

# Immediate $\beta$ -Blockade in Patients With Myocardial Infarctions: Is There Evidence of Benefit?

Richard Sinert, DO, David H. Newman, MD, Ethan Brandler, MD, Lorenzo Paladino, MD

From the Department of Emergency Medicine, SUNY–Downstate Medical Center, Brooklyn, NY (Sinert, Brandler, Paladino); and Columbia University, Department of Emergency Medicine, St. Luke’s–Roosevelt Hospital Center, New York, NY (Newman).

**Study objective:** The American Heart Association recommends the initiation of  $\beta$ -blockade to all patients with an ST-segment elevation myocardial infarction (STEMI) without contraindications to  $\beta$ -blocking agents. The present study seeks to systematically review the medical literature to determine the efficacy of treating STEMI patients with a  $\beta$ -blocker within the first 24 hours.

**Methods:** We searched databases for articles through MEDLINE with the PubMed interface and from 1966 through May 2009 and EMBASE from 1980 to August 2009 with the Ovid Technologies interface, using a search strategy derived from the following PICO (Patient-Intervention-Comparator-Outcome) clinical question: In patients presenting with STEMI (P), does immediate treatment with  $\beta$ -blockers (I) followed by standardized care beginning on day 2 or 3 compared with placebo or no treatment followed by standardized care on day 2 or 3 (C) reduce the risk of death, reinfarction, or cardiogenic shock (O)? The methodological quality of the studies was assessed.

**Results:** From more than 2,000 references identified in the search, only a single randomized trial met the inclusion criteria. There were no statistically significant differences in mortality; the relative risk for the combined endpoint (mortality and reinfarction) was 0.67 (95% confidence interval 0.44 to 1.03) at 6 days and 0.74 (95% confidence interval 0.53 to 1.06) at 6 weeks. Outcomes for cardiogenic shock were not reported.

**Conclusion:** Evidence from a single randomized trial failed to demonstrate a reduction in mortality or reinfarction with administration of  $\beta$ -blocker within the first 24 hours after STEMI. [Ann Emerg Med. 2010;56:571-577.]

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## CLINICAL SCENARIO

A 56-year-old woman presents complaining of acute onset chest pain and mild shortness of breath. Her history is significant for hypertension and cigarette smoking. She presents with normal vital signs but appears anxious and diaphoretic; her physical examination is otherwise normal. The ECG demonstrates a normal sinus rhythm at 89 beats/min, with normal PR interval and QRS durations and 3-mm ST-segment elevations in the anterior leads, with 1- to 2-mm ST depressions in leads II, III, and aVF. The chest radiograph result is unremarkable. The nearest cardiac catheterization facility is 2 hours away by ground transport, and the local medical transport helicopter is grounded because of the weather.

In accordance with your hospital ST-segment elevation myocardial infarction (STEMI) protocol, you order antiplatelet, anticoagulant, and thrombolytic therapy and place the call to the tertiary cardiology service. The accepting cardiologist agrees with the plan to transfer but suggests that, in accordance with the most recent American Heart Association (AHA) recommendations, you administer oral metoprolol before the

patient leaves the emergency department (ED). As requested, 50 mg of metoprolol is administered before the patient is loaded onto the ambulance, but you wonder whether the benefits of immediate administration of a  $\beta$ -blocker was worth the risk of adverse events during the 2-hour transport. You decide to review the evidence for this recommendation the following day.

## FORMULATING THE QUESTION

The evidence-based question was derived using the “PICO” (Patient-Intervention-Comparator-Outcome) format, in which P represents the target patient population; I, the intervention; C, the comparison intervention (if any); and O, the most relevant patient-important outcome measures. STEMI is believed to represent a biologic and clinical entity in which time-sensitive interventions are particularly important, making patients with STEMI most relevant to our inquiry. We chose to focus on studies that enrolled patients with STEMI without evidence of active heart failure because our patient would likely respond similarly to the early administration of  $\beta$ -blockers.

