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SAFETY OF BETA-BLOCKER THERAPY WITH AND WITHOUT THROMBOLYSIS: A COMPARISON OF BISOPROLOL AND ATENOLOL IN ACUTE MYOCARDIAL INFARCTION

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ON BEHALF OF THE BISOPROLOL AND ATENOLOL IN ACUTE MYOCARDIAL INFARCTION GROUP

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ABSTRACT

In the current era of widely used thrombolytic therapy, the new beta-blocker bisoprolol was compared with the well-established beta-blocker atenolol in the treatment of acute myocardial infarction (AMI). A total of 334 patients were enrolled in this international, multicenter, randomized, double-masked, controlled study of 7 days' duration in two parallel groups. The purpose of the study was to compare the tolerability and safety of the two beta-blockers given to patients with AMIs who either were (281 patients) or were not (53) given concurrent thrombolytic agents. A statistically significant decrease in heart rate was seen with both bisoprolol and atenolol. Beta-blocker therapy had to be interrupted in 70 patients, 36 receiving bisoprolol and 34 atenolol, because of serious adverse effects. The difference in incidence of adverse events between groups was not significant. A logistic regression analysis based on conditions at admission predicted an increase in the risk of critical events occurring during the first week after an AMI for patients with a positive family history of AMI, a moderate-sized myocardial infarction, or a heart rate >70 beats/min, and for patients pretreated with dihydropyridine calcium antagonists. Bisoprolol was found to be as effective as atenolol in reducing heart rate, an important goal of intervention in AMI. Furthermore, some characteristics that might influence the decision to use beta-blockers in addition to thrombolytic agents were identified.

INTRODUCTION

The numerous studies of reperfusion, patency, and mortality conducted to date have firmly established thrombolysis as the cornerstone therapy for evolving myocardial infarction in eligible patients.[1–4] Before thrombolytic therapy attained this prominence, it was determined that early treatment

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with beta-blockers reduces infarct size, the incidence of arrhythmia, ventricular rupture, and overall mortality.[5–7] The extent of the reduction in mortality appears to be related to the degree of reduction in heart rate.[8] Most of the studies on beta-blockade in acute myocardial infarction (AMI) were performed before thrombolysis was established as a treatment for myocardial infarction. The Thrombolysis in Myocardial Infarction trial[9,10] demonstrated that after initial thrombolysis, conservative therapy was the most appropriate treatment for patients with AMI.

Combination therapy with thrombolysis and beta-blockade has not yet been investigated. The use of a placebo-controlled study to demonstrate the efficacy of a new beta-blocker in the treatment of AMI is no longer ethically justifiable. Thus we conducted a study of the new beta-1-selective beta-blocker bisoprolol and one of the most studied beta-1-selective beta-blockers, atenolol, to compare their tolerability and safety in the treatment of patients with AMI who either were or were not clinically able to receive concurrent thrombolytic agents. On admission to the study, certain patient characteristics were recorded to analyze whether they could be used to predict an adverse outcome of myocardial infarction when beta-blocker therapy was combined with thrombolysis.

PATIENTS AND METHODS

A total of 334 patients with AMI (age range, 18 to 75 years) were enrolled in this multicenter study.

Eligibility

Patients were eligible for the study if they had signs typical of an AMI and if the signs and symptoms had started within 6 hours before inclusion in the study. Additionally, at least 2 of the 3 following criteria had to be present: (1) nitrate-resistant anginal pain lasting longer than 30 minutes; (2) electrocardiographic (ECG) signs of a myocardial infarction (ST-segment elevation >1 mm in lead I or aV_L or >2 mm in 2 of the 3 inferior leads [II, III, aVF] or in at least 2 adjacent precordial leads, or the presence of new Q waves in at least 3 leads); or (3) persistent ST-segment depression after administration of nitroglycerin sublingually or intravenously (IV).

