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Beta-Adrenergic Blocking Agents in the Treatment of Patients After a Myocardial Infarction

Sidney Goldstein, MD*

Beta-adrenergic blocking agents have been widely used in ischemic heart disease. They have achieved their greatest benefit in the secondary prevention of recurrent events in patients following acute myocardial infarction (MI). This is a review of the major clinical investigations exploring the effects of beta-adrenergic blocking agents in patients following acute MI and in a variety of patient subsets. These data indicate that the routine use of beta-adrenergic blocking agents in postinfarction patients results in a 25% to 35% decrease in mortality and has increased relative and absolute benefit in patients with ventricular ectopy and left ventricular dysfunction. The adverse effects of beta-adrenergic blocking agents are discussed which indicate that these drugs are well tolerated with little or no side effects. This review supports the observation that beta-adrenergic blocking agents have an important role in the treatment of patients following an acute MI, with the exclusion of those with chronic lung disease and severe left ventricular dysfunction. (Henry Ford Hosp Med J 1991;39:200-5)

Beta-adrenergic blocking agents represent the current therapeutic foundation for the treatment of patients with acute and chronic coronary heart disease. Although this review deals with the use of these agents in the secondary prevention of postinfarction morbidity and mortality, their use in the treatment of hypertension and chronic angina pectoris should also be emphasized.

Clinical investigation of beta-blockers in ischemic heart disease began almost three decades ago with the initial observations by Ahlquist (1) who demonstrated the presence of β -adrenergic receptors in the cardiovascular system. The presence of β -adrenergic receptors led Black et al (2) to develop drugs that could block these receptors, thereby decreasing blood pressure, pulse rate, and the metabolic requirements of the heart. A series of preliminary clinical studies almost two decades ago described the benefit of β -adrenergic blocking agents in the treatment of patients who have sustained acute myocardial infarction (MI) (3-6). The results of these studies were confirmed by two major clinical trials of almost 7,000 patients, the Norwegian Multicenter Study (7) and the Beta-Blocker Heart Attack Trial (8) which examined the beta-blockers timolol and propranolol, respectively. Since these initial studies, reexamination of the original beta-blocker studies confirmed the initial observations of their benefit when administered to patients after an acute MI.

Mechanism of Action of Beta-Blockers

The initial studies by Black et al (2) demonstrated that beta-blockers lower heart rate and blood pressure. These two physiologic effects result in the modification of myocardial oxygen demands resulting in a salutary effect on the jeopardized ischemic myocardial tissue. It has been proposed that the degree to which pulse rate decreases as a result of beta-blocker therapy is a mea-

sure of its effect on improving survival (9) (Fig 1). In addition to limiting infarct size, they modify the expression of ventricular ectopy both in the acute and chronic phases of MI. Whether this is a result of modifying myocardial ischemia or due to an independent antiarrhythmic effect is not entirely clear. Animal studies demonstrate that beta-blockers exhibit a dose response effect on ventricular fibrillation threshold when studied in both ischemic and nonischemic states (10). It is therefore clear that β -adrenergic blocking agents have the potential of modifying two of the major risks facing patients with ischemic heart disease: the progression of myocardial ischemia and the development of life-threatening arrhythmias. In addition, Kaplan et al (11) demonstrated that propranolol therapy was able to modulate diet-induced coronary atherosclerosis in male cynomolgus monkeys by altering their behavioral response to stress. Cruickshank (12) reviewed the multiplicity of potential effects that these agents have on altering the progression of coronary artery disease.

Beta-adrenergic blocking agents differ in their physiologic and pharmacologic effects. The major difference relates to the presence of β_1 selectivity. Metoprolol, atenolol, and betaxolol, for instance, are considered drugs which have β_1 receptor blocking ability. These drugs tend to have a predominant, but not exclusive, effect on chronotropic and inotropic blockade without affecting β_2 receptors which cause peripheral vasoconstriction and bronchial constriction. The nonselective drugs such as propranolol, timolol, and nadolol do not have this selectivity and block both β_1 and β_2 receptors. It should be emphasized, how-

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ever, that this β_1 selectivity is expressed at relatively low doses and is usually lost in the higher dose range. An additional unique characteristic of these agents is the intrinsic sympathomimetic or β -agonist effect. This can be expressed to a varying degree by a positive inotropic or chronotropic effect as seen with oxprenolol, pindolol, or acebutolol. All of these characteristics provide a spectrum of drugs available to the physician in the treatment of many forms of cardiovascular disease including hypertension, angina, and arrhythmias. The only drugs which have been tested on mortality in the chronic phase of acute MI are propranolol (8), timolol (7), metoprolol (13), atenolol (14), sotalol (15), acebutolol (16), pindolol (17), and oxprenolol (18). All but pindolol and oxprenolol have demonstrated a salutary effect on mortality.

