therapeutic role in the management of oedema and hypertension in chronic renal disease.

We are grateful to the patients and volunteers who took part in this study and to Mr L. Doig and Mr M. McMahon, some of whose surgical patients were volunteers. We thank nursing staff and dietitians at the General Infirmary and St James's Hospital, Leeds; Professor D. B. Morgan and staff of the department of chemical pathology; and Miss K. Milner, Miss C. Pollard, and Miss A. Calderwood, who typed the manuscript.

References

(Accepted 27 October 1982)
also been shown in dogs pretreated with atenolol. The increase in circulating catecholamine values in patients with acute myocardial infarction is associated with an increase in the severity of cardiac arrhythmias, and in several non-randomised clinical studies intravenous beta-blocking agents were effective in the treatment of some of these arrhythmias. Randomised controlled trials, however, have shown no benefit in reducing ventricular arrhythmias in the first 24 hours after acute myocardial infarction. These disappointing results may be due to (a) the use of an initial oral dose of the trial drug leading to delay in achieving effective beta-blockade; (b) the inclusion of patients late after the onset of chest pain, at a time when ventricular arrhythmias have considerably decreased; and (c) the small numbers of patients actually included in the arrhythmia studies.

The main aim of this study was to assess the antiarrhythmic effect of an initial intravenous dose of atenolol followed by oral treatment, when administered early in the course of acute myocardial infarction when ventricular arrhythmias are prevalent. Other end points were morbidity and infarct size, of which a preliminary report has been published.

### Patients and methods

All patients admitted to the coronary care units of the John Radcliffe Hospital, Oxford, and to the Regional Cardiac Centre, Wythenshawe Hospital, Manchester, presenting with chest pain suggestive of acute myocardial infarction were eligible. 

Patients were considered unsuitable for beta-blockade if the heart rate was less than 60 beats/min, if the systolic blood pressure was below 90 mm Hg, if second-degree or third-degree heart block was present, or if heart failure requiring digoxin or more than 80 mg of frusemide was present. Patients already taking a beta-blocker on admission or requiring immediate beta-blockade were not eligible for study. Open data were blank due to faulty cable, and four others had less than three hours of recording, leaving 182 tapes for the final analysis. At entry an electrocardiogram was taken and patients allocated at random to a treatment or control group according to instructions kept in sealed envelopes. Patients randomised to treatment received 5 mg atenolol intravenously (slowly over five minutes) followed by an oral dose of 50 mg immediately and 12 hours later, and 100 mg daily from the second to tenth day. 

Data are presented as follows: all patients randomised (n = 182); patients who had electrocardiographic signs of acute myocardial infarction at entry (n = 121); and patients who were admitted with characteristic chest pain but without definite electrocardiographic changes (threatened infarction, n = 61). 

### Results

**Entry characteristics**—Of 182 patients randomised, 95 received atenolol and 87 were allocated to the control group. The patients were matched for age, sex, systolic and diastolic blood pressures, heart rate, presence of heart failure on admission and previous medical history of myocardial infarct or diabetes mellitus, primary ventricular fibrillation before randomisation, prior antiarrhythmic treatment, and site of infarct based on the initial electrocardiogram. The mean time after the onset of chest pain to randomisation was similar in both groups—5.5 hours in the atenolol group and 5.1 hours in the control group (table I).

