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**Post–myocardial infarction β -blocker therapy:
The bradycardia conundrum.**

**Rationale and design for the
Pacemaker & β -blocker therapy post-MI (PACE-MI) trial**

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This article describes the rationale and design of the NIH sponsored PACE-MI trial. For more information regarding the PACE-MI trial please visit: <http://www.pace-mi.org>.

Post-myocardial infarction β -blocker therapy: The bradycardia conundrum. Rationale and design for the Pacemaker & β -blocker therapy post-MI (PACE-MI) trial

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Multiple clinical trials have demonstrated β -blockers improving survival after myocardial infarction (MI). Patients with "bradycardia-related" contraindications to β -blockers, such as those with asymptomatic bradycardia or AV conduction abnormalities, have been excluded from clinical trials of β -blockers and continue to be excluded from post-MI β -blocker therapy in routine clinical practice. These patients tend to be elderly and have a high 1-year mortality. If β -blockers provide benefit to the post-MI patient independent of their heart rate-lowering effect, then these patients could benefit substantially from initiation of β -blocker therapy. However, in this particular group of patients, β -blockers can be safely initiated *only if* more severe or significant bradycardia can be prevented by pacemaker implantation. It is unclear whether adverse effects related to pacemaker implantation could also negate some or all of the hypothesized benefit of β -blocker therapy. Although β -blockers are particularly effective in the elderly, the benefit of β -blocker therapy in patients with bradycardia-related contraindications to β -blockers has not been established. The PACE-MI trial is a randomized controlled trial that will address whether β -blocker therapy enabled by pacemaker implantation is superior to no β -blocker and no pacemaker therapy after MI in patients with rhythm contraindications to β -blockers or in those who have developed symptomatic bradycardia due to β -blockers. The trial will randomize 1124 patients to standard therapy (not to include β -blockers as patients must have a contraindication to be enrolled) or standard therapy plus pacemaker implantation and β -blocker. The primary end point is the composite end point of total mortality plus nonfatal reinfarction. (*Am Heart J* 2008;155:455-64.)

Groundbreaking advances in the care of patients with acute myocardial infarction (MI) over the last several decades have resulted in dramatically improved outcomes. One of these advances is the establishment of the utility of β -blockers in improving survival after MI. Patients with "bradycardia-related" contraindications to β -blockers, such as those with asymptomatic bradycardia or AV conduction abnormalities, have been excluded

from clinical trials of β -blockers and continue to be excluded from post-MI β -blocker therapy in routine clinical practice. There are conflicting opinions whether β -blocker therapy would be effective in this population of patients. It has been argued that β -blockers would be beneficial in these patients, but the potential for causing bradycardia-related complications represents a contraindication. On the other hand, it has also been argued that the resting bradycardia in these patients already provides the pathophysiologic benefit that would be conferred by β -blocker therapy, and therefore, their use in these patients is unnecessary. In the former case, these patients would benefit from β -blocker therapy if (1) a pacemaker were implanted first to provide rate support, thereby removing the barrier to therapy, and (2) the benefits of β -blocker therapy outweigh the risks of pacemaker implantation (and subsequent pacing). In the latter case, there would be no benefit to implanting a pacemaker to facilitate β -blocker treatment. These issues have not been addressed in prior clinical trials as these patients have always been excluded from participation. Because of the lack of data, the Center for Medicare and Medicaid Services has also determined

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(www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=17) that it will not cover pacemaker implantation in post-MI patients with asymptomatic bradycardia to initiate β -blocker therapy. In addition, emerging data suggest that in some settings, pacing in patients without indications for antibradycardia pacing may be harmful.¹ Therefore, the specific aim of the PACE-MI trial is to test the hypothesis that pacemaker-facilitated β -blocker therapy after MI reduces the combined end point of total mortality and nonfatal reinfarction in the subgroup of post-MI patients who currently do not routinely receive β -blocker therapy because of bradycardia or conduction abnormalities and in whom the benefit of β -blocker therapy has not been established.