Effect of Beta-Blockers on Mortality and Morbidity

A series of clinical trials examined the effect of different beta-blockers on mortality (Table 1). The largest body of information has been reported by the Norwegian Multicenter Study Group (7) and the Beta-Blocker Heart Attack Trial (8). Timolol was administered in doses of 10 mg twice daily and propranolol in doses of 60 to 80 mg three times a day. These two studies indicate that when either timolol or propranolol was administered within two to three weeks postinfarction, a decrease in mortality between 25% and 36% in the first two years could be achieved, when compared to control patients receiving placebo (Figs 2 and 3). In addition, in the timolol study a significant reduction in reinfarction and sudden death was observed in the active treatment group.

The relative benefit of these drugs has been examined prospectively and retrospectively in a number of different patient subsets and found to be consistently similar in almost all subgroups studied. The use of beta-blockers relative to infarct location supports their efficacy, regardless of anterior or inferior infarction. Anterior infarcts, in general, have a placebo mortality rate twice that of inferior infarctions. The absolute benefit of these drugs relates to the inherent mortality risk of the particular subgroups. For example, patients who have experienced an anterior MI or who are older have a higher placebo mortality rate and therefore will achieve a greater total decrease in mortality as a result of beta-blocker therapy. The one exception are patients

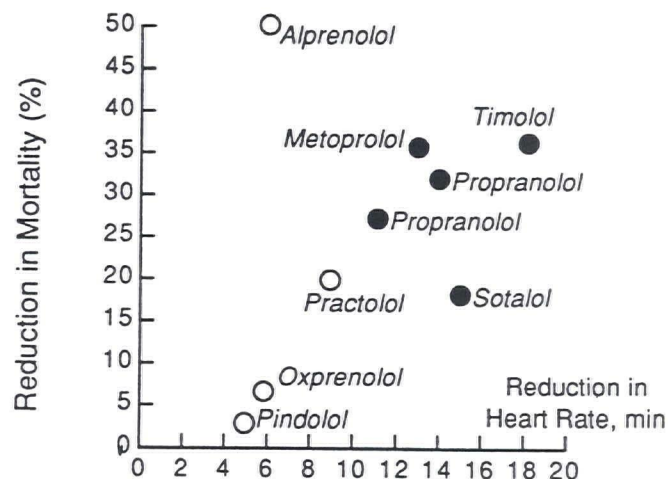


Fig 1—Relationship between heart rate and reduction in mortality induced by beta-blockers in survivors of acute MI. Note that beta-blockers with significant intrinsic sympathomimetic activity (open circles) with little or no bradycardic effect exert little effect on mortality. Beta-blockers without intrinsic sympathomimetic activity (closed circles) with bradycardic effect have the most significant effect on mortality. (From Kjekshus JK. Importance of heart rate in determining beta-blocker efficacy in acute and long-term myocardial infarction intervention trials. *Am J Cardiol* 1986;57:43F-49F. Reprinted with permission.)

who experienced a non-Q wave MI who achieve a less apparent benefit. Subgroup analyses demonstrate no significant effect of propranolol or metoprolol in patients with a non-Q wave acute MI (19,20). In contrast, the timolol-treated patients with a non-Q wave acute MI experienced a significant reduction in mortality (21).

