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EUROPEAN COLLABORATIVE TRIAL OF MULTIFACTORIAL PREVENTION OF CORONARY HEART DISEASE: FINAL REPORT ON THE 6-YEAR RESULTS

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Summary In a randomised controlled evaluation of multifactorial prevention of coronary heart disease (CHD) among 60 881 men employed in 80 factories in Belgium, Italy, Poland, and the UK intervention was associated with reductions of 10·2% in total CHD, 6·9% in fatal CHD, 14·8% in non-fatal myocardial infarction, and 5·3% in total deaths, with a neutral result for non-CHD deaths. Benefit was significantly related to the extent of risk factor change. The observed reduction in total CHD was 62% of that predicted by means of a multiple logistic function summary of risk factor changes. Advice on risk factor reduction in middle-aged men is effective to the extent that it is accepted and it appears to be safe.

Introduction

IN 1983 we reported incomplete incidence and mortality results from the World Health Organisation European Collaborative Trial of Multifactorial Prevention of Coronary Heart Disease.[1] (The trial was still in progress in Warsaw, which started 2 years after other centres.) The analysis in the interim report considered only the overall differences between the intervention and control groups to try to see what happens when an attempt is made to change a community's coronary risk factors. In the large Belgian centre there was a 24% reduction in total incidence of coronary heart disease (CHD), significant at the 5% level. Similar reductions in the Rome and Cracow centres did not individually reach significance because there were fewer factories. The absence of a positive result from the UK centre reduced the overall benefit to a non-significant level. The UK centre was the least successful in reducing risk factor levels, so that its result was not surprising.

The trial in Warsaw is now finished. The present report gives the first complete results from all centres, and analyses them in an attempt to see what happens when coronary risk factors in a community are changed. For this we related the magnitude of incidence reduction to the magnitude of risk factor change.

Subjects and Methods

60 881 working men aged 40 to 59 years entered the trial.[2] One-half received preventive advice on a cholesterol-lowering diet, control of smoking, overweight and blood pressure, and regular exercise. The other half formed a control group, 10% of whom were screened at entry and at intervals during the trial to assess their risk factor levels; the other 90%, who were not examined during the trial, formed the at-risk population for incidence measurements. For the analysis the changes in the various risk factors were summarised with a single number for each factory. To do this, data from the European cohorts of the Seven Countries Study[3] were used to assign weighting coefficients to each factor so as to predict the risk of CHD associated with any given levels of the risk factors. A multiple logistic function (MLF), calculated for each factory with the use of these coefficients, gives the best prediction for the expected CHD rate. Thus the net difference in this function between intervention and control men estimates the predicted reduction in CHD incidence, if risk is wholly and immediately reversible when risk factors are reduced.

The recruitment units for the trial were 80 factories (or other large occupational groups), ranging in size from 69 to 2508 men. These were arranged in matched pairs, and in each pair one was randomly allocated to intervention. (The implications of cluster allocation for

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TABLE I—CUMULATIVE 6-YEAR INCIDENCE OF CHD AND THE NET DIFFERENCE BETWEEN INTERVENTION AND CONTROL GROUPS

Country	Group	At-risk population†	Fatal CHD		Non-fatal MI		Fatal CHD + non-fatal MI		All deaths	
			%	No	%	No	%	No	%	No
Poland	Control	7309	0·89	64	2·02	132	2·65	191	4·78	349
	Intervention	9115	0·92	82	1·52	126	2·24	201	4·52	412
	Δ	..	+3·4	..	−24·8	..	−15·5	..	−5·4%	..
	p	..	0·7	..	0·1	..	0·08	..	0·2	..
Whole trial	Control	26 971	1·50	398	2·11	505	3·27	873	4·40	1186
	Intervention	30 489	1·41	428	1·93	505	3·08	927	4·34	1325
	Δ crude	..	−6·0%	..	−8·5%	..	−5·8%	..	−1·4%	..
	Δ adjusted*	..	−6·9%	..	−14·8%	..	−10·2%	..	−5·3%	..
	p	..	0·8	..	0·06	..	0·07	..	0·4	..

*Adjusted for effect of allocating groups not individuals. †Excludes screened control men (10%).

the statistical power of the trial will be discussed elsewhere—M. J. Shipley, personal communication.) Each pair of factories yielded an independent estimate of changes in risk factors and incidence. Risk factor change was obtained from the calculation for each individual of the MLF change from entry to the 2-year, 4-year, and final examination. Individual changes were then averaged to estimate the overall net change for each intervention factory.