Rationale for the PACE-MI trial

Efficacy of β -blockers post-MI

In the early 1980s, several large-scale trials^{2,6} demonstrated that β -blocker therapy after MI improves survival. In an overview of results from randomized controlled trials in >50 000 patients,⁷ there was a substantial reduction in mortality due to β -blocker treatment (relative risk 0.81, 95% confidence interval 0.75-0.87, $P < .00001$). A subsequent analysis⁸ also including >50 000 patients demonstrated a substantial reduction in mortality associated with β -blocker treatment (relative risk 0.77, 95% CI 0.69-0.85). The Norwegian Multicenter Study Group⁵ reported that this survival benefit was evident for at least 6 years after MI. Similar results were observed in the extended 5-year follow-up of the APSI trial.⁹ Large-scale observational reports have confirmed that the benefits that have been observed with β -blocker therapy in clinical trials are actually achieved in clinical practice.¹⁰⁻¹² The largest report includes >200 000 patients in the Medicare database.¹¹ After adjusting for baseline differences, β -blocker therapy was associated with a 40% decrease in mortality at 2 years. In the GUSTO-I trial,¹³ the use of atenolol was associated with a 47% reduction in 30-day mortality (after adjusting for baseline characteristics and excluding deaths within 48 hours). The benefits of β -blocker therapy persist despite the advent of newer therapies such as thrombolytic therapy,¹³ angiotensin-converting enzyme inhibitors,¹⁴⁻¹⁸ and revascularization.^{19,20} The early-randomized clinical trials evaluating the efficacy of β -blockers excluded some populations that could benefit from this therapy. For example, patients with left ventricular dysfunction were typically excluded. CAPRICORN,²¹ a more recent randomized clinical trial, addressed this issue and demonstrated a significant reduction in mortality with carvedilol treatment post-MI in patients with an ejection fraction of $\leq 40\%$ (hazard ratio 0.77, 95% CI 0.60-0.98). As a result of the overwhelming evidence in favor of β -blocker therapy, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines²²⁻²⁴ suggest that essentially all patients

without contraindications to β -blockers after MI should be treated indefinitely with β -blockers. This has become an established metric for assessing clinical quality performance.²⁵

Mechanism of benefit of β -blockers

Despite the well-documented effects of β -blockers on reduction of total and cardiac mortality,^{2,8,10-12} sudden death,²⁶⁻²⁸ and reinfarction,^{21,28,29} the precise mechanism for these clinical benefits has not been clarified. One hypothesis^{29,31} is that β -blockers achieve their clinical benefits through their heart rate-lowering effects, thereby reducing myocardial oxygen demand. Heart rate reduction may prevent ischemia and ischemic-related arrhythmias. Kjekshus²⁹ summarized the relationship of heart rate lowering to therapeutic effect. Reduction in infarct size by acute administration of β -blockers has been related to the degree of heart rate lowering. Similarly, in long-term trials, the reduction in mortality and reinfarction was also related to the reduction in heart rate. Although heart rate reduction clearly represents a pharmacologic response to the administration of β -blockers, the question arises whether heart rate reduction is both a necessary and sufficient condition required to achieve therapeutic benefit. Other drugs that slow the heart rate have been evaluated as potential prophylactic agents in patients after MI. Calcium-channel blockers, such as diltiazem and verapamil, that slow the heart rate have not proven to be beneficial in this setting.^{12,32-34} Amiodarone also lowers heart rate and has not been shown to have a beneficial effect on total mortality.^{35,36} Thus, rate slowing by itself may not be a sufficient treatment goal to provide a survival advantage.

Little direct evidence is available to assess whether heart rate reduction is necessary to achieve therapeutic benefit from beta-blockade. Rathore et al³⁷ reported that β -blocker therapy did improve survival in patients who presented with a paced rhythm at the time of their infarction. Although pre- and posttreatment heart rates were not reported, the fact that patients presented with a paced rhythm raises a strong possibility that significant heart rate reduction was not achieved with β -blocker therapy. Data from the CIBIS-II trial are also particularly enlightening.³⁸ In this large, randomized clinical trial in patients with congestive heart failure (most had coronary artery disease), it was shown that the survival benefits of β -blockers are not dependent on the initial heart rate nor on the extent of heart rate lowering achieved by β -blocker treatment. In fact, even patients who had an increase in their heart rate on β -blocker therapy experienced a survival benefit. MERIT-HF also noted no relation of the benefit of metoprolol based on initial or achieved heart rate.³⁹ If heart rate reduction were necessary for the therapeutic benefit of β -blocker therapy after MI, one might also expect to observe a dose-dependent effect of treatment. In an analysis of the database from the northern California Kaiser Permanente