A number of different subgroups have been analyzed in order to identify those patients who can achieve the greatest benefit from beta-blocker therapy. In postinfarction patients between 65 to 75 years of age, timolol exerted a similar decrease in reinfarction and death (22), indicating its efficacy regardless of age. Jafri et al (23) examined the effect of propranolol on smokers (Fig 4) and observed that the greatest beneficial effect of pro-

Table 1
Selected Results of Long-Term Beta-Blocker Trials for Secondary Prevention After Acute Myocardial Infarction

Trial	Number of Patients	Beta-Blocker	Entry From MI (Days)	Mean Follow-up (Months)	Mortality (%)		Reinfarction (%)	
					Drug	Placebo	Drug	Placebo
Multicentre International Study (1975) (6)	3,053	Practolol	1.0	24	6.3	8.2*	4	4
Norwegian Multicenter Study (1981) (7)	1,884	Timolol	11.5	17	10.4	16.2*	10	14*
Julian et al (1982) (15)	1,456	Sotalol	8.3	12	7.3	8.9	3	4
Beta-Blocker Heart Attack Trial (1982) (8)	3,738	Propranolol	13.8	25	7.2	9.8*	4	5*
Taylor et al (1982) (18)	1,103	Oxprenolol	14 months	48	9.5	10.2	11	12
Boissel et al (1990) (16)	607	Acebutolol	2-22	10	5.7	11.0*	2	1.3

*Statistically significant difference.

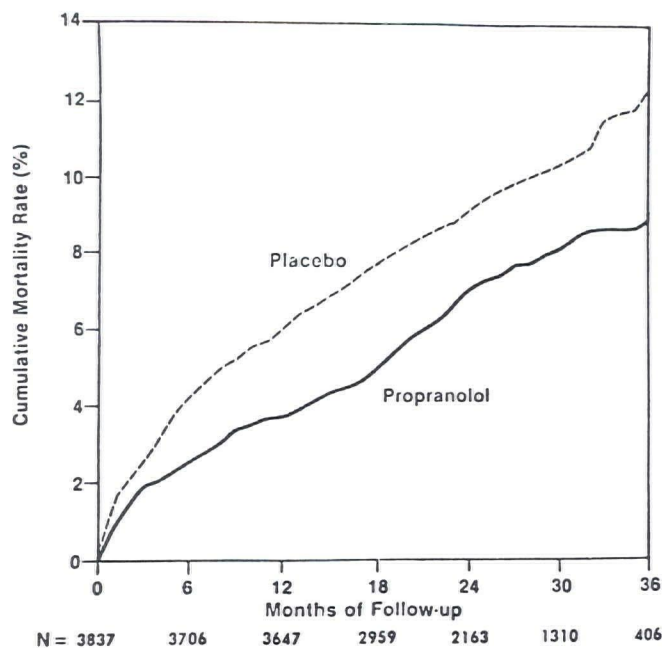


Fig 2—Life-table cumulative mortality curves for groups receiving propranolol hydrochloride or placebo. N indicates total number of patients followed-up through each time point. (From the Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA* 1982;247:1707-14. Reprinted with permission.)

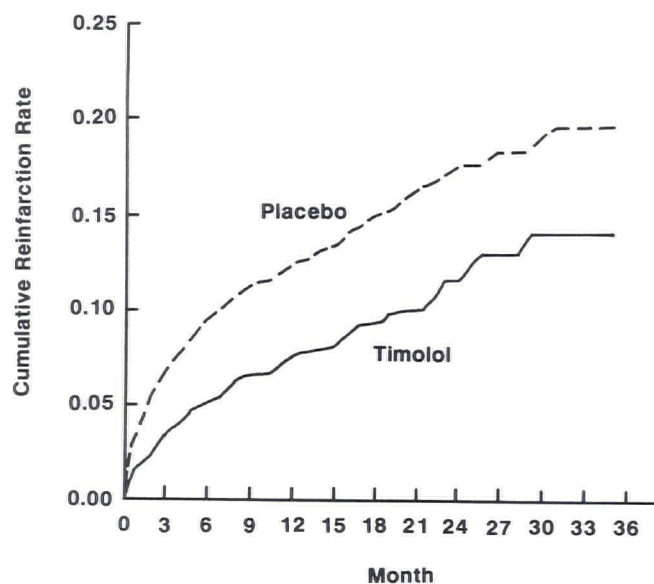


Fig 3—Effect of timolol on mortality from all causes. (From the Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med* 1981;304:801-7. Reprinted with permission.)

pranolol on mortality was achieved in patients who smoked before their MI and those who continued to smoke after the event. Similar observations with timolol treatment were made by Ronnevik et al (24).

