ABSTRACT Three hundred and one patients who had been hospitalized for acute myocardial infarction, were less than 70 years old, were in sinus rhythm, and did not have complete bundle branch block were stratified before discharge according to age, size of infarction, and type of ventricular arrhythmias as determined on a 6 hr electrocardiogram (ECG). They were thereafter randomly assigned to double-blind treatment with 100 mg bid metoprolol or placebo. Repeat 6 hr ECGs were recorded 3 days and 1, 6, and 12 months after treatment had begun. In the placebo group there was a significant increase in the proportion of patients with complex premature ventricular complexes (PVCs) (i.e., multiform, paired and R-on-T PVCs, or ventricular tachycardia) as well as increased numbers of PVCs in the patients during the follow-up. In contrast, an initial decrease in the number of PVCs (p < .001) was found in the metoprolol group, whereas the complexity of PVCs was constant in those patients who continued on metoprolol therapy throughout the follow-up period. We conclude that the increase in complexity and number of PVCs that is part of the natural clinical course after myocardial infarction is counteracted by long-term treatment with metoprolol.

*Circulation* 69, No. 6, 1129–1134, 1984.

MOST DEATHS after acute myocardial infarction are due to ventricular fibrillation.1 Patients who have suffered myocardial infarction show increasing numbers of ventricular arrhythmias as well as increased complexity of these arrhythmias with time.2–4 Unsuccessful attempts have been made to reduce mortality by the prescription of antiarrhythmic drugs such as procainamide,5 phenytoin,6 disopyramide,7, 8 mexiletine,9 and tocainide.10 In contrast, three studies completed in the middle 1970s showed a reduction in sudden death rates among postmyocardial infarction patients treated with the β-adrenoceptor blockers alprenolol11, 12 and practo-
lol.13 These results have been confirmed in three large, well-controlled interventional trials with timolol,14 metoprolol,15 and propranolol.16 Today it is evident that both total mortality and sudden death rate can be reduced by intervention with some β-adrenoceptor antagonists in the postinfarction phase. There are, however, still unresolved questions concerning this therapy, including the actual beneficial mechanisms, identification of patients in whom treatment is beneficial, and the necessary duration of treatment.

The early studies with alprenolol and practolol11–13 and the information on the natural course and prognostic value of predischarge premature ventricular complexes (PVCs) in patients with myocardial infarction2–4, 17–20 formed the basis for this study. The study was designed to evaluate the influence of long-term postinfarction treatment with metoprolol on ventricular arrhythmias. This report deals with the 1 year follow-up data.

**Material and methods**

Between May 1976 and December 1980 301 consecutive patients who had suffered an acute myocardial infarction were entered in a study of double-blind treatment with 100 mg bid metoprolol (120 men and 34 women) and placebo (122 men and 25 women). The first 221 patients had been in the Coronary Care Unit (CCU) at the Serafimer Hospital in Stockholm from May 1976 until the hospital closed in December 1979. In 1980 80 consecutive patients were included from the CCU at Danderyd's Hospital.

The following were the inclusion criteria for the study. (1) Patients were required to be less than 70 years old and to be living in the catchment areas. (2) Admission to the CCU had to be within 48 hr of onset of symptoms and development of acute myocardial infarction according to the World Health Organization criteria.21 (3) Patients had to be in sinus rhythm without
complete bundle branch block. (4) The following were required to be absent: systolic blood pressure less than 100 mm Hg, severe cardiac failure that did not respond to conventional treatment with digitalis and diuretics, intermittent claudication, bronchial asthma, and apparent need for β-adrenoceptor blockade.

Four days before discharge from the hospital a 6 hr electrocardiogram\(^2\) with telemetry was recorded on paper (at 2:00 to 5:00 A.M. and 9:30 A.M. to 12:30 P.M.). After this investigation the patients were stratified according to age (less than 65 years or 65 to 69 years), estimated size of infarction (maximum thermostable lactate dehydrogenase <20 or ≥20 μkat/liter), and type of ventricular arrhythmias (six groups: no PVCs, uniform PVCs, multiform PVCs [i.e., initial and mean axis of the QRS complex and the T-wave differed between two PVCs in one channel of the recording], R-on-T PVCs, or ventricular tachycardia [i.e., runs of ≥3 PVCs of rate >100 beats/min]).