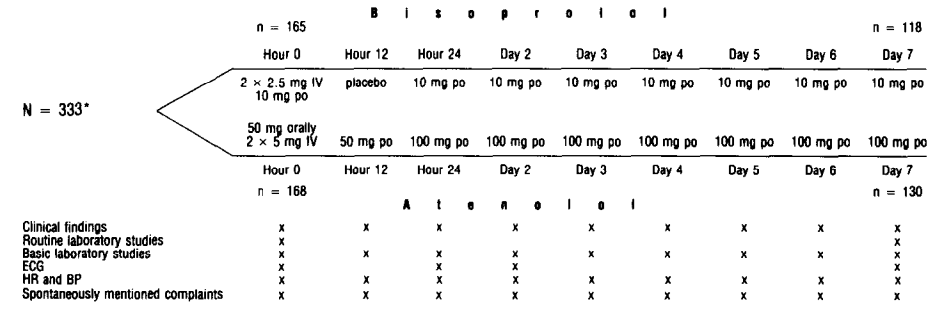
Patients with the standard contraindications for beta-blocker therapy—bradyarrhythmia, second- and third-degree atrioventricular block, bifascicular block, manifest heart failure, or a history of severe chronic obstructive airway disease—were excluded. During the study the concomitant administration of beta-blockers and calcium-channel blockers, other than dihydropyridines, was not allowed.

All patients included in the study were asked for their informed consent in writing or verbally in the presence of a witness. The study protocol was approved by the hospital ethics committee of each center.

The diagnosis of AMI had to be confirmed by an increase in the MB isoenzyme of creatine phosphokinase (CPK-MB) to a value of at least twice the upper limit of the normal range. A committee of independent cardiologists evaluated the data on enzyme levels and ECG time intervals under masked conditions. The diagnosis of definite AMI required the presence of abnormal Q waves with evolutionary ST- and T-wave changes on serial ECG tracking and enzyme evidence. CPK-MB <40 U/L indicated a small infarction and CPK-MB ≥82 U/L indicated a moderate-to-large infarction.

Study Design

This international multicenter study was designed as a randomized, double-masked, controlled study of 7 days' duration. Patients were assigned, on the basis of a randomization schedule performed in blocks per center, to one of two parallel groups to receive either bisoprolol or atenolol (Figure 1). Patients were admitted to the coronary care unit, where the thrombolytic treatment was or was not administered according to the recommended clinical routine, and were enrolled directly into the study. The choice of thrombolytic agent depended on the standard thrombolytic agent in each center. A standard 12-lead ECG was recorded, blood samples were collected, and clinical findings were reported. Upon admission, the patients received either bisoprolol 2.5 mg or atenolol 5 mg by slow IV injection over 5 minutes (2 mL/min). Blood pressure and heart rate were registered with mercury sphygmomanometers and pulse counts, respectively, at 5-minute intervals. If none of the withdrawal criteria—heart rate <50 beats/min, systolic blood pressure <95 mm Hg, P–Q interval >0.24 sec, or congestive heart failure resistant to diuretics—were present, a second IV dose of bisoprolol 2.5 mg or atenolol 5 mg was given 15 minutes after the first administration. Ten minutes after the last IV administration of the



* Thrombolysis, n = 281; no thrombolysis, n = 52. One patient was excluded before the study medication was given because of bradycardia and hypotension.

Figure 1. Study design. IV = intravenously; po = orally; ECG = electrocardiography; HR = heart rate; BP = blood pressure.

beta-blocker, the first oral treatment with bisoprolol 10 mg or atenolol 50 mg was started. The patient received the second capsule, either placebo (if randomized to bisoprolol) or atenolol 5 mg, after 12 hours. After another 12 hours, a third capsule of either bisoprolol 10 mg or atenolol 100 mg was given. ECG at rest was performed and blood samples were obtained. From the third through the seventh day after the AMI, patients received bisoprolol 10 mg or atenolol 100 mg orally once daily. After the seventh day, treatment with beta-blockade was continued or discontinued at the physician's discretion.

A subgroup of 70 patients (all the randomized patients from two university centers) had a 48-hour ambulatory ECG recording during the first 2 days of treatment. The recording was started just before the administration of the beta-blocker.