For the particular model used in the analysis the effect of intervention in each factory pair was expressed by the logarithm of the ratio of the intervention to the control rate. (This assumes that in each factory pair the percentage change in incidence rate due to intervention is independent of the magnitude of the underlying rates.) The rates actually observed in each factory are only estimates of the true underlying event rates; and since the study has randomised whole factories rather than individuals, the analysis must allow for variation in their underlying event rates. The relation of outcome to risk factor change was therefore assessed by means of a modification of the maximum likelihood regression method of Pocock et al:[4]

$$\text{Log}_e\,(p_I/p_C) = a + b\,(\Delta_{MLF}) + e$$

where p_I = rate in intervention factory

p_C = rate in control factory

a = a constant (represents any effect of intervention for zero net change in risk factors, as measured)

Δ_{MLF} = net mean change in risk factors (summarised by a multiple logistic function)

b = slope of the regression (estimates the strength of the relation between risk factor change and outcome)

e = error term.

The maximum likelihood method is equivalent to a weighted regression, in which the incidence difference is weighted according to the inverse of its variance for each factory pair. Since the weights themselves depend on the goodness of fit of the regression they must be calculated by iteration.

This method was also used to estimate the overall effect of intervention, ignoring risk factor changes. It provides tests of significance that take account of the randomisation of factories rather than individuals. In this case the regressions simplify and become equivalent to weighted means of the change in incidence.

Results

Table I shows the complete incidence and mortality results from Poland, together with the final totals for the whole trial. The 6-year rates have been calculated actuarially.

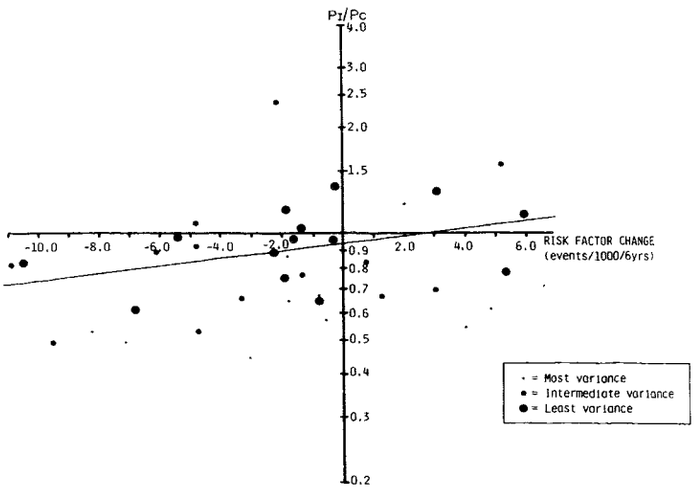
In Poland (Cracow and Warsaw) the incidence of fatal CHD was much lower than in the rest of the trial, with a small, non-significant excess in the intervention group. In contrast, non-fatal myocardial infarction (MI) was lower in the intervention group by 24·8% (p = 0·1). Total CHD (death + non-fatal MI) was 15·5% lower in the intervention group. Non-CHD mortality in Poland was higher than in the rest of the trial and gave the trial's highest rate for total mortality; this rate was 5·4% lower in the intervention than in the control group.

The total experience of the whole trial indicates an overall reduction in fatal CHD associated with intervention of 6·9% (95% confidence interval −19% to +7%). Non-fatal MI was reduced by 14·8% (95% confidence interval −28% to +1%). The combined result for total CHD was intermediate. Non-CHD mortality was almost equal in the intervention (2·93%) and control groups (2·90%), leaving a 5·3% advantage to the intervention group for total mortality.

The maximum likelihood regression method already described was used to study the relation between the degree of risk factor change and the impact on CHD incidence. This tests whether the intervention factories with better control of risk factors also tended to get more benefit.

The result for total CHD is set out graphically in the figure. The method of analysis gave different weights to each factory-pair difference, and this is indicated by different sizes of point. The fitted regression line is described by two statistics. The first is the slope, which measures the strength of the relation between risk factor change and outcome; and the second is the intercept, which measures whether intervention had any effect on outcome not accounted for by the MLF summary of the measured risk factor changes.

For total CHD the regression indicates that when risk



Regression of outcome difference for total CHD (log incidence ratio intervention/control) on net risk factor change (multiple logistic function summary) for 40 pairs of factories.

