Should β-Blockers Be Given Immediately and Concomitantly With Thrombolytic Therapy in Acute Myocardial Infarction?

Elliot Rapaport, MD

The efficacy of β-blockers in the setting of acute myocardial infarction has been extensively studied. Over 50 randomized clinical trials involving more than 50,000 patients have been carried out to evaluate either β-blockers begun intravenously early after infarction or their long-term chronic oral use as secondary prevention. Pooled data from trials in which therapy was usually initiated before hospital discharge and generally maintained for at least 1 year indicate that mortality can be reduced by an average of 21% and reinfarction by 24%.1 Trials of the early use of intravenous β-blockers on mortality in the prethrombolytic era have been less impressive. Pooled data from 27 trials involving approximately 27,000 patients reveal only a 13% reduction in mortality ($p<0.01$).2 The three largest of these trials were the Göteborg Metoprolol Trial,3 the Metoprolol in Acute Myocardial Infarction (MIAMI) Trial,4 and the first International Study of Infarct Survival (ISIS-I) Trial.5

In the Göteborg Trial3 intravenous and then oral metoprolol was used. Among 697 patients randomized to placebo, the 7-day mortality rate was 3.3% and the mortality rate in the 698 patients receiving metoprolol was 2.6%.6 Initiation of therapy took place after a mean time lapse of 11.3 hours. This led the same group of investigators to carry out a much larger study, the MIAMI Trial,4 with the express purpose of studying very early intervention.

The MIAMI Trial4 involved 2,901 patients who received placebo and 2,877 patients randomized to receive intravenous and then oral metoprolol. The median delay time from onset of symptoms to randomization was 7 hours. Seven-day mortality was 3.2% among controls and 2.7% among those on the β-blockers. At 15 days these mortality rates were 4.9% and 4.3%, respectively. This 13% reduction in mortality was not statistically significant. A high-risk subgroup in this study was retrospectively defined. This group consisted of patients who had three or more of the following variables: age more than 60 years, history of past infarction, electrocardiographic indication of myocardial infarction, previous angina, congestive heart failure, diabetes, or being on diuretics or digitalis. A significant 29% reduction in mortality was observed among the metoprolol-treated patients in this subgroup.7

The largest study of early β-blocker intervention was ISIS-I.5 In this trial, 7,990 patients were randomized to the control group and 8,037 received intravenous and then oral atenolol. Thirty-eight percent of those treated with atenolol received it within 4 hours and 81% within 8 hours of symptom onset. Seven-day mortality was 4.6% in the controls and 3.9% among those on atenolol.6 This represented an approximately 15% reduction in vascular mortality and primarily reflected prevention of cardiac rupture and ventricular fibrillation. Furthermore, the beneficial effects of β-blockers on mortality occurred mainly in the first 24 hours. Analysis of the pooled data also indicates that there was a comparable reduction in the incidence of in-hospital nonfatal reinfarction among those receiving β-blockers.

The above observations encouraged the TIMI investigators to assess early treatment with the β-blocker metoprolol in their multicenter study comparing a post–thrombolytic therapy strategy of “watchful waiting,” designated as a conservative strategy, with an invasive approach involving early arteriography followed by immediate angioplasty if suitable anatomy was found. Patients in both strategy arms deemed suitable to receive a β-blocker were subrandomized to either immediate intravenous and then oral metoprolol or to therapy delayed until day 6, when the control group was started on metoprolol. The article by Roberts and his coinvestigators in this issue of Circulation presents the detailed results of this aspect of the trial.8

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From the Department of Medicine, University of California, San Francisco, School of Medicine, and the Cardiology Division, Medical Service, San Francisco General Hospital, San Francisco, Calif.

Address for correspondence: Elliot Rapaport, MD, Cardiology Division, Room 5G1, San Francisco General Hospital, San Francisco, CA 94110.
The multicenter Thrombolysis in Myocardial Infarction Phase II Trial, or TIMI II-B, enrolled 2,948 patients for treatment with recombinant tissue plasminogen activator (rt-PA). However, only 1,434, or 49%, were considered eligible to receive \( \beta \)-blockers with thrombolytic therapy because of the exclusionary criteria used in this study. It is not uncommon for clinical trials to be conservative in their exclusionary criteria for reasons of safety and to maximize the likelihood of a positive trial. Thus, in clinical practice it is inappropriate to assume that immediate \( \beta \)-blocker administration cannot be given simply because the patient had been receiving a \( \beta \)-blocker or diltiazem at the time of admission, as was done in this study. If there is any question of whether a \( \beta \)-blocker can be tolerated in the acute infarct patient, one can initiate therapy with the ultra-short-acting \( \beta \)-blocker esmolol. An infusion of 100–200 \( \mu \)g/kg/min can be titrated to observe whether a therapeutic effect can be achieved without significant adverse effects. If troublesome side effects occur, the drug can be stopped, and a return to pre-esmolol conditions will occur within 15–30 minutes, because the half-life of the drug is only 9 minutes.

The primary endpoint in the TIMI II-B \( \beta \)-blocker arm trial was the global left ventricular ejection fraction just before hospital discharge. The results were examined both by pooling the invasive and conservative arms and for each strategy separately. In addition, patients were also categorized, as in the MIAMI Trial, into a low-risk or a "not low-risk" subgroup. Approximately two thirds of the patients fell into the "not low-risk" risk classification. Intravenous metoprolol was started a mean of 42 minutes after the initiation of rt-PA administration, while in the deferred treatment group oral therapy was begun on the sixth day after study entry.