Table I. Contraindications and withdrawal rates from β -blockers after MI in large-scale β -blocker trials

Study reference no.	4	6	2	3	56	57
Number	2619	3647	16 400	4355	26 439	2948
Time of randomization post-MI	within 48 h	6-27 d	5-21 d	after 4 d	within 24 h	immediate
Age limits (y)	40-74	20-75	30-69	35-70	<75	<75
Mean age (y)	60		55		60	55
Distribution of ages	35% 65-74	40% 65-75		75%-80% <65		
Contraindications to β -blockers	14%	18%	18%	28.3%	29.4%	27.7%
Heart rate cut-point (beat/min)	<45	<50	–	<50	<65	<55
Bradycardia	0.8%	–	–	0.4%	15.8%	13.9%
AV block	1.7%	–	–	5.5%	1.7%	6.4%
Total rhythm-related contraindications	2.5%	–	–	5.9%	17.5%	20.3%
Withdrawal from β -blockers due to bradycardia or AV block	5%	4.9%	0.8%	3.6%	5%	–

hospitals,⁴⁰ the beneficial effect of β -blocker therapy was evaluated relative to the dose given. In patients given 1% to 49% of the dose found to be effective in clinical trials, the long-term mortality was 3.4%, whereas in those given \geq 50% of the dose found to be effective in clinical trials, the mortality was 6.9%; in those not treated with β -blockers, the mortality was 18.8%. Rochon et al⁴¹ also reported similar reductions in mortality in patients treated with low-, standard-, and high-dose β -blocker therapy after MI. Although heart rate reduction was not reported in these studies, it is likely that those patients who received the lower doses had less heart rate reduction than those who received the higher doses. These data raise the possibility that heart rate reduction is not the mediator of all the clinical benefits of β -blocker therapy after an MI.

Post-MI β -blocker trials that have evaluated cause-specific mortality have shown that most of the survival benefit of β -blocker therapy is due to a reduction in sudden death.^{2,6,26,27,42} In a compilation of 7 studies that reported on sudden death,²⁶ it was found that β -blocker therapy led to a 28% reduction in mortality with a 33% reduction in sudden death and a 20% reduction in nonsudden death. β -Blockers would not be expected to confer any protection from sudden death resulting from bradyarrhythmias. Thus, as most sudden deaths are due to ventricular tachyarrhythmias,⁴³ the reduction in sudden death from β -blockers is due to protection from ventricular tachyarrhythmias. The important role of β -blockers in the prevention of ventricular tachyarrhythmias has been established in multiple settings.⁴⁴⁻⁴⁷ Thus, it is likely that not all the benefits of β -blocker therapy are related to the slowing of heart rate. Yet, this has never been tested in a clinical trial because patients with preexisting bradycardia have routinely been excluded from trials of β -blocker therapy after MI.

“Bradycardia-related” contraindications to β -blockers

Despite the tremendous benefit associated with β -blocker therapy, numerous studies indicate that many patients are not treated with a β -blocker.^{11,40,48-52} In some

of these reports, more than half the patients who had an acute MI were not treated with a β -blocker. Underuse of β -blockers is particularly prominent in older patients.^{12,53-55} There are a number of absolute and relative contraindications to the use of β -blockers after an MI. One of the main reasons for exclusion from treatment is the presence of significant resting bradycardia or AV block. Table I shows the incidence of these findings in some of the initially reported randomized clinical trials. Another group of patients not treated with β -blockers are those in whom the drugs are withdrawn because of side effects, such as symptomatic heart block or bradycardia (Table I). In a report from a Minnesota community,⁵¹ 51% of patients were placed on β -blockers during their hospital stay, but only 40% were on therapy at discharge. At 1 year, only 34% of patients were taking a β -blocker. These findings indicate that the ability to maintain patients on β -blockers may be limited by the development of bradycardia or heart block and/or other side effects in a substantially high percentage of patients.¹⁰