TABLE II—SLOPE AND INTERCEPT VALUES FOR THE REGRESSION OF CHANGE IN INCIDENCE* OF CHD ON DIFFERENCES IN RISK FACTOR CONTROL FOR TRIAL AS A WHOLE

Outcome	Slope†	(SE)	Intercept‡	(SE)
Fatal CHD	+0·310§	(0·138)	−0·028	(0·069)
Non-fatal MI	+0·260	(0·179)	−0·116	(0·083)
Total CHD	+0·246§	(0·118)	−0·064	(0·057)
Total deaths	+0·151	(0·133)	−0·027	(0·060)
Non-CHD deaths	+0·026	(0·179)	−0·017	(0·078)

*$[\log_e(p_t/p_c)]$.
†Slope = change in log (incidence ratio) per predicted fall (net MLF change) of 10 events/1000/6yr.
‡Intercept = change in log (incidence ratio) for zero net MLF change.
§$p<0·05$ (2-tailed).

factor change was greater (MLF change more negative), the ratio of intervention to control rates was smaller. This is unlikely to be due to chance ($p=0·04$, 2-tailed test). The value of the intercept is small and negative, which indicates that there might have been a slight additional reduction in CHD associated with intervention, other than that accounted for by the MLF summary of measured risk factor changes. A regression of the difference in the intervention-control rates (rather than the logarithm of their ratio) against the measured risk factor changes (with the method already described) indicated that for each reduction in risk factors corresponding to a predicted decline in total CHD of 10 cases per 1000 over the trial period, there was an observed decline of 6·2 per 1000.

More results for the various outcome measures are set out in table II. For fatal CHD and total CHD (primary trial end-points) the relation of benefit to risk factor change is significant at the 5% level (2-tailed), or the 2% level (1-tailed). For non-fatal MI (not a primary end-point) the relation is of similar strength but it is less consistent and does not reach the same level of significance ($p=0·15$, 2-tailed). Mortality from causes other than CHD is almost the same in intervention and control factories, and it is unrelated to change in risk factors. As a result, the fall in total mortality shows an intermediate and positive relation to risk factor change, but this is not significant.

Table III shows results for individual countries. For none of the end-points is there any significant heterogeneity between countries ($p\geqslant 0·2$). Within the UK, Belgium, and Italy the relations with CHD are all positive (that is, better control of risk factors favours the outcome), but the individual results are mostly not significant. In Poland the relation between outcome and compliance is negative, despite a strong overall reduction for total CHD in the intervention group (see table I), but the effect is not significant.

Discussion

Three other randomised primary prevention trials have studied the effects of multiple risk factor control on CHD incidence. The Oslo study[5] was in high-risk men. It achieved a large fall in serum cholesterol level and a smaller reduction in smoking, which corresponded to a net change in MLF of −38%; the incidence of CHD was halved. The MRFIT trial,[6] also in high-risk men, was weakened by large risk factor reductions in the control group, which resulted in a net change in MLF of only −20%; after 6 years the incidence of fatal CHD was 7% lower in the intervention group, a change that was not significant statistically. The Göteborg trial,[7] based, like ours, on a cross-section of all levels of risk, achieved only small risk factor differences between its two groups; and, not surprisingly, the two CHD rates were essentially the same. Taken together, these trials are consistent with the theory that benefit is proportional to reduction in risk factors; and where this reduction is large, the fall in CHD in high-risk men can also be large and statistically significant.

The WHO collaborative trial is the largest randomised trial of CHD prevention to date, with centres in 4 countries (60 881 subjects) following the same protocol. Because of international differences in baseline characteristics and the delivery of intervention, it was planned from the start that the national results should be considered individually as well as collectively.

With the collective results and a conservative 2-tailed significance test, we found that the intervention effort was associated with reductions of 10·2% in total CHD ($p=0·07$), 6·9% in fatal CHD ($p=0·8$), 14·8% in non-fatal MI ($p=0·06$), and 5·3% in total mortality ($p=0·4$). These benefits are large enough to be of great public health importance, in relation to the small costs of intervention; but they do not achieve the conventional level of significance, and therefore by themselves they constitute only moderate evidence that intervention is effective. (For total CHD and for non-fatal MI they achieve the same significance levels as the LRC trial,[8] which reported results with a 1-tailed test.)

