lack rigor in defining and adjudicating clinical endpoints and angiographic results. All these factors may have exaggerated the relative benefit of angioplasty.

To determine the true magnitude of the benefit, the GUSTO IIb investigators performed a large, randomized trial comparing primary angioplasty vs fibrinolytic therapy

BRIEF ANALYSIS OF THE GUSTO IIb FINDINGS

Among patients assigned to angioplasty, 94% underwent emergency angiography, followed by angioplasty in 82%. Almost 4% received fibrinolytic therapy before arriving in the angiography suite. Compliance with the assignment to fibrinolytic therapy was near-complete (98%), and only 1.4% of the patients allocated to t-PA received primary angioplasty.
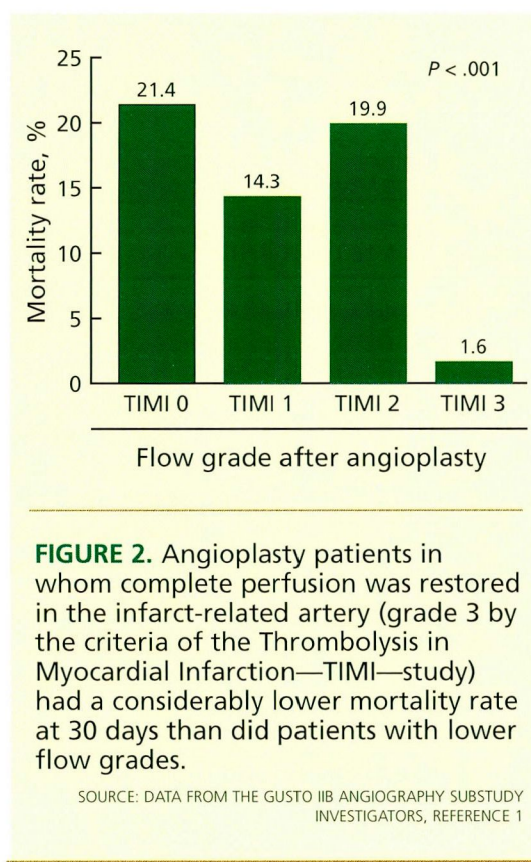
In the fibrinolytic therapy group, a median of 3 hours elapsed between the onset of symptoms and the start of the t-PA infusion; in the angioplasty group, 3.8 hours elapsed between symptom onset and the first balloon inflation—nearly 50 minutes longer. One should note, though, that although the first balloon inflation almost always restores blood flow immediately, fibrinolytic agents achieve patency only 30 to 40 minutes from the initiation of therapy. Thus, the difference in the beginning of therapy translates to essentially equivalent time to reperfusion in the two groups.

Angioplasty patients had significantly fewer deaths, reinfarctions, or disabling strokes

By 30 days after treatment, 54 (9.6%) of the patients in the angioplasty group had either died or suffered a reinfarction or disabling stroke, compared with 78 (13.6%) in the t-PA group, for an odds ratio of 0.67 ($P = .033$). None of these endpoints—death, reinfarction, or stroke—reached statistical significance by itself, but the trial was not designed to detect such a difference. There was an insignificant trend toward fewer events in angioplasty patients who received hirudin than in angioplasty patients who received heparin.

The benefit from angioplasty in reducing the composite endpoint became evident between days 5 and 7 (**FIGURE 1**). However, by 6 months, the difference was no longer statistically significant: 13.3% of the angioplasty patients had died or had a reinfarction or disabling stroke, compared with 15.7% of the patients who received t-PA.

Prespecified subgroup analysis was per-

FIGURE 2. Angioplasty patients in whom complete perfusion was restored in the infarct-related artery (grade 3 by the criteria of the Thrombolysis in Myocardial Infarction—TIMI—study) had a considerably lower mortality rate at 30 days than did patients with lower flow grades.

formed based on age, infarct location, high-risk clinical characteristics, hospital angioplasty volume, and time from symptom onset to presentation. Although most of the subgroups benefited more from angioplasty than from fibrinolytic therapy, none of the trends reached statistical significance.

