EDITORIAL COMMENT

Rescue Angioplasty

Does the Concept Need to Be Rescued?*

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During the 1980s, thrombolytic therapy became the initial treatment for patients with acute myocardial infarction (AMI). Toward the end of the decade, primary percutaneous coronary intervention (PCI) was shown to be effective (1,2), and a recent analysis of 23 randomized trials demonstrated improved rates of reinfarction, stroke, and death compared with thrombolytic therapy (3). However, because of limited facilities and trained interventionists, many hospitals continue to initiate thrombolytic therapy for patients with AMI.

Unfortunately, not all arteries respond to thrombolytic therapy, and approximately 40% have less than Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 after 90 min. Patients with an occluded infarct artery (TIMI flow grade 0 to 1) or suboptimal flow (TIMI flow grade 2) 90 min after thrombolytic therapy have worse left ventricular (LV) function and increased early mortality (4). Rescue PCI is performed for patients with failed thrombolysis to establish reperfusion, to salvage myocardium, and hopefully to improve prognosis.

A post hoc analysis of patients from the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trials demonstrated that the in-hospital and late mortality of patients who left the catheterization laboratory with a patent infarct artery were similar in groups who had reperfusion established by successful thrombolysis (n = 607) or by rescue PCI after failed thrombolysis (n = 169) (5). However, patients requiring rescue PCI to achieve patency had a twofold greater rate of reocclusion, which was associated with less regional and global LV functional recovery. Moreover, in patients who failed rescue PCI, the mortality was 39%.

In a review of 12 early observational studies (6), short-term patency was restored by rescue PCI in 71% to 100% of occluded coronary arteries after failed thrombolysis (mean, 80%). However, 18% of vessels reoccluded, ejection fraction often failed to improve by hospital discharge, and in-hospital mortality averaged 10.6%. Over the years, better understanding of the importance of aspirin, higher-dose heparin, and angioplasty technique have resulted in lower reocclusion rates. In the Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries (GUSTO) angiographic substudy, there was no difference in immediate patency or inhospital reocclusion among various thrombolytic regimens (7). Likewise, reocclusion at 24 h occurred in only 4% of patients having TIMI flow grade 3 (8).

Few randomized trials of rescue PCI have been reported (9–13). In the TAMI-5 study group (9), 575 thrombolytic patients were randomized to either immediate angiography with rescue PCI for failed thrombolysis or a deferred predischarge catheterization strategy. Rescue PCI was performed in 18% of the immediate group with an 85% success rate. As a result, 96% of the immediate catheterization group left the catheterization laboratory with a patent infarct artery. At hospital discharge, the immediate angioplasty group had greater predischarge patency, improved regional motion in the infarct zone, and a reduced rate of recurrent ischemia. Immediate catheterization appeared to be safe, with similar nadir hematocrit and transfusion requirement between the two groups.

In the multicenter international Randomized Evaluation of Salvage angioplasty with Combined Utilization of Endpoints (RESCUE) study, 151 anterior myocardial infarction (MI) patients with angiographically documented TIMI flow grades 0 to 1 after lytic therapy were randomized to either rescue PCI or medical therapy (10). The benefits of rescue PCI were most likely underestimated by this study as a result of the exclusion of patients with previous MI by protocol and investigator bias to dilate (and therefore not to randomize) 134 other high-risk patients with left anterior descending occlusion. Despite this, at 30 days, the patients undergoing rescue PCI had a higher exercise ejection fraction (45% vs. 40%, p = 0.04) and a reduction in the combined end point of death or New York Heart Association functional class III to IV heart failure (6.4% vs. 16.6%, p = 0.05). These differences were apparent up to one year of follow-up.

In the late 1990s, two European studies were conducted comparing three different management strategies in AMI patients who were admitted to hospitals without a catheterization laboratory (12,13). Although transfer for primary PCI was the best approach, patients who were randomly assigned to thrombolysis with routine transfer for rescue PCI demonstrated a trend for improved outcomes compared with those assigned to thrombolysis alone.

Thus, a strategy of immediate catheterization followed by rescue PCI for failed thrombolysis has been demonstrated to be safe, have a high success rate, and improve regional wall motion and exercise LV function. Moreover, a pooled analysis of randomized trials suggested improvement in severe heart failure, reinfarction, and one-year mortality (14). However, patients requiring rescue PCI remain at increased risk for reocclusion and early death, especially if
the PCI is unsuccessful. The high rate of death and reocclusion may partly be explained by the selection of a high-risk group of patients who have already demonstrated resistance to pharmacologic reperfusion, possibly as a result of hypotension, large thrombus burden, or platelet-rich thrombi, factors that are unfavorable to the performance of PCI.

