PAPERS AND ORIGINALS

Reduction in mortality after myocardial infarction with long-term beta-adrenoceptor blockade

Multicentre international study: supplementary report

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Summary

In a controlled multicentre trial carried out to assess the value of long-term practolol treatment after myocardial infarction the provisional results showed a significant reduction in mortality, though some of the data were lacking. These have now been included and the results updated.

The final figures for all deaths were 78 in the placebo group of 1533 patients and 48 in the practolol group of 1520 patients. The reduction in mortality (38%) was significant at the 1% level. The figures for non-fatal reinfarction (97 in the placebo group, and 75 in the practolol group) were not significantly different. Patients with pre-entry anterior infarction, and especially those with a diastolic blood pressure equal to or below the mean (78 mm Hg) at entry to the trial, were at high risk but benefited particularly well from beta-adrenoceptor blockade. After pre-entry inferior infarction the percentage reduction in deaths occurring within two hours after symptoms of a new event was similar to that after anterior infarction, but the incidence of death more than two hours after the event was greater in the practolol-treated group. Thus the difference between groups in total deaths after pretrial inferior infarction was marginal.

Until the results of further trials are reported long-term beta-adrenoceptor blockade (possibly up to two years) is recommended after uncomplicated anterior myocardial infarction.

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Introduction

We previously reported the results of an international multicentre placebo-controlled trial of long-term beta-adrenoceptor blockade in 3038 patients who had recovered from the acute phase of myocardial infarction.[1] The planned end-points of the trial were death and reinfarction. Mortality was found to be significantly reduced in the practolol-treated group ($P < 0{\cdot}02$), though data on some patients were lacking. That information has now been received and we report here an analysis of the final results.

Methods

A full description of the methods employed was given previously. Entry to the trial was one to four weeks after the acute episode (mean 13 days). The main reasons for exclusion were age over 70, bronchospasm, congestive heart failure, bradycardia, severe heart block, and serious intercurrent disease.

Results and comment

Table I shows the numbers of patients at risk at different stages of the trial. Most had completed the trial after one year. The progressive reduction in numbers over the first 12 months was due to death and reinfarction; withdrawal because of angina pectoris, arrhythmias, other medical conditions, and suspected adverse reactions; and defaulting. In addition 152 patients had not completed 12 months when the trial was closed.

There were highly significant differences between the placebo and drug-treated groups in the numbers of patients withdrawn because of real or suspected adverse reactions (76 in the placebo group compared with 134 in the practolol group: $P<0.001$), angina pectoris (84 compared with 39: $P<0.001$), and dysrhythmias (55 compared with 28: $P<0.01$). Similar numbers of patients in the two groups defaulted (55 in the placebo group and 49 in the practolol group).

TABLE I—*Numbers of patients at risk in the two treatment groups up to 24 months after entry to trial*

	At entry to trial	Months after entry					
		1	3	6	12	18	24
No on practolol	1533	1421	1334	1234	1071	609	478
No on placebo	1520	1401	1294	1188	1038	608	481

MORTALITY AND NON-FATAL REINFARCTION

Further follow-up inquiries disclosed six additional deaths, which widened the gap between the placebo and drug-treated groups, the difference between them (78 *v* 48) being significant at the 1% level (table II). The difference in numbers of non-fatal reinfarctions between the placebo and drug-treated groups (97 *v* 75) failed to reach the 5% level of significance ($P<0.09$).

TABLE II—*Numbers of deaths and reinfarctions in the two treatment groups*

	Placebo	Practolol	Significance
Cardiac deaths (sudden)	78 (55)	48 (31)	$P<0.01$ ($P<0.01$)
Non-fatal myocardial infarction	97	75	$P<0.09$
All events (deaths + myocardial infarction)	175	123	$P<0.001$
Deaths from other causes	5	6	NS
Cardiac deaths after withdrawal	41	42	NS

NS = Not significant.

SITE OF PRE-ENTRY INFARCT AND PROGNOSIS

The numbers of patients with pretrial anterior and inferior infarcts were almost equal (1539 and 1501), though in 13 cases the site was unknown. Table III shows the mortality in relation to the pre-entry infarction site and the time that elapsed between entry to the trial and death. Deaths that occurred within two hours of symptoms of a new event were regarded as "sudden."

In the placebo group pre-entry anterior infarction was associated with a significantly higher mortality than inferior infarction (50 *v* 28 deaths: $P<0.02$), particularly in the first month after entry (18 *v* 1).

