PAPERS AND SHORT REPORTS

One year's treatment with propranolol after myocardial infarction: preliminary report of Norwegian multicentre trial

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Abstract

A prospective, randomised, double-blind study was performed to compare the effects of propranolol and placebo on sudden cardiac death in a high-risk group of patients who survived acute myocardial infarction. Altogether 4929 patients with definite acute myocardial infarction were screened for inclusion: 574 (11·6%) died before randomisation, and 3795 (77%) were excluded. Five hundred and sixty patients aged 35 to 70 years were stratified into two risk groups and randomly assigned treatment with propranolol 40 mg four times a day or placebo. Treatment started four to six days after the infarction. By one year there had been 11 sudden deaths in the propranolol group and 23 in the placebo group ($p < 0·038$, two-tailed test analysed according to the "intention-to-treat" principle). Altogether there were 25 deaths in the propranolol group and 37 in the placebo group ($p < 0·12$), with 16 and 21 non-fatal reinfarctions respectively. A quarter of the patients were withdrawn from each group. Withdrawal because of heart failure during the first two weeks of treatment was significantly more common among propranolol-treated patients than among the controls, but thereafter the withdrawal rate was the same.

The significant reduction in sudden death was comparable with that after alprenolol, practolol, and timolol, which suggests that the mechanism of prevention is beta-blockade rather than any other pharmacological property of the individual drugs.

Introduction

Many studies have shown that mortality during the first year after acute myocardial infarction is substantial.[1 2] Some studies have shown a correlation between electrical or mechanical complications in the acute phase and an increased risk of late sudden death.[3-5] Many of these deaths are inevitable, caused by advanced myocardial failure, but more than half are sudden and unexpected and presumably caused by ventricular fibrillation.[5 6]

Although various antiarrhythmic drugs may be effective in treating ventricular arrhythmias in the acute phase, none have been proved to have a preventive effect on sudden death. In addition, the high incidence of side effects makes existing drugs unsuitable for routine long-term treatment.

Recently several long-term clinical trials have indicated that beta-adrenoceptor blocking drugs may reduce the sudden death rate in survivors of myocardial infarction,[7-12] while other studies have failed to show this effect.[13-16] It is still not clear whether the inconsistency of the results is due to differences in patient selection, sample size, duration of trial, or to specific pharmacological properties of the beta-adrenoceptor blockers tested.

A major criticism of the practolol[9] and recent propranolol[15] trials has been that "good risk" patients have been selected. In the timolol trial[12] the patients were stratified into three risk groups before randomisation. The total cardiac death rate in the placebo-treated patients of the highest risk group was more than twice that in the placebo groups of the practolol[9] and propranolol[15] trials.

Because the medical and economic consequences would be considerable if all survivors of myocardial infarction were to be treated with beta-adrenoceptor blocking drugs, we thought that new and larger trials in high-risk patients were necessary. The objective of the present trial was to study whether treatment with propranolol for one year after a myocardial infarction could reduce the sudden death rate in a defined high-risk group of patients.

Methods

PATIENT SCREENING AND SELECTION

Patients were selected from 12 Norwegian hospitals serving a population of 1·2 million people. There was no overlap or double-counting between our trial and the timolol trial,[12] and no hospital participated in both trials. Screening of patients started on 1 December 1977, and recruitment was completed on 30 July 1980. Patients with

definite acute myocardial infarction according to WHO criteria[17] treated in the intensive care unit were screened on the fourth day after the infarction, but only patients with an increased risk of death were included. In total, 4929 patients were screened for participation. Of these, 574 (11·6%) died before randomisation, mostly from cardiogenic shock. Of the remaining patients 3795 (77%) were excluded because of contraindications to beta-blockade or for other reasons (table I), and 560 patients (11·4%) were included.

