Significance of Arrhythmias During the First 24 Hours of Acute Myocardial Infarction Treated With Alteplase and Effect of Early Administration of a β-Blocker or a Bradycardiac Agent on Their Incidence

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Background Although early intravenous β-blocker therapy during acute myocardial infarction (AMI) reduces the incidence of fatal arrhythmias in patients not treated with thrombolytic agents, its antiarrhythmic effect in thrombolysed patients remains controversial. We investigated prospectively the arrhythmia incidence in 244 patients with AMI receiving alteplase and a double-blind randomized adjunctive therapy with intravenous atenolol, alinidine, or placebo. Moreover, the characteristics and prognostic significance of early arrhythmias and their relation with infarct size and coronary patency were evaluated.

Methods and Results All patients underwent 24-hour Holter monitoring on day 1 and were clinically followed in the hospital for 10 to 14 days. Coronary angiography was performed on day 10 to 14. Atenolol and alinidine significantly decreased the basic heart rate without causing more sinus arrest or higher-degree atrioventricular block. The prevalence of atrial fibrillation in alinidine patients was lower than in the atenolol patients (P=.007) but not lower than in placebo patients (P=.11). There was no effect of either agent on the incidence and frequency distribution of ventricular or supraventricular premature beats or on the incidence and characteristics of nonsustained ventricular tachycardia, accelerated idioventricular rhythm, sustained ventricular tachycardia (VT), or ventricular fibrillation (VF). On day 1, seven VF episodes were recorded in six patients (2.5%) and five VT episodes in five patients (2%). VF always started at <2.5 hours after start of thrombolytic treatment and VT always at >2.5 hours (average of 6 hours). Five of the seven VF and three of the five VT episodes started with an R-on-T. However, for all VT, the morphology of the first beat was the same as that of the following beats, suggesting that the sustained arrhythmia was not induced by an extrasystole. After day 1 and before hospital discharge, VF and VT developed in one and six patients, respectively. Three of the seven patients who developed VF during the first 2 weeks underwent coronary angiography; all three had an occluded infarct-related artery. In contrast, only one of nine patients with early or late VT had an occluded vessel. Patients with VT and VF on day 1 had a significantly larger enzymatic infarct size than those without the arrhythmia (P=.02), and a similar trend was noted for VT or VF after day 1 (P=.19). However, none of the patients with VT or VF on day 1 developed a life-threatening arrhythmia later during the hospital stay. Also, none of the seven patients with VT or VF after day 1 had experienced a major rhythm disturbance during the first 24 hours.

Conclusions (1) Our data do not support the hypothesis that β-blockers or bradycardiac agents might reduce the incidence of major arrhythmias when used in conjunction with thrombolytic therapy. (2) The pathogenees of VT and VF early during AMI are clearly distinct. (3) VT or VF during the first 2 weeks is a marker for a larger infarct. (4) We could not detect a relation between malignant arrhythmias on day 1 and recurrences within the following 2 weeks. (Circulation. 1994;89:1051-1059.)

Key Words • arrhythmia • thrombolysis • atenolol • alinidine

It is generally accepted that β-blocker therapy started immediately after an acute myocardial infarction prevents fatal arrhythmias and that this contributes to the reduction of early and late mortality.1,2 Mortality rates for acute myocardial infarction are especially high during the first hours and are mainly the result of arrhythmic events.3 In the prethrombolytic era, the MIAMI4 and ISIS-15 investigators have shown that early intravenous administration of a β-blocker during the course of an acute myocardial infarction was associated with a reduction in early death (within 24 to 48 hours), cardiac rupture, and ventricular fibrillation. In the TIMI II-B trial, however, early administration of a β-blocker in combination with thrombolytic therapy did not further reduce the incidence of fatal arrhythmias compared with thrombolysis alone.2,6

Although reperfusion frequently induces arrhythmias, the incidence of serious arrhythmias like ventricular fibrillation (VF) and/or ventricular tachycardia (VT) during hospital stay is usually lower in thrombolysed patients than in conventionally treated patients. However, no continuous Holter monitoring has been
performed systematically in large groups of these patients.

The present prospective study reports on a group of patients with acute myocardial infarction, all treated with thrombolytic therapy, who were double-blindly randomized to early intravenous administration of a β-blocker (atenolol), a specific bradycardiac agent (alindidine), or placebo. The incidence of arrhythmias during the first 24 hours was evaluated by continuous Holter recording. Afterward, all serious arrhythmias between day 1 and hospital discharge on day 10 to 14 were reported on the record form.

