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Multicentre post-infarction trial of propranolol in 49 hospitals in the United Kingdom, Italy, and Yugoslavia

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SUMMARY A multicentre study of survivors of an anterior myocardial infarction is reported. The trial consisted of 720 patients and was a double-blind, placebo-controlled study with propranolol 40 mg three times a day. Trial entry was at two to 14 days (mean 8·5 days) and follow-up at one, three, and in most centres, six and nine months. The trial was designed to detect a 50 per cent reduction in mortality and this was not shown. The non-fatal reinfarction rate was similar in both groups. Subgroup analysis identified several prognostic risk factors for death, none of which interacted with treatment.

There have been 15 studies with four beta-adrenergic blocking drugs (propranolol, practolol, alprenolol, and oxprenolol) after acute myocardial infarction.[1–15] In 11 of these studies,[1–9 14 15] the drugs were started within the first 24 to 48 hours. Only in the first study with propranolol[1] was a reduction in mortality claimed. In another early intervention trial an important subgroup with an initial high heart rate also had a reduced mortality with practolol.[14] In the other four studies,[10–13] treatment was started two weeks or more after recovery from the acute attack and was continued for up to three years. Three of these trials yielded significant reductions in mortality with practolol[13] and alprenolol.[11 12] The present studies were undertaken to see whether propranolol gave comparable results with those of practolol[13] in patients with anterior infarction.

Patients and methods

From a total of 49 hospitals, 720 patients (609 men, 111 women) aged 70 or less entered a double-blind placebo-controlled study at two to 14 days (mean 8·5) after anterior infarction. They were started on propranolol or placebo according to a separate random code for each centre, with a dose of 40 mg propranolol thrice daily. Follow-up was at one, three, six, and nine months in 28 centres (Table 1). Outpatient facilities were restricted in 21 hospitals

Table 1 *Number of patients*

	Patients in trial	
	Placebo	*Propranolol*
Entry	365	355
1 month	345	328
3 months	295	299
6 months*	147	146
9 months*	122	123

* In a total of 374 patients the trial duration was only three months.
Mean duration in trial: patients on propranolol 172 days; patients on placebo 169 days.

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and so hospital follow-up was made at one and three months only. Subsequent mortality and morbidity in patients beyond three months from these 21 centres was ascertained by direct communication with the doctor and, if necessary, with the patient's general practitioner. At the hospital visits blood pressure, heart rate, side effects, and drug compliance were recorded. Patients withdrawn for various reasons were also followed up and their fate determined.

PATIENT SELECTION

Diagnosis of anterior myocardial infarction was based on electrocardiographic abnormalities of an anterior infarction defined as "very probable" on WHO electrocardiographic criteria,[16] plus either a typical history or serum enzyme levels (AST and LDH) at least twice the accepted upper limit of normal or three times if CK was used.

Critera for exclusion included :* (1) bronchospasm; (2) atrioventricular block greater than first degree; (3) sinus bradycardia (< 55/minute); (4) persistent heart failure; and (5) beta blockade at time of infarction.

Withdrawal criteria : (1) angina requiring treatment with a beta blocker; (2) bradycardia less than 50 beats/min or heart block greater than first degree; (3) other clinical indications, for example heart failure; and (4) discontinuation of treatment for more than 10 days.

STATISTICAL METHODS

It was estimated that 1000 patients in each group would be needed to give adequate power to detect a reduction in three month mortality from 4 per cent in the placebo group to 2 per cent in the propranolol group[17]; this assumed reduction was based on the earlier practolol trial results.[13] A precautionary sequential analysis of mortality was also used to avoid excessive prolongation of the study. Analysis of mortality included all deaths in all randomised patients, whether or not they withdrew from the trial. Analysis of potential risk factors and their interaction with treatment was carried out by means of stepwise regression,[18] and confirmed by means of Cox's proportional hazard regression model.[19] In stepwise regression the most significant factors are deliberately selected from a large set of possible factors. This leads to significance levels which are too high and which, therefore, must be interpreted cautiously.[20] *

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Results

GROUP COMPARISON

The two groups were similar in all the factors shown in Table 2.

TRIAL TERMINATION

When the double-blind trial reached the statistical end-point of no difference, patient recruitment was stopped.

TOTAL DEATHS AND REINFARCTIONS

The difference in total mortality between the two double-blind groups was not statistically significant (Table 3). The 90 per cent confidence limits on the mortality difference in the trial ranged from a 41 per cent decrease to a 54 per cent increase. There were no significant intergroup differences for timing or mode of death or reinfarction (Tables 3 and 4).

