The Only Better Alternative to Rescue Percutaneous Coronary Intervention Is Primary Percutaneous Coronary Intervention*

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The superiority of primary percutaneous coronary intervention (PCI) over thrombolysis as a reperfusion strategy in patients with ST-segment elevation myocardial infarction (STEMI) has been sufficiently documented (1). However, thrombolysis still remains a frequently used therapeutic option for patients with STEMI, for the most part due to constraints in offering PCI in a timely manner (2,3). Even with the use of advanced fibrin-specific thrombolytic agents, thrombolysis restores normal epicardial blood flow—Thrombolysis In Myocardial Infarction (TIMI) flow grade 3—in only slightly more than one-half of patients with STEMI (4). The efficacy of thrombolysis is highly time-dependent, with drastic attenuation in benefit if the interval from onset of symptoms exceeds 6 h (5). Available evidence shows that patients with an occluded infarct-related artery (TIMI flow grade 0 to 1) and those with suboptimal blood flow restoration (TIMI flow grade 2) have increased mortality compared with patients with complete restoration of anterograde flow (TIMI flow grade 3) (6). It has recently been estimated that nearly 125,000 patients with STEMI will have suboptimal reperfusion with thrombolytic therapy in the U.S. per annum (7). Despite the frequent occurrence and clinical impact, the therapeutic options for patients with failed thrombolysis continue to be a much debated issue.

Over the years, the concept of rescue PCI as a treatment for failed thrombolysis has evolved from a “conscience tranquilizer” to a valuable therapeutic option with the capacity to improve the health of patients (8). The efficacy of rescue PCI has been investigated in the settings of large thrombolytic trials, trials of systematic and facilitated PCI, trials of transfer for primary PCI, and randomized trials specifically designed to investigate rescue PCI. In the last 5 years, 2 trials of rescue PCI for failed thrombolysis have been published: the MERLIN (Middlesbrough Early Revascularisation to Limit Infarction) trial (9) and the REACT (Rescue Angioplasty Versus Conservative Treatment or Repeat Thrombolysis) trial (10). Although these trials came to opposite conclusions with regard to the efficacy of rescue PCI, mostly due to substantial differences in their design and the risk of patients included, they are instrumental to the understanding of the place of rescue PCI in the treatment of STEMI patients with failed thrombolysis, and to some extent, they reflect the contemporary practice of interventional cardiology.

In this issue of the Journal, Carver et al. (11) report on the long-term results of the REACT trial. Briefly, the REACT trial included 427 patients, 21 to 85 years of age, with STEMI within 6 h of symptom onset and 90-min electrocardiographic criteria (<50% ST-segment resolution in the lead with previous maximal ST-segment elevation) for failed thrombolysis. Patients were randomly assigned to rescue PCI (n = 144), repeat thrombolysis (n = 142), or conservative therapy (n = 141). Due to problems with the recruitment of patients and funding, the trial was prematurely terminated. In the present article, the authors report on the primary composite end point of death, recurrent myocardial infarction, cerebrovascular events, and severe heart failure at 1 year, and mortality at a median of 4.4 years. From 6 months to 1 year, there were few events in each of the study arms, so that the 6-month advantage in event-free survival was maintained at 1 year of follow-up (81.5%, 67.5%, and 64.1% in rescue PCI, conservative therapy, and repeat thrombolysis arms, respectively; p = 0.004). Of note, the most important finding of this study was a significant reduction in long-term mortality: 11.2% for rescue PCI, 22.4% for conservative therapy, and 22.3% for repeat thrombolysis. Also, of importance but not unexpected was the finding that repeat thrombolysis did not offer any benefit compared with conservative therapy (11).

Almost all prior rescue PCI trials used an outdated PCI technology and adjunctive antithrombotic therapy and therefore are not reflective of current practice. With coronary stent use in 68.5% of patients and glycoprotein IIb/IIIa receptor blocker (abciximab) administration in 43.4% of patients, the REACT trial better reflects the contemporary practice of interventional cardiology. In a randomized trial of rescue stenting versus rescue balloon angioplasty, both with the adjunct use of abciximab, Schömig et al. (12) showed that the use of stents was associated with a significantly greater myocardial salvage compared with angio-

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plasty alone. Moreover, glycoprotein IIb/IIIa receptor blockers may reduce the excessive risk of thrombus formation seen after failed lytic therapy, which is consequent on post-thrombolytic platelet activation (13). These factors could be instrumental to the understanding of the superior results of rescue PCI in the REACT trial.

Several aspects of rescue PCI for failed thrombolysis need further clarification in future studies. A loading dose of thienopyridines (clopidogrel and more recently prasugrel)—a standard adjunct of current periprocedural antithrombotic therapy during PCI—has not been investigated in the setting of rescue PCI. The role of thrombus aspiration also needs to be evaluated in the setting of rescue PCI. Although the new strategies including drug-eluting stents certainly deserve to become the focus of future studies on rescue PCI, for the time being, the REACT trial remains the most mature, contemporary, and important trial on the management of patients with failed thrombolysis.

The most recent guidelines of the Task Forces of the American College of Cardiology/American Heart Association (2) and the European Society of Cardiology (3) assign a Class IIA recommendation to rescue PCI. This is because not all randomized trials on rescue PCI were able to show such a clear advantage from this form of therapy as did the REACT trial. We performed a meta-analysis using data on mortality at the longest available follow-up obtained from the most recent updated reports on 6 existing trials: the trial of Belenkie et al. (14), the MERLIN trial (15), the REACT trial (11), the RESCUE (Randomized Comparison of Rescue Angioplasty With Conservative Management of Patients With Early Failure of Thrombolysis for Acute Anterior Myocardial Infarction) 1 and 2 trials (16), as well as the TAMI (Thrombolysis and Angioplasty in Myocardial Infarction) trial (16). As shown in Figure 1, in the pooled sample of 908 patients, there was a nonsignificant, slightly more than 25% risk reduction in 1- to 4-year mortality from rescue PCI. This is enough to recommend rescue PCI as the best option after failed thrombolysis, yet none of the trials and even the pooled population provided sufficient power to assess mortality. The failure to enroll more patients in randomized trials on rescue PCI in the past, when thrombolysis was the dominant reperfusion treatment of patients with STEMI, makes the realization of larger trials in the future unlikely. The use of thrombolysis as a reperfusion strategy in patients with STEMI has markedly decreased. As recently reported in GRACE (Global Registry of Acute Coronary Events), which included 10,954 patients with STEMI presenting within 12 h of symptom onset, the use of primary PCI increased from 15% to 44%, and the use of thrombolysis decreased from 41% to 16% over the period between April 1999 and June 2006 (17). Although these trends reduce the chances of having large studies conducted on rescue PCI, they strengthen the hope that rescue PCI will be needed increasingly less in the future. The recent story of thrombolysis is far from being a success story. In patients with STEMI, thrombolysis was proven to be inferior to PCI as stand-alone therapy (1) and even harmful if used in an effort to “facilitate” subsequent PCI (18). With this in mind, the only better alternative to rescue PCI is primary PCI. Until this concept is universally accepted and applied, PCI after failed thrombolysis will indeed continue to save patients’ lives. However, the survival of thrombolysis
as a treatment strategy in STEMI may largely be dependent on the effectiveness of rescue PCI.

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