Examining the age limits for enrollment in the post-MI trials, it is evident that most were biased to exclude the elderly. The mean age in these trials was 55 to 60 years. In contrast, the mean age reported in the National Registry of MI from 1994 to 1999 ranged from 66.5 to 68 years.⁵⁸ As the incidence of conduction system disease would be expected to be higher in the older patients, the data in the table should represent lower bounds for the incidence of bradycardia and AV block precluding the use of β -blockers MI. Of note, the trials that initiated β -blocker therapy early after MI have a very high incidence of rhythm-related contraindications to β -blocker therapy. Those that initiated β -blockers several days remote from the event have a much lower incidence of rhythm-related contraindications.

The best recent data regarding contraindications to β -blocker therapy come largely from studies that have reported on the underuse of β -blocker therapy after an MI. Viskin et al⁵² reported that sinus bradycardia of <50 beat/min and AV block precluded β -blocker therapy in 4% and 5%, respectively, of 606 patients

Table II. Mortality reduction associated with β -blocker therapy in older patients

Study	Population	Dates	Follow-up	Mortality reduction
Gottlieb et al ¹¹	Medicare-national	1994-1995	2 y	40% (adjusted for differences in risk)
Soumerai et al ¹²	NJ Medicare "eligible for β blockers"	1986-1990	2 y	43% (adjusted for other predictors of mortality)
Krumholz et al ¹⁰	Medicare-national	1995	1 y	41% (unadjusted), 33% (adjusted for age, sex, and race)
BHAT ²	Ages 60-69	1978-80	25 m	36%
Norwegian ⁶⁵	Ages 65-75	1978-79	17 m	32.2%

discharged after an MI. Venturini et al⁵⁹ reported patterns of practice in 9 European countries and Canada. Among 1976 patients admitted with acute MI, 14.4% had AV conduction abnormalities or bradycardia of <60 beat/min precluding the use of β -blockers (analysis included evaluation of discharge medications). Rochon et al⁴¹ noted that 12% (1630/13623) of their postinfarction patients had bradycardia or heart block "contraindications" to β -blockers, but only 7.7% were not treated with a β -blocker. Heller et al⁶⁰ identified secondary *International Classification of Diseases, Ninth Edition* codes in acute MI survivors that have been considered to be contraindications to β -blocker therapy; 12.1% had codes for conduction disorders and SA node dysfunction. Fehrenbach et al⁶¹ noted that 5% to 6% of the patients they reviewed had more than first-degree heart block or bradycardia that precluded β -blocker therapy after MI. Thus, the range of reported bradycardia contraindications is 5% to 15%. The reported withdrawal rate from β -blockers has recently been reported to be in the 12% to 20% range,^{15,21} although not all withdrawal is due to development of bradycardia. Phillips⁶² performed an economic modeling analysis of the benefits of β -blocker use. Their analysis assumed that all patients with MI without absolute contraindications to β -blockers would be eligible for treatment. These absolute contraindications were more than first-degree heart block, heart rate <60 beat/min, asthma, or allergy/intolerance. Based on available evidence, their best estimate was that 8% of patients would be excluded because of these absolute contraindications. In addition, their best estimate based on available evidence was a 12% withdrawal rate among patients with no relative contraindications and a 30% withdrawal rate among patients with relative contraindications.

β -Blocker use and efficacy in the elderly

White et al⁶³ described a variety of characteristics in the GUSTO-I population, which included >30 000 participants stratified by age. The incidence of significant bradyarrhythmias increased with age as did the 1-year mortality. Because conduction system abnormalities are more prevalent in the elderly, it is important to examine the efficacy of β -blockers in this population. Randomized clinical trials have consistently demonstrated that the mortality reduction conferred

by β -blocker therapy is greater in the older subgroups.⁶⁴ Table II provides data on the expected risk reduction of β -blockers in the elderly population. The registry data suggest a 33% to 43% reduction of 1- to 2-year mortality associated with β -blocker therapy. The data from older randomized trials of β -blockers suggest a 32% to 36% reduction in total mortality.