The intervention (I) of interest is  $\beta$ -blockers, and we are focused specifically on their effect when given immediately. Six

hours seems a reasonable cutoff, and we will have to be attentive to this variable, though perhaps flexible, in our search. In addition, the agents may have differing effect when given intravenously versus orally, but before we seek to answer a specialized question about  $\beta$ -blockade (ie, effect based on route of administration), we must first attempt to establish whether there is utility in any form.

As mentioned, interventions for STEMI often have differential effect according to timing; therefore, the C in our PICO question will have to be carefully crafted. Because most patients with STEMI are also candidates for reperfusion therapy (either mechanical or pharmacologic), we will accept patients undergoing reperfusion therapy for STEMI as being most relevant to our clinical question. We know, for instance, that pharmacologic and mechanical reperfusion is more beneficial when performed earlier. This emphasis on time urgency distinguishes our clinical question from those of other systematic reviews<sup>1,2</sup> because ample trial data have demonstrated a benefit to administration of  $\beta$ -blockers initiated at hospital discharge after STEMI.  $\beta$ -Blockers therefore clearly have a beneficial effect after STEMI<sup>3,4</sup> begins, but at what point? The essential component of our comparison is a question of timing. In the First International Study of Infarct Survival Collaborative Group (ISIS-1)<sup>5</sup> and Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT),<sup>6</sup> the 2 largest trials of immediate  $\beta$ -blockade, treatment groups received  $\beta$ -blockade immediately and continued for 1 week. Control groups received placebo or no treatment during the entire first week after STEMI. These data address benefit or harm with respect to a full week of  $\beta$ -blocker therapy but do not focus on whether immediate (ie, ED)  $\beta$ -blockade is beneficial. If, for instance,  $\beta$ -blockade increases cardiogenic shock in the first day (as observed in COMMIT and ISIS-1) but reduces arrhythmias and reinfarction on the second day (also observed in COMMIT and ISIS-1), then the benefits of  $\beta$ -blockade may begin only after day 2, yet there may be potential for harm when used in the immediate phase.

The comparison (C) group of greatest relevance is therefore patients receiving either placebo or no  $\beta$ -blocker therapy in the immediate phase but receiving equal treatment beginning 2 to 3 days after onset of symptoms (rather than having the comparison period extend through the first week of management). Therefore, the ideal data would compare immediate  $\beta$ -blockade with placebo for the first 24 to 48 hours, followed by continual  $\beta$ -blockade for both groups starting on day 2 to 3.

Finally, the outcomes (O) of greatest interest should always be those of greatest import to patients. In this case, death, reinfarction, and cardiogenic shock all seem clinically relevant, and the timing of these endpoints is important to both patients and physicians. Endpoints of 30 days and 6 months both seem reasonable; however, the timing of cardiogenic shock and arrhythmias or cardiac arrest events should also be tracked closely in the peri-infarct period.

In summary, to best answer our clinical evidence question we will be seeking high-quality research that attempts to answer the following PICO question: In patients presenting with STEMI (P), does immediate treatment with a  $\beta$ -blocker, followed by standardized care beginning on day 2 or 3 (I), compared with placebo or no treatment followed by standardized care on day 2 or 3 (C), reduce death, reinfarction, or cardiogenic shock (O)?

## SEARCHING FOR THE BEST EVIDENCE

We searched MEDLINE with the PubMed interface for articles from 1966 through May 2009 and EMBASE from 1980 to August 2009, using the Ovid Technologies interface (see Appendix E1, available online at <http://www.annemergmed.com>, for complete MEDLINE and EMBASE search strategies). We also searched the Cochrane Central Register of Controlled Trials and the Cochrane Review addressing the topic of antihypertensives during acute cardiovascular events and checked the bibliographies of the included articles and reviews.