Practolol was more effective in the higher-risk group of patients with anterior infarction; this group accounted for nearly all the reduction in overall mortality among patients treated with practolol as opposed to placebo.

The proportionate reduction in "sudden" deaths after pre-entry anterior infarction was similar to that after inferior infarction (34 *v* 20, and 21 *v* 11).

Among patients with inferior infarction the incidence of deaths more than two hours after a new event was greater in the practolol group than in the placebo group (14 *v* 7), almost cancelling out the apparent advantage in sudden deaths.

With regard to the time between entry to the trial and death after pre-entry inferior infarction, more patients in the practolol group died within a month of entering the trial than in the placebo group (7 *v* 1). After the first month the distribution between the groups was reversed, with 18 deaths in the practolol group and 27 in the placebo group. This change, however, was not significant (Wilcoxon rank sum test on number of days to death).

BLOOD PRESSURE AND PROGNOSIS

Patients with anterior infarction and a diastolic blood pressure equal to or below the mean for the trial (78 mm Hg) at the time of entry were at higher risk than other patients (table IV), but the prognosis was greatly improved with practolol treatment.

ASSOCIATIONS WITH ARRHYTHMIAS

The arrhythmias that had been observed during the acute phase of the pre-entry infarction were recorded on the entry record forms. Forty per cent of all patients had had atrial or ventricular fibrillation, tachycardia, or ectopic beats. Table V shows the relationships between mortality during the first year of the trial and the presence or absence of these atrial and ventricular arrhythmias associated with pretrial infarction.

The numbers of deaths in the six categories of arrhythmia were too small to justify individual comment. Atrial arrhythmias taken as a whole, however, appeared to be prognostically similar to ventricular arrhythmias. Both were associated with a higher mortality than for all other patients and a greater reduction in deaths with treatment. Further analysis of the presence or absence of arrhythmia without regard to origin was therefore carried out in relation to the two main prognostic factors already mentioned—namely, site of pretrial infarct and blood pressure (table IV). Again the numbers of deaths in the subgroups were small and differences should be interpreted with caution. Nevertheless, the highest mortality among placebo-treated patients and the lowest among practolol-treated patients occurred in those with anterior infarction associated with arrhythmias and a blood pressure of 78 mm Hg or less at entry to the trial. In contrast, pre-entry inferior infarction carried a much better prognosis, which was not appreciably altered by blood-pressure category, the presence of

TABLE III—*Deaths related to site of pre-entry infarct and time after entry to trial*

Time from entry (months)	No of deaths and death rates							
	Pre-entry anterior infarcts				Pre-entry inferior infarcts			
	Placebo		Practolol		Placebo		Practolol	
	No of deaths	Death rate (%)†	No of deaths	Death rate (%)†	No of deaths	Death rate (%)†	No of deaths	Death rate (%)†
Under 1	18	28·8	12	19·5	1	1·7	6	11·3
1–	8	7·0	3	2·7	4	3·6	3	1·7
3–	10	6·3	2	1·3	8	5·2	1	0·6
6–	5	1·8	3	1·1	9	3·3	8	2·7
12–	9	1·8	3	0·8	5	1·4	5	1·3
24	0		0		1		1	
Total	50 (34)		23 (20)		28 (21)		25 (11)	
Total for first year	43	6·1	20	3·0	22	3·5	19	2·9

Greater accuracy in calculating times of death has resulted in minor but important changes to this table as compared with its original.
Sudden deaths (≤2 h) in parentheses.
†Death rates based on average number at risk and expressed on an annual basis.

TABLE IV—*Deaths in first year related to site of pre-entry infarct, presence of arrhythmias, and diastolic blood pressure at entry to trial in the two treatment groups*

Site of infarct	Diastolic BP (mm Hg)	Arrhythmias*	Placebo		Practolol	
			No of deaths	Death rate (%)†	No of deaths	Death rate (%)†
Anterior	≤78	Absent	10	6·3	3	2·1
		Present	14	10·0 } 8·1	1	0·7 } 1·4
	>78	Absent	8	3·6	9	4·0
		Present	9	6·0 } 4·5	7	4·6 } 4·2
Inferior	≤78	Absent	8	4·6	3	1·8
		Present	2	1·9 } 3·6	4	3·4 } 2·4
	>78	Absent	7	3·0	8	3·4
		Present	5	4·2 } 3·4	4	3·0 } 3·2

*Types of arrhythmia defined in text.
†Death rates based on average numbers at risk during first year.