The duration of therapy in these trials was limited to two to three years. The beneficial effects of therapy persisted throughout that time. The Norwegian Multicenter Study on timolol was later extended to seven years, during which a continued beneficial effect was observed (25). The effect of withdrawal of metoprolol in postinfarction patients was investigated after five to six years of therapy (26). Associated with metoprolol withdrawal was an observed increase in symptoms and mortality in patients, when compared to patients who continued therapy. A recent study examined the risk of hospital death in patients taking a beta-blocker before a MI (27). That study indicated that prior beta-blocker therapy reduced the risk and severity of the subsequent acute infarction. Although ventricular fibrillation was similar in patients regardless of prior beta-blocker therapy, patients taking a beta-blocker at the time of admission had a reduced extent of infarction and risk of death during the 28-day period after an acute MI.

Effect of Beta-Blockers on Ventricular Arrhythmias

Ventricular ectopy, of course, has been a major predictor of both sudden death and long-term mortality in patients following MI. Observations in the Beta-Blocker Heart Attack Trial (28) demonstrated that the use of propranolol decreased the frequency of ventricular ectopy in the first six weeks after the event. In patients with complex ventricular ectopy, propranolol therapy resulted in a greater decrease in mortality rate when compared to those patients without complex ventricular premature beats (29) (Fig 5). The effect of beta-blockers on mortality in patients with high-frequency ventricular ectopy is not solely related to ventricular ectopic beat suppression. It appears that they may also modify the biological milieu in which ventricular ectopy occurs, presumably rendering them less malignant.

A number of studies examined the relationship of beta-blocker therapy on arrhythmias and hypokalemia and their effect on hypokalemia in patients receiving concomitant diuretic therapy. Patients taking a beta-blocking agent prior to their MI had higher serum potassium and less frequent ventricular ectopy on admission (30). This is presumably due to the interference with NaK ATPase by β_2 receptor blockade, preventing the intracellular movement of K^+ which occurs in the setting of increased serum catecholamine associated with stress (31).

Effect of Beta-Blockers in Patients with Decreased Left Ventricular Function

Treatment with beta-blockers in postinfarction patients with left ventricular dysfunction has been of particular interest. Some concern was initially raised regarding the potential dangers of beta-blockers in patients with heart failure. Patients with severe left ventricular dysfunction manifested by shock and overt congestive heart failure were excluded from most beta-blocker trials. In the Beta-Blocker Heart Attack Trial, patients were in-