Dose dependency of β -blocker effect

In randomized, clinical trials of β -blocker therapy after an MI, the doses of β -blockers were generally titrated up to doses equivalent to 200 mg of metoprolol or 160 mg of propranolol daily. However, in clinical practice, most patients do not achieve these targets. Most patients who are treated with blockers after an MI receive $\leq 50\%$ of the dose found to be effective in the randomized clinical trials.^{40,52} In an analysis of the database from the northern California Kaiser Permanente hospitals,⁴⁰ low-dose β -blocker therapy for MI was shown not only to be beneficial, but, in that study, the mortality was actually lower in patients receiving low-dose β -blockers (25% of the dose used in large-scale clinical trials). Similarly, in another study of elderly people receiving low-, standard-, and high-dose β -blocker therapy after MI, there was a 60% reduction in mortality in the low-dose group with similar reductions in the standard- and high-dose groups.⁴¹ Finally, in the observational studies^{11,12} in the Medicare population, it is unlikely that full-dose β -blockers were used in most patients and a marked survival benefit was demonstrated.

Defining "bradycardia" contraindications to β -blocker therapy

As noted above, there is a wide range of reported cutoffs for heart rate as a contraindication to β -blocker therapy. The relevant issue is the risk of developing symptomatic and/or dangerous bradycardia when someone with underlying conduction system disease is treated with β -blockers. β -Blockers slow the sinus rate and depress AV nodal conduction.⁶⁶ Depending on whether their effects are measured in the supine, sitting, or standing position, a decrease in heart rate of 8 to 25 beat/min may develop with β -blocker therapy⁶⁷⁻⁷⁰ in subjects without sinus node dysfunction. In a study on 8 individuals with normal AV

conduction,⁷¹ propranolol (0.1 mg/kg) was associated with a 20% increase in AV nodal conduction time (P-H interval). A 17% increase in P-H interval was noted in 10 patients with ischemic heart disease who received only 0.05 mg/kg of propranolol.⁷² The Boston Collaborative Drug Surveillance Program^{73,74} documented adverse reactions in 319 patients treated with β -blockers. Life-threatening complications included bradycardia and shock in 3, bradycardia and angina in 1, and complete heart block in 1. Non-life-threatening complications included asymptomatic bradycardia in 5 and 2:1 heart block in 1. Given the known effects of β -blockers on sinus rate and AV conduction, they are not recommended to patients with marked sinus or AV nodal conduction abnormalities.

Several post-MI β -blocker trials provide important information about the effects of β -blocker therapy on sinus and AV nodal function in this population. In the BHAT trial,² β -blocker treatment was associated with an 11 beat/min drop in heart rate from baseline (pretreatment) to 1 year. β -Blocker therapy may result in adverse bradyarrhythmic events, even in patients without manifest underlying sinus or AV nodal conduction disease. In the MIAMI trial,⁵⁶ patients were excluded if their heart rate was ≤ 65 beat/min. In this cohort, 12.9% of the patients treated with metoprolol had an adverse reaction due to the development of a heart rate < 45 beat/min, and 5.6% developed second- or third-degree AV block. In the Norwegian Multicenter Study Group,⁶ patients with heart rate < 50 beat/min or any second- or third-degree AV block were excluded. Six percent of patients developed an adverse reaction related to sinus node dysfunction (heart rate < 40 beat/min or SA block). An additional 0.4% developed AV block. Withdrawal of active β -blocker therapy was required in 78% of patients with these reactions. Patients who have already manifested conduction system disease before initiation of β -blocker therapy can only be expected to have more frequent and severe bradyarrhythmias than those without conduction system disease. For this reason, it is unsafe to initiate β -blocker therapy in these patients. In 1995, the Canadian Cardiovascular Society published an update to their 1991 consensus report on the management of the post-MI patient.⁷⁵ The absolute contraindications to β -blockers were listed as sick sinus syndrome and second- or third-degree AV block, whereas a heart rate of < 60 beat/min represented a relative contraindication. The 1999 ACC/AHA guidelines²⁴ refer to but do not define criteria for a contraindication to β -blocker therapy. The 1990 ACC/AHA guidelines⁷⁶ list heart rate < 60 beat/min, PR interval > 220 milliseconds, and type I second-degree AV block as contraindications to β -blocker therapy.

