Editorial Comment

Do We Need to Intervene After Thrombolysis in Acute Myocardial Infarction?

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In this issue of Circulation, the TIMI II investigators describe the results and 1-year follow-up of the subsity TIMI II-A. The main TIMI II trial compared two strategies—a delayed (48-hour) invasive strategy and conservative management—in the treatment of 3,339 patients who had undergone thrombolysis with recombinant tissue-type plasminogen activator (rt-PA), and they concluded that there was no advantage in the early invasive strategy.2

TIMI II-A (approximately 600 patients) compared three strategies—very early (<2 hours) angiography and percutaneous transluminal coronary angioplasty (PTCA) (including attempted reopening of totally occluded infarct-related arteries, so-called “rescue” PTCA), 48-hour angiography and PTCA (but no rescue PTCA), and a conservative regime in which angiography without PTCA was carried out at 8–10 days predischarge, but intervention occurred only on clinical indications (rest- or exercise-induced ischemia).1 The 194 and 197 patients in the latter two groups were included in the main TIMI II comparison.

The TIMI II-A study was carried out at seven U.S. centers that had personnel who were highly experienced in PTCA, with matched randomization at each site. An unspecified number of patients were randomized by an envelope system and the remainder by microcomputer. The baseline characteristics were generally well matched except for a greater degree of stenosis being present in the patients randomized to the immediate (<2 hours) invasive strategy.

To be eligible for TIMI II, patients had to be less than 76 years old, be within 4 hours of the onset of pain lasting more than 30 minutes, have ST segment elevation, and have none of the usual contraindications to thrombolysis. Genentech rt-PA (total dose, 150 mg for the first third of patients randomized and 100 mg for the remainder) was administered at a mean time of 2.9 hours from pain onset. Ancillary treatment was specified (where not contraindicated) to include routine and immediate morphine (87% of patients were still in pain on entry to the study), sublingual nitrate, intravenous followed by subcutaneous heparin, and prophylactic lidocaine; nifedipine 10–20 mg three times daily for 96 hours; and predischarge metoprolol 50 mg and then 100 mg b.i.d. for 1 year. It should be noted that from overviews published after the trial was designed, the routine use of lidocaine4 or nifedipine5 seems questionable and possibly harmful. Sixty-six percent of patients were classified as “not low risk” because of anterior myocardial infarction (MI), previous MI, or age of more than 70 years. Although 99% and 90% in the 2- and 48-hour groups, respectively, had angiography, only 76%, 64%, and 24% (the latter is the conservative group) received PTCA by time of discharge from hospital.

The 21-day results of the two invasive arms of TIMI II-A have been published and show no differences between these two strategies.5 This report1 adds the results of the conservative strategy, quantitative data on early and late left ventricular ejection fraction, coronary artery anatomy, and survival and other events to 1 year, including exercise test data.

In general, there was no significant advantage in using either invasive arm over the conservative strategy. Despite a high initial success rate in opening stenotic or closed arteries, there was a high rate of rethrombosis. The predischarge angiograms showed no differences in the percentage of open infarct-related arteries in all three groups, which somewhat surprisingly was nonsignificantly higher (87.7%) in the conservative group! There was, however, a statistically significant higher degree of residual stenosis in the conservative group, which correlated well with the predischarge exercise test data. We should note that by the end of the first year, a cumulative 39% of the conservative group had had PTCA or coronary artery bypass graft surgery (CABG) on clinical grounds; perhaps because of these interventions, there were no differences in a full symptom-limited protocol exercise test at 1 year among the three treatment arms. Angina class, activity level, and days of hospitalization were also similar. These TIMI II-A results, which show no significant advantages for more aggressive treatment after thrombolysis, also confirm the results of the Thrombolysis and Angio-

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plasty in Myocardial Infarction study and the similar European Cooperative trial, which also reported no early benefit from PTCA after thrombolysis.

The results are in line with the recently reported Should We Intervene Following Thrombolysis (SWIFT) trial, which randomized 800 patients treated with anistreplase to conservative management (PTCA and CABG only for symptoms) and compared this conservative group with patients receiving early angiography and PTCA and/or CABG. At 3 months, the intervention rates were strikingly different—only 4.2% of the conservative group received intervention for clinical indications (12 PTCA and five CABG) compared with 57.4% (169 PTCA and 59 CABG) of the intervention group. Although at 3 months there was marginally less angina in the intervention group (18% vs. 24.3%; p=0.046), mortality was nonsignificantly higher (4.8% vs. 3.2%). As in TIMI II, there was no difference in radionuclide ejection fraction (at 3 months), and mortality from entry to 3 months was low.