Discontinuation of Therapy

The study medication was discontinued if a severe side effect occurred at any time during the study. These side effects were a heart rate <50 beats/min, systolic blood pressure <95 mm Hg, P–Q interval >0.24 second, or persistent signs of congestive heart failure despite treatment with diuretics.

An adverse event was defined as any sign or symptom observed by the investigator or reported by the patient during treatment, whether or not the event was related to the study medication. Critical events, defined as events associated with a high risk for an adverse outcome, included death, the recurrence of angina pectoris, the recurrence of myocardial infarction, signs of heart failure, atrioventricular conduction disorders, arrhythmia, and hypotension.

Statistical Analysis

Data are reported as mean ± 1 SD, unless otherwise noted. A two-sided probability level of 0.05 or less was considered to indicate statistical significance. For the comparison of clinical characteristics associated with the study medications, chi-square analysis, two-tailed Fisher's exact test, Wilcoxon-rank sum test, or Student's t test was used as appropriate. Repeated measurement analysis of variance with the baseline as covariate was used for the analysis of the efficacy data, which were derived from measurements of heart rate, systolic blood pressure, and the rate-pressure product at different time points.

To determine parameters related to the cumulative safety data, logistic regression analysis was performed with the covariates being family history, CPK-MB release, and heart rate. (Only variables with coefficients with $P \leq 0.05$ are reported.) The regression analysis began with an examination of univariate distributions to identify potential errors indicated by outlying values, appropriate categorization guided by frequencies of rep-

resentation, and assessment of missing data, considering their frequencies as a basis for choosing subject deletion or the modeling approach by using an indicator method. Variables modeled as continuous were assessed by determining the quartiles or, if necessary, the deciles of the distribution using the lowest quartile as the reference group. In the case of a linear trend in the estimated coefficients, the variable was introduced as continuous. If no linearity was demonstrated, the variable was categorized by combining the estimated coefficients and, therefore, the quartiles or deciles that were similar in magnitude. Adjusted-rate ratios and 95% confidence intervals are presented.

All analyses were made using the Statistical Analysis System (SAS Institute, Cary, North Carolina) and the Epidemiologic Graphics Estimation and Testing (EGRET® Circ and Cytel) package.

RESULTS

A total of 334 patients from 38 centers in eight European countries were randomized to receive treatment with bisoprolol or atenolol. The mean time from the onset of AMI until the study medication was started was 1.97 ± 0.2 hours. One patient was excluded from further analysis after the randomization and before the study medication was given because of bradycardia and hypotension. Thus 333 patients were evaluated for safety. In 29 patients the diagnosis of AMI could not be confirmed by the committee of independent cardiologists. These patients completed the trial according to the protocol and their data were included in the safety analysis and the regression analysis but not in the analysis for the efficacy of heart rate reduction.

The study medication was discontinued in 70 patients because of adverse events. Their data were included in the safety analysis and evaluated in the regression analysis. Fifteen patients did not receive their medication at the intervals prescribed in the study protocol, meaning that data for 248 patients were included in the analysis of hemodynamic variables.

With respect to the baseline characteristics of age, body weight, height, and the location and size of the infarction, no relevant difference was found between the bisoprolol- and the atenolol-treated patients (Table I). Two hundred eighty-one patients were treated with thrombolytic agents and a beta-blocker, while 52 were treated with a beta-blocker only. Streptokinase was administered in 74.5% of the patients, anisoylated plasminogen streptokinase activator complex in 11.5%, recombinant tissue plasminogen activator in 11.5%, and urokinase in 2.5%.

Heart Rate Reduction

A total of 248 patients completed the study according to the protocol and were included in the analysis of hemodynamic variables. The mean

Table I. Patient characteristics, location of infarction, and serum creatine phosphokinase (CPK) and the MB isoenzyme of creatine phosphokinase (CPK-MB) values.

