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THE NORWEGIAN PROPRANOLOL TRIAL IN SELECTED PATIENTS

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The objective of our trial was to study whether treatment with a β-adrenoceptor blocker could reduce the risk of sudden death in survivors of myocardial infarction. Patients with an increased risk of death or reinfarction were selected.

We estimated that the number of patients we needed to include was 700. This assumption was based on an estimated sudden death rate in the placebo group of 10 to 12% and a calculated reduction in mortality in the actively treated group of one half. This would give an 80% chance of detecting a difference between the two groups significant at the 5% level.

Patients and methods

Patients with an increased risk of death were selected from 12 Norwegian hospitals serving an area of 1.2 million people. The recruitment period started on 1 December 1977 and closed on 31 July 1980. In total 4929 patients with definite acute myocardial infarction according to the criteria of The World Health Organization (1971) were screened on the fourth day after the infarction. Of these, 574 patients died before randomization, mostly from advanced pump failure, and 3795 were excluded because they were of too 'low risk' or for other reasons (Table 1). The remaining 560 patients were included in the trial. This number was lower than expected, because the exclusion criteria proved more restrictive than originally planned.

The patients were divided into two risk groups according to complications occurring before randomization. Group 1 consisted of patients who had been treated for ventricular fibrillation, asystole, or prolonged ventricular tachycardia before randomization. Group 2 comprised patients treated for one or more of the following complications: ventricular tachycardia of short duration, 'complicated premature ventricular contractions' (Lown *et al.*, 1967), atrial fibrillation or flutter not previously diagnosed, persistent sinus tachycardia exceeding 120 beats/min for more than three hours, and left ventricular failure (moist rales over the lungs or radiological signs of pulmonary congestion).

The patients in the two risk groups were randomized separately with two codes at each participating centre in balanced blocks of 10, using a double-blind design. Treatment started on the fourth to sixth day after the infarction (the day of randomization) with propranolol 40 mg four times a day or matching placebo tablets. The patients were reexamined before discharge, and they returned for follow-up after 2, 6, and 12 months. For all patients information on death and reinfarction during the 12 months' follow-up was obtained regardless of whether they withdrew from the study. Information on cause of death was obtained from hospital records or from relatives or witnesses when the patient died outside hospital. Necropsies were performed in 30% of the patients who died.

The end-points used are shown in Table 2. The results were analysed according to 'intention to treat' (Peto *et al.*, 1976). In a second analysis only events occurring on treatment or within one month after withdrawal were included. Survival data were analysed according to the two-tailed log rank test

Table 1 Patients excluded from the 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 β-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 antiarrhythmic drugs	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
No. of patients	3795	
No. of reasons	5155	

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Table 2 End-points

Sudden cardiac death:
Type 1: Instantaneous, witnessed
Type 2: Chest pain < 1 h, witnessed
Type 3: Death 12 h, no pain, unwitnessed
Fatal reinfarction
Total death
Non-fatal reinfarction
Total no. of cardiac events

method (χ^2-approximation). Differences between proportions were tested by Yates's corrected z tests using estimates of variance from pooled groups, and Fisher's exact test was used in the case of small numbers.

Results

Comparison of the groups

A large number of patient characteristics presumed to be related to risk of death were compared in the two groups (Table 3). There were no significant or systematic differences between the groups, except that the relative heart size was slightly greater in the propranolol group. X-ray examination of the heart was, however, performed after the start of treatment, and the difference therefore might have been caused by the treatment with propranolol.

Deaths

The total number of deaths was 25 (9.0%) in the propranolol group and 37 (13.1%) in the placebo group (Table 3). Three patients on propranolol and two on placebo died from non-cardiac causes. The differences in total deaths and total cardiac deaths were not significant ($P=0.117$ and 0.079 respectively), but there was a definite trend in favour of the propranolol treated group.

The total number of sudden deaths was significantly reduced in the actively treated group (11 deaths on propranolol, 23 on placebo, $P=0.038$). When restricted to deaths on treatment or within one month after withdrawal the figures were 10 and 19 sudden deaths respectively ($P=0.097$). Survival curves are shown in Figures 1 (total death) and 2 (sudden cardiac death). A flow diagram of all patients with definite acute myocardial infarction considered for the trial is shown in Figure 3.

The number of fatal reinfarctions was the same in the two groups (11 on propranolol, 10 on placebo), while non-fatal reinfarction occurred slightly but not significantly more often among patients on placebo treatment (16 on propranolol, 21 on placebo).

When sudden cardiac deaths, fatal and non-fatal reinfarctions, and other cardiac deaths were combined that is, the total number of cardiac events was considered, there was a definite difference between the groups in favour of propranolol (38 on propranolol, 56 on placebo, $P=0.054$). In addition, 10 patients suffered more than one reinfarct (four on propranolol, six on placebo), and five patients (one propranolol, four placebo) were successfully resuscitated from ventricular fibrillation while on treatment. The incidence of major events was not significantly correlated to age, sex, or to the site of the index infarct.

Table 3 Events

	In-trial		*Ex-trial*		*Total*		
	Propranolol	*Placebo*	*Propranolol*	*Placebo*	*Propranolol*	*Placebo*	*P Value*
Sudden death							
Type 1	8	14	1	3	9	17	0.115
Type 2	1	2	0	1	1	3	N.S.
Type 3	1	3	0	0	1	3	N.S.
Total	10	19	1	4	11	23	0.038
Fatal reinfarction	10	6	1	4	11	10	N.S.
Other cardiac deaths	0	1	0	1	0	2	N.S.
Other deaths	3	2	0	0	3	2	N.S.
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	N.S.
Total no. of cardiac events	34	47	4	9	38	56	0.054

P Values analysed according to 'intention to treat'.