Methods

Patient Population

Twenty-four-hour Holter recording was started as soon as possible after the administration of the thrombolytic agent (recombinant tissue plasminogen activator, alteplase) in 244 patients with acute myocardial infarction (symptoms lasting <5 hours). The patients formed a subgroup of the 292 patients reported on previously who received a β-blocker (atenolol) or a specific bradycardiac agent (alindidine) as adjunct to thrombolytic therapy in acute myocardial infarction.7 The participating centers, the inclusion criteria, and the contraindications for thrombolytic therapy were described in a previous report.7 Eligible patients (≤70 years old) were randomized by use of a “double-dummy” technique to receive, in conjunction with thrombolytic and antithrombotic therapy (100 mg alteplase over a period of 3 hours plus heparin, 5000 IU bolus followed by continuous infusion of 1000 IU/h during at least 48 hours), one of the following: (1) the β-selective adrenergic receptor blocker atenolol (5 mg IV over 5 minutes, repeated after 10 minutes by a second dose of 5 mg if heart rate and systolic blood pressure did not decrease below 60 beats per minute and 90 mm Hg, respectively); (2) a specific bradycardiac agent, alindidine* (N-allyl derivative of clonidine; 20 mg IV over 5 minutes possibly followed by a second dose of 20 mg [same criteria as for atenolol]); (3) matching placebo (again one or two intravenous injections according to the same criteria). The acute intravenous administration was followed by an oral regimen for 10 to 14 days (atenolol 25 to 50 mg b.i.d., alindidine 20 to 40 mg t.i.d., or placebo), of which the first dose was given immediately after the intravenous dose if heart rate and systolic blood pressure did not decrease below 60 beats per minute and 90 mm Hg, respectively; otherwise, the first oral dose was postponed for 8 to 12 hours. The study protocol allowed the use of intravenous or oral antiarrhythmic medication at the discretion of the responsible clinician. No specific criteria were formulated, nor which type of drug had to be used. No routine prophylactic use of antiarrhythmic drugs was recommended (eg, for runs of nonsustained ventricular tachycardia).

All patients gave informed consent to the protocol, which was approved by the Ethical Committee of the University of Leuven.

Holter Analysis

Two bipolar derivations were recorded. The same equipment was used in all centers and in all patients (Biomedical Systems, St Louis, Mo). The tapes were analyzed by a Century device. Full-disclosure printouts of the tapes were manually validated by four cardiologists, both for arrhythmias and for ST-segment interpretation (measured 60 milliseconds after the J point). ST-segment changes of >0.1 mV toward baseline that occurred over a time period of 15 minutes or less and that remained stable for another 30 minutes were considered possible markers for reperfusion.

Other Investigations

In addition to the Holter recordings during the first 24 hours reported here, enzymatic infarct size, coronary angiography and left ventriculography (with calculation of ejection fraction), scintigraphic left ventriculography, and exercise testing were performed within 10 to 14 days in all patients. The methodologies used for these additional investigations have been described previously.7,9,10 the study data form, which had to be filled out by the responsible clinician, also asked for the presence of major arrhythmias (sustained VT and VF) during the hospital stay.

Follow-up

The end point of this substudy was a comparison of the incidence of bradyarrhythmias and tachyarrhythmias within the three treatment groups during the first day. In addition, we wanted to evaluate whether arrhythmias documented during the first 24 hours were correlated to arrhythmic events or outcome later during the hospital stay. Moreover, since ST-segment normalization and accelerated idioventricular rhythms (AIVR) might predict the presence of reperfusion, we wanted to investigate in which percentage of cases these signs were detectable on Holter recording and whether they were correlated with the angiographic findings.

Definitions

Ventricular or supraventricular premature beats (VPB and SPB) were defined as being >20% premature and wide (or not, respectively) by more than 25% in either or both Holter channels. VT was defined as three or more consecutive VPBs at a rate of ≥120 beats per minute. It was considered sustained if it lasted more than 30 seconds or required DC cardioversion because of hemodynamic collapse. Accelerated idioventricular rhythm was defined as three or more consecutive VPBs at a rate of ≤120 beats per minute.

Statistical Methods

As pointed out in our previous report,7 the goal of the study was to investigate how β-blockers might be beneficial when used early during myocardial infarction, the primary end points being global and regional left ventricular function and infarct size. The arrhythmia evaluation was added as a secondary end point. Every patient was prospectively planned to have a Holter recording as part of the original study protocol, and all patients with analyzable Holter recordings are part of this study. The sample size, however, was calculated on the basis of the expected treatment effect on the primary end points (ejection fraction), based on three treatment groups (power, 80%; α=.05).

Given our data and assuming expected treatment benefits from previous studies with β-blockers of 30%,4,5,11–14 and for an α=.05, we calculated the power of our Holter substudy for some variables (using a categorized approach and three treatment groups): it is 83% for runs of nonsustained VT, 24% for runs of AIVR, and 27% for the average number of VPBs per hour. To have an 80% power for the last two variables, the treatment effect had to be 60%; hence, reductions or increases of the number of AIVR or of VPBs <60% may have been unnoticed by our analysis.