TABLE V—*Deaths in first year related to arrhythmias associated with pre-entry infarct in the two treatment groups*

Type of arrhythmia	Placebo		Practolol	
	No of deaths*	Death rate (%)†	No of deaths*	Death rate (%)†
Supraventricular ectopic beats	5	4·5	2	1·6
Supraventricular tachycardia	5	8·9	0	0·0
Atrial fibrillation	8	12·6	1	1·8
Any atrial arrhythmia	14	6·9	3	1·4
Ventricular ectopic beats	21	5·5	14	3·6
Ventricular tachycardia	4	5·5	2	2·9
Ventricular fibrillation	3	8·5	0	0·0
Any ventricular arrhythmia	24	5·7	14	3·4
Both atrial and ventricular arrhythmias	8	7·3	1	1·1
Atrial or ventricular arrhythmia	30	5·8	16	3·0
Arrhythmia absent	33	4·2	23	3·0

*Types of arrhythmia not mutually exclusive: thus numbers of deaths are not additive.
†Death rates based on average number of patients at risk during first year of trial.

TABLE VI—*Cumulative effect on mortality one year after entry of anterior site of infarction, associated arrhythmias, and diastolic blood pressure ≤78 mm Hg in the two treatment groups*

	Placebo		Practolol	
	No	%	No	%
All myocardial infarctions	63	4·8	39	3·0
Pretrial anterior myocardial infarction	41	6·1	20	3·1
Anterior myocardial infarction plus diastolic blood pressure ≤78 mm Hg	24	8·1	4	1·4
Anterior myocardial infarction plus diastolic blood pressure ≤78 mm Hg plus arrhythmia in acute phase	14	10·0	1	0·7

arrhythmias, or treatment with practolol.

Table VI shows the cumulative effect of anterior infarction, below-average blood pressure, and arrhythmia on mortality and the effect of treatment.

Discussion

These final results support our previous conclusion that long-term practolol treatment after myocardial infarction was successful in reducing mortality. Patients with pre-entry anterior infarction derived most benefit. The proportionate reduction in sudden deaths was similar irrespective of infarct site. After pre-entry inferior infarction, however, the number of deaths occurring more than two hours after symptoms of a new event was greater in the practolol-treated group than in the placebo group. Thus the total reduction in mortality after inferior infarction was marginal. Another peculiarity about mortality after pre-entry inferior infarction was related to the interval between the start of medication and death. In the first month after entry to the trial more deaths occurred in the practolol group than in the placebo group (7 *v* 1), but after the first month there were 18 deaths in the practolol group compared with 27 in the placebo group. The results *after* the first month were consistent with the results of a Swedish trial[2] in which treatment with alprenolol was started six weeks after the acute event: that trial showed no influence of the pre-entry infarct site on the results of treatment.

Our results in relation to the presence or absence of clinically obvious arrhythmias in the acute phase after the pre-entry infarction are interesting. All the clinically serious arrhythmias had disappeared before the patients were entered into the trial. Nevertheless, the patients with anterior infarction who had previously exhibited them were shown ultimately to have a poorer prognosis.

The lifesaving effects of practolol were probably related to its antiarrhythmic activity as a beta-adrenoceptor blocker. The careful study by Barber *et al* supports this.[3] Theoretically the use of a drug that prevents death from arrhythmia after new ischaemic events might be expected to result in a proportionately greater incidence of *non-fatal* reinfarction. In our trial the incidence of non-fatal reinfarction was not increased by beta-adrenoceptor blockade: surprisingly, a small reduction occurred, though this did not reach statistical significance.

Because of its serious side effects practolol is now absolutely contraindicated for long-term use and indeed is no longer commercially available in tablet form. Extensive evidence from experiments on animals[4–8] and trials on man[2 9] support the view that other beta-adrenoceptor blocking agents may be as effective as practolol, though the differing additional properties of currently available beta-adrenoceptor blocking drugs may result in differences in safety in some cases and effectiveness in others.

Until the results of further trials are reported long-term beta-adrenoceptor blockade is recommended after anterior infarction unless specifically contraindicated. Treatment should begin when it is clear that there is no serious impairment of conduction and no immediate prospect of congestive failure; it should probably be continued for up to two years (the extent of our experience). We can make no recommendations about treatment after inferior infarction.

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