## SELECTING THE BEST EVIDENCE

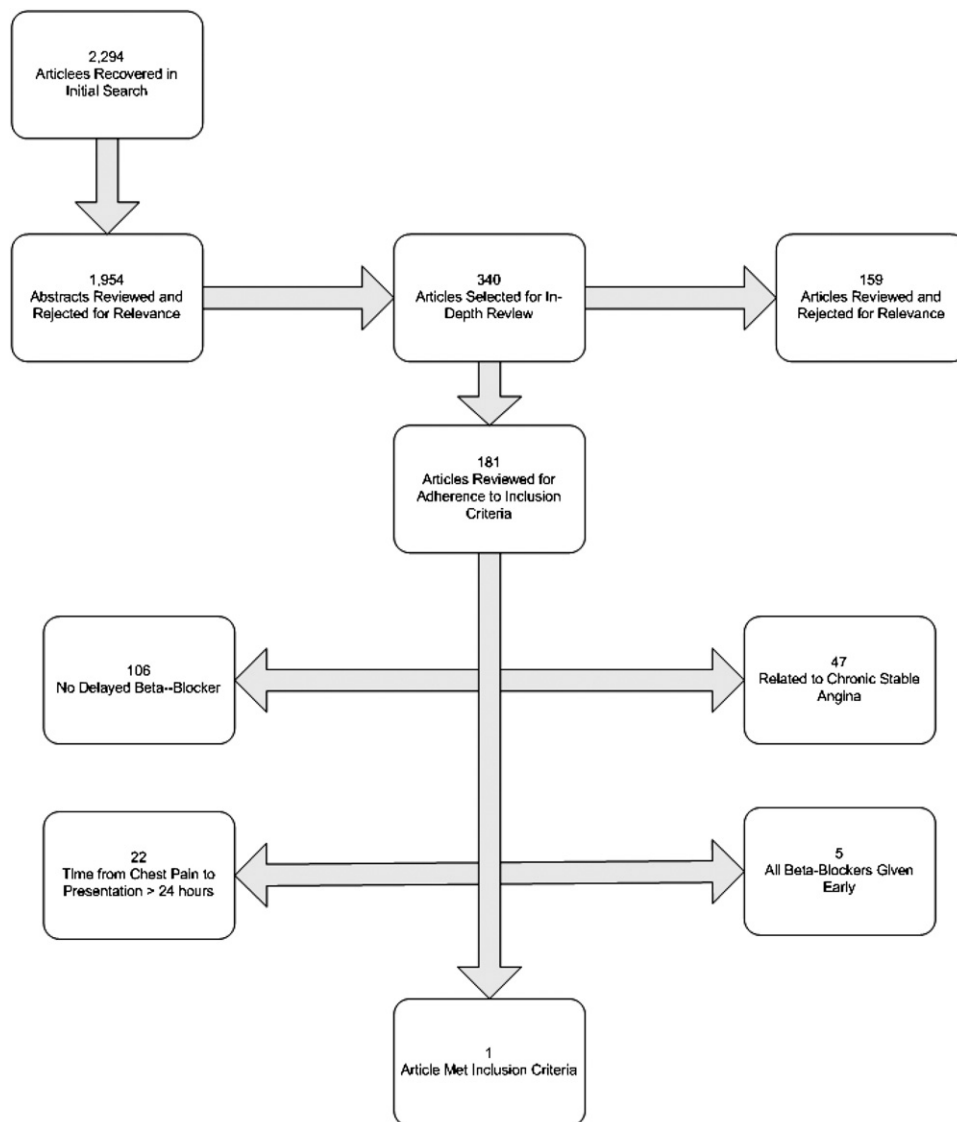
Our MEDLINE search returned 2,294 studies. EMBASE and the search of the Cochrane trial registry did not return any additional relevant studies. We considered only randomized trials that enrolled adult (aged  $\geq 18$  years) patients who had a recent ( $< 24$  hours) onset of chest pain consistent with an acute myocardial infarction. To be included in this review, studies were required to compare the effects of  $\beta$ -blockers with that in patients who received either standard medical therapy with or without a placebo.  $\beta$ -Blockers were defined as agents possessing  $\beta$ -1 antagonist properties whether they also had any  $\beta$ -2 effect or not. We also included studies of combined  $\alpha$ - and  $\beta$ -blocking agents such as labetalol and carvedilol. The use of other agents for secondary cardiac prophylaxis or therapies such as thrombolysis or angioplasty was not an exclusion criterion. We excluded studies of patients without documented ST-segment myocardial infarctions. Our primary endpoint was mortality, whether it was the primary or the secondary endpoint of the respective trials.