	Bisoprolol		Atenolol	
Sex				
Female	25	15.1%	24	14.3%
Male	140	84.9%	144	85.7%
Age (y) (mean ± SEM)	58.50 ± 1.3		57.20 ± 4.0	
Height (cm) (mean ± SEM)	171.99 ± 0.62		172.17 ± 0.58	
Body weight (kg) (mean ± SEM)	77.41 ± 0.91		75.64 ± 0.81	
Smoking history				
No	39	23.5%	42	25.0%
Yes	91	55.4%	85	50.6%
Ex-smoker	35	21.1%	41	24.4%
Thrombolysis				
Without thrombolysis	27	16.3%	25	14.9%
With thrombolysis	138	83.7%	143	85.1%
Location of new infarction				
Inferior, inferior posterior, posterior	63	38.1%	62	36.9%
Anterior, anteroseptal, anterolateral	66	40.0%	78	46.4%
No infarction	15	9.1%	12	7.1%
Other locations	19	11.5%	13	7.7%
Missing date	2	1.2%	3	1.9%
Time to hospitalization (h) (mean ± SEM)	1.93 ± 0.2		1.99 ± 0.4	
CPK				
On admission	206.60 ± 93.2		185.60 ± 5.8	
Maximum (mean ± SEM)	1268.80 ± 100.1		1167.30 ± 85.9	
CPK-MB				
On admission	27.80 ± 6.5		21.50 ± 6.9	
Maximum (mean ± SEM)	110.27 ± 9.19		116.89 ± 11.02	

heart rate at baseline was comparable in both the bisoprolol and atenolol groups in both stratified groups (the patients who did and did not receive thrombolysis). The heart rate decreased significantly ($P < 0.001$) 1 hour after the first IV dose in all patients. In the bisoprolol group the heart rate decreased from a mean of 78.5 ± 1.4 beats/min at baseline to a mean of 66.3 ± 1.3 beats/min, and in the atenolol group from a mean of 80.5 ± 1.2 beats/min at baseline to a mean of 67.3 ± 0.9 beats/min 1 hour after the first dose of the beta-blocker was administered. The significant decrease in heart rate was maintained during both the IV and oral phases of the study (Figure 2). Throughout the study, no statistically significant differences in heart rate were found between the bisoprolol- and the atenolol-treated groups. Although the average heart rate in the patients treated with both thrombolysis and beta-blockade was higher on the first day than that in the patients not given thrombolysis, this difference was not statistically significant ($P = 0.31$). Repeated measurement analysis of variance during the IV and oral phases revealed no differences in heart rate reduction between the bisoprolol and the atenolol groups or between the groups that did and did not receive thrombolysis.

The mean systolic and diastolic blood pressures decreased significantly ($P < 0.001$) during the first 24 hours in both the bisoprolol and the

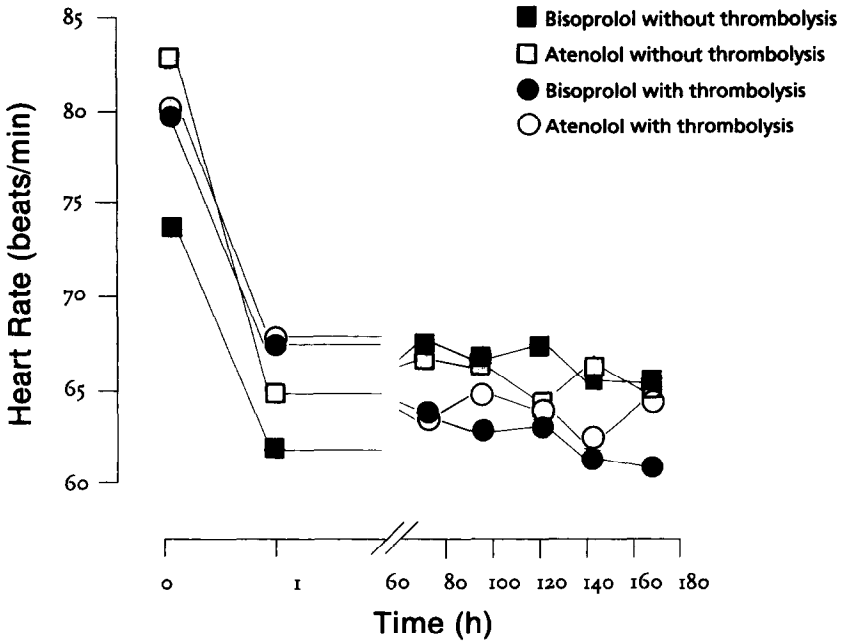


Figure 2. Heart rate.