Continuous data are presented as mean±SD if normally distributed; otherwise, the median and 90% range are reported. For categorical data, the three treatment groups were compared by an extension of the Fisher’s Exact Test. For continuous measurements, a one-way ANOVA was performed if the (possibly transformed) data appeared to be normally distributed in each group. Normality was assessed by the Shapiro-Wilk test. If a normalizing transformation could not be found, the Kruskal-Wallis test was used. For correlation analysis of the ranks of variables, Spearman correlation coefficients were calculated. In all other cases, pairwise signifi-
TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Atenolol (n=83)</th>
<th>Alinidine (n=84)</th>
<th>Placebo (n=77)</th>
<th>All Holter Patients (n=244)</th>
<th>All Thrombolysed Patients (n=292)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59 (32-69)</td>
<td>56 (39-68)</td>
<td>57 (41-68)</td>
<td>57 (40-68)</td>
<td>58 (39-68)</td>
<td>NS</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>68 (82)</td>
<td>73 (87)</td>
<td>67 (87)</td>
<td>208 (85)</td>
<td>246 (84)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous myocardial infarction, n (%)</td>
<td>3 (4)</td>
<td>2 (2)</td>
<td>3 (4)</td>
<td>8 (3)</td>
<td>8 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>Site of present infarction, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>24 (29)</td>
<td>29 (35)</td>
<td>24 (31)</td>
<td>77 (32)</td>
<td>95 (33)</td>
<td>NS</td>
</tr>
<tr>
<td>Inferoposterior</td>
<td>58 (70)</td>
<td>54 (64)</td>
<td>47 (61)</td>
<td>159 (65)</td>
<td>188 (64)</td>
<td>NS</td>
</tr>
<tr>
<td>Lateral</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>4 (5)</td>
<td>5 (2)</td>
<td>5 (2)</td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>2 (3)</td>
<td>3 (1)</td>
<td>4 (1)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>132 (100-170)</td>
<td>133 (100-170)</td>
<td>140 (100-180)</td>
<td>135 (100-170)</td>
<td>130 (100-170)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>80 (60-100)</td>
<td>80 (60-100)</td>
<td>80 (60-100)</td>
<td>80 (60-100)</td>
<td>80 (60-100)</td>
<td>NS</td>
</tr>
<tr>
<td>History of diabetes mellitus, n (%)</td>
<td>2 (2)</td>
<td>8 (10)</td>
<td>4 (5)</td>
<td>14 (6)</td>
<td>17 (6)</td>
<td>NS</td>
</tr>
<tr>
<td>Time from onset of pain to initiation of treatment, min</td>
<td>159 (88-285)</td>
<td>162 (70-274)</td>
<td>165 (50-315)</td>
<td>160 (75-300)</td>
<td>160 (80-305)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>74 (55-110)</td>
<td>72 (56-120)</td>
<td>75 (53-102)</td>
<td>74 (54-104)</td>
<td>73 (54-105)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum [K+]</td>
<td>4 (3.3-5.2)</td>
<td>4 (3.4-5.1)</td>
<td>4 (3.1-4.8)</td>
<td>4 (3.2-5.2)</td>
<td>4 (3.1-5.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Enzymatic infarct size*</td>
<td>530 (105-1192)</td>
<td>421 (72-1310)</td>
<td>546 (5-1540)</td>
<td>514 (60-1335)</td>
<td>527 (60-1434)</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>58 (31-77)</td>
<td>80.5 (37-79)</td>
<td>59.5 (41-80)</td>
<td>59 (35-77)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Holter recording time, h</td>
<td>23.8 (4-24)</td>
<td>23.9 (14-24)</td>
<td>23.8 (17-24)</td>
<td>23.8 (12-24)</td>
<td>...</td>
<td>NS</td>
</tr>
<tr>
<td>Antiarrhythmic drugs on day 1, n (%)</td>
<td>23 (27)</td>
<td>27 (33)</td>
<td>19 (25)</td>
<td>69 (28)</td>
<td>...</td>
<td>NS</td>
</tr>
<tr>
<td>Antiarrhythmic drugs after day 1, n (%)</td>
<td>12 (14)</td>
<td>9 (11)</td>
<td>11 (14)</td>
<td>32 (13)</td>
<td>...</td>
<td>NS</td>
</tr>
</tbody>
</table>

bpm indicates beats per minute. Values are median values (and 90% range) or numbers (percentages) of patients.

* Determined by the cumulative release into plasma of a-hydroxybutyrate dehydrogenase up to 72 hours after onset, expressed in units per liter.

cance tests combined with a Bonferroni correction were used. The nominal significance level was fixed at P<.05.

Results

Patient Characteristics

From June 1988 through December 1990, 244 patients with an acute myocardial infarction underwent 24-hour Holter recording starting at the beginning of the administration of alteplase. In addition, 83 received atenolol, 84 alinidine, and 77 placebo. Table 1 lists their baseline characteristics: the three groups were similar with respect to age, sex distribution, incidence and site of previous infarction, systolic and diastolic blood pressures, incidence of diabetes mellitus, time interval between start of the pain and initiation of thrombolytic therapy, pulse rate and serum potassium concentration on admission, enzymatic extent of the present infarction, and ejection fraction (as measured on day 10 to 14). The mean ambulatory ECG recording time was similar in the three treatment groups (overall median of 23 hours and 48 minutes). The proportions of patients receiving antiarrhythmic drugs (mainly lidocaine) during the first 24 hours, or after day 1, were not statistically different. All but one patient, randomized to atenolol, received the study drug. Seventy-three percent of the patients in the atenolol group and 86% of the alinidine patients tolerated the full intravenous dose.