Pacemaker morbidity and mortality

In theory, conduction system abnormalities that preclude the use of β -blockers could be resolved by pacemaker implantation. The risks and benefits of such

an approach have to be carefully considered. Pacemaker implantation is associated with low morbidity and minimal mortality, even in elderly populations^{77,78}; of 853 patients who underwent pacemaker implantation, there was only one death that occurred 3 days after implant with a presentation of dyspnea and asystole. Complications include pneumothorax, lead dislodgment, cardiac perforation, sensing/capture problems, vein thrombosis, pacemaker erosion/infection, and wound hematoma requiring an intervention in approximately 5% of patients. Although pacemaker implantation has low morbidity, recent data have raised the possibility of adverse effects related to right ventricular pacing, the standard site for ventricular pacing. In the MADIT-II,⁷⁹ the incidence of new or worsened heart failure was 14.9% in the control group (those who did not receive a device) and was 19.9% in those implanted with a device ($P = .09$). Because there were no significant differences in clinical characteristics or medications used in the 2 groups, it is plausible that the increased heart failure was due to "inadvertent" right ventricular pacing that might occur in patients with an implantable defibrillator. Supporting this concept, Saad et al⁸⁰ recently reported worsening symptoms of congestive heart failure in 44% of those patients who receive an implantable defibrillator and were exposed to right ventricular pacing compared to 5% of those not exposed to ventricular pacing ($P < .01$). Finally, the DAVID trial¹ demonstrated that patients undergoing defibrillator implantation who do not also have indications for antibradycardia pacing had a higher incidence of the combined end point of mortality and first hospitalization for heart failure when their devices were programmed to dual-chamber rate-responsive pacing rather than ventricular back-up pacing at 40 beat/min (hazard ratio 1.61, 95% CI 1.06-2.44). This adverse outcome was related to right ventricular pacing that was observed in the dual-chamber pacing group.⁸¹ However, ventricular pacing is not uniformly associated with worse outcomes. For example, patients who undergo AV node ablation and pacemaker implantation do not have an increase in mortality compared to patients who are treated with medications for rate control, despite experiencing 100% ventricular pacing.⁸²

Post-MI patients with bradycardia-related contraindications to β -blocker therapy may either not be treated with these agents or require insertion of a pacemaker to provide rate support for β -blocker treatment. The purpose of the PACE-MI trial is to assess which of these strategies is associated with better outcomes.

PACE-MI study design

End points

The primary objective of the PACE-MI trial is to determine if, in patients after an acute MI who have either bradycardia or heart block precluding the use

Table III. Secondary end points for PACE-MI

Total mortality plus nonfatal reinfarction plus rehospitalization due to congestive heart failure
Major adverse cardiac events—cardiac mortality plus nonfatal reinfarction plus rehospitalization due to unstable angina or congestive heart failure
Major adverse cardiac event plus rehospitalization due to new-onset atrial fibrillation or sustained ventricular arrhythmias
Total mortality
Cardiac mortality
Sudden death mortality
Rehospitalization due to congestive heart failure, re-infarction, unstable angina, new onset atrial fibrillation, or sustained ventricular arrhythmias
Quality of life, economics

of β -blockers, treatment with a pacemaker and a β -blocker will reduce the combined end point of total mortality and nonfatal reinfarction compared to no β -blocker therapy and no pacemaker therapy. Other secondary end points are in [Table III](#).

Study population

All patients with an acute MI at the participating sites will be followed in a registry. Patients who meet the inclusion and none of the exclusion criteria ([Table IV](#)) will be eligible for enrollment in the PACE-MI trial. Given that the bradycardia or heart block contraindications defined in [Table IV](#) could represent either relative or absolute contraindications to β -blocker therapy, at the time of enrollment, the managing physician will be asked to determine if the enrollment criteria for that patient represent relative or absolute contraindications to β -blocker therapy. This will be determined by assessing the individual patient's clinical condition and comorbid conditions. If the managing physician determines that even low-dose β -blockers cannot be safely initiated, the patient may proceed to randomization. If low-dose β -blockers can be safely initiated, the patient will be followed in the PACE-MI observational arm. However, if a patient in the observational arm develops symptomatic bradycardia with ≤ 50 mg/d of metoprolol, the patient may proceed to randomization.