Through a review of titles and abstracts, 1,954 studies were rejected for relevance. The remaining 340 were reviewed and assessed for inclusion and exclusion criteria (Figure 1). Only a single study, the Thrombolysis in Myocardial Infarction (TIMI)II-B Study trial,<sup>7</sup> met our selection criteria.

## ANALYZING THE EVIDENCE

### Description of the Study

The TIMI-II-B trial was a randomized, controlled trial designed to assess the benefits of early versus delayed angiography and percutaneous transluminal coronary angioplasty in patients receiving recombinant tissue-type plasminogen activator for acute myocardial infarction. A total of 2,934 subjects receiving recombinant tissue-type plasminogen activator were enrolled and randomized for this purpose. As an additional aim, the trial examined  $\beta$ -blocker therapy by



**Figure 1.** Selection process to obtain articles for review.

randomizing further within the enrolled subject group to early versus delayed  $\beta$ -blocker therapy. Exclusion criteria for this substudy were patients receiving  $\beta$ -blockers or calcium channel blockers, patients with implanted pacemakers, those with pulse rates less than 55 beats/min at baseline or heart block, systolic blood pressure less than 100 mm Hg, wheezing, or evidence of pulmonary edema. Of the 2,934 subjects initially randomized into TIMI-IIB, 1,434 met the inclusion criteria for enrollment in the  $\beta$ -blocker substudy. Table 1 shows no significant differences between the immediate and deferred  $\beta$ -blocker groups for baseline demographics or risks for and history of coronary artery disease.

The study protocol called for metoprolol given intravenously as soon as possible after recombinant tissue-type plasminogen activator in the immediate group and metoprolol given orally beginning on day 6 in both groups (Figure 2). The primary

endpoints for both the  $\beta$ -blocker substudy and the overall trial were left ventricular ejection fraction as assessed by resting radionuclide ventriculography at hospital discharge and at 6 weeks. Mortality and reinfarction, secondary endpoints, were also recorded at 6 days, 6 weeks, and 1 year.

### APPRAISING THE EVIDENCE

From Table 2 we assess the risk of bias in the TIMI-IIB trial by determining appropriate generation of random allocation sequence; concealment of the allocation sequence; blinding of participants, health care providers, data collectors, and outcome adjudicators; proportion of patients lost to follow-up; stopping of trials early for benefit; and whether the analysis followed the intention-to-treat principle.

There is a risk of bias if the group assignment was not truly random and if there was no concealment of allocation. Neither