The 244 patients formed a subgroup of 292 patients described in a previous report on left ventricular function, infarct size, and clinical outcome among the three treatment groups.7 Dropouts from the Holter study were a result of technical failure, nonavailability of the recorder, or death early after randomization (17 in the atenolol arm, 14 in the alinidine arm, and 17 in the placebo group). Table 1 also lists the characteristics of the 292 original patients: it is clear that the Holter subgroup did not differ statistically from the original population.

Basic Electrophysiological Parameters in the Three Treatment Groups

Table 2 shows the main pharmacological effect of the administration of the study drugs alinidine and atenolol: a significant decrease in heart rate was found in the atenolol group (66.1 beats per minute; P=.0001) and in the alinidine group (69.4 beats per minute; P=.0001) compared with the placebo group (76.6 beats per minute). In 137 of the 244 patients (56%), the minimal heart rate dropped below 50 beats per minute during the time of Holter recording. There was a statistically higher incidence of bradycardia in the atenolol than in the alinidine patients, but it did not reach statistical significance.
### Table 2. Basic Rhythm Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Atenolol (n=83)</th>
<th>Alinidine (n=84)</th>
<th>Placebo (n=77)</th>
<th>All Holter Patients (n=244)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average heart rate, bpm</td>
<td>66 (51-80)</td>
<td>68 (54-96)</td>
<td>75 (59-96)</td>
<td>69 (53-95)</td>
<td>.0001*</td>
</tr>
<tr>
<td>Atrial fibrillation (permanent or paroxysmal)</td>
<td>7 (8.4)</td>
<td>0 (0)</td>
<td>3 (3.9)</td>
<td>10 (4.1)</td>
<td>.01†</td>
</tr>
<tr>
<td>Bradycardia (heart rate &lt;50 bpm)</td>
<td>59 (71.1)</td>
<td>48 (57.1)</td>
<td>30 (39.0)</td>
<td>137 (56.0)</td>
<td>.0002‡</td>
</tr>
<tr>
<td>Pauses of ≥3 s</td>
<td>11 (13.3)</td>
<td>8 (9.5)</td>
<td>9 (11.7)</td>
<td>28 (11.5)</td>
<td>NS</td>
</tr>
<tr>
<td>First-degree AV block</td>
<td>1 (1.2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Second-degree AV block</td>
<td>1 (1.2)</td>
<td>1 (1.2)</td>
<td>1 (1.3)</td>
<td>3 (1.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Third-degree AV block</td>
<td>1 (1.2)</td>
<td>0 (0)</td>
<td>1 (1.3)</td>
<td>1 (0.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Intraventricular conduction disturbance</td>
<td>2 (2.4)</td>
<td>3 (3.6)</td>
<td>3 (3.9)</td>
<td>8 (3.3)</td>
<td>NS</td>
</tr>
</tbody>
</table>

bpm indicates beats per minute; AV, atrioventricular. Values are median values (and 90% range) or numbers (percentages) of patients.  
*Atenolol-placebo, .0001; alinidine-placebo, .0001; atenolol-alinidine, NS.  
†Atenolol-placebo, NS; alinidine-placebo, NS (P=.11); atenolol-alinidine, .007.  
‡Atenolol-placebo, <.0001; alinidine-placebo, .03; atenolol-alinidine, NS (P=.08).

(P=.08). However, the proportion of patients with sinus arrest causing pauses of 3 seconds or more (eventually with junctional escape) was not different among the three groups. The incidence of atrioventricular nodal block was also similar in the three treatment groups (Table 2). The incidence of intraventricular conduction disturbances, defined as a QRS duration of ≥120 milliseconds, was comparable for the three treatment groups (overall mean was 3.3%; Table 2).

Ninety-six percent of the patients remained in a sinus basic rhythm throughout the first day after admission; the remaining 4% had atrial fibrillation during the whole first 24 hours or had self-terminating bouts of this arrhythmia. The prevalence of atrial fibrillation was significantly lower in the alinidine group than in the atenolol patients (P=.007), but the difference did not reach statistical significance compared with the placebo group (P=.11). The enzymatic infarct size and ejection fraction were not significantly different between patients with atrial fibrillation and patients with sinus rhythm. Major ventricular arrhythmias (sustained VT and VF) or death within the first 14 days occurred in 2 of the 10 patients with atrial fibrillation (20%) and in 6.4% of the patients with sinus rhythm (15 of 234). This difference was not statistically significant.

### Ventricular and Supraventricular Premature Beats

The median of the VPB frequency per hour was 8.7 per hour for the 244 patients, with a 90% range of 0.1 to 92 VPB per hour (Table 3). There was no difference among the three treatment groups, nor was there any difference in the number of ventricular couplets. The frequency distribution for VPB is listed in Table 3: half of the patients had a mean number of <10 VPBs per hour. Table 3 also shows the mean number and the frequency distribution of SPBs in the different treatment groups and in the whole population: again, no significant differences were present.