### Table 1—Entry characteristics. Mean values expressed ± SEM. (Percentages in parentheses)

<table>
<thead>
<tr>
<th></th>
<th>Atenolol (n = 95)</th>
<th>Control (n = 87)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average age (range)</strong></td>
<td>55.6 (32-73)</td>
<td>55.1 (26-75)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>85 (89)</td>
<td>89 (79)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (11)</td>
<td>18 (21)</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mm Hg)</strong></td>
<td>140 ± 2</td>
<td>141 ± 2</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure</strong></td>
<td>89 ± 1</td>
<td>89 ± 1</td>
</tr>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td>77 ± 1</td>
<td>75 ± 1</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td>13 (14)</td>
<td>13 (15)</td>
</tr>
<tr>
<td><strong>Previous myocardial infarction</strong></td>
<td>15 (16)</td>
<td>10 (11)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>4 (4)</td>
<td>3 (3)</td>
</tr>
<tr>
<td><strong>Ventricular fibrillation</strong></td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td><strong>Antiarrhythmic drugs</strong></td>
<td>5 (5)</td>
<td>2 (2)</td>
</tr>
<tr>
<td><strong>Site of infarct</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>39 (41)</td>
<td>38 (44)</td>
</tr>
<tr>
<td>Inferior</td>
<td>43 (45)</td>
<td>38 (44)</td>
</tr>
<tr>
<td>Indefinite</td>
<td>12 (13)</td>
<td>10 (11)</td>
</tr>
<tr>
<td><strong>Time from onset of chest pain (hours):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>3 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>2-4</td>
<td>35 (36)</td>
<td>38 (40)</td>
</tr>
<tr>
<td>4-6</td>
<td>27 (28)</td>
<td>25 (27)</td>
</tr>
<tr>
<td>6-8</td>
<td>19 (20)</td>
<td>17 (18)</td>
</tr>
<tr>
<td>8-10</td>
<td>7 (8)</td>
<td>10 (11)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>4 (4)</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

*Notes lost for one patient in each group.*

**Heart rate** was significantly reduced from 77 ± 1 beats/min at entry to 65 ± 1 beats/min in the first hour (2p < 0.0001) after atenolol, and this reduction was maintained throughout the 24-hour period; heart rate in the control group did not change significantly from the initial value (75 ± 1 to 74 ± 2 beats/min).

### Ventricular extrasystoles and R-on-T ventricular extrasystoles

Since ventricular extrasystoles are not normally distributed in patients with acute myocardial infarction, the individual total values were transformed into logarithms to the base 10 and standard t tests for statistical analysis of the differences then applied. The total number of ventricular extrasystoles was reduced from a mean log10 of 2.12 ± 0.10 in the control group to 1.67 ± 0.09 in the atenolol group (2p < 0.001). A similar reduction was observed whether the patients had electrocardiographic evidence of acute myocardial infarction or "threatened infarction" at entry (fig 1). 

**Ventricular extrasystoles and R-on-T ventricular extrasystoles**—Since ventricular extrasystoles are not normally distributed in patients with acute myocardial infarction, the individual total values were transformed into logarithms to the base 10 and standard t tests for statistical analysis of the differences then applied. The total number of ventricular extrasystoles was reduced from a mean log10 of 2.12 ± 0.10 in the control group to 1.67 ± 0.09 in the atenolol group (2p < 0.001). A similar reduction was observed whether the patients had electrocardiographic evidence of acute myocardial infarction or "threatened infarction" at entry (fig 1). 

**Incidence of repetitive ventricular arrhythmias**—There was a significant reduction in the incidence of complexes from 72% (63 patients) in the control group to 48% (46 patients) in the atenolol
group ($\chi^2 = 10.88; \text{df} = 2; p < 0.001$), and of triplets from 41% (36 patients) to 20% (19), respectively ($\chi^2 = 9.84; \text{df} = 2; p < 0.005$). The incidence of ventricular tachycardia was reduced from 44% (38 patients) in the control group to 33% (31) in the atenolol group ($\chi^2 = 2.35; \text{df} = 2; p = 0.05$).

There was, however, a significant reduction in the incidence of ventricular tachycardia in patients admitted with threatened infarction from 34% (11 patients) in the control group to 7% (2 patients) in the treated group ($\chi^2 = 6.85; \text{df} = 2; p < 0.01$). There was a significant reduction in the incidence of repetitive ventricular arrhythmias as a whole from 74% (64 patients) in the control group to 58% (55) in the treated patients ($\chi^2 = 4.92; \text{df} = 2; p < 0.05$) (fig 3).

Frequency of repetitive ventricular arrhythmias—The total number of episodes of repetitive ventricular arrhythmias per patient were transformed to $\log_{10}$ in the two groups. There was a significant reduction in the mean $\log_{10}$ values of couplets from 0.479 ± 0.05 in the control group to 0.241 ± 0.04 in the atenolol group (2p < 0.001), and the mean $\log_{10}$ for triplets from 0.177 ± 0.03 to 0.303 ± 0.01, respectively (2p < 0.02). There was a reduction in the mean $\log_{10}$ for episodes of ventricular tachycardia from 0.127 ± 0.03 in the control group to 0.078 ± 0.02 in the atenolol group (2p < 0.02). There was a highly significant reduction in the total number of repetitive ventricular arrhythmias as a whole, from a mean $\log_{10}$ of 0.601 ± 0.06 in the control group to 0.327 ± 0.04 in the treated patients (2p < 0.001) (fig 4).