**Table 1.** Summary TIMI II-B trial.

<b>Roberts et al, 1991 (n=1,434), TIMI-II-B Trial (95% Confidence Interval)</b>		
<b>Study Characteristics</b>	<b>Immediate <math>\beta</math>-Blocker (n = 720)</b>	<b>Deferred <math>\beta</math>-Blocker (n = 714)</b>
<b>Included Patients</b>		
Age, y	54.8	55.2
Race, % white	85.3 (82.5–87.7)	87.7 (85.1–89.9)
Sex, % male	86.1 (83.4–88.5)	84.5 (81.6–86.9)
Not low risk, %	64.0 (60.5–67.5)	64.7 (61.1–68.1)
Age >70 y	8.5 (6.6–10.7)	9.2 (7.3–11.1)
Previous myocardial infarction, %	6.5 (4.9–8.6)	8.8 (6.9–11.1)
Anterior myocardial infarction, %	56.0 (52.3–59.6)	56.0 (51.2–60.7)
History of angina, %	43.5 (39.9–47.1)	43.9 (40.2–47.25)
History of congestive heart failure, %	0.8 (0.3–1.9)	1.4 (0.7–2.6)
History of hypertension, %	30.0 (26.8–33.5)	30.7 (27.4–34.2)
History of diabetes mellitus, %	10.7 (8.6–13.2)	11.5 (9.3–14.9)
<b>Excluded patients</b>		
Rales >1/3 of lung field, %	0.4 (0.1–1.3)	0.3 (0.0–1.1)
Hypotension and sinus tachycardia, %	1.3 (0.6–2.4)	1.0 (0.4–2.1)
Atrial fibrillation/flutter, %	1.7 (0.9–2.4)	1.5 (0.8–2.8)
Pulmonary edema, %	0.4 (0.1–1.3)	0.1 (0.0–0.1)
Cardiogenic shock, %	0.0 (0.0–1.1)	0.1 (0.0–0.1)
Procedures common to all patients: Treated with recombinant tissue-type plasminogen activator (rt-PA), heparin, and aspirin <4 h after the onset of chest pain. Then randomized to (1) invasive strategy (routine angiography and PTCA, where indicated, at 18–48 h) or (2) conservative-strategy-only medical therapy (angiography for possible angioplasty only in the event of recurrent ischemic symptoms or an ischemic response to predischARGE submaximal exercise study). Then each subgroup (invasive, conservative) was randomized to the intervention (immediate) or comparison (deferred) $\beta$ -blocker subgroups (Figure 2).		
Intervention	Immediate $\beta$ -blocker: Metoprolol was given as soon as possible after initiation of rt-PA. Three intravenous injections of 5 mg metoprolol were given at 2-minute intervals, for a total intravenous dose of 15 mg. Fifteen minutes after the administration of the third intravenous dose of metoprolol, patients received 50 mg orally every 12 h during the first 24 h and 100 mg orally every 12 h thereafter.	
Comparison	Deferred $\beta$ -blocker: Metoprolol started on day 6 (at least 48–72 h before the radionuclide ventriculogram); all patients received 50 mg metoprolol twice daily for 1 day and then 100 mg metoprolol twice a day for as long as they remained within the study and tolerated this agent clinically.	
Outcome measures	Primary endpoint: Global left ventricular ejection fraction as measured by resting radionuclide ventriculography performed before hospital discharge. Secondary endpoints: Included resting left ventricular ejection fraction at 6 weeks, left ventricular ejection fraction on exercise both at hospital discharge and at 6 weeks, and regional left ventricular ejection fraction in the infarcted area at rest and on exercise before hospital discharge and at 6 weeks. Patients were also monitored for clinical events, including myocardial ischemia. Mortality and reinfarction: These were evaluated alone and in combination for the two $\beta$ -blocker groups and for each of the 4 treatment groups at 6 days, 6 weeks, and 1 year.	

PTCA, Percutaneous transluminal coronary angioplasty.

of these issues is clarified in the study methods. An additional risk of bias occurred in the TIMI-II-B trial according to a lack of blinding of both subjects and providers, which may have led to differential treatment based on group assignment. There was evidence for blinding of the outcome adjudicators for mortality but not for the determination of ventricular ejection fraction.