### Nonsustained Ventricular Tachycardia

Of the 244 patients, 184 (75%) had at least one episode of nonsustained VT on their Holter recordings;
the incidence was similar in the three subgroups (Table 4). Among the patients who had runs, the number ranged from 1 to 78 (90% interval) over a 24-hour period (overall median was 7). The number of runs of nonsustained VT did not differ statistically among the treatment groups either when calculated for all (244) patients or only for the 184 patients with at least one run. The median length and the rate of the longest run of nonsustained VT were 9 beats (90% range, 3 to 29) and 150 beats per minute (90% range, 120 to 200) for the whole group; they were similar in all subgroups. The frequency distribution of the VT rates is also listed in Table 4: although the majority of VTs are faster than 150 beats per minute, only 6% of patients had runs that were faster than 200 beats per minute. There was a trend toward fewer runs with a rate of >200 beats per minute in the atenolol group, but it did not reach significance ($P = .09$). Self-limiting episodes of polymorphic VT were recorded in 4.5% of patients.

**Accelerated Idioventricular Rhythm**

Of the 244 patients, 174 (71.3%) had at least one episode of AIVR on their Holter recordings. There seems to be a trend toward a lower incidence of runs of AIVR in the placebo group, but this difference was not statistically significant ($P = .08$) (Table 5). Among the patients with at least one run, the median number of runs of AIVR was three over a 24-hour period (90% range, 1 to 65); it was similar for the three groups. The frequent competition with normal sinus rhythm (in at least 40% of cases) precluded an accurate determination of the length (in number of beats) or duration (in minutes) of the runs of AIVR. In half of the patients with AIVR, bouts of arrhythmia were present for more than 30 minutes (eventually in competition with sinus rhythm). Since there is frequent waxing and waning of the rate of AIVR, we determined the minimal rate of the longest run: it was 80 beats per minute for the whole group (90% range, 58 to 100) and was very similar in the three subgroups. The frequency distribution of the minimal rate of AIVR shows that the vast majority of episodes is slower than 100 beats per minute (93%; Table 5). Surprisingly, 5.3% of the broad-QRS tachycardias had runs with a rate of <120 beats per minute—the definition for AIVR—were reported to have a polymorphic appearance.

If the longest run of AIVR was associated with a concomitant ST-segment normalization of >0.1 mV

<table>
<thead>
<tr>
<th>Table 4. Nonsustained Ventricular Tachycardia</th>
</tr>
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<tbody>
<tr>
<td></td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Proportion of patients with the arrhythmia</td>
</tr>
<tr>
<td>Number of runs of nonsustained VT in patients with at least one run</td>
</tr>
<tr>
<td>Number of runs of nonsustained VT in all patients</td>
</tr>
<tr>
<td>Longest run of nonsustained VT</td>
</tr>
<tr>
<td>Number of beats</td>
</tr>
<tr>
<td>Rate, bpm</td>
</tr>
<tr>
<td>120-149, n (%)</td>
</tr>
<tr>
<td>150-199, n (%)</td>
</tr>
<tr>
<td>≥200, n (%)</td>
</tr>
<tr>
<td>Polymorphic, n (%)</td>
</tr>
</tbody>
</table>

VT indicates ventricular tachycardia; bpm, beats per minute. Values are median values (and 90% range) or numbers (percentages) of patients.

<table>
<thead>
<tr>
<th>Table 5. Accelerated Idioventricular Rhythm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Proportion of patients with the arrhythmia</td>
</tr>
<tr>
<td>Number of runs of AIVR in patients with at least one run</td>
</tr>
<tr>
<td>Longest run of AIVR</td>
</tr>
<tr>
<td>Minimal rate, bpm</td>
</tr>
<tr>
<td>&lt;100, n (%)</td>
</tr>
<tr>
<td>100-120, n (%)</td>
</tr>
<tr>
<td>Polymorphic, n (%)</td>
</tr>
<tr>
<td>Presumed reperfusion*, n (%)</td>
</tr>
</tbody>
</table>

AIVR indicates accelerated idioventricular rhythm; bpm, beats per minute. Values are median values (and 90% range) or numbers (percentages) of patients.

*Reperfusion was assumed if the longest run of AIVR was associated with a concomitant ST-segment normalization of >0.1 mV over 15 minutes in at least one of the two Holter channels.
over 15 minutes in at least one of the two Holter channels, this was considered a noninvasive marker of reperfusion. By this criterion, the time of reperfusion could be tentatively assigned in 68 of the 244 thrombolysed patients (28%). There was no statistical difference in the proportion of patients presenting this combined phenomenon among the three treatment groups. The median time period from start of treatment/Holter recording to the ECG reperfusion event was 81 minutes (90% range, 10 to 470 minutes), and about 75% occurred during the 3-hour alteplase infusion; the timing was not statistically different among the three treatment groups.