VENTRICULAR FIBRILLATION was observed in five control patients and in one patient in the atenolol group after randomisation (2p < 0.01).

**TABLE II**—Ancillary treatment in coronary care unit (Percentages in parentheses)

<table>
<thead>
<tr>
<th></th>
<th>Atenolol</th>
<th>Control</th>
<th>$\chi^2$</th>
<th>2p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmic drugs</td>
<td>13 (14)</td>
<td>24 (27)</td>
<td>5.42</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>Diuretics</td>
<td>30 (31)</td>
<td>32 (37)</td>
<td>0.95</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diabetic</td>
<td>5 (2)</td>
<td>9 (10)</td>
<td>8.43</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>Atropine</td>
<td>9 (9)</td>
<td>7 (8)</td>
<td>0.11</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Temporary pacemaker</td>
<td>5 (5)</td>
<td>1 (1)</td>
<td>4.44</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**TABLE III**—Cardiac events in hospital. (Percentages in parentheses)

<table>
<thead>
<tr>
<th></th>
<th>Atenolol</th>
<th>Control</th>
<th>$\chi^2$</th>
<th>2p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital mortality</td>
<td>5 (5-3)</td>
<td>11 (12-9)</td>
<td>3.08</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>1 (1-0)</td>
<td>5 (5-7)</td>
<td>1.14</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Hospital mortality and ventricular fibrillation*</td>
<td>6 (6-3)</td>
<td>15 (17-2)</td>
<td>5.31</td>
<td>&lt;0.025</td>
</tr>
</tbody>
</table>

*Patients who developed ventricular fibrillation but were discharged alive.
FIG 4.—Frequency of repetitive ventricular arrhythmias in first 24 hours after acute myocardial infarction. Patients randomised to beta-blocker group had fewer episodes of repetitive arrhythmias irrespective of subgroup analysis. Note that the greatest effect is shown when these arrhythmias are analysed as groups (couplets, triplets, and ventricular tachycardia). Values expressed as log, mean ± SEM. All p values two-tailed (2p).

Ancillary treatment after randomisation.—There was a significant reduction in the use of other antiarrhythmic drug treatment in the atenolol-treated patients (such as lignocaine, disopyramide, mexiletine, or a combination of these—13 patients in the atenolol group, 24 in the control group). Fewer atenolol-treated patients required digoxin (2 ± 9). No difference was found in the use of diuretics, atropine, or inotropic agents. One control patient and five treated patients had a temporary pacemaker inserted (table II).

Hospital mortality.—Five patients in the treated group (5.3%) and 11 in the control group (12.6%) died in hospital. Six patients in the atenolol group and 15 in the control group either died or had ventricular fibrillation and were discharged alive (χ² = 5.31; 2p < 0.025) (table III).

Discussion

Our results show that intravenous atenolol followed by oral treatment significantly reduced the number of ventricular extrasystoles, the incidence and frequency of R-on-T extrasystoles, and the incidence and frequency of repetitive ventricular arrhythmias in the first 24 hours after acute myocardial infarction. The reduction in incidence (fig 3) and frequency (fig 4) of repetitive ventricular arrhythmias was consistent in all subgroups analysed. Patients admitted with threatened infarction and receiving atenolol had a significantly reduced incidence of ventricular tachycardia, and this may be attributed, in addition to the antiarrhythmic effect, to prevention of myocardial infarction in a proportion of these patients by beta-blockade.14

The reduction in early ventricular arrhythmias was supported by a significant decrease in the requirements for further antiarrhythmic drug treatment during the first 24 hours, and also by a trend in the reduction of ventricular fibrillation. Our data show that ventricular arrhythmias regarded as serious (R-on-T, couplets, and ventricular tachycardia) were very frequent in patients with acute myocardial infarction. Of the 55 patients in the control group who showed electrocardiographic evidence of acute myocardial infarction at entry, 45 (82%) had at least one episode of repetitive ventricular arrhythmia, though most had two or more episodes. R-on-T extrasystoles were detected in 44 (80%) of these patients. These results show a slightly higher but comparable incidence of serious ventricular arrhythmias in previous clinical trials: 64% to 76%19,38 for serious ventricular arrhythmias, and 53%38 and 59%40 for R-on-T extrasystoles alone. We found a significant reduction of R-on-T extrasystoles in the treated group, and the clinical importance of this merits consideration. Though undoubtedly ventricular fibrillation can be initiated by a late coupled ventricular extrasystole, it will more frequently do so by an early coupled extrasystole,31,32 and an increased prevalence of R-on-T extrasystoles before the onset of primary ventricular fibrillation has recently been described.23