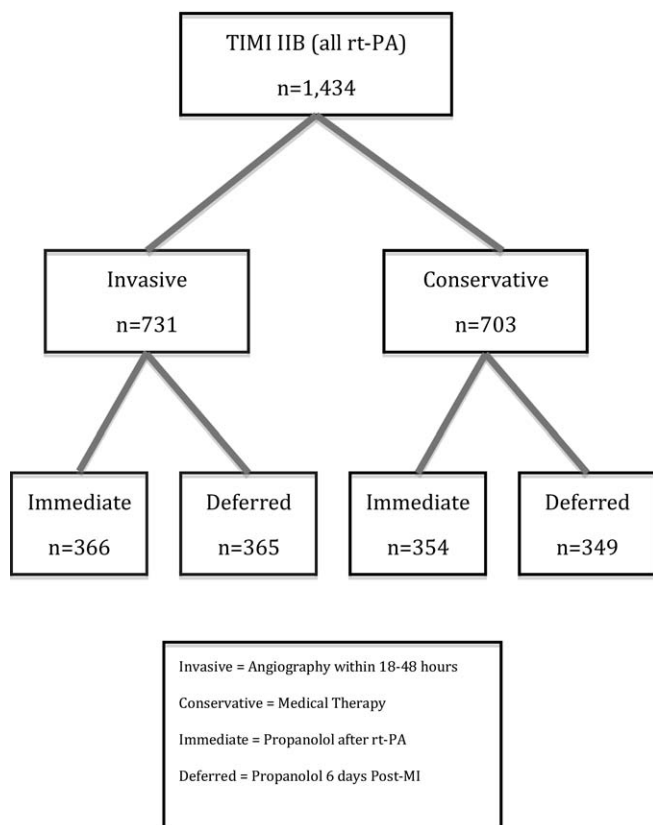
The TIMI-II-B trial reports an intention-to-treat analysis; it appears no patients were lost to follow-up at hospital discharge, 6 weeks, and 1 year.

The TIMI-II-B's factorial design added a layer of complexity by comparing conservative versus invasive strategies. We do not believe that this challenged the study's internal validity because when the  $\beta$ -blocker data were analyzed by these subgroups, the results were unchanged. It therefore seems unlikely that the

trial's factorial design had any important effect on the comparison between  $\beta$ -blocker groups.

## RESULTS OF THE TRIAL

Among the 1,434 subjects enrolled, 720 were randomized to immediate  $\beta$ -blocker therapy, whereas 714 were randomized to delayed therapy. The 2  $\beta$ -blocker groups were similar with respect to age, race, sex distribution, and risk status (Table 2). The patients assigned to invasive (731) or conservative strategies (703) were evenly distributed among the 2 groups. In Table 3, we recalculated the trial data comparing relative risks between the immediate and deferred  $\beta$ -blocker groups. Mortality and reinfarction rates and radionuclide ventriculography results at hospital discharge (the study's primary endpoint) were similar.



**Figure 2.** TIMI-IIB trial. *MI*, Myocardial infarction.

**Table 2.** Susceptibility to bias of TIMI II-B trial.

Potential Bias	Roberts et al, 1991, TIMI-IIB Trial
Randomization	Factorial design to provide equal numbers of patients in the 4 treatment groups: (1) immediate intravenous $\beta$ -blockade with metoprolol and invasive strategy, (2) immediate intravenous $\beta$ -blockade with metoprolol and conservative strategy, (3) deferred oral $\beta$ -blockade with metoprolol and invasive strategy, and (4) deferred oral $\beta$ -blockade with metoprolol and conservative strategy (Figure 2).
Concealment	Methods used for allocation concealment not stated
Blinding	Blinding of only outcome adjudicators
Intention to treat	Yes
Baseline comparisons	Well balanced for risk factors for primary and secondary endpoints
Cointerventions	Similar
Completeness of follow-up	No patients lost to follow-up at 6 days, 6 weeks, and 1 year

Although cardiogenic shock was posed as a patient-important outcome in the formulation of our PICO clinical question, this outcome was not reported in the trial results.

**APPLYING THE EVIDENCE**

The 1999 AHA/American College of Cardiology ST Elevation Myocardial Infarction guidelines recommended early

**Table 3.** Results of TIMI II-B trial.

Mortality and Reinfarction	Roberts et al, 1991, TIMI-IIB Trial		
	Immediate $\beta$ -Blocker (%)	Deferred $\beta$ -Blocker (%)	Relative Risk (95% Confidence Interval)
Death			
Conservative strategy			
6 Days	4/354 (1.1)	9/349 (2.6)	0.44 (0.14–1.41)
6 Weeks	8/354 (2.3)	11/349 (3.2)	0.78 (0.29–1.76)
Invasive strategy			
6 Days	13/366 (3.6)	8/365 (2.2)	1.63 (0.68–3.87)
6 Weeks	18/366 (4.9)	14/365 (3.8)	1.28 (0.65–2.53)
Death or Reinfarction			
Conservative strategy			
6 Days	11/354 (3.1)	20/349 (5.7)	0.54 (0.26–1.11)
6 Weeks	22/354 (6.2)	30/349 (8.6)	0.72 (0.43–1.23)
Invasive strategy			
6 Days	23/366 (6.3)	30/365 (8.2)	0.76 (0.45–1.29)
6 Weeks	30/365 (8.2)	39/365 (10.7)	0.77 (0.49–1.21)