**Sustained Ventricular Tachycardia and Ventricular Fibrillation**

Sustained VT was recorded in five patients (2%): two receiving atenolol, one receiving alinidine, and two on placebo (not significant). Three of the five episodes started at the end of the preceding T wave and two late after it. The average time period between start of treatment and occurrence of the VT was 6 hours; the earliest episode occurred after >2.5 hours. All episodes were monomorphic, and the morphology of the first beat always was similar to that of the consecutive beats. The rate of the five tachycardias was 170, 150, 145, 135, and 126 beats per minute; the 135–beat per minute episode showed waxing and waning of the rate; the average duration was 6 minutes 52 seconds (the shortest episode lasted 35 seconds), indicating that these VTs were hemodynamically well tolerated. Only one tachycardia required DC cardioversion (after about 13 minutes of tachycardia). None of the patients with early VT developed a life-threatening arrhythmia later during the hospital stay, and none of them died during this time period. Six patients (two from each group) developed VT after the first day; none of them had shown major rhythm disturbances during the first 24 hours.

Seven episodes of VF were recorded in six patients (2.5%): two in atenolol patients, one in the alinidine group, and three in the placebo group (one patient with two episodes) (not significant). All episodes required electrical defibrillation. Six of the seven episodes developed within the first hour after start of treatment and one after 2.5 hours. Five of the seven episodes started with a VPB on or shortly after the preceding T wave. One of the VF episodes that started late after the T wave first had a slower rate (polymorphic VT; about 220 beats per minute) that degenerated into VF; also, after DC shock, there was first a 15-second slow polymorphic VT (about 100 beats per minute) before resumption of normal sinus rhythm. In three patients, both VF (occurring early) and VT (occurring later on day 1) were present. None of the patients with early VF developed a major arrhythmia after day 1, and none of them died during the hospital stay. One patient of the placebo group developed VF and died after the first day; he had not had major rhythm disturbances during the first 24 hours.

The combined incidence of major ventricular arrhythmias (sustained VT and VF) during the hospital stay was 6.2%. The mortality rate during this time period was <1% (2 of 244).

**Arrhythmia Incidence Related to Enzymatic Infarct Size**

There was a weak but significant correlation between the infarct size (determined enzymatically) and the average number of VPBs per hour (r = .38) and number of runs of nonsustained VT (r = .40) (P < .0001 for both). There was no correlation between infarct size and the total number of runs of AIVR. Patients developing sustained VT or VF within the first 24 hours had significantly larger infarctions (median calculated cumulative release into plasma of α-hydroxybutyrate dehydrogenase up to 72 hours was 1251.5 versus 586.5 U/L; P = .02); the same trended to be true for patients developing these arrhythmias or dying after the first day (773.5 versus 600.6 U/L; P = .19).

**Arrhythmia Incidence Related to Coronary Patency Determined Angiographically After 10 to 14 Days**

Of the 244 Holter patients, 225 underwent angiography after 10 to 14 days. All patients were heparinized between the day of admission and the day of angiography. Table 6 lists the arrhythmia incidence and frequency during the first 24 hours according to the patency state of the infarct-related artery stratified according to the TIMI classification. There were no differences in the incidence or in the frequency of
VPBs, runs of nonsustained VT, or runs of AIVR between patients with an open or occluded infarct-related artery.

Three of the six patients who had VF during the first 24 hours underwent coronary angiography; all three had an occluded infarct-related vessel. In contrast, of the five patients who had VT during the first 24 hours, three had angiography, and only one had an occluded infarct-related vessel; this patient also had VF 1 hour before the episode of VT. Interestingly, all six patients who developed VT after the first day had an open vessel. No angiogram could be made in the single patient who had VF and died after the first day.

Applying our noninvasive criteria to assess the time of reperfusion (see above), 31% of the TIMI class 2 or 3 patients fulfilled the criteria for “presumed reperfusion” during or immediately after thrombolytic therapy. Remarkably, 21% of the patients with an occluded vessel at angiography (performed between days 10 and 14) were also noninvasively diagnosed as having “presumed reperfusion.”

Discussion
Effects of Atenolol and Alinidine on the Incidence of Arrhythmias During Acute Myocardial Infarction Treated With Thrombolysis

This study shows that effective drug action is exerted by atenolol and alinidine, as indicated by the significant bradycardiac effect in the active treatment groups. However, we did not find different incidences of ventricular arrhythmias during the first 24 hours or during the first 14 days after the acute event compared with placebo. Hence, our data do not support the hypothesis, raised mainly after the MIAMI and ISIS trials, that β-blockers might reduce the incidence of fatal arrhythmias when used in conjunction with thrombolytic therapy.

The ISIS-1 and the MIAMI investigators had studied the effect of β-blocker administration during the acute phase of myocardial infarction in patients not treated with thrombolytic agents. In ISIS-1, this intervention reduced mortality from VF within the first 2 days; for the 5778 MIAMI patients, it led to a (nonsignificant) reduction of late VF (between days 6 and 15), although there was no difference in the incidence of VF during the first 5 days. The antiarrhythmic potency of β-blockers without thrombolysis was further evaluated in Holter studies by many authors.11-13,16,17 It is clear that the early use of β-blockers in the absence of thrombolytic therapy significantly reduces nonfatal and fatal ventricular arrhythmias late after acute myocardial infarction, and it is likely that this adjunctive therapy also reduces arrhythmias during the first 24 hours.