TABLE I—*Reasons why 3795 patients were excluded from trial*

Reason	No (%) of patients
Good risk patients	1367 (36·0)
Age <35 or >70 years	1370 (36·1)
Acute phase data:	
Uncontrolled heart failure	457 (12·0)
Need for beta-blockade	404 (10·6)
Atrioventricular block II and III or sinoatrial block	240 (6·3)
Systolic blood pressure <100 mm Hg	188 (5·0)
Need for other anti-arrhythmics	151 (4·0)
Unwilling to participate	22 (0·6)
Resting heart rate <50 beats/min	18 (0·5)
Preadmission data:	
Diabetes mellitus	246 (6·5)
History >48 hours before admission	160 (4·2)
Alcoholism, mental disease	156 (4·1)
Obstructive airways disease	83 (2·2)
Neoplastic disease	28 (0·7)
Other reasons	265 (7·0)

The number of patients to be included in the study was calculated in advance to 700. This assumption was based on an expected sudden death rate on placebo at one year of 10-12% and a calculated 50% reduction in mortality in the actively treated group. This would give an 80% chance of detecting a difference between the two groups significant at the 5% level (two-tailed test). The duration of the recruitment period (one year) was based on an estimated inclusion rate of 30% among the screened patients.

The exclusion criteria proved more restrictive than originally planned, however, and the recruitment period had to be prolonged. To keep up the interest and enthusiasm of the participating centres, we decided to stop recruitment after two and a half years, although the number of patients was only 560.

For patients included in the study a special record for later computer processing was filled in. The clinical details were based on information from the patient and from earlier hospital records. A 12-lead electrocardiogram (ECG) was recorded and serum aspartate aminotransferase activities (upper normal limit 40 U/l) were measured daily for the first three or four days. The site of the infarct was recorded as anterior, inferior, or other or uncertain, and the infarct size was calculated from a combination of maximum enzyme values and ECG changes.[18]

The patients were divided into two risk groups. Group 1 consisted of patients who had been treated for ventricular fibrillation, asystole, or prolonged ventricular tachycardia in the intensive care unit. Group 2 comprised patients with one or more of the following complications: ventricular tachycardia of short duration, "complicated ventricular extrasystoles,"[19] atrial fibrillation or flutter not previously diagnosed, sinus tachycardia exceeding 120 beats/minute for more than three hours, and left ventricular failure (moist râles over the lungs or radiological signs of pulmonary congestion). (Patients who presented with heart failure on admission or during the initial phase of the infarction were included if the signs of failure had disappeared at the time of randomisation. Patients with severe heart failure—that is, cardiogenic shock or pulmonary oedema—and patients who still presented with signs of heart failure at the time of randomisation, though treated with digitalis and frusemide 40-80 mg/day, were excluded.)

Groups 1 and 2 were randomised separately with two codes at each participating centre, in balanced blocks of 10. A double-blind design was used. Treatment started on the day of randomisation, between day 4 and day 6 after the infarction, and the patients received either propranolol 40 mg four times a day or matching placebo tablets. Informed consent was obtained from all patients, and the study received approval from the steering committee and from the National Centre for Medical Products Control.

TABLE II—*Comparison of the groups. Results are numbers (and percentages) of patients unless otherwise stated*

Characteristics	Propranolol (n = 278)	Placebo (n = 282)
Group 1	26	23
Group 2	252	259
Sex:		
Male	235 (84·5)	241 (85·5)
Female	43 (15·5)	41 (14·5)
Mean age	161 (58·0)	166 (58·8)
35–64 years	218 (78·4)	203 (72·0)
65–69 years	60 (21·6)	79 (28·0)
Clinical history:		
No previous coronary heart disease	143 (51·4)	137 (48·6)
Angina pectoris	85 (30·6)	90 (31·9)
Previous myocardial infarction	50 (18·0)	55 (19·5)
Hypertension (treated)	62 (22·3)	51 (18·1)
Intermittent claudication	24 (8·6)	16 (5·7)
Cerebrovascular disease	9 (3·2)	7 (2·5)
Drug treatment before admission:		
Digitalis	17 (6·1)	16 (5·7)
Diuretics	53 (19·1)	45 (16·0)
Other antihypertensives	22 (7·9)	18 (6·4)
Smoking habits:		
Daily smoker	162 (58·3)	183 (64·9)
Ex-smoker	78 (28·1)	68 (24·1)
Infarct complications:		
Ventricular fibrillation	22 (7·9)	20 (7·1)
Ventricular tachycardia or extrasystoles	204 (73·3)	205 (72·7)
Atrial fibrillation or flutter	58 (20·9)	44 (15·6)
Atrioventricular or sinoatrial block (pacemaker-treated)	7 (2·5)	6 (2·1)
Left ventricular failure	110 (39·6)	116 (41·1)
Site of infarct:		
Anterior	144 (51·8)	124 (44·0)
Inferior	90 (32·4)	108 (38·3)
Other or uncertain	44 (15·8)	50 (17·7)
Estimated infarct size:		
Large	26 (9·4)	31 (11·0)
Medium	209 (75·2)	209 (74·1)
Small or unclassified	43 (15·5)	41 (14·6)
Heart rate (beats/min):		
On admission	79·2	77·0
At randomisation	81·5	78·7
Mean heart size (ml/m² body surface)	516·1*	493·7
Mean maximal aspartate aminotransferase value (IU)	274·0	263·9