(within 12 hours) intravenous followed by oral  $\beta$ -blockade for all patients.<sup>8,9</sup> In 2004 this became a class IA (highest level) recommendation for oral agents.<sup>10,11</sup> The Centers for Medicare & Medicaid Services then designated early  $\beta$ -blockade a “core measure” for public tracking in 2005. However, the COMMIT<sup>6</sup> trial in late 2005, the largest-ever study of immediate metoprolol versus placebo for acute myocardial infarction, demonstrated no effect on mortality and the AHA softened its guideline language, recommending caution in the use of intravenous  $\beta$ -blockade in the immediate period. Accordingly, in 2009 the Centers for Medicare & Medicaid Services rescinded their core measure.<sup>12</sup> A Cochrane Review<sup>13</sup> was also published in 2009, examining 20 trials of immediate (<24 hours from the onset of chest pain)  $\beta$ -blocker therapy. The review found no mortality benefit over placebo.

The multiple modifications in AHA guidelines and in the Centers for Medicare & Medicaid Services core measures on the subject of early  $\beta$ -blockade have occurred in the absence of substantive changes in the relevant evidence. Indeed, by carefully framing and identifying the proper clinical question, we can see that despite numerous trials addressing the  $\beta$ -blocker issue, there is only one study that directly assesses the efficacy of the timing of drug administration in the acute care setting. The  $\beta$ -Blocker Heart Attack Trial (BHAT)<sup>3</sup> and Norwegian timolol<sup>4</sup> studies, for example, demonstrate statistically significant 2.6% and 6.2% mortality reductions over placebo at 27 and 33 months, respectively, for patients receiving  $\beta$ -blockers in the weeks and months after their infarction.  $\beta$ -Blockade in this period appears to decrease ventricular arrhythmias and therefore reduce mortality. These and other data therefore strongly support  $\beta$ -blocker therapy in the period after myocardial infarction, but these data leave open the question of when it should start. Virtually all other trials of

“immediate”  $\beta$ -blockade, though often cited in guidelines as supporting or not supporting immediate administration, have compared a group that received  $\beta$ -blockade immediately and throughout the postinfarction period with a group that did not receive  $\beta$ -blockade immediately and also did not receive  $\beta$ -blockade during the postinfarction period. When 30-day outcomes and any longer-term endpoints are examined, this conflates the question of whether immediate  $\beta$ -blockade is beneficial, with the known benefits of postinfarction  $\beta$ -blockade. Unfortunately, this conflation has led not only to confusion and changes in the AHA guidelines but also to a decades-long conventional wisdom that there was a proven benefit to immediate  $\beta$ -blockade.

Our comprehensive literature search identified only a single study comparing immediate (<6 hours) to delayed (6 days) initiation of  $\beta$ -blockers for STEMI patients. Although there were areas of potential bias identified and the study was not powered to address our primary outcome (mortality), the trial was unable to demonstrate benefit or harm for immediate  $\beta$ -blocker administration. This result may represent a type II error for the outcome of mortality rate.

Returning to our opening scenario, we are disappointed to have found minimal evidence to support any concrete initiation time for  $\beta$ -blockade in STEMI patients. However,  $\beta$ -blockade should be initiated at some point after the first 24 to 48 hours after symptom onset in myocardial infarction patients, and further study aimed at determining the appropriate timing of  $\beta$ -blocker initiation will be needed before evidence-based recommendations can be made.