The patients were randomly assigned to receive double-blind treatment with metoprolol (100 mg bid) or placebo. All tablets were identical in shape and color. After 3 days of therapy (i.e., the day before discharge) another 6 hr ECG with telemetry was recorded on paper. Long-term follow-up ECGs for the same 6 hr periods mentioned above were repeated after 1, 6, and 12 months of therapy. In the first 170 patients the 6 and 12 month recordings were made, by telemetry on paper, while the patients were in the hospital. According to changes in routine due to the closing of the Serafimer Hospital, the remaining 6 and 12 month ECGs as well as all 1 month recordings were obtained from ambulatory patients with an Oxford Medilog 1 tape recorder (two channels). The tapes were manually evaluated by specially trained nurses who used the Oxford Medilog analyzing system. In the evaluation of ventricular arrhythmias we analyzed data (1) from patients still on study treatment after 12 months ("on drug 12 months") and (2) according to initial drug allocation irrespective of future therapy ("intention to treat"). Both total number of PVCs/registration and complexity of PVCs were evaluated. Multiform, paired, and R-on-T PVCs and ventricular tachycardias have been denoted complex PVCs. To further investigate the pharmacologic effect of the treatment, intragroup differences in PVC incidence were evaluated in patients on drug 12 months. More than 75% differences in mean hourly PVC incidence in patients with more than one PVC/hour were considered relevant.

Clinical investigations were performed and blood samples were drawn for determination of standard biochemistry 1, 3, 6, and 12 months after myocardial infarction. The total follow-up period comprises 3 years of double-blind treatment.

All patients gave their informed consent to participate in the study, which was approved by the Ethical Committee at the Serafimer Hospital in Stockholm.

In the statistical analyses the chi-square test and Wilcoxon matched-pairs test\(^2\) were used. A p value less than .05 was regarded as indicative of a significant difference. Results are mean ± SD. The data were analyzed without breaking the study code for individual patients.

**Results**

Clinical characteristics of the entire study population are given in table 1. No significant differences between the groups were found for any variable. During the 1 year follow-up 26 and 28 patients in the placebo and the metoprolol groups, respectively, were withdrawn due to side effects (table 2). Withdrawal due to uncontrolled angina tended to be more common in the placebo group, whereas withdrawal due to cardi-decompensation tended to be more common in the metoprolol group, although no differences were significant. Antiarrhythmic drugs were used in a few cases, mainly to prevent episodes of atrial fibrillation.

Twenty-six patients died (table 3) and 28 nonfatal reinfarctions (3 patients with 2 reinfarctions) were registered during the first year in the study patients. One hundred nine and 117 surviving patients in the placebo and metoprolol groups, respectively, were still on the study treatment after 12 months. Of the 109 placebo-treated patients, eight, one, and three had nonanalyzable ECGs at the 1, 6, and 12 month recordings, respec-

| TABLE 1 |
|------------------|------------------|
| Characteristics of patients |
| Variables | M (n = 154) | P (n = 147) |
| Age (yr) | 60.1 ± 6.7 | 59.2 ± 7.2 |
| LD<sub>max</sub> (μkat/l) | 19.8 ± 14.0 | 19.6 ± 13.7 |
| Heart volume (ml/m<sup>2</sup>) | 471 ± 89 | 470 ± 88 |
| Site of infarction (%) | | |
| Anterior | 44 | 51 |
| Inferior | 38 | 31 |
| Unknown | 18 | 18 |
| VF in the CCU (%) | 3.2 | 2.7 |
| VT in the CCU (%) | 36.4 | 45.9 |
| Pulmonary congestion in CCU (%) | 64.7 | 66.7 |
| Complex PVCs at randomization (%) | 38 | 33 |

| TABLE 2 |
|------------------|------------------|
| Reasons for patient withdrawal during the 12 month follow-up |
| Attributed cause | P | M |
| Uncontrolled angina | 11 | 4 |
| Cardiac decompensation | 3 | 8 |
| Hypertension | 1 | |
| Arhythmia | 3 | 2 |
| Hypotension | 2 | |
| Mental discomfort | 2 | 5 |
| Claudication | 1 | 3 |
| Suspected allergic reactions | 1 | 1 |
| Asthma | 1 | |
| Impotence | 1 | 1 |
| Refusal | 3 | 1 |
| Total | 26 | 28 |

P = placebo group; M = metoprolol group.
respectively. In the metoprolol group the corresponding figures were 11, six, and one.