Table 2 *Comparability of groups*

History before infarct	*Placebo*	*Propranolol*
No. of patients	365	355
Mean age (y)	54·8	55·0
Percentage male	83	86
Percentage female	17	14
Mean weight (kg)	72	73
Mean height (cm)	170	170
Previous angina:		
Percentage positive	40	35
Percentage with angina more than three months	19	15
Previous infarct (%)	16	15
History of cardiac failure (%)	2	1
Concurrent disease:		
Percentage hypertension	15	13
Percentage peripheral artery disease	2	1
Percentage with diabetes	4	3
Smokers (%)	65	64
Data on original infarct and post-infarct state		
Earliest mean (±SE) systolic and diastolic blood pressure after infarct (mmHg)	144·5 (1·4) / 91·4 (0·9)	142·7 (1·3) / 91·4 (0·8)
Earliest mean (±SE) heart rate (beats/min)	84·0 (1·0)	82·2 (0·9)
Treatment during acute phase:		
Percentage DC shock	4	5
Percentage drug treatment other than beta blockers	88	86
Percentage receiving beta blockers	7	5
Percentage with cardiac failure in acute phase	21	19
Mean no. of days from infarct to entry	8·4	8·4
Mean (±SE) systolic BP at entry (mmHg)	124·2 (1·0)	122·8 (0·9)
Mean (±SE) diastolic BP at entry (mmHg)	79·7 (0·6)	79·2 (0·6)
Mean (±SE) heart rate at entry	81·9 (0·6)	81·3 (0·7)
Percentage with ventricular ectopics at entry	7	6

Table 3 *Total deaths and reinfarctions in all randomised patients at 9 months*

	Placebo		Propranolol	
	No.	*Per cent*	*No.*	*Per cent*
Cardiac deaths in trial	18	4·9	19	5·4
Non-cardiac deaths in trial	2	0·5	3	0·8
Cardiac deaths after withdrawal	7	1·9	6	1·7
Non-cardiac deaths after withdrawal	0	0	0	0
Total deaths	27	7·4	28	7·9
Non-fatal reinfarctions in trial	14	3·8	15	4·2
Non-fatal reinfarctions after withdrawal	1	0·3	0	0

Per cent expressed as a percentage of number entering the study.

Table 4 *Time from entry to death—total mortality*

Time from entry (months)	*Placebo*	*Propranolol*
1	14	18
1 to 3	6	3
3 to 6	6	4
6 to 9	1	3

PROGNOSTIC FACTORS AND RELATION TO TREATMENT

Six prognostic factors independent of a treatment effect were identified (Table 5). The overall mortality correlated positively with age and with entry heart rate. Mortality was also higher in patients with arrhythmias at entry.

Attempts were made to relate any effect of treatment on mortality to the six prognostic factors above and also to other factors such as blood pressure (Table 6) (immediately on admission and at entry) and congestive cardiac failure (Table 7). However, no statistically significant relation was found for any of the factors ($p > 0.05$).

Table 5 *Risk factors for mortality independent of treatment*

Age	Definite
Heart rate at trial entry	$p < 0.005$
Arrhythmias at entry	
Female sex	Possible
Smoking	$p < 0.1$
History of myocardial infarction	

Table 6 *Deaths related to acute systolic and entry diastolic blood pressures*

	Placebo	Propranolo
No. (%) deaths with acute systolic blood pressure above mean	14 (8·2)	10 (6·7)
No. (%) deaths with acute systolic blood pressure below mean	13 (6·7)	18 (8·8)
No. (%) deaths with entry diastolic blood pressure above mean	21 (9·5)	15 (7·3)
No. (%) deaths with entry diastolic blood pressure below mean	6 (4·2)	13 (8·7)

Table 7 *Death rate by signs of congestive cardiac failure in acute phase*

	Placebo		Propranolol	
	No.	*Per cent*	*No.*	*Per cent*
Congestive cardiac failure:				
Absent	22	7·6	21	7·3
Present	5	6·5	7	10·6

WITHDRAWALS (Table 8)

There were no statistically significant differences between the two groups.

OPEN TRIAL

In parallel with the double-blind, placebo-controlled trial, an open study, using 40 mg propranolol three times a day, was also conducted in 500 patients by doctors in 37 hospitals who, because of the practolol multicentre trial findings,[13] were unwilling to consider randomising. There were three findings of particular interest from this study:

(1) Comparability of patients at trial entry (8·5 days) with both groups of the double-blind trial.
(2) A similar total mortality (31/501 entered: 6·2%) at nine months.
(3) A more precise estimate of risk factors independent of treatment was possible by inclusion of this group (Table 5).