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*Address for correspondence:* Richard Sinert, DO, Department of Emergency Medicine, Box 1228, SUNY–Downstate Medical Center, 450 Clarkson Ave, Brooklyn, NY 11203; 718-245-2973, fax 718-245-4799; E-mail [Richard.Sinert@Downstate.edu](mailto:Richard.Sinert@Downstate.edu).

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## Critically Appraised Topic (CAT): Immediate $\beta$ -blockade in patients with myocardial infarctions—is there evidence of benefit?

<b>Question</b>	In patients presenting with STEMI, does immediate treatment with a $\beta$ -blocker, followed by standardized care beginning on day 2 or 3, compared with placebo or no treatment followed by standardized care on day 2 or 3, reduce death, reinfarction, or cardiogenic shock?
<b>Reviewed by</b>	Sinert RH, Newman D, Brandler E, Paladino L
<b>Date of search</b>	August 2009
<b>Expiration date</b>	August 2011
<b>Clinical bottom line</b>	Evidence from a single randomized trial did not demonstrate benefit or harm with administration of $\beta$ -blocker after STEMI in the first 24 hours. However, $\beta$ -blockade should be initiated at some point after the first 24 to 48 hours after symptom onset in myocardial infarction patients.
<b>Search strategy</b>	MEDLINE, EMBASE, the Cochrane Library from the dates of origin through May 2009.
<b>Citations</b>	Roberts R, Rogers WJ, Mueller HS, et al. Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) II-B Study. <i>Circulation</i> . 1991;83:422-437.
<b>Primary study characteristics</b>	<p><b>Study Population</b> Patients older than 18 years with STEMI.</p> <p><b>Interventions</b> Immediate (after thrombolysis) vs deferred (6 days after thrombolysis) <math>\beta</math>-blocker.</p> <p><b>Outcome Measures</b> Mortality and reinfarction at 6 days and 6 weeks.</p>
<b>Critical appraisal</b>	Fair quality as a result of a lack of blinding and inadequate reporting of concealment.

## Results

<b>Intervention</b>	<b>Follow-up</b>	<b>Relative Risk of Death or Reinfarction: Invasive and Conservative Arms Combined (95% Confidence Intervals)</b>
Immediate vs deferred	6 Days	0.67 (0.44–1.03)
$\beta$ -blockade	6 Weeks	0.74 (0.53–1.06)

No significant difference in mortality at 6 days and 6 weeks. Outcomes for cardiogenic shock not reported.

**Appendix E1.** Search strategy.

**MEDLINE-PubMed**

“angina pectoris”[MeSH Terms] OR (“angina”[All Fields] AND “pectoris”[All Fields]) OR “angina pectoris”[All Fields] OR “angina”[All Fields]

“coronary artery disease”[MeSH Terms] OR (“coronary”[All Fields] AND “artery”[All Fields] AND “disease”[All Fields]) OR “coronary artery disease”[All Fields]

“chest pain”[MeSH Terms] OR (“chest”[All Fields] AND “pain”[All Fields]) OR “chest pain”[All Fields]

“myocardial infarction”[MeSH Terms] OR (“myocardial”[All Fields] AND “infarction”[All Fields]) OR “myocardial infarction”[All Fields]

#1 or #2 or #3 or #4

“humans”[MeSH Terms] OR “humans”[All Fields]

#5 and #6

“adrenergic beta-antagonists”[MeSH Terms] OR (“adrenergic”[All Fields] AND “beta-antagonists”[All Fields]) OR “adrenergic beta-antagonists”[All Fields] OR (“beta”[All Fields] AND “blocker”[All Fields]) OR “beta blocker”[All Fields] OR “adrenergic beta-antagonists”[Pharmacological Action]

#7 and #8

(randomized controlled trial [pt] or controlled clinical trial [pt] or randomized controlled trials [mh] or random allocation [mh] or double-blind method [mh] or single-blind method [mh])

#9 and #10

**EMBASE**

‘beta blocker’/exp AND ‘acute myocardial infarction’/exp AND ‘prevention and control’/exp AND ‘human’/exp AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [1995-2008]/py