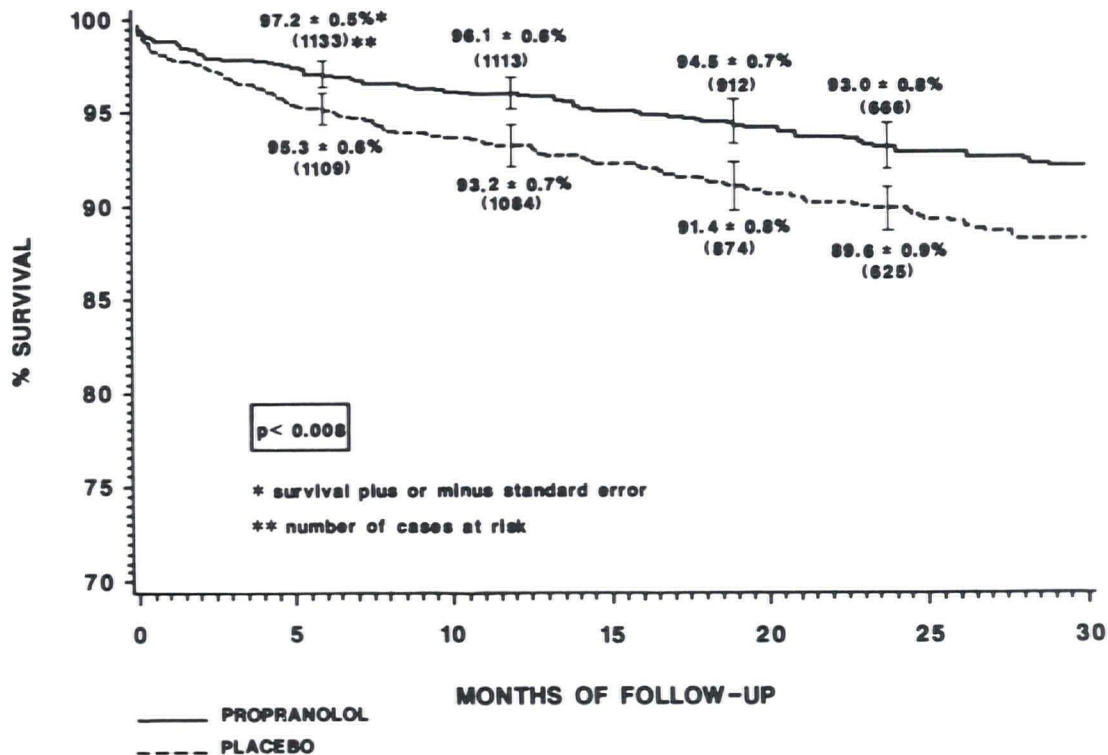


Fig 4—Survival in smokers following MI was better in patients receiving propranolol in comparison to placebo. (From Jafri SM, Tilley BC, Peters R, Schultz LR, Goldstein S. Effects of cigarette smoking and propranolol in survivors of acute myocardial infarction. *Am J Cardiol* 1990;65:271-6. Reprinted with permission.)

cluded who had congestive heart failure but whose heart failure was stabilized with digitalis and diuretic therapy. In those patients with a history of heart failure, propranolol therapy had the most profound beneficial effect on mortality (32) (Fig 6). Although there was a slight increase in mortality in heart failure in the initial phases of the treatment of these patients, beta-blockers were well tolerated. In a similar study in patients with complex arrhythmias and ventricular dysfunction, propranolol was also demonstrated to decrease sudden death significantly (33). A recent analysis of the patients who received placebo in the Multicenter Diltiazem Postinfarction Trial (34) further confirmed these observations. Patients with evidence of heart failure and a left ventricular ejection fraction less than 30% and who received a beta-blocker had approximately a 50% decrease in mortality when compared to those who were not taking beta-blockers (Fig 7). Although beta-blockers should be used cautiously in patients with left ventricular dysfunction, these patients have the greatest potential for benefit.

Side Effects of Beta-Blocker Therapy

Although it is suggested that beta-blockers are poorly tolerated due to a host of presumed adverse effects, blinded randomized placebo-controlled trials fail to support this presumption. The Beta-Blocker Heart Attack Trial extensively examined the

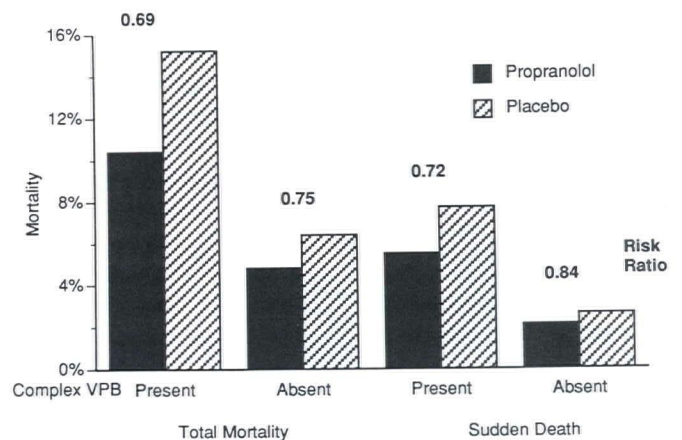


Fig 5—Effect of propranolol on mortality and sudden death in relation to the presence of complex ventricular premature beats (VPBs), > 10/hr or runs or multiforms on 24-hour Holter monitor at baseline. (Adapted from Freidman LM, Byington RP, Capone RJ, Furberg CD, Goldstein S, Lichstein E, for the Beta-Blocker Heart Attack Trial Research Group. Effect of propranolol in patients with myocardial infarction and ventricular arrhythmia. *J Am Coll Cardiol* 1986;7:1-8. Reproduced with permission.)

adverse effects of propranolol (8). Although patients with obstructive pulmonary disease were excluded from the study, there was a slight increase in bronchospasm and tiredness in patients taking propranolol (Table 2). Neuropsychiatric symptoms such as depression, nightmares, and insomnia did not occur any more frequently in patients receiving propranolol than in those receiving placebo. It is therefore clear that these drugs are well tolerated. Much of the perceived psychological reactions associated with beta-blocker therapy may in fact be related to the increased occurrences of these symptoms in patients who experience a MI.