atenolol groups. In the bisoprolol group, systolic blood pressure decreased from a mean of 135.4 ± 1.9 mm Hg to 115.3 ± 1.4 mm Hg, and diastolic blood pressure decreased from a mean of 84.3 ± 3.7 mm Hg to 72.6 ± 3.2 mm Hg 12 hours after the first IV dose. In the atenolol group, systolic blood pressure decreased from a mean of 134.0 ± 2.0 mm Hg to 111.0 ± 1.3 mm Hg, and diastolic blood pressure decreased from a mean of 82.9 ± 2.4 mm Hg to 75.0 ± 2.3 mm Hg. The decreases were comparable in the bisoprolol and the atenolol groups and were maintained in the oral phase. Repeated measurement analysis of variance revealed no difference between the two drug regimens in the IV or the oral phase. The rate-pressure product (heart rate × systolic blood pressure) decreased significantly ($P < 0.001$) for both drug regimens after the first IV dose; the reduction was maintained during the oral phase. The analysis of variance for repeated measurements revealed no difference between the two drug regimens at any time point. In the subpopulation of 70 patients in whom a 48-hour ambulatory ECG recording was performed, repeated measurement analysis of variance revealed no difference between the bisoprolol and the atenolol groups in minimum, maximum, and average heart rate.

Safety

All 333 patients were included in the safety analysis. Treatment with beta-blockers had to be interrupted in 70 patients—36 receiving bisoprolol

and 34 atenolol—because of serious adverse events. (The occurrence of an adverse event did not necessarily lead to discontinuation of the medication.) There was no significant difference in the occurrence of serious adverse events between the bisoprolol and the atenolol groups (Table II). Similarly, the stratification for patients who received thrombolytic therapy versus those who did not showed no statistically significant difference in the occurrence of critical events in the bisoprolol and atenolol groups.

In the total population, no statistically significant change was found in the P–Q interval between the bisoprolol and the atenolol groups either with or without thrombolysis.

During the first 24-hour ECG recording, 72.2% of the patients receiving bisoprolol and 82.4% receiving atenolol had Lown class IVb rhythm disturbances.[11] During the second 24-hour ECG recording, Lown class IVb rhythm disturbances were found in 13.3% of the bisoprolol-treated patients and 38.5% of the atenolol-treated patients. This difference was not statistically significant ($P = 0.10$).

Subanalyses

Using multivariate analysis, the thrombolysis and non-thrombolysis treatment groups were tested for a change in the degree of risk of critical events, defined as death, myocardial infarction, recurrence of angina pectoris, atrioventricular conduction disorders, hypotension, arrhythmia, and signs of heart failure. Thrombolysis was found to have no influence on the occurrence of an adverse event; the risk was −.5238 ($P = 0.111$; confidence interval 0.3312–1.127).

A logistic regression analysis was performed to determine the value of the different baseline characteristics (Table III) in predicting an adverse outcome. An adverse outcome was defined as the occurrence of any critical event, cumulative (sum of all adverse events), or unique per patient (same event occurring more than once in the same patient was considered as one

Table II. Adverse events.

	Thrombolysis		No Thrombolysis	
	Bisoprolol %	Atenolol %	Bisoprolol %	Atenolol %
Death	0.7	2.1	0	4.0
Myocardial infarction	0.7	2.8	0	0
Angina	5.1	2.8	7.4	8.0
Bradyarrhythmias	12.3	12.6	29.6	16.0
Atrioventricular conduction disorders	2.2	2.1	0	0
Heart failure	7.2	3.5	3.7	8.0
Hypotension	15.1	13.3	11.1	12.0
Ventricular arrhythmias	1.8	2.4	0	0.3

Table III. Patient data recorded on admission to the study.