The 30-day mortality rate in angioplasty patients who achieved TIMI grade 3 flow was strikingly lower than in patients with lower TIMI flow grades (**FIGURE 2**).
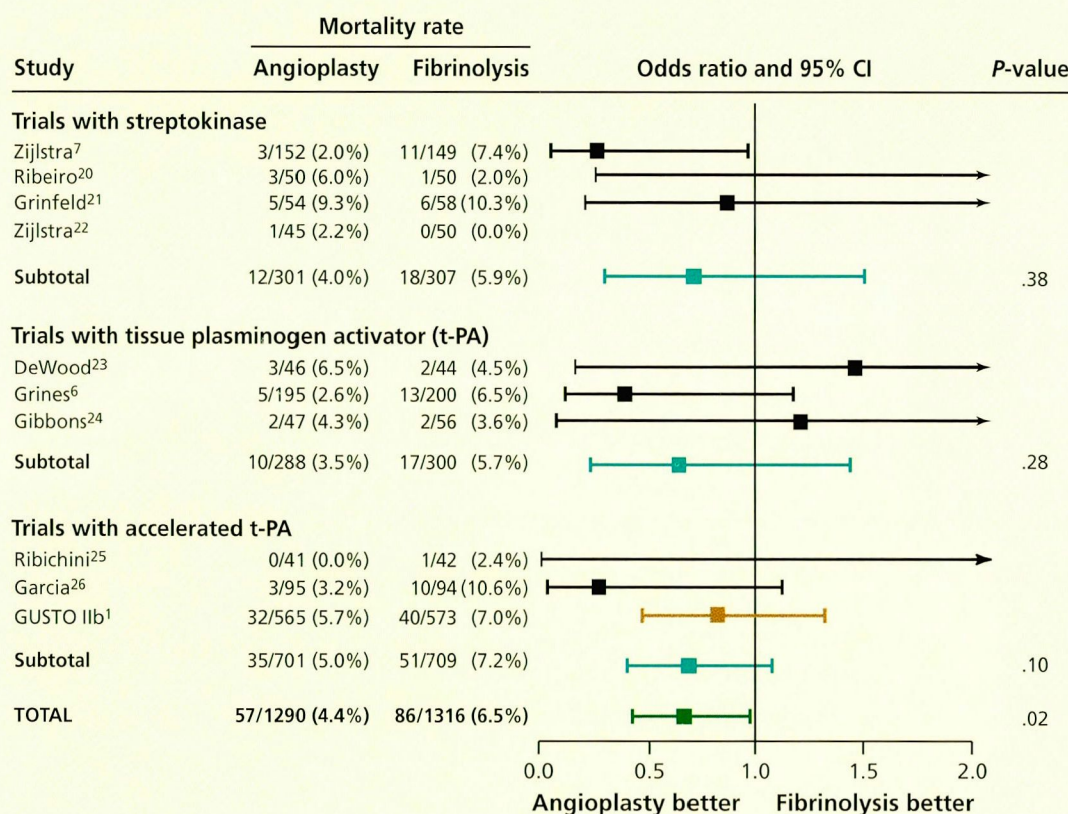
Bleeding complications common in both groups

Intracranial hemorrhage occurred in 1.4% of the t-PA group and 0% of the angioplasty group. Moderate or severe bleeding was noted in 9.5% of the t-PA group and 12.3% of the angioplasty group. Most of the patients with moderate or severe bleeding received blood products. Recurrent ischemia was more common in the t-PA group (9.0% vs 5.5%), while new congestive heart failure developed in similar proportions (4.9% and 4.3%, respectively).

The mortality rate was significantly lower in patients with TIMI grade 3 flow than in those with lower grades in the angioplasty group

Angioplasty vs fibrinolysis in acute MI

Study	Mortality rate		Odds ratio and 95% CI	P-value
	Angioplasty	Fibrinolysis		
Trials with streptokinase				
Zijlstra[7]	3/152 (2.0%)	11/149 (7.4%)		
Ribeiro[20]	3/50 (6.0%)	1/50 (2.0%)		
Grinfeld[21]	5/54 (9.3%)	6/58 (10.3%)		
Zijlstra[22]	1/45 (2.2%)	0/50 (0.0%)		
Subtotal	12/301 (4.0%)	18/307 (5.9%)		.38
Trials with tissue plasminogen activator (t-PA)				
DeWood[23]	3/46 (6.5%)	2/44 (4.5%)		
Grines[6]	5/195 (2.6%)	13/200 (6.5%)		
Gibbons[24]	2/47 (4.3%)	2/56 (3.6%)		
Subtotal	10/288 (3.5%)	17/300 (5.7%)		.28
Trials with accelerated t-PA				
Ribichini[25]	0/41 (0.0%)	1/42 (2.4%)		
Garcia[26]	3/95 (3.2%)	10/94 (10.6%)		
GUSTO IIb[1]	32/565 (5.7%)	40/573 (7.0%)		
Subtotal	35/701 (5.0%)	51/709 (7.2%)		.10
TOTAL	**57/1290 (4.4%)**	**86/1316 (6.5%)**		**.02**