In patients on drug 12 months, 31% in the placebo group and 41% in the metoprolol group had complex PVCs before therapy. Compared with pretreatment findings there was a significant increase in the proportion of patients with complex PVCs after 6 (48%, p < .05) and 12 months (52%, p < .01) in the placebo group. In the metoprolol group the values obtained on the 1 (36%), 6 (40%), and 12 month (49%) recordings did not differ statistically from pretreatment values. The same pattern was found when the data were evaluated according to intention to treat (figures 1 and 2). Complex PVCs in the placebo group were registered in 33% before treatment, 40% after 3 days, 36% after 1 month, 52% after 6 months, and 50% after 12 months of treatment as compared with in 38%, 33%, 37%, 42%, and 51% (p < .05 compared with pretreatment) in the metoprolol group.

The total number of PVCs was significantly increased on the 1 month (p < .01), 6 month (p < .001), and 12 month (p < .001) ECGs in the placebo group (figure 3). In the metoprolol group there was a decrease in number of PVCs at 1 month as compared with before treatment (p < .001, figure 4). In the evaluation of the proportions of patients with individual changes in PVC incidence (patients on drug 12 months), the pattern in the two groups was significantly different.

### TABLE 3

<table>
<thead>
<tr>
<th></th>
<th>Deaths (n = 26)</th>
<th>Nonfatal reinfarction (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncomplex PVCs</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Complex PVCs</td>
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<td>9</td>
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<td>12</td>
<td>13</td>
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<tr>
<td>LD&lt;sub&gt;t&lt;/sub&gt; ≥ 20 µkat/l</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
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<td>5</td>
<td>21</td>
</tr>
<tr>
<td>LD&lt;sub&gt;t&lt;/sub&gt; ≥ 20 µkat/l + complex PVCs</td>
<td>21*</td>
<td>17</td>
</tr>
</tbody>
</table>

LD<sub>t</sub> = thermostable lactate dehydrogenase.

*<p < .05.

### FIGURE 2

Proportion of patients in the metoprolol group with complex PVCs. Patients on drug 12 months: n = 117, 106, 111, and 116 at the initial, 1, 6 and 12 month recordings, respectively. Intention to treat: n = 154, 133, 134, and 137 at the initial, 1, 6 and 12 month recordings, respectively. PT = pretreatment status; 3d = after 3 days treatment; 1 m = after 1 month treatment; 6 m = after 6 months treatment; 12 m = after 12 months treatment; M = metoprolol group; P = placebo group. *<p < .05.

### FIGURE 1

Proportion of patients in the placebo group with complex PVCs. The numbers of patients on drug 12 months were 109, 101, 108, and 106 at the initial, 1, 6, and 12 month recordings, respectively. The numbers of patients whose data were analyzed based on intention to treat were 147, 130, 130, and 126 at the initial, 1, 6, and 12 month recordings, respectively. PT = pretreatment status; 3d = after 3 days treatment; 1 m = after 1 month treatment; 6 m = after 6 months treatment; 12 m = after 12 months treatment. *<p < .05; **<p < .01.

### FIGURE 3

Mean number of PVCs in the placebo group during the 6 hr ECGs. The numbers of patients examined are as in figure 1. **<p < .01; ***<p < .001. Abbreviations are as in figure 1.

Vol. 69, No. 6, June 1984
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have shown that 36% to 42% of predischarge long-term ECG recordings contain complex PVCs,22,24-25 Furthermore, complex ventricular arrhythmias have been shown to carry independent prognostic weight for subsequent mortality and morbidity.2,4,17,18,20,26,27 The lack of influence on mortality of true antiarrhythmic agents,5-10 contrary to the beneficial effects of β-adrenoceptor antagonists,11-13 especially on sudden death rates, encouraged us to investigate the influence of metoprolol on ventricular arrhythmias in postmyocardial infarction patients. Although β-adrenoceptor blockers are regarded as less effective in suppressing chronic ventricular arrhythmias than the classic antiarrhythmic drugs,28 a reduction in PVC incidence after a single dose or short-term treatment has been reported in patients with ischemic heart disease during exercise testing and Holter monitoring.29-30 However, no previous study has evaluated the effect of long-term postinfarction treatment with β-blocking therapy on ventricular arrhythmias with the use of serial long-term ECG recordings during the first year after acute myocardial infarction.