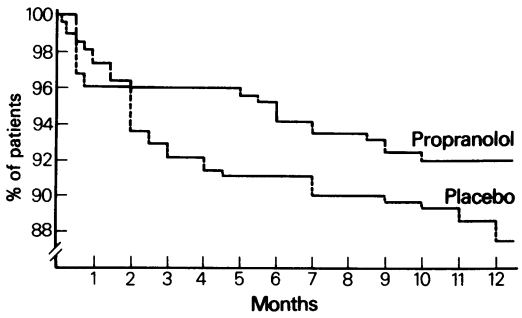

Figure 1 Survival curve for total death (intention to treat) (Hansteen *et al.*, *Br. Med. J.* with permission).

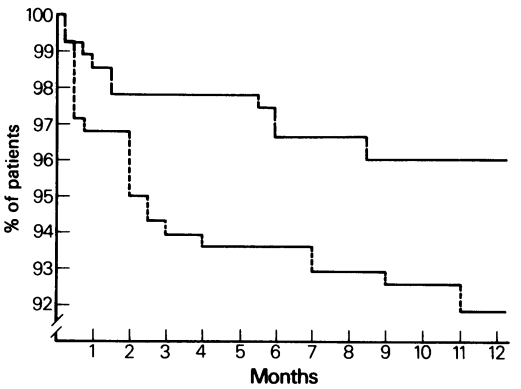

Figure 2 Survival curve for sudden cardiac death (intention to treat) (Hansteen *et al.*, *Br. Med. J.* with permission).

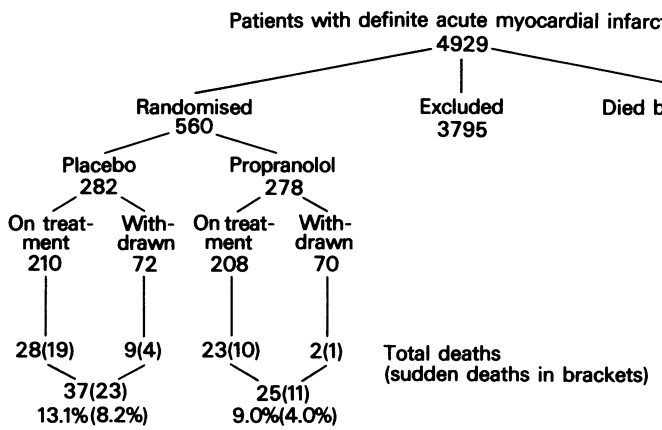

Figure 3 Flow diagram for all patients with acute myocardial infarction. (Hansteen *et al.*, *Br. Med. J.* with permission).

Withdrawal

The number of withdrawals was almost the same in the two groups, 70 patients on propranolol (25.2%), 72 on placebo (25.5%), but the pattern of withdrawal was different. Angina pectoris requiring additional drug treatment and serious arrhythmias were significantly more common in the placebo group, while significantly more patients in the propranolol group were withdrawn because of severe heart failure during the first two weeks of treatment. Most of these withdrawals occurred within the first few days of treatment. Overall, however, heart failure occurred with the same frequency in the two groups.

Adverse effects

Adverse effects spontaneously admitted by the patient or objectively recorded by the doctor were recorded. They were called mild when withdrawal was not required, and severe when withdrawal was necessary.

Adverse effects, mostly mild, were common in both groups, and occurred in 57% of the propranolol-treated and 51% of the placebo-treated patients. Hypotension, constipation, dry eyes or mouth, dizziness or asthenia, and depression, all classified as mild, were more common in the propranolol group. Severe effects were few and occurred with equal frequency in the two groups,

the only exception being early heart failure and severe sinus bradycardia, which were more common among propranolol treated patients.

Patient compliance

Tablet counts at each follow-up visit indicated a high degree of compliance, as 80% of the patients in both groups had taken more than 95% of the prescribed dose. This was supported by the mean resting heart rates which were 12 to 17 beats/min lower at discharge and follow-up visits in the propranolol group than in the controls. Only 2% of the patients on propranolol but 30% of those on placebo had resting heart rates above 80 beats/min. On the other hand, 25% of the propranolol treated patients as against 2% of the placebo-treated patients had resting heart rates below 50 beats/min.

Comment

Our study showed that treatment with propranolol for one year after a recent myocardial infarction in selected patients with a presumed increased risk of death may reduce the incidence of sudden cardiac death and probably even the risk of reinfarction. These findings support the results of earlier trials with alprenolol (Wilhelmsson *et al.*, 1974; Ahlmark & Saetre, 1976; Andersen *et al.*, 1979) and practolol (Green *et al.*, 1975) and recently published trials with timolol (Norwegian Multicenter Study Group, 1981), metoprolol (Hjalmarson *et al.*, 1981), and propranolol (Beta-blocker Heart Attack Study Group, 1981).

The exact protective mechanism of β-blockade in patients who have suffered an infarction is not known, although the most probable explanation is an antiarrhythmic effect. The same effect has been recorded with different β-blockers. It seems reasonable to conclude, therefore, that blockade of cardiac β-receptors is responsible for the benefits shown, rather than any other individual pharmacological property of each drug. (A more detailed presentation of the results of this trial and a thorough dicussion of their implications have been published recently Hansteen *et al.*, 1982).

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