0.0 0.5 1.0 1.5 2.0

Angioplasty better   Fibrinolysis better

FIGURE 3. Most smaller studies conducted prior to the GUSTO IIb trial, comparing angioplasty with fibrinolytic therapy, found a greater advantage for angioplasty than was found in the larger GUSTO IIb trial. The chart above indicates the odds ratio for each of the different studies, the pooled subtotals for different fibrinolytic regimens, and overall pooled total. In the studies by Ribeiro and Ribichini, the odds ratios are beyond the boundaries of the chart. In the second Zijlstra study, there is no odds ratio or confidence interval listed because the denominator in the odds ratio was zero.

The true advantage of angioplasty may be smaller than once thought, but it is considerable nevertheless

■ WHY SHOULD ANGIOPLASTY BE BETTER THAN FIBRINOLYSIS?

Mechanical restoration of antegrade coronary flow addresses some of the limitations of fibrinolytic therapy, and thus has the potential to improve outcome. However, both have been shown to reduce the mortality rate in acute MI and are reasonable therapies.

Angioplasty: pros and cons

Although angioplasty is more often successful in restoring coronary flow and in reducing adverse clinical outcomes, its advantages are offset by a high rate of restenosis (30% to 50%) in the infarct-related artery, necessitating repeat revascularization procedures. (This process can be substantially altered by the use of stents.)

Fibrinolytic therapy: pros and cons

Fibrinolytic therapy is logistically easy to administer, does not require special equipment, and can be given even in the patient's home.[11] It has been investigated in almost 200,000 patients worldwide in well-executed,

randomized, controlled clinical trials and is now known to reduce 30-day mortality after acute myocardial infarction by approximately 20% compared with placebo.[12]

On the other hand, fibrinolytic therapy leaves behind a significant coronary stenosis, which serves as a substrate for future ischemic events. Consequently, from 40% to 60% of patients who receive fibrinolytic therapy need revascularization procedures before or soon after hospital discharge.[13]

Fibrinolytic reperfusion is associated with a significantly lower initial rate of TIMI grade 3 flow (approximately 50%, vs at least 75% for angioplasty). Moreover, even the 50% estimate may be overly optimistic: of the patients who achieve TIMI grade 3 flow, there is reocclusion in 5% to 10% and impaired flow at the capillary level ("no-reflow phenomenon") in 23%.[14] Thus, only 25% of treated patients achieve full reperfusion with fibrinolytic therapy, a phenomenon that Lincoff and Topol[15] have termed "the illusion of reperfusion."

Fibrinolytic therapy is associated with a small but important incidence of intracranial bleeding, especially in elderly patients with uncontrolled hypertension.[16,17] This hazard is much lower with primary angioplasty.

■ INSIGHTS FROM GUSTO IIB

As shown in FIGURE 3, earlier, smaller studies that compared angioplasty with less-than-optimal fibrinolytic regimens indicated larger benefits for angioplasty than did the GUSTO IIb study.[18] For example, in the Primary Angioplasty in Myocardial Infarction Study Group (PAMI 1),[6] the second-largest study with 395 patients enrolled, the in-hospital mortality rate was 6.5% in patients who received t-PA vs 2.6% for patients who received angioplasty—an astounding 60% relative risk reduction (P = .06). Similarly, the Dutch Primary Angioplasty Study found a 73% reduction in mortality in patients treated with angioplasty (7.4% for streptokinase to 2.0% for angioplasty).[7]

In contrast, the advantage of angioplasty was more modest in the GUSTO IIb trial: a 30% reduction in the composite endpoint by 30 days (P = .033), a 19% reduction in the mortality rate (P = NS), and a 31% reduction in the reinfarction rate (P = NS). These results are probably more realistic than the earlier findings.

Complete, brisk, stable reperfusion is essential

The GUSTO IIb findings reaffirm the importance of complete, brisk, and stable reperfusion of the infarcted artery (TIMI grade 3 flow). GUSTO I was the first thrombolytic study to incorporate an angiographic substudy designed to explain the mechanism of improvement in outcome with better fibrinolysis.[9] Subsequent analyses[19] of previous lytic studies concurred with the finding that patients with brisk, complete, stable reperfusion (TIMI grade 3 flow) have a significantly higher rate of survival at 35 days than do patients with lesser degrees of infarct-artery recanalization. Since angioplasty can restore TIMI grade 3 flow in at least 20% to 30% more patients than fibrinolytic therapy, it is reasonable to expect an absolute advantage in mortality of 2% to 3%.