Medication	Systolic blood pressure
Thrombolysis	Diastolic blood pressure
Angina pectoris	Heart rate
Myocardial infarction	Diabetes mellitus
Atrioventricular conduction disturbances + sinoatrial block etc.	Time to hospitalization
	Creatine phosphokinase and the MB isoenzyme of creatine phosphokinase
Hypotension	Arrhythmias
Death	Cardiac surgery
Heart failure	Valvular defect
Bradyarrhythmias	Cardiac failure
Sex	Cerebral circulatory disorder
Height	Thrombosis
Body weight	Migraine
History of myocardial infarction	Raynaud's phenomenon
Location of old infarction	Family history
Location of new infarction	Smoking history
Angina pectoris: stable or unstable	

event) (Table IV). There was a significant increase in relative risk for an adverse outcome for family history ($P = 0.01$; odds ratio, 1.942, confidence interval, 1.162–3.699) and for patients receiving dihydropyridine-like calcium antagonists ($P = 0.04$; odds ratio, 2.711, confidence interval, 1.032–7.124). A reduction in the risk of adverse outcome was found in patients with heart rate ≥70 beats/min ($P < 0.03$; odds ratio, 4.269, confidence interval, .2423–.7522) and a moderate-to-large infarction CPK-MB ≥40 and <82 U/L ($P = 0.04$; odds ratio, 2.530, confidence interval, 1.344–4.760) but not for large myocardial infarctions with CPK-MB ≥82 U/L ($P = 0.99$; odds ratio, −.9897, confidence interval, 0.4775–2.052).

DISCUSSION

In this study of 333 evaluable patients with AMI, of whom a substantial number received thrombolysis, a comparable reduction in heart rate was

Table IV. Results of logistic regression analysis.

	Adjusted Odds Ratio	95% Confidence Interval	P
Family history*	1.942	1.162–3.699	0.01
CPK-MB ≥40 and <82†	2.530	1.344–4.760	0.04
CPK-MB ≥82	−.9897	.4775–2.052	0.99
HR ≥70 beats/min‡	4.269	.2423–.7522	0.03
Calcium antagonist	2.711	1.032–7.124	0.04
Thrombolysis	−.5238	.3312–1.127	0.11

CPK-MB = the MB isoenzyme of creatine phosphokinase; HR = heart rate.
* Reference category no family history with an adjusted odds ratio of 1.0.
† Reference category CPK-MB <40 with an adjusted odds ratio of 1.0.
‡ Reference category heart rate of <70 beats/min with an adjusted odds ratio of 1.0.

demonstrated with the two beta-blockers bisoprolol and atenolol. Thrombolysis appeared to have no additional effect on adverse outcome when combined with beta-blocker therapy.

Beta-blockers reduce the oxygen demand of the myocardium by decreasing the rate-pressure product; they also counterbalance the direct adverse effects of catecholamines and have anti-arrhythmic properties.[5,12] In the last several decades it has been demonstrated that beta-blockers cause a reduction in infarct size, decrease myocardial wall stress, and prevent cardiac rupture.[13] When started within 12 hours of the onset of chest pain, a variety of beta-blockers have been shown to reduce the direct indexes of myocardial damage (ie, enzymatic or electrocardiographic changes) in humans.[6,7] The magnitude of the effect has been shown to correlate with the magnitude of the reduction in heart rate and systolic blood pressure; it has been suggested that the beta-blocker that produces the greatest reduction in heart rate is the most effective in treating AMI.[8]

We found that bisoprolol and atenolol were equally effective in reducing heart rate and the rate-pressure product. This suggests that the two drugs would be similar in their effectiveness in reducing overall mortality, size of the infarction, and complications after AMI.