Previous randomised beta-blocker trials using oral11–13 or intravenous propranolol14 have failed to show a reduction in ventricular arrhythmias. These studies adopted conventional monitoring in the coronary care unit to record ventricular arrhythmias, and the unreliability of this method is well recognised.29,30 Our findings also contrast with the two disappointing reports from Nottingham11,13 in which continuous recordings of the electrocardiogram were used. This may have been due to (a) the administration of an initial oral dose resulting in inadequate beta-blockade in the early hours of infarction, when ventricular arrhythmias are common30,31; (b) the inclusion of patients late after the onset of chest pain (mean times from pain to electrocardiographic recordings 17 hours12 and 19 hours11 compared with five hours in our study); and (c) electrocardiographic recordings in only a small number of patients, an average of 18 patients11 and 30 patients13 with definite and probable myocardial infarction in their treatment group.

Our results are in accordance with a previous report utilising intravenous acebutolol in a non-randomised but controlled trial16 and support the concept that an initial intravenous dose is essential to achieve a reduction in ventricular arrhythmias by producing rapid and adequate beta-adrenergic blockade.

In addition there was a significant reduction in enzyme activities in patients with electrocardiographic signs of myocardial infarction at entry, confirming earlier reports from our study11 and from other workers.3 The antiarrhythmic action of atenolol in acute myocardial infarction is in part probably due to competitive antagonism of circulating catecholamines. Catecholamine concentrations are abnormally high in acute myocardial infarction, which may cause an increase in the severity of cardiac arrhythmias14 and is also associated with an increase in antiarrhythmic drug requirements. The arrhythmogenic actions of catecholamines in acute myocardial infarction may be attributed to a direct effect on the myocardial cell membrane increasing automaticity29 or indirectly by its metabolic effects. Catecholamine-mediated lipolysis increases circulating free fatty acids28,29 and, although the arrhythmogenic properties of free fatty acids in myocardial ischaemia are disputed,30–32 these increase myocardial oxygen consumption in the presence of catecholamine stimulation in man.41 Low plasma potassium concentrations have been associated with serious cardiac arrhythmias in patients with acute myocardial infarction,42 an alteration which may be induced by adrenaline and has been shown to be inhibited by beta-blocking drugs.42 Intravenous beta-blockade produces an immediate decrease in the high concentrations of circulating catecholamines and a concomitant decrease in plasma free fatty acids in patients with acute myocardial infarction.43

Although this trial was not designed to study mortality, an encouraging trend was observed in favour of atenolol; and when we combined hospital mortality with patients resuscitated from ventricular fibrillation and discharged alive we found a significant result (table III). Such a retrospectively identified subgroup benefit, however, must await confirmation from prospective studies.

In conclusion, the results of this randomised clinical trial using early intravenous atenolol followed by oral treatment for 10 days...
showed a reduction in the incidence and frequency of severe ventricular arrhythmias (some of which have been shown to precede ventricular fibrillation) in the initial 24 hours of acute myocardial infarction in man. This antiarrhythmic effect, in addition to our preliminary report of a reduction in enzyme activities in patients with definite myocardial infarction and prevention of myocardial infarction in patients with threatened infarction, and reduction in chest pain in early intravenous atenolol confirm that beta-adrenergic blockade is beneficial in the early hours of acute myocardial infarction and that a worthwhile reduction in mortality is possible. Unfortunately, reliable information on the effects of intravenous beta-blockade on mortality may not be obtained unless a large trial in which several thousands of patients have been randomised is completed.

We thank the following for their help: Mr R Motwani, ClinPath Laboratories; the house officers and physicians of both hospitals; and the nursing staff of both coronary care units. This work was supported by the British Heart Foundation and ICI Pharmaceuticals. Dr Rossi is supported by grant CBE 11400/81 from CAPES, Ministerio de Educucao e Cultura, Brazil.

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