Of interest, in the GUSTO IIb trial, the local cardiologists tended to assign higher TIMI flow grades (85% TIMI grade 3 flow) than did the core angiographic laboratory (73% TIMI grade 3 flow).

### Benefit of angioplasty seen only after day 5

In earlier studies the excess mortality in the fibrinolytic arm was concentrated in the first 48 hours from admission, reflecting the occurrence of stroke and cardiogenic shock. In contrast, in GUSTO IIb the cumulative outcome curves started to separate only on day 5, indicating that the reduction in adverse events is mostly due to prevention of recurrent ischemia and infarction and their accompanying complications.

Why did the GUSTO IIb findings differ from those in previous studies?

Part of the difference in outcome between GUSTO IIb and previous smaller studies can be explained by the more rigorous examination of endpoints in GUSTO IIb, and part can be attributed to the fact that this study was

The GUSTO IIb trial reflects the "real world" of acute MI care
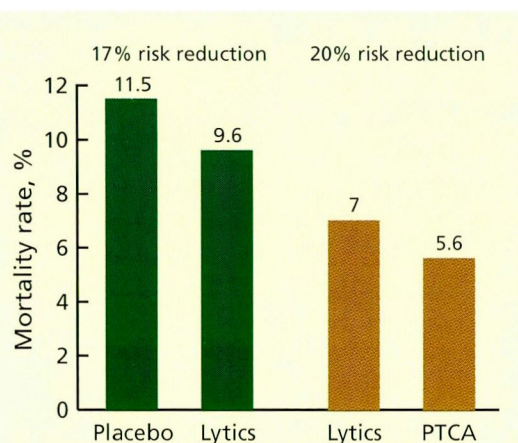
FIGURE 4. The reduction in mortality with angioplasty vs fibrinolytic therapy in the GUSTO IIb trial (gold bars) is comparable to the reduction in mortality in the earlier trials that compared fibrinolytic therapy with placebo (green bars).

SOURCE: DATA FROM THE GUSTO IIB ANGIOGRAPHY SUBSTUDY INVESTIGATORS, REFERENCE 1, AND THE FIBRINOLYTIC THERAPY TRIALISTS' (FTT) COLLABORATIVE GROUP, REFERENCE 12

Fibrinolysis will remain the mainstay of MI therapy in most hospitals

performed in institutions with a wider range of experience with primary angioplasty, in which support personnel may not have been immediately available (ie, more representative of the "real world") than those represented in the earlier studies.

Although the true advantage of angioplasty may be smaller than once thought, it is comparable to the improvement conferred by other interventions for acute myocardial infarction (**FIGURE 4**). For example, in randomized trials that compared fibrinolytic therapy with placebo, the 35-day mortality rate in patients who received placebo was 11.5%, vs 9.6% in patients who received fibrinolytic therapy—a 17% relative risk reduction.[12] In comparison, in GUSTO IIb, the 30-day mortality rate in patients who received fibrinolytic therapy was 7%, vs 5.6% in patients who received angioplasty—a 20% relative advantage. This further reduction in mortality is even more impressive because it occurs on the background of an already successful intervention in acute MI patients.

WHAT SHOULD PHYSICIANS AND PATIENTS DO?

Primary angioplasty is a valuable intervention and, should be considered in all patients with acute ST elevation MI, if it can be performed within 60 to 90 minutes of presentation. It is the preferred approach in patients with cardiogenic shock, late presentation, or absolute contraindications to fibrinolytic therapy.

Nevertheless, because of the logistic difficulties associated with primary angioplasty, prompt administration of fibrinolytic therapy will remain the mainstay of therapy for acute myocardial infarction in most hospitals around the world.

Patients at risk of having an MI should be educated to go to the closest hospital as soon as symptoms appear, and not to delay seeking medical attention.
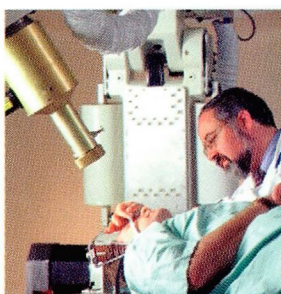
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