Reperfusion is the most effective way to treat the ischemic myocardium.[14] However, in both GISSI and ISIS-2,[2–4] an excess number of deaths were reported in the early period after thrombolysis. In our study, we found a slightly higher heart rate (not statistically significant) in the patients who received thrombolysis compared with those who did not. This might indicate that thrombolysis causes a further increase in catecholamine release. Before thrombolysis was available, the benefit of early IV beta-blocker therapy was particularly apparent in the first 24 to 36 hours after drug administration. In our study, significant reduction in heart rate in the patients who received thrombolysis and beta-blocker therapy implies a complementary role for beta-blockers and thrombolytic therapy. Therefore, patients receiving thrombolysis could be expected to benefit at least as much from beta-blocker therapy as did the patients before thrombolysis became available.

A second important issue to address is whether the risk of adverse events changes with combination therapy using a beta-blocker and thrombolytic agent compared with monotherapy with one or the other of these treatments. Compared with beta-blockers alone, the combination of thrombolytic agents and beta-blockers may lead to an increase in adverse outcome due to an accumulation of complications or adverse events. In patients with AMI, it is difficult to distinguish whether beta-blocker therapy contributed to the complications resulting from an AMI or caused the adverse event directly. However, we found that the addition of the beta-blockers to throm-

bolytic treatment appeared not to influence the adverse outcome. This result indicates that beta-blockers can safely be given to all patients with or without thrombolysis, and we may expect to find the same benefits from beta-blockade today as was found before thrombolysis became widely available. The combination of either bisoprolol or atenolol with thrombolysis did not influence the risk for critical events, the lengths of the P–Q interval, nor the occurrence of arrhythmias.

A logistic regression analysis was performed to identify patients who benefited most from the administration of beta-blockers in addition to thrombolytic agents. A family history positive for cardiovascular diseases was shown to be a predictor for a higher risk of adverse events. This finding was independent of any drug regimen, indicating that the clinician should closely monitor these patients. An increased risk for critical events was found for patients pretreated with calcium antagonists. This finding was difficult to interpret. Previous studies[15,16] have shown that combination therapy with a calcium antagonist and a beta-blocker is beneficial in patients with unstable angina. Whether this is also true for AMI should be investigated in a properly designed study. However, the pharmacology and adverse-reaction profiles of beta-blockers and dihydropyridine calcium antagonists predict increased toxicity when combined. In this regard, the current finding is not surprising, regardless of the results in other studies.

Based on the results of the ISIS-2 trial,[3] in which aspirin was shown to reduce cardiovascular mortality in AMI, we expected beneficial outcomes for patients pretreated with acetylsalicylic acid products. This could not be demonstrated in the current study.

In patients with AMI, a heart rate <70 beats/min at admission indicates a low mortality risk. In these patients, careful titration and monitoring of heart rate are of more immediate concern than the decision to administer beta-blockers. We found that the reduction in heart rate was independent of the thrombolysis. Although during the first hours after AMI the heart rate was slightly (not significantly) higher, in the groups receiving thrombolysis than in those without thrombolysis, beta-blocker therapy resulted in a comparable reduction in heart rate.

Because a patient's enzyme levels can be determined quickly, CPK values can be used as an indicator of the risk of an adverse event. Although the CPK values for the area under the curve might be more relevant, these only become available during the following hours. This analysis shows that patients with a moderate-sized myocardial infarction, defined as CPK-MB ≥ 40 U/L and <82 U/L at admission, have an increased risk of adverse outcome. Patients with a large infarction (CPK-MB ≥ 82 U/L) have no increase in this risk. The latter observation may indicate that in patients in whom thrombolysis is successful, reperfusion might cause a rapid washout of enzymes, which should be considered a positive sign. The other

baseline characteristics tested had no influence on the risk for adverse outcome of AMI.

CONCLUSIONS

Bisoprolol and atenolol are equally effective in reducing heart rate in patients with AMI. Patients who benefit most from beta-blockade during the acute phase of myocardial infarction are characterized by a positive family history of cardiovascular diseases, a moderate-size myocardial infarction, a high initial heart rate (>70 beats/min), and pretreatment with dihydropyridine calcium antagonists. The presence of any of these factors might influence the decision to use beta-blocker therapy in addition to thrombolysis.

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