*p<0·05.

COMPARISON OF THE GROUPS

Table II shows a list of patient characteristics presumed to be related to risk of death. The two groups were comparable in all respects, except that the mean heart size at the time of discharge was slightly greater in the propranolol group ($p < 0·05$). The randomisation procedure thus assured equal distribution between the propranolol and placebo groups, so we thought that it was justifiable to present the results of the two risk groups together.

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CHOICE OF BETA-ADRENOCEPTOR BLOCKER

Propranolol was the first beta-adrenoceptor blocking drug registered in Norway, and reports on its efficacy, safety, and pharmacokinetic and pharmacodynamic properties are extensive.[20] These aspects were considered to be of paramount importance, as practolol was withdrawn during the planning stages of this trial. We also regarded it an advantage to use a drug without intrinsic sympathomimetic activity. The weak membrane-stabilising activity was thought to be without practical importance in the dosage chosen.[21]

FOLLOW-UP

Patients were discharged from hospital between days 10 and 24 and returned for follow-up at 2, 6, and 12 months after discharge. At follow-up their histories were taken, including a recording of spontaneously admitted adverse effects (see table V). They were examined and their tablets were counted. Blood pressure was measured supine after 10 minutes resting and after one minute standing. A 12-lead ECG and standard haematological and biochemical tests in the non-fasting state were performed at each visit and a chest *x*-ray examination at 2 and 12 months. Relative heart size was calculated as volume per square metre of body surface.

WITHDRAWALS

Patients were withdrawn according to predetermined criteria defined as follows: severe angina—angina pectoris requiring treatment with beta- or calcium-blockers in addition to glycerol trinitrin; arrhythmias—serious arrhythmias (mostly rapid atrial fibrillation, recurrent ventricular tachycardia, and ventricular fibrillation) requiring additional anti-arrhythmic therapy; heart failure—left ventricular failure not responding adequately to treatment with digitalis and diuretics; sinus bradycardia—sinus rhythm below 40 beats/minute causing symptoms (dizziness or fainting); drop outs—patients who had stopped the treatment for more than 10 days; reinfarction; and atrioventricular or sinoatrial block.

EVALUATION OF EVENTS

For all patients information on reinfarction and death up to 12 months after the original infarction was obtained regardless of whether they withdrew from the study. Information on mode of death was obtained from hospital records, or from relatives or witnesses if the patient died outside hospital. Necropsies were performed in 30% of the patients who died.

The following definitions were used.

Sudden death was divided into three subgroups: type 1—witnessed, instantaneous death; type 2—death witnessed but preceded by chest pain of less than one hour's duration; type 3—patients found dead, but seen alive and free of chest pain less than 12 hours earlier.

Fatal reinfarction occurred when death was more than one hour after the onset of chest pain, but less than four weeks after recurrence of symptoms and confirmed by WHO criteria.[17]

Non-fatal reinfarction was one or more episodes of reinfarction according to WHO criteria.[17] These patients were not withdrawn from the trial.

Data were analysed according to the "intention-to-treat" principle[22]—that is, cases of death or reinfarction were assigned to the original test group whether or not the patient had been withdrawn from the study at the time of the event. In a second analysis the incidence of events included only patients on treatment or within one month after withdrawal.

DATA PROCESSING AND STATISTICS

The data for this summary report were processed by hand. The records were, however, prearranged for later computer processing.