Table 8 *Reasons for withdrawal from trial (these are not mutually exclusive)*

	Placebo	Propranolol
Reinfarction	9	10
Cardiac failure	22	22
Cardiac failure alone	17	10
Angina	13	7
Arrhythmias	11	7
Adverse reaction	5	12
Other	38	42
Total number of patients withdrawn	88 (24%)	82 (23%)

Discussion

The findings indicate no difference in mortality throughout the nine months of follow-up after anterior myocardial infarction, between those given propranolol (40 mg thrice daily) and placebo. These results merit close examination, because they demonstrate some important features in the design, execution, and interpretation of such trials.

The design of the study took into account the experience gained from the practolol multicentre study.[13] The number of patients required was estimated on the basis that propranolol might produce a comparable reduction in mortality to that of practolol, that is 50 per cent.

Propranolol may produce a reduction in mortality of less than 50 per cent, and this is still possible within the confidence limits of the result (Fig). The dismissal of potentially useful agents because of an inadequate sample size or the reporting of "no difference" between treatment and control when only very large differences have been considered, has been recently reviewed.[21] In the example given in that reference (which was a propranolol post-infarction trial) there was a 77 per cent risk of missing a real difference of 25 per cent reduction in mortality, and a 42 per cent risk of missing a difference of 50 per cent. The Figure gives the 90 per cent confidence limits for the true percentage difference in mortality rates for all propranolol trials. In seven of the eight trials, a 25 per cent reduction in mortality cannot be excluded; in six of the eight studies, a 50 per cent reduction cannot be excluded.

In the present study the lower confidence limit does not exclude a possible reduction of 40 per cent but much larger numbers of patients would have been required to show this smaller difference (approximately 1700 per group). It is pertinent to ask whether a smaller reduction in mortality, if proven, would warrant the widespread use of a beta-blocking agent for all anterior infarction patients. A recent editorial by Rose[22] develops this argument. The annual mortality after an uncomplicated anterior infarction is about 6 per cent,[13] and if a 30 per cent reduction in this mortality could be achieved, then in every 100 patients treated, two patients would benefit.

Another consideration concerns the possibility that harm to specific patient subgroups outweighs benefit to others. However, this was not shown in this trial. In particular, there was no evidence that more patients died in congestive cardiac failure or were withdrawn from the trial because of this complication in the propranolol group compared with placebo.

In the practolol multicentre study, patients with an anterior infarction whose trial entry diastolic blood pressure was equal to or below the mean (78 mmHg) and who received practolol, had only one-sixth the mortality, compared with their respective placebo group (24 deaths on placebo versus four deaths on practolol). Interactions of blood pressure and treatment were sought in the present study, but none of these reached significance at the 5 per cent level.

Detailed comparison with the practolol trial is not appropriate, but possible pertinent differences include: size of trials, differences between patient groups, differences in pharmacological profiles, and differences in the time courses of beta blockade.[23 24]

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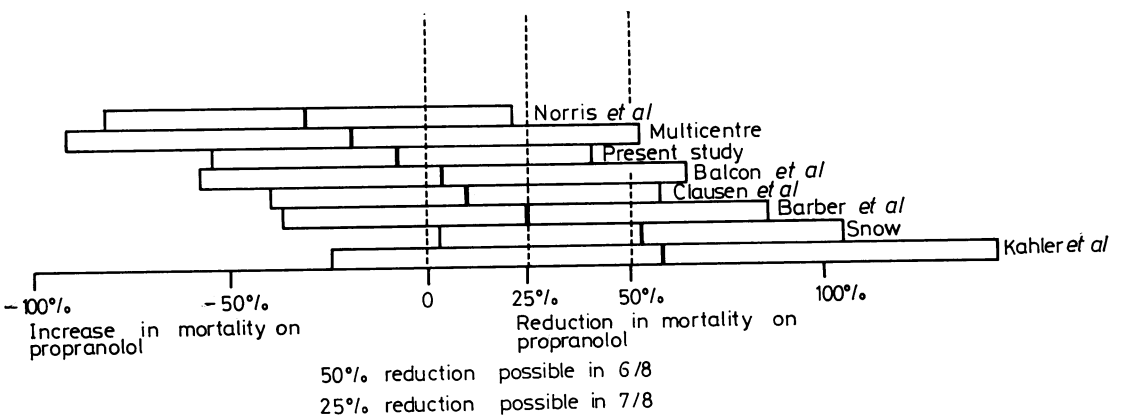

Fig. *Difference in mortality rates with 90 per cent confidence limits expressed as a percentage of observed control rate in eight controlled trials of propranolol.*

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