Our data do not show any antiarrhythmic effect of β-blockers in thrombolysed patients, either for early events (as analyzed by Holter recordings during the first 24 hours) or for late events (such as clinically reported VT and VF during the hospital phase). The observation that the need for antiarrhythmic drug treatment was the same in the three groups (both on day 1 and later) underscores this conclusion. Our results are in agreement with those of Hohnloser et al10 (reporting on the first Holter study in patients treated with β-blockers and thrombolysis) and of those of the TIMI II-B trial.6 However, some limitations may have precluded the detection of drug effects on arrhythmia incidence, not only in our study but probably also in others. First, our population was a low-risk group (eg, with a rather low proportion of anterior myocardial infarctions) because of possible randomization to negative inotropic β-blockers and the age limit of 70 years. Second, the sample size for the three treatment groups was based on calculations for the primary end points of the study, LV function and infarct size.7 Hence, the power for some of the comparisons in this arrhythmia substudy may be low. Reductions or increases of 30% in the incidence of nonsustained VT could have been detected with a power of 83%, but to detect changes in AIVR or VPB incidence with a power of at least 80%, for instance, treatment effects had to be larger than 60% (ie, the incidence of these arrhythmias had to be more than halved or doubled). Moreover, treatment effects on the less frequently occurring arrhythmias (particularly sustained VT and VF) are even more likely to have been unnoticed by our study. It is important to note that this limitation applies to all Holter studies published so far concerning the use of β-blockers in acute myocardial infarction. A possible explanation for the absence of any major drug effect could be that the antiarrhythmic effect of β-blockers in nonthrombolysed patients is the result of their anti-ischemic action but that this beneficial effect is blunted by the reduction in infarct size caused by reperfusion. This hypothesis is supported by our data on infarct size and left ventricular function in the same patients: atenolol did not result in a significant improvement of these parameters compared with thrombolysis alone. Interestingly, Norris et al12 reported that the occurrence of VF was significantly reduced during the first 27 hours of acute myocardial infarction by the non-β1-selective blocker propranolol in nonthrombolyzed patients. Since no continuous ECG monitoring was performed, these authors had no data on the incidence of VPBs, runs of VT, or runs of AIVR. However, their preliminary findings warrant further investigation as to whether nonselective β-blockers might have an antiarrhythmic potential during the early course of acute myocardial infarction, in contrast to the more frequently studied selective agents.

Our study did not show any significant effect of atenolol on the prevention of supraventricular arrhythmias. This is in contrast with the reported reduction in the incidence of atrial fibrillation in two previous studies,14,20 but it confirms the findings of Norris et al19 that propranolol did not reduce the incidence of atrial fibrillation.

Specific bradycardiac agents like alinidine block the hyperpolarization-activated nonspecific cation current, i, partly responsible for the spontaneous diastolic depolarizations in nodal, atrial, and proximal His bundle cells. Antiarrhythmic actions have been attributed to alinidine in regard to focal arrhythmias originating in these cells. However, antiarrhythmic effects on ischemia-related arrhythmias, caused largely by reentrant mechanisms, are very unlikely.21 Therefore, no a priori effect on arrhythmic events was expected in this arm of our trial. Surprisingly, we found a lower incidence of atrial fibrillation in the alinidine patients. Although we have no basic electrophysiological explanation for this finding, it warrants further study. Moreover, alinidine-
treated patients tended to have smaller infarcts compared with placebo and atenolol patients.7

The trend toward a higher incidence of AIVR in the active treatment groups can be explained by the bradycardiac effect, which increases the probability of AIVR to break through the sinus rhythm, and does not appear to be the expression of a proarrhythmic effect. The same observation was made in the TIMI II-B trial.8 Remarkably, the rate of the AIVR runs was not changed by β-blocker therapy or by alimidine. These reperfusion arrhythmias are thought to be generated by delayed afterdepolarizations in calcium-overloaded cells. Sympathetic stimuli are known to lead to an increased calcium load of the cells (eg, by an increased calcium current). The lack of effect of atenolol may be an indicator that ischemia in itself is such a strong factor leading to calcium overload in partially depolarized tissue that the excess effect of β-stimulation is negligible.