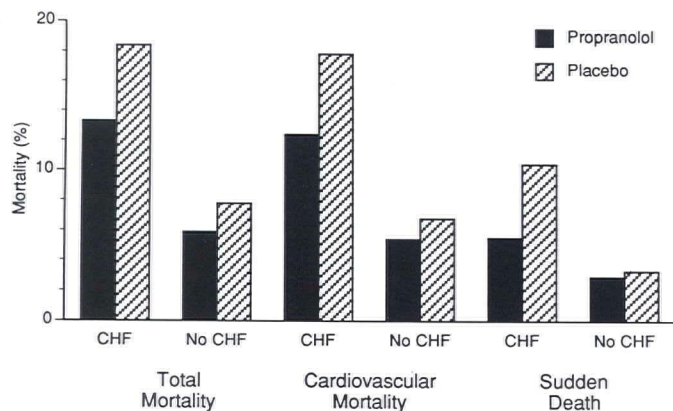


Fig 6—The effect of propranolol on mortality in relation to a history of heart failure (CHF) at baseline in the Beta-Blocker Heart Attack Trial. (Adapted from Chadda K, Goldstein S, Byington R, Curb JD. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. *Circulation* 1986;73:503-10. Reproduced with permission.)

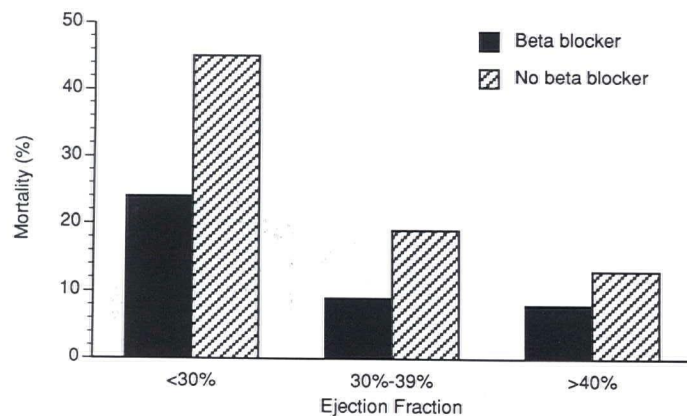


Fig 7—Risk of mortality was lower for patients receiving a beta-blocker than for those not receiving a beta-blocker for each subgroup of left ventricular ejection fraction. (Adapted from Lichstein E, Hager WD, Gregory JJ, Fleiss JL, Rolnitzky LM, Bigger JT, for the Multicenter Diltiazem Postinfarction Research Group. Relation between beta-adrenergic blocker use, various correlates of left ventricular function and the chance of developing congestive heart failure. *J Am Coll Cardiol* 1990;16:1327-32. Reproduced with permission.)

One additional concern has been the effect of these drugs on blood lipids. A recent analysis by Byington et al (35) of the Beta-Blocker Heart Attack Trial indicates that although there is a slight decrease in high-density lipoprotein cholesterol and an increase in triglycerides, there is no change in low-density lipoprotein cholesterol. When mortality data were analyzed relative to these changes, propranolol continued to exert a profound beneficial effect on mortality regardless of its effect on blood lipids. It appears, therefore, that these effects on serum lipids are of no importance either in the short- or long-term therapy of MI patients.

These studies, as well as retrospective examinations of clinical trials of beta-blockers, continue to develop data to support the benefits of the routine use of these drugs in postinfarction patients. Their use appears to be indicated in all patients except those who have contraindications to their use. Beta-blockers appear to have their most significant absolute effect on high-risk patients including those with complex ventricular ectopy and left ventricular dysfunction. Therapy should be continued for the life of the patient, based on residual beneficial effects observed at seven years following the acute event.

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Table 2
Side Effects of Beta-Blockers*

Side Effect	Propranolol (%)	Placebo (%)	P-Value
Shortness of breath	66.8	65.5	NS
Bronchospasm	31.3	27.0	<0.005
Cold hands, feet	10.0	7.7	<0.005
Tiredness	66.8	62.1	<0.005
Reduced sexual activity	43.2	42.0	NS
Depression	40.7	39.8	NS
Insomnia	21.1	18.8	NS
Diarrhea	5.5	3.6	<0.01

*Adapted from Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA* 1982;247:1707-14.
NS = not significant.

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