Survival data were analysed according to the two-tailed log-rank test method with the slightly conservative χ^2 approximation. Differences between proportions were tested by Yates's corrected z tests using estimates of variance from pooled groups. In the case of small numbers Fisher's exact test was used.

Results

A flow diagram of all patients with definite acute myocardial infarction is shown in fig 1.

Deaths—Table III summarises the major events. The total number of deaths was 25 (9%) in the propranolol group and 37 (13·1%) in the placebo group. Of all deaths 88% in the propranolol and 95% in the placebo group were cardiac. Five patients died from non-cardiac causes (two patients receiving propranolol from dissecting aortic aneurysm, and one from acute leukaemia; one patient on placebo from dissecting aortic aneurysm, the other from bronchial carcinoma). The differences in total deaths and total cardiac deaths between the groups were not significant (p = 0·117 and 0·079 respectively), but there was a definite trend in favour of the propranolol group.

TABLE III—*Events in each group*

	Patients remaining in trial		Patients withdrawn from trial		Total		
	Propranolol	Placebo	Propranolol	Placebo	Propranolol	Placebo	p Value
Sudden death	10	19	1	4	11	23	0·038
Type 1	8	14	1	3	9	17	0·115
Type 2	1	2	0	1	1	3	NS
Type 3	1	3	0	0	1	3	NS
Fatal reinfarction	10	6	1	4	11	10	NS
Other cardiac deaths	0	1	0	1	0	2	NS
Other deaths	3	2	0	0	3	2	NS
Total deaths	23	28	2	9	25	37	0·117
Total cardiac deaths	20	26	2	9	22	35	0·079
Non-fatal reinfarctions	14	21	2	0	16	21	NS
Total No of cardiac events	34	47	4	9	38	56	0·054

p Values analysed according to intention to treat.

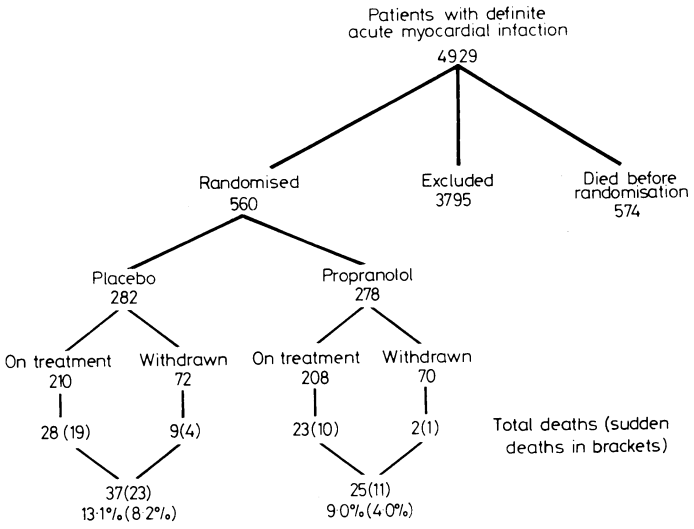

FIG 1—Flow diagram for all patients with acute myocardial infarction.

The total number of sudden deaths (groups 1 and 2 combined) were 11 in the propranolol group and 23 in the placebo group ($p = 0.038$). When only cases of sudden death occurring on treatment or within one month after withdrawal were included, there were 10 deaths in the propranolol group and 19 in the placebo group ($p = 0.097$).

Life-table curves for sudden and total cardiac death according to intention to treat are shown in figs 2 and 3.