The two methods used for detection of arrhythmias, telemetry on paper and tape-recorded ambulatory monitoring, may not be absolutely comparable. However, this should not have interfered with our results. Both groups were subjected to the same change in registration technique and the same arrhythmia profiles were observed during both the former and latter parts of the study. Also, manual and semiautomated evaluation methods for ECG analysis have previously been compared, and the diagnostic yields have been very similar.31 We have shown that the consistency is high when classifying two different ECG recordings into arrhythmic classes (i.e., complex and noncomplex PVCs in patients with ischemic heart disease).32 Similar results were recently reported for patients with aortic valve disease.33 In the evaluation of complex PVCs in a study of 72 hr recordings, Winkle et al.34 proposed that not only the presence but also the frequency of complex PVCs is of importance in identifying high-risk patients. However, during a shorter period of ECG recording, as in our study, the presence of complex PVCs may also yield information on frequency merely by appearing during this shorter observation time. We therefore consider the increasing proportion of patients with complex PVCs in the placebo group to be significant and of clinical relevance.

In the evaluation of antiarrhythmic efficacy in individual patients, the spontaneous variability of the arrhythmias must be considered. According to previous studies a 65% to 83% reduction in PVC frequency

(figure 5). There were significantly more patients in the placebo group with increased PVC incidence and fewer with decreased PVC incidence as compared with those in the metoprolol group during the first 6 months. The PVC pattern in either group was not influenced by the rare occasion when antiarrhythmic drugs were used.

Serum potassium levels during the follow-up varied between 4.1 ± 0.4 to 4.4 ± 0.4 mmol/liter and 4.2 ± 0.4 to 4.4 ± 0.4 mmol/liter in the placebo and metoprolol groups (NS), respectively.

Discussion

PVCs are common in patients in the postinfarction period. Congruent with our findings, previous reports

FIGURE 4. Mean number of PVCs in the metoprolol group during the 6 hr ECGs. The numbers of patients examined are as in figure 2. *** p < .01. Abbreviations are as in figure 1.

FIGURE 5. Proportion of patients on drug 12 months with increased, decreased, or unchanged PVC-incidence according to individual changes greater than 75% when PVC frequency was more than one per hour. Abbreviations are as in figure 1.

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during a 24 hr monitoring period is required in "stable patients" with frequent PVCs to establish a statistically significant effect of a treatment in an individual patient.\textsuperscript{35, 36} During shorter monitoring periods this figure is proposed to be even higher — 90%.\textsuperscript{37} In our study, in which monitoring periods and patients' characteristics differed from those in these earlier studies,\textsuperscript{35-37} we have used a change in PVC incidence of more than 75% in an individual patient to detect trends of changed PVC incidence in the study population. This does not necessarily mean a statistically significant reduction in number of PVCs in the individual patient according to definitions used by others,\textsuperscript{35-37} but an evaluation of group drug effect has previously been suggested to be adequate in determining drug effectiveness.\textsuperscript{38} By using the same hours of the day for the ECG evaluations we have tried to minimize the spontaneous variability that might occur during the day.\textsuperscript{36} In accordance with others,\textsuperscript{2-4, 39} we have interpreted the increased proportion of individual patients with a significant increase in PVC incidence in the placebo group to be an expression of the dynamic situation in the first year after a myocardial infarction.

Since the patient characteristics were similar in the two groups at inclusion and the potassium levels were similar and stable during the follow-up, we find the present data compatible with an antiarrhythmic action of long-term postinfarction therapy with metoprolol. The effect is not one of complete abolition of preexisting PVCs, but of reduction in the progression rate of both complexity and incidence of PVCs. The increase in ventricular arrhythmias found during the follow-up may therefore be interpreted as a marker of progression of ischemic heart disease. This assumption is supported by the high consistency of PVC frequency in healthy subjects older than 40 years of age.\textsuperscript{40}

In contrast to our findings, Roland et al.\textsuperscript{41} found no antiarrhythmic effect of propranolol or atenolol treatment in patients in the postinfarction period. However, this may be due to the low doses of \(\beta\)-adrenoceptor blocker used and to small patient numbers in combination with a short follow-up period, since in another study\textsuperscript{42} results similar to ours were found. The antiarrhythmic effects of \(\beta\)-adrenoceptor blockade have previously been demonstrated mainly in patients with supraventricular arrhythmias; in patients with chronic ventricular arrhythmias but without ischemic heart disease the efficacy for abolition of PVCs seems low compared with that of true class I antiarrhythmic drugs.\textsuperscript{28} In patients with ischemic heart disease, however, PVCs may have different underlying mechanisms and are probably often catecholamine depend-
procainamide following acute myocardial infarction. Circulation 47: 1204, 1973


Ventricular arrhythmias during the first year after acute myocardial infarction: influence of long-term treatment with metoprolol.
G Olsson and N Rehnqvist

Circulation. 1984;69:1129-1134
doi: 10.1161/01.CIR.69.6.1129

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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