As noted in this issue of the Journal (15), the Middlesbrough Early Revascularization to Limit INfarction (MERLIN) trial is the largest trial conducted to date of “rescue angioplasty.” Unfortunately, this is not a trial of classic rescue PCI, in that patients were randomized very early (60 min after thrombolysis) and were not required to have chest pain at the time of arrival in the catheterization laboratory or have an occluded infarct artery. The definition of “failed thrombolysis” required only the lack of 50% improvement in the ST-segment elevation, meaning that a patient with only 0.5 mm of ST-segment elevation (50% improvement in 1 mm of ST-segment elevation) would be eligible for enrollment. On the other hand, the MERLIN trial addresses important clinical questions faced by physicians who use thrombolytics: Should this patient be transferred to a tertiary care center? Should this patient undergo emergency catheterization?

The most serious limitation of the MERLIN trial is the fact that the primary end point is stated to be “mortality.” Although the authors themselves gave an estimated range of mortality of 2% to 12% and commented that 3,000 patients would be needed to show a mortality benefit, only 300 patients were enrolled! It is misleading for the authors to state that the primary end point is negative, when in fact the trial was obviously underpowered at the beginning.

An additional concern is that the majority of patients enrolled were inferior MIs. Randomized trials and American Heart Association/American College of Cardiology guidelines suggest that the clinical benefit is confined to anterior MI patients. Despite knowing this, the investigators did not omit small infarcts, stratify at the time of randomization for infarct location, or consider this as a prespecified subgroup analysis.

Virtually every thrombolytic and angioplasty trial has shown an extremely low mortality (typically 2.5%) in patients with TIMI flow grade 3. Despite numerous patients having TIMI flow grade 3 at baseline, the mortality and complication rates in the MERLIN trial were quite high. Even in patients who had no angioplasty because of the presence of baseline TIMI flow grade 3, mortality was 8%. Furthermore, the majority of reinfarction events in the rescue arm occurred in patients who never underwent rescue angioplasty but were treated conservatively.

Why would mortality be higher in the MERLIN trial? Chance may play a role because the study was greatly underpowered. The selection of patients with persistent ST-segment elevation despite a patient infarct vessel may indicate reperfusion injury, hemorrhagic infarction, or microvascular plugging events, none of which can be improved with PCI.

The choice of thrombolytics also may be responsible. Streptokinase was the thrombolytic agent used in 90% of patients enrolled in the MERLIN trial. Randomized trials of PCI combined with streptokinase or urokinase have demonstrated increased major adverse cardiac events (MACE) compared with primary angioplasty (1,12,13,16). However, several recent studies that used fibrin-specific thrombolytic agents have shown that early PCI is safe (17–19) and improves MACE compared with conservative care (20,21).

Increasing data exist that myocardial perfusion may be abnormal, even in the setting of TIMI grade 3 epicardial coronary flow. Gibson et al. (22) reviewed 90-min angiography in 865 patients treated with fibrin-specific thrombolytic agents in the TIMI-10B trial. They reported that two-year survival was predicted not only by TIMI flow grade but also by improved myocardial perfusion and rescue PCI. Accordingly, many investigations and clinical sites have abandoned “rescue angioplasty alone” in lieu of combinations of new devices and drugs to stabilize the coronary lumen and improve tissue perfusion. Coronary stenting causes stabilization of the coronary lumen, resulting in less recurrent ischemia, reocclusion, and restenosis (23–25).

Abciximab (compared with no abciximab) during rescue PCI after failed fibrin-specific thrombolysis may lower 30-day mortality (26,27). Distal protection during PCI avoids distal embolization and reduces MACE (28). Mechanical thrombectomy improves flow, reduces thrombus burden, and improves MACE (29). Several trials designed to determine the effectiveness of these new technologies in patients with AMI have just been completed, and results will be available shortly.

Therefore, it is premature to abandon the open-artery hypothesis. Perhaps the concept of rescue angioplasty is correct, but well-designed trials with appropriate patient selection and use of contemporary adjunctive pharmacologic agents and devices are lacking.

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REFERENCES