Bradycardia is a frequent complication of acute myocardial infarction, especially when located inferiorly. It can be induced by spontaneous or pharmacological reperfusion,23 or it can result from a reflex increase in vagal over sympathetic tone. Neither alimidine nor atenolol proved to be associated with an increased risk of pauses caused by sinus arrest or atrioventricular block. The high proportion of inferior myocardial infarctions, however, may have blunted real drug side effects in our series, being more obvious in anterior infarctions. Bradycardiac complications were reported in some6,19 but not all previous β-blocker studies.13

General Remarks on Arrhythmias During Acute Myocardial Infarction

To the best of our knowledge, this study is the largest series of Holter recordings during evolving acute myocardial infarction. Since there were no statistical differences in the incidence of arrhythmias among the treatment groups, some general conclusions can be drawn. We must, however, take into consideration that 28% and 13% of the patients received antiarrhythmic drugs (mainly lidocaine) during the first 24 hours and after day 1, respectively, although no routine prophylactic use (eg, for nonsustained VT) was recommended in the study protocol. This proportion is comparable to observations in analogous trials.4,6,11,23

The incidence of VF is low in our series: 2.5% during the first day and 2.9% within the first 14 days. In previous studies (albeit without the use of Holter recording), it was reported to occur in 2.3% to 5.3% of patients during the first day11,24 and in 2.5% to 15% of patients during the first 2 weeks.22,25–28 The incidence is always lower in thrombolysed patients (eg, in the ISAM study, 4.3% versus 5.3% on day 134; in the ISIS-2 study, 4.4% versus 5.0% within 10 days23), but the very low incidence in our series may also be related to (1) the low-risk profile of our patients as discussed above and (2) a delayed start of the recording, missing the first 2.5 hours of chest pain.3

The incidence of nonsustained VT (75%) or of AIVR (71%) in our series is much higher than the previously reported data of trials without Holter recording24 or with recording during a limited time period,28 since the benign hemodynamic effect of these arrhythmias may leave them unnoticed. Our data agree well with the calculated figures in some smaller studies using Holter: 70% to 90% for nonsustained VT22,27,30 and 77% to 90% for AIVR.22,27,30,31

A noteworthy observation is that none of the patients with major arrhythmias during the first day had malignant recurrences during the ensuing 2 weeks (and vice versa). The limited size of our study and the low incidence of major events in our low-risk patients, however, may have masked such a relation. The infarcts of the patients with early major arrhythmias were significantly larger than those of patients not showing arrhythmias, suggesting a poorer long-term outcome. Unfortunately, we have no long-term follow-up data.

Ventricular Arrhythmias According to Coronary Patency

Many authors have shown that all types of ventricular arrhythmias are more frequent in patients with reperfusion than in those with a permanently occluded artery.18,29–31 We did not find such a difference. This may be because of delayed time of angiography: late spontaneous reocclusion and late reperfusion (an unknown percentage at present) may have weakened the relation. Nevertheless, some interesting conclusions can be drawn. We found a remarkable contrast in patency rate between patients with early or late VF (all examined patients had an occluded artery) and sustained VT (only one of nine did not show reperfusion, but this patient also developed VF). Moreover, most VF episodes occurred within the first hour after start of treatment and started with an R-on-T phenomenon, underscoring the importance of massive electrical heterogeneity induced by acute ischemia in larger regions of the myocardium. In contrast, sustained VT always developed more than 2.5 hours after start of treatment (in fact, half of them even between day 2 and day 10), and they were always monomorphic, implying a specific reentrant circuit with stable electrophysiological characteristics in the border zone between viable and infarcted tissue.

It has been shown that the type of ventricular arrhythmia is not a very useful tool to predict coronary reperfusion noninvasively but that the presence of longer-lasting runs of AIVR can be a noninvasive diagnostic marker for reperfusion.22,27 Moreover, Zehender et al22 and Shah et al52 showed that sudden ST-segment changes during Holter monitoring could reliably predict the time of reperfusion, whereas patients without reperfusion infrequently show such a sudden ST-segment change.22,52,53 Since runs of AIVR are frequently interrupted by sinus beats, we felt that the classification of “long runs of AIVR” was too unreliable to be used with confidence. We therefore combined the presence of the “longest run” with “ST-segment normalization” as a tentative double criterion to assess reperfusion.15

Our results from this much larger database confirm the findings of Zehender et al: 63 of the 225 patients who underwent coronary angiography (28%) showed an ST-segment normalization of >0.1 mV over 15 minutes combined with the occurrence of a long run (or of a long period with multiple runs) of AIVR. Eighty-one percent of them had an open infarct-related coronary artery at late angiography. Thus, the specificity of this double criterion for reperfusion is 79% and the sensitivity 31%. However, one must take into account a reocclusion rate
of ≈15% within the first week. Hence, if coronary patency had been assessed early, the specificity and sensitivity could have been much better. These results indicate that continuous ECG recording is a valuable and specific (albeit not very sensitive) noninvasive tool to predict the efficiency of thrombolytic therapy.

Summarizing, we may conclude that (1) our data do not support the hypothesis that β-blockers or bradycardic agents might reduce the incidence of arrhythmias when used in conjunction with thrombolytic therapy, with the possible exception of atrial patency had presence of marker for a larger infarct; (2) we could not detect a relation between malignant arrhythmias on day 1 and recurrences within the following 2 weeks; and (5) the presence of ST-segment normalization combined with the occurrence of a long run of AIVR predicts coronary reperfusion.

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Significance of arrhythmias during the first 24 hours of acute myocardial infarction treated with alteplase and effect of early administration of a beta-blocker or a bradycardiac agent on their incidence.

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