It is not surprising that this trial failed to demonstrate any difference in either rest or exercise ejection fraction between the immediate- and deferred- \( \beta \)-blocker patient groups. Mean global ejection fraction for all patients just before hospital discharge was a relatively high 50.5%, which presumably already reflected some myocardial salvage resulting from the thrombolytic therapy itself. Whatever salvage can occur has probably already occurred by the time of discharge. This interpretation is strengthened by the observation that chest pain resulting from rt-PA administration was similar with or without concomitant intravenous metoprolol therapy. However, trials of early intravenous administration of \( \beta \)-blockers without thrombolytic treatment demonstrate a significant reduction in immediate chest pain. Furthermore, the concept that immediate administration of \( \beta \)-blockers limits infarct size has not been well substantiated either in the experimental animal model or in humans.

More disappointing in this study was the failure to demonstrate that early intravenous administration of \( \beta \)-blockers reduced the likelihood of myocardial rupture. In ISIS-I, proven and probable cases of myocardial rupture were more than 2.5-fold more frequent in controls than in those allocated to intravenous atenolol. A similar trend was found in the Göteborg Metoprolol and MIAMI trials. This fits with the theory that \( \beta \)-blockers, by decreasing the heart rate and the force of cardiac contraction, should decrease the risk of myocardial rupture. Furthermore, in the large thrombolytic treatment trials such as ISIS-II and GISSI-I, despite the dramatic reduction in mortality in those receiving streptokinase, more deaths actually occurred in the first day or so among those receiving thrombolytic treatment than among the controls. A high proportion of these appear to have resulted from myocardial rupture. Because patients receiving thrombolytic drugs may have an increased likelihood of early myocardial rupture, one would anticipate a demonstrable reduction in myocardial rupture in the immediate \( \beta \)-blocker treatment group. In reality, the trend was in the opposite direction. However, there were so few early deaths, the power of this study to detect a difference in myocardial rupture was too low. Clearly, this issue cannot be adequately addressed from this substudy.

There was also no difference in total mortality between the immediate and delayed treatment at 6 days, 6 weeks, and 1 year. However, cautiously downplayed by the investigators as a subgroup analysis of a secondary endpoint was the observation that the incidence of death or reinfarction within 6 weeks among the patients in the immediate \( \beta \)-blocker group treated with intravenous metoprolol within 2 hours of onset was 5.4% (10 of 186) compared with 13.7% (26 of 190) in the delayed therapy group \( (p=0.01) \). The lack of emphasis on this observation probably reflected the fact that by 1 year this difference had largely disappeared. However, the likelihood that this was a real effect and not simply an artifact of innumerable subgroup analyses is strengthened by the fact that the secondary endpoints of nonfatal reinfarction and fatal or nonfatal reinfarction were also significantly lower in the entire immediate \( \beta \)-blocker group both at 6 days and at 6 weeks. However, once again, this was no longer seen at the end of 1 year. Finally, among the higher risk patients recurrent ischemia during hospitalization was significantly lower in the immediate \( \beta \)-blocker group, a result similar to the results of \( \beta \)-blocker trials in the pre–thrombolytic therapy era.

Why did the benefits of immediate \( \beta \)-blockade on reducing recurrent ischemia disappear after hospitalization and the difference in the incidence of reinfarction disappear between 6 weeks and 1 year? Both groups during this interval were on the same dose of oral metoprolol. One can only speculate, but it is noteworthy that there were 50 additional cases among the 720 immediate \( \beta \)-blocker group \( (6.9\% \) who either died or reinfarcted between the end of the hospitalization period and 1 year. These patients presumably were no longer bound to a specific protocol on leaving the hospital. Nevertheless, there may
have been some reluctance to be aggressive in uncovering latent ischemia or managing clinical ischemia due to concern that one might introduce late management variables that could confound long-term outcome comparisons of the original invasive and conservative strategies. Whatever the explanation, these events between the time of hospital discharge and 1 year later might be preventable.

I believe one should adopt any management strategy that decreases the likelihood that a patient undergoing a myocardial infarction would develop a fatal or nonfatal reinfarction or recurrent ischemia during the initial hospitalization period. I appreciate that the benefits in absolute percentage differences are small. However, this substudy also established that immediate concomitant therapy with β-blockers in infarct patients undergoing reperfusion is safe and generally well tolerated. In fact, there was some suggestive evidence that the occurrence of a hemorrhagic stroke within the first 6 days was decreased in those receiving immediate β-blocker therapy. Furthermore, it would appear that if such therapy is initiated within 2 hours of symptom onset, the benefit can be substantial. One should therefore be aware of the possibility that such patients may be more prone to ischemic events in the year that follows and to be correspondingly more aggressive in follow-up strategies. Therefore, barring the usual contraindications to its use, this study in my judgment supports the view that one of the earliest interventions in the emergency room should be administration of an intravenous β-blocker along with aspirin and nitroglycerin. If thrombolytic therapy is subsequently withheld for whatever reason, the β-blocker should still prove beneficial.

References
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E Rapaport

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