Randomization and treatment protocol

Patients who meet inclusion criteria will be randomized to 1 of 2 arms:

1. Control group—therapy in this group will be conventional, guideline-based treatment of MI but will not include a β -blocker (eligible patients must have either contraindications to β -blockers or be intolerant of β -blockers).
2. Treatment group—therapy in this group will be conventional treatment of MI plus implantation of a transvenous pacemaker, followed by initiation of β -blocker therapy. The study β -blocker will be metoprolol, starting at 25 to 50 mg BID with a target

Table IV. Inclusion and exclusion criteria for PACE-MI

Inclusion criteria

1. Patients (age >30 y) with a recent (within 30 d^{*}) history of an MI documented by both the following:
 - a. Cardiac enzymes (creatinine phosphokinase elevation >2 times or troponin elevation >3 times the upper limit of normal for the laboratory value)
 - b. Electrocardiographic changes and/or symptoms consistent with MI (ie, chest pain, shortness of breath)
2. Patients must have either of the following:
 - a. Bradycardia or heart block contraindication to β -blocker therapy defined by (at least one of the following):
 - Resting (awake) heart rate ≤ 55 beat/min on 2 consecutive days in the absence of treatment with rate-slowing medications (ie, diltiazem, verapamil)
 - Sinus pauses (> 2 s) during the day
 - PR interval ≥ 260 ms in the absence of medications that prolong AV nodal conduction time (digoxin, diltiazem, verapamil)
 - Second-degree AV block, type I at rest (and awake)
 - b. Documented symptomatic bradycardia due to β -blocker therapy

Exclusion criteria

1. Patients with unstable or class IV angina
2. Patients with absolute medical contraindications to β -blockers (ie, severe bronchospastic disease, systolic blood pressure <90 mm Hg)
3. Patients with clinical indications for either a pacemaker or an implantable defibrillator and those who are known to imminently have indications for an implantable defibrillator (ie, ejection fraction $<30\%$)
4. Any medical condition that, in the investigators' judgment, would seriously limit life expectancy (poor 6-m survival)
5. Patients with class IV congestive heart failure
6. Patients with a contraindication or relative contraindication to a transvenous pacemaker (ie, inadequate venous access, bleeding disorder)
7. Patients who have had coronary artery bypass surgery within 2 weeks of enrollment in the study
8. Patients who are scheduled for coronary artery bypass surgery within 3 m of enrollment in the study
9. Patients with marked valvular heart disease ($>3+$ aortic or mitral insufficiency, aortic stenosis with valve area ≤ 1 cm²)
10. Current alcohol or drug abuse
11. Patients unavailable for follow-up for the duration of the trial
12. Patients participating in other trials of "experimental" therapy (not to exclude patients who are in trials of diagnostic techniques or approved therapies)
13. Patients unwilling or unable to provide informed consent

*Patients with a left ventricular ejection fraction $<35\%$ peri-MI whose ejection fraction reevaluated in >40 days after MI is $>35\%$ and still meet the rhythm enrollment criteria for PACE-MI may be enrolled up to 90 days after the MI. This adjustment was made so that patients who will "imminently" have an indication for an implantable defibrillator (ie, those with ejection fraction $<35\%$ determined >40 days after MI) would not be enrolled, whereas those whose initial peri-MI ejection fraction is $<35\%$, but improves to $>35\%$ determined >40 days after MI, could still be enrolled if the rhythm enrollment criteria are still satisfied.

of 200 mg daily (of Toprol XL [AstraZeneca, Los Angeles, CA]).

In patients randomized to the treatment group, a transvenous pacemaker will be implanted using standard techniques and Food and Drug Administration-approved devices. β -Blocker treatment will commence after the pacemaker has been implanted. Guidelines for pacemaker

programming have been developed to minimize ventricular pacing.

Patients will be followed at 1 month, 3 months, 6 months, and then semiannually until the termination date of the study.