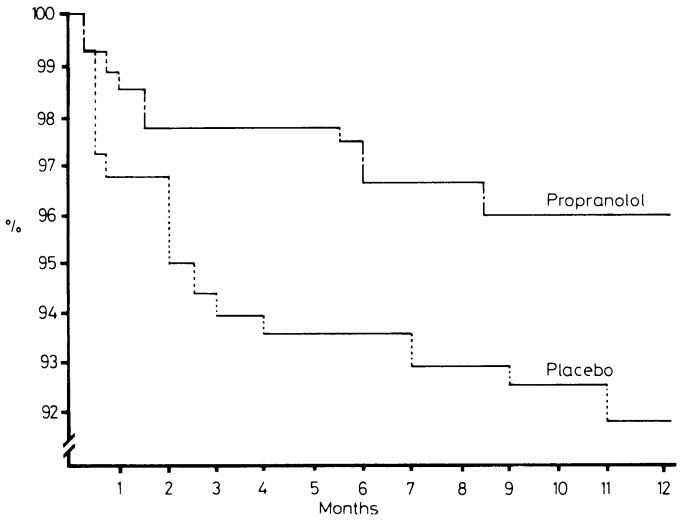

FIG 2—Life table for cummulated sudden cardiac death rate (intention to treat).

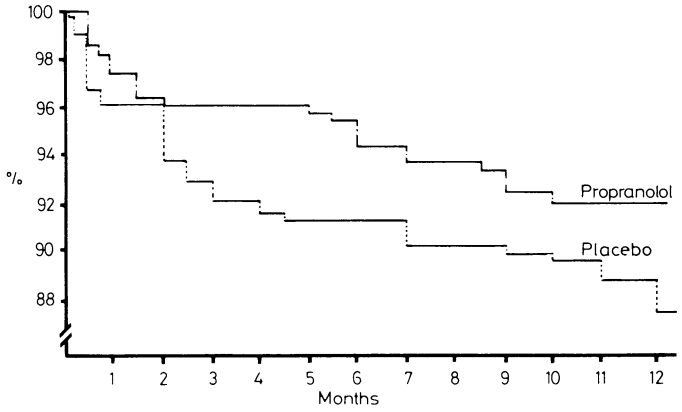

FIG 3—Life table for cummulated total death rate (intention to treat).

Fatal and non-fatal reinfarction—There was no significant difference in the number of fatal reinfarctions between the two groups (table III). Ten patients suffered more than one reinfarct, six on placebo, and four on propranolol. Only the first reinfarction is listed in table III.

Total number of cardiac events—The total number of sudden cardiac deaths, fatal and non-fatal reinfarctions, and other cardiac deaths was lower among the propranolol-treated patients than among the placebo-treated patients ($p = 0.054$). In addition, one patient in the propranolol group and four in the placebo group were successfully resuscitated from ventricular fibrillation while on treatment. The event occurred between day 6 and day 270 after randomisation. All these patients were withdrawn.

Effects of age, sex, and site of original infarct—The incidence of major events in the treatment groups was not significantly different in patients above and below 65 years of age or in either sex. There were fewer sudden deaths in the propranolol group in both age groups. The major events were not related to the site of the original infarct.

Withdrawal—Seventy patients (25·2%) were withdrawn from the propranolol group and 72 (25·5%) from the placebo group (table IV). Angina pectoris requiring treatment with a beta-adrenoceptor blocker and serious arrhythmias were more common in the placebo group than in the propranolol group ($p < 0.05$). Overall heart failure occurred with similar frequency in the two groups, but there were significantly more patients withdrawn during the first two weeks in the propranolol group (6·5% *v* 1·8%; $p < 0.05$). Most of these withdrawals occurred within the first few days. Sinus bradycardia was more frequent in the propranolol group. Other causes of withdrawal were evenly distributed between the two groups.

TABLE IV—*Reasons for withdrawal. Results are numbers (and percentages) of patients*

	Propranolol (n = 278)	Placebo (n = 282)
Severe angina	7 (2·5)*	17 (6·0)
Arrhythmias	2 (0·7)*	11 (3·9)
Reinfarction	6 (2·2)	4 (1·4)
Drop outs	7 (2·5)	8 (2·8)
Heart failure before 2 weeks	18 (6·5)*	5 (1·8)
Heart failure after 2 weeks	4 (1·4)	11 (3·9)
Atrioventricular or sinoatrial block	3 (1·1)	3 (1·1)
Sinus bradycardia	7 (2·5)*	1 (0·4)
Other effects	13 (4·7)	8 (2·8)
Other reasons	3 (1·1)	4 (1·4)
Total No of withdrawals	70 (25·2)	72 (25·5)

*$p < 0.05$ propranolol *v* placebo.