All these trials were designed in the hope (subsequently dashed) that ejection fraction would prove a surrogate for mortality and thus reduce the study population required for these necessarily complex trials. Comparison of the ejection fraction data (at both rest and exercise) measured initially (rest only), after discharge, and at 6 weeks is generally disappointing, with little evidence of recovery of myocardial function (i.e., no evidence of “stunning” or myocardial salvage from PTCA).

Can we infer anything from the mortality data presented in these relatively small trials? TIMI II-A was analyzed by intention-to-treat analysis, but it should be noted that the 1-year intervention rate was about 40% in patients assigned “conservative” management compared with 85% and 72% in those allocated to 2- and 48-hour PTCA, respectively, reflecting the aggressive attitude in the seven TIMI centers chosen for their expertise in PTCA. The 1-year mortality figures for these same groups were 8.2%, 7.7%, and 10.2%, nonsignificantly favoring aggressive treatment; again, there was a nonsignificant trend to worse left ventricular function in the conservative group. Those patients considered unsuitable for PTCA received CABG, and it is interesting to note that the 7.7% of the 2-hour invasive group who received this early elective CABG had a low 1-year mortality rate of 2.3% with no perioperative MI. In contrast, those needing CABG after attempted PTCA had a high (16.7%) mortality rate and a 25% perioperative MI rate.

It is interesting to note that the nonsignificant advantage in 1-year mortality (~8% vs. 10%) favoring aggressive therapy is very similar to that achieved by thrombolysis itself, which is now widely accepted as standard therapy as a result of trials large enough to convince physicians that this 20–25% benefit was real and clinically worthwhile. The approximately 600 patients randomized in TIMI II-A are an inadequate population for detecting a real difference in mortality of 25% (the GISSI-1, ISIS-2, and ASSET trials randomized approximately 12,000, 17,000, and 5,000 patients, respectively).

Until the details of the SWIFT trial (800 patients) are published, we can make only cautious inferences. One thing that is quite clear from SWIFT is that there was much less intervention in the conservative group, in which the PTCA and CABG rate (4.2%) was less than one tenth the rate (52%) in the aggressive treatment arm. In contrast, the intervention rate in the conservative arm of TIMI II was as much as one half that of the aggressive arm (39% vs. 78%), reflecting a difference of both philosophy and perhaps available resources between North America and Europe. The SWIFT centers are undoubtedly less proficient in angioplasty than the seven TIMI II-A centers. Unlike TIMI II-A, the 3-month mortality results in SWIFT were nonsignificantly better in the conservative group (3.2%) than in the invasive arm (4.8%). In the larger 50-hospital TIMI II study, there was also a nonsignificant advantage for conservative management (6-week mortality, 4.7% for conservative vs. 5.2% for invasive).

Despite some disquiet over the possibility of a false-negative result in TIMI II-A, the conclusion in favor of “watchful waiting” is correct for the majority of hospitals treating patients with MI, particularly hospitals with limited expertise in angioplasty. This conclusion is supported by results from the European Cooperative, TAMI, and TIMI II trials and by preliminary results from the SWIFT trial, in which the collaborating hospitals were not necessarily centers of excellence in angioplasty, and (in the SWIFT trial) the confounding effects of patient crossover were much less. Crossover may be the wrong term because late intervention for clinical indications was part of the design strategy for the conservative group.

It may be that early intervention still has a place (albeit expensive) in highly specialized centers. It should also be remembered that these trials of early intervention versus conservative management were carried out in patients who were less than 75 years old (and, therefore, relatively good risks) and in patients after thrombolysis when reperfusion by PTCA might hold more complications than PTCA alone. Nor is it known whether early aggressive PTCA without thrombolysis is better or worse than thrombolysis with or without 48-hour PTCA. These are potentially expensive questions, both in money and in trained personnel, and perhaps in morbidity. For the present, health care providers will have a sigh of relief at the TIMI II-A data.

References


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