Statistical design and analysis

The primary end point for this trial is the composite end point of total mortality plus nonfatal reinfarction. There is only one modern-day randomized clinical trial of β -blockers post-MI—CAPRICORN.²¹ In this trial, patients within 3 to 21 days of an acute MI and ejection fraction $\leq 40\%$ were randomized to receive carvedilol or no β -blocker. The 1- and 2-year composite end point of death plus nonfatal MI was noted in 15% and 24% of the placebo group (estimated from the Kaplan-Meier curve). Although this population was restricted to those having ejection fraction $\leq 40\%$, the average age was only 63 years. It is likely that the expected combination of more advanced age in our proposed study population and the concomitant conduction system disease will confer at least as great a risk for increased events as the ejection fraction criteria used in CAPRICORN. Hjalmarson et al³¹ demonstrated almost a doubling of mortality 1-year postdischarge in patients with a heart rate < 50 beat/min versus those with heart rates of 50 to 70 beat/min. Thus, we estimate the 1- and 2-year event rates for the composite end point in this trial at 15% and 24%. Regarding the expected benefit of β -blockers, CAPRICORN reported a hazard ratio of 0.71 for total mortality and nonfatal MI. Of note, all β -blocker trials that have reported age-based mortality reductions have shown greater benefit in the older population (Table II). In MERIT-HF patients who were post-MI, total mortality was reduced by 40% and the composite end point of cardiac death plus nonfatal MI was reduced by 45%. Thus, a conservative estimate for the hazard ratio in this trial is 0.70.

With a constant hazard ratio of 0.70, the expected event rates in the intervention group are 10.75% at 1 year, 17.48% at 2 years, and 23.70% at 3 years (the estimated average length of follow-up), assuming exponential survival during each period. The expected event rate in the control group at 3 years is 32.05%. The sample-size calculation is based on a 2-tailed test with 85% power. Uniform entry of patients into the trial is assumed for a 2-year period. The follow-up period continues for 2 years after accrual is complete for a total study length of 4 years and thus an estimated average follow-up of 3 years. In these calculations, it has been assumed that 4 interim analyses will be done, after 20%, 40%, 60%, and 80% of the events have occurred. An O'Brien-Fleming-type α spending function is being used. Based on the above assumptions, the required number of events is 290, which based on the assumed event rates and exponential survival, yields a total sample size of 1044, or 522 per group. As the primary end point includes total mortality

and mortality data can be obtained from the National Death Index, little dropout is expected. However, some crossovers may occur. The primary analysis will be based on intention to treat. Thus, the planned sample size for the trial will be increased by 40 per group to 562, for a total sample size of 1124 patients.

Study organization and support

The clinical and data coordinating centers for this study are the Clinical Trials Unit at Northwestern University (Chicago, IL). The economics and quality-of-life coordinating center is the Duke Clinical Research Institute (Durham, NC). A steering committee and its subcommittees (events committee, publications committee) will oversee the study. A Data and Safety Monitoring Board is appointed by and reports to the National Heart, Lung, and Blood Institute. It is responsible for the independent assessment of the progress of the study, its scientific appropriateness, the safety of the participants, and the review of interim analyses. Participants will be enrolled at approximately 60 sites in the United States, Canada, and Israel. Recruitment will start in summer 2007 and will continue for 2 years, followed by an additional 2-year follow-up. The results are thus expected by the end of 2011.

Summary

It appears that the patients who cannot take β -blockers post-MI because of bradycardia contraindications tend to be an elderly population with a high 1-year mortality. Furthermore, if β -blockers provide benefit to the post-MI patient independent of their heart rate-lowering effect, then these patients could benefit substantially from initiation of β -blocker therapy. However, in this particular group of patients, β -blockers can be safely initiated *only if* more severe or significant bradycardia can be prevented by pacemaker implantation. It is unclear whether adverse effects related to pacemaker implantation could also negate some or all of the hypothesized benefit of β -blocker therapy. The PACE-MI trial is a randomized controlled clinical trial that will address whether β -blocker therapy enabled by pacemaker implantation is superior to no β -blocker and no pacemaker therapy after MI in patients with rhythm contraindications to β -blockers or in those who have developed symptomatic bradycardia due to β -blockers.

Pacemakers for the PACE-MI trial have been donated by Boston Scientific, Natick, MA; Medtronic, Minneapolis, MN; and St Jude Medical, St. Paul, MN.

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