Adverse effects—Adverse effects were divided into mild (not requiring withdrawal) and severe (requiring withdrawal). Adverse effects occurred in 57% of the propranolol-treated patients and 51% of these on placebo. Symptoms of hypotension, constipation, dry eyes or mouth, dizziness and asthenia, and depression, all classified as mild, were more common in the propranolol group (table V; $p < 0.05$). Severe effects were of equal frequency in the two groups, except for early heart failure and sinus bradycardia.

Patient compliance—Tablet counts at each visit indicated that 80% of the patients in both groups had taken more than 95% of the prescribed dose. The number of tablets taken by the individual patient varied from 37% to 172% of the prescribed dose. Good

TABLE V—*Adverse effects. Results are numbers of patients who experienced effect on one or more occasion*

	Propranolol (n = 278)		Placebo (n = 282)	
	Mild	Severe	Mild	Severe
Atrioventricular or sinoatrial block	0	3	0	3
Sinus bradycardia	88*	7*	13	1
Heart failure	18	22	25	16
Hypotension	23*	1	9	1
Bronchospasm	10	1	10	1
Intermittent claudication	11	2	14	0
Cold hands or feet	31	1	30	0
Nightmares	0	3	0	3
Sleep disturbances	24	0	15	0
Constipation	7*	0	0	0
Dry eyes or mouth	7*	0	2	0
Depression	6*	0	0	0
Dizziness, asthenia	38	2	19	1
Other symptoms	26	3	29	2

*$p < 0.05$ propranolol *v* placebo.

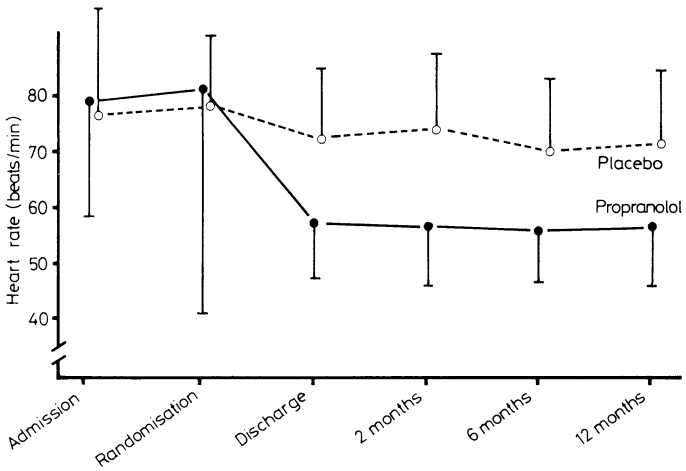

FIG 4—Mean heart rates (±SD) at admission, randomisation, and discharge and at 2, 6, and 12 months' follow-up.

compliance was confirmed by presence of bradycardia in most of the propranolol-treated patients (and by plasma propranolol concentrations, which will be reported separately).

Degree of beta-adrenergic blockade—Resting heart rates on admission to the intensive care unit and at randomisation, discharge, and follow-up visits are shown in fig 4. Heart rates during exercise were not measured to try to prevent our discovering which group the patient was in. The differences in the mean resting heart rates after randomisation were highly significant ($p < 0.001$) and varied from 12 to 17 beats/minute. Only 2% of patients on propranolol had heart rates above 80 beats/minute compared with 30% placebo. On the other hand, 25% of the patients on propranolol but only 2% of those on placebo had resting heart rates below 50 beats/minute.

Smoking habits—As stopping smoking may affect the prognosis favourably after a myocardial infarction, smoking habits were followed. Almost half of the smokers in both groups stopped smoking after the infarction. The percentage did not change throughout the study period.

Discussion

This study has shown a significant reduction in the number of sudden cardiac deaths in high-risk patients treated with propranolol after a myocardial infarction. The reduction was maintained during the observation period and was not accompanied by an increase in other cardiac deaths, indicating a real net reduction in mortality and not merely a short postponement of the time of death. The reduction in the sudden death rate was 51%. This is of the same magnitude as in the recently published timolol study[12] and confirms the results from this as well as other studies.[7 9 11] The difference in the sudden death rate between the groups increased gradually up to six months but did not change significantly after that (fig 2). The difference was more pronounced when all deaths according to intention to treat were included than when only in-trial deaths were counted. This is surprising, as we would have expected the opposite. The difference was significant, however, and most probably coincidental, due to small numbers.

The one-year total mortality in the placebo group was 13·1%. A higher mortality might have been expected with such high-risk patients, but this discrepancy may be explained by the high incidence of contraindications to beta-blocker treatment in high-risk patients who have suffered myocardial infarction. The one-year mortality in the placebo group was, however, higher than in the timolol study (10%),[12] which also included many high-risk patients.

Patients were stratified, before randomisation, into two risk groups. Comparison between the groups showed that the patients were well matched, except for heart size at the time of discharge. The incidence of left ventricular failure, however, was the same in the two groups. The reduction in the numbers of sudden deaths thus cannot be attributed to differences in pretreatment risk factors.

In the alprenolol study by Andersen *et al*[11] a reduction in cardiac mortality was confined to patients below 65 years of age, while in the practolol study[9] a significant reduction in mortality occurred in patients with anterior infarctions. These findings were not confirmed in our study.

Our results contrast with those of the recently reported propranolol post-infarction trial in patients with anterior infarcts,[15] in which no effect on mortality was found. One possible explanation for the discrepancy is that the British propranolol study covered relatively good-risk patients, as shown by a total cardiac mortality of 6·8% in the placebo group compared with a mortality of 12·4% in our placebo group. Propranolol was also given in a lower dose (40 mg three times a day) and the follow-up period was shorter (9 months) in the British study.

In the timolol study[12] there was a significant reduction in the incidence of non-fatal reinfarction in the actively treated group (38%). In our study the percentage reduction in the propranolol group was only slightly lower (25%) but did not reach the 5% level of significance. This could be explained by minor differences in the inclusion and exclusion criteria between the two studies, though the number of patients in our study may have been too small to prove a modest reduction of the reinfarction rate (to prove a 25% reduction, at least 1700 patients in each group would have been required[15 23]). On the other hand, the effect of beta-blockade on the reinfarction rate has varied in different trials,[7–9] and this effect can still be argued.

The dose of propranolol which suppresses serious ventricular arrhythmias without depressing myocardial function is open to debate.[24] The bioavailability of propranolol varies considerably both within and between patients after long-term treatment,[25] and adequate beta-blockade cannot be achieved in all patients if a fixed dose is used. Nevertheless, for practical purposes, we chose a regimen of 40 mg four times a day. As judged by resting heart rate at follow-up, most patients were adequately beta-blocked. Thus, it seems improbable that any additional effect could have been obtained by increasing the dose of propranolol. (Plasma propranolol concentrations were studied in a subgroup of patients, and their relation to heart rate and arrhythmias will be reported later.)

The withdrawal rate in this study was high (25%), but equal in the two groups, and it is similar to that reported in the practolol,[9] propranolol,[15] and timolol[12] trials. A high withdrawal rate for different reasons in the two groups may lead to reduced comparability in patients remaining at risk. This is largely overcome by using the intention-to-treat principle in the analysis. A high withdrawal rate also reduces the number of patients on treatment and may thus mask significant drug effects. More patients were withdrawn in the placebo group because of angina pectoris and serious arrhythmias (40% of all withdrawals). The overall incidence of heart failure was similar, but early withdrawal for heart failure was significantly more common in the propranolol-treated patients. This highlights the dilemma of starting long-term beta-blockade in high-risk patients. On the one hand, beta-blockade may suppress potentially fatal arrhythmias at the time of a new ischaemic event; on the other, it may depress myocardial function and provoke heart failure.

Whenever possible, the test substance was withdrawn gradually over a week. Some of the patients on propranolol experienced worsening angina of effort, and a few developed unstable angina. No cases of death or reinfarction could be directly associated with withdrawal.[26]

Adverse effects were more common in the propranolol-treated patients. Sinus bradycardia and hypotension are expected pharmacological effects of beta-blockade, but only in the former case was there a significant difference in the number of patients withdrawn (7 propranolol, 1 placebo). Dry eyes were reported more frequently in the propranolol group. This was not associated with the oculomucocutaneous syndrome of practolol, and no patients were withdrawn.

An increasing number of controlled trials have presented evidence that beta-adrenoceptor blocking drugs may reduce long-term mortality in patients who have had a myocardial infarction. The effect seems to be primarily connected with a reduction in the risk of sudden cardiac death. It is generally accepted that sudden death is due to ventricular fibrillation,[27] and though the exact mechanism is not known the bulk of evidence is in favour of an antiarrhythmic effect. As the same effect has been found with different beta-blockers,[7 9 12] it seems an inescapable conclusion that beta-blockade, rather than any individual pharmacological property of each drug, is responsible for the benefits shown. This is also supported by the reduction of arrhythmias shown in this as well as in other studies.[9] But if the main effect of beta-blockade in the post-infarction patient is a protection against malignant arrhythmias, we do not know whether the dose sufficient to produce adequate beta-blockade as expressed by a reduction in heart rate is the same as the dose necessary to prevent fatal arrhythmias.

Our study was specifically designed to study patients with high-risk complications of acute myocardial infarction. An

effect shown in highly selected subgroups of patients cannot, however, be extrapolated to other groups of patients, although other studies, including those with a wider, less selected population,[9 12] indicate that even low-risk patients may profit from long-term beta-adrenoceptor blockade.

There has been much debate about analysis, presentation, and interpretation of beta-blocker post-infarction trials.[28-30] We have presented our data so that end-point differences based on both the "intention-to-treat" and "in-trial" differences can be calculated, but we have chosen to analyse the results according to intention to treat. We hope that our results will make a small contribution to an important debate.

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SHORT REPORTS

Sinus arrest during treatment with amiodarone

Amiodarone (Cordarone X) is widely used for treating resistant cardiac tachyarrhythmias and is generally assumed to have few limiting side effects.[1] We report two cases of sinus arrest, with depressed automaticity of escape foci, that required pacing after administration of amiodarone.

Case reports

Case 1—A 61-year-old man with a remote anteroseptal myocardial infarction presented with recurrent sustained ventricular tachycardia. A week before admission a permanent ventricular pacemaker had been inserted for transitory complete heart block. Electrocardiography showed right bundle-branch block, left posterior hemiblock, and evidence of an old anteroseptal infarction. When not paced his rhythm was sinus with first-degree atrioventricular block. Comprehensive intracardiac electrophysiological study disclosed a corrected sinus node recovery time of 220 ms (normal <525 ms), A-H interval 120 ms (normal 60-140 ms), and H-V interval 85 ms (normal 30-55 ms). Two morphologically distinct types of ventricular tachycardia could be induced. Quinidine, procainamide, propranolol, digoxin, disopyramide, mexiletine, and several combinations of these failed to suppress the tachycardia. Amiodarone 600 mg daily was started. Six weeks later ventricular extrastimulation induced poorly tolerated ventricular tachycardia. In the meantime no spontaneous ventricular tachycardia had occurred and ambulatory electrocardiography showed complete suppression of ventricular ectopic activity. At that time no sinus node activity was present and the patient was pacemaker-dependent without an escape focus. Apart from amiodarone the only known cardioactive agents that he was taking were metoprolol and digoxin, both in conventional dosage and for several months before these studies. Electrolyte concentrations were normal. The patient was discharged taking these agents as no non-pharmacological treatment was indicated.

Case 2—A 67-year-old man with a history of myocardial infarctions in 1968 and 1977 presented with recurrent drug-resistant ventricular tachycardia that required numerous cardioversions. He was in congestive cardiac failure and had severe peripheral vascular disease and mild chronic renal failure. Electrocardiography showed normal sinus rhythm with an intraventricular conduction defect and evidence of old anteroseptal and inferior infarctions. Electrophysiological study showed a corrected sinus node recovery time of 270 ms, A-H interval 125 ms, and H-V interval 80 ms. Sustained ventricular tachycardia (160/min) was induced by ventricular extrastimulation. Serial drug testing with many agents failed to suppress his arrhythmia. Treatment was initiated with amiodarone 1 g daily. Ventricular ectopy was suppressed, and nine days later repeat ventricular stimulation disclosed inducible ventricular tachycardia (125/min). Amiodarone was continued, and two days