The pooled result was non-significant because the large UK centre had little success in sustained risk factor control (Δ_{MLF} −4%), so that its failure to reduce CHD was not surprising. The other countries did much better and each reported a substantial reduction in total CHD. This suggested a need for an analysis, reported for the first time in this paper, which relates the net risk factor reduction to the changes in CHD incidence across the 40 pairs of factories, each of which constituted an independent trial. For each of the coronary event groups (total, fatal, and non-fatal), the relation proves to be strong; that is, the degree of benefit depends on the degree of risk factor control. For total CHD

TABLE III—SLOPES FOR THE REGRESSION OF CHANGE IN INCIDENCE* OF CHD ON DIFFERENCES IN MLF RISK FACTOR CHANGE BY COUNTRY†

Outcome	Slopes‡ (SE)				Test for heterogeneity	
	UK	Belgium	Italy	Poland	χ^2_3	p
Fatal CHD	0·263 (0·162)	0·129 (0·394)	1·301 (0·828)	−0·371 (0·701)	2·49	0·5
Non-fatal MI	0·222 (0·205)	0·788 (0·618)	1·286 (0·801)	−0·594 (0·656)	4·10	0·3
Total CHD	0·195 (0·134)	0·339 (0·358)	1·322 (0·592)	−0·543 (0·484)	6·09	0·2
Total deaths	0·202 (0·164)	0·310 (0·341)	0·404 (0·673)	0·297 (0·432)	2·17	0·6
Non-CHD deaths	0·131 (0·235)	−0·612 (0·444)	0·025 (0·876)	0·481 (0·503)	3·08	0·5

*$[\log_e(p_t/p_c)]$.
†The Spanish Centre participated only in the study of risk factor changes, not incidence.
‡Slope = change in log (incidence ratio) per net MLF change of 10 events/1000/6 yr.

and for fatal CHD the result is significant at the 5% level (or 2%, if a 1-tailed test is preferred).

The MLF statistic offers a best-estimate of the predicted fall in CHD if the benefit of risk factor reductions is instantaneous and complete. Over the 6 years of the trial the observed benefit in total CHD was 62% of this predicted value. The shortfall can be explained by measurement defects (estimates of change were subject to sampling error), by delay in risk reversal (already suggested for smoking in numerous observational studies), and by the disappointing effect of antihypertensive drugs on CHD risk.[9] The apparent benefit was surprisingly large and quick to appear, especially since most of the deaths were in men with CHD at entry to the trial. It is possible that the effect of dietary advice on CHD risk is not confined to the reduction in serum cholesterol level, but also involves thrombotic mechanisms.

In Poland there was a large overall benefit to the intervention group, but this tended to be negatively related to the MLF estimate of risk factor reduction. This could well have happened by chance; or it may be that the relation of risk factors to disease is qualitatively or quantitatively different in Poland, and that the MLF coefficients which we used—and which were derived from other European countries—may not have been appropriate.

Except for hypertension control, our intervention methods were based on lifestyle changes. There was no evidence of any adverse effects on non-coronary mortality. In this respect dietary methods of lipid control may differ from pharmacological methods.[10]

This trial has yielded strong experimental evidence that, among ordinary middle-aged men, advice on risk factor control is effective to the extent that it is accepted, and it appears to be safe.

A more complete report of the trial will be published by WHO.

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ENALAPRIL, ATENOLOL, AND HYDROCHLOROTHIAZIDE IN MILD TO MODERATE HYPERTENSION

A Comparative Multicentre Study in General Practice in Norway

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Summary Enalapril, atenolol, and hydrochlorothiazide were compared in a double-blind randomised parallel study in general practice. 436 patients with mild to moderate hypertension were included at 76 centres. A two-week placebo run-in period was followed by 16 weeks of monotherapy. The initial doses were: enalapril 20 mg; atenolol 50 mg; and hydrochlorothiazide 25 mg. These were doubled if treatment was not effective after 4 weeks. Adverse reactions were the main reason for withdrawal from the study (9 on enalapril, 19 on atenolol, and 8 on hydrochlorothiazide). Systolic and diastolic blood pressures were significantly reduced in all three groups. The reduction in systolic blood pressure was greater on enalapril than on atenolol. Serum potassium was reduced and uric acid increased on hydrochlorothiazide. Fasting blood sugar rose on atenolol but fell on enalapril. The frequency of adverse reactions was acceptable in all three groups. After 16 weeks on treatment significantly more adverse reactions were recorded in the atenolol group than in the enalapril group. Enalapril is effective and well tolerated in patients with mild to moderate hypertension.

Introduction

ANTIHYPERTENSIVE treatment with conventional drugs has been shown to be effective in the prevention of cerebrovascular disease. The preventive effect with coronary heart disease (CHD) has, however, been disappointing[1-5] especially since in hypertensives below 65 years of age CHD is a much more common complication than cerebrovascular disease.[6] Drug-induced metabolic effects have been suggested as possible explanations for this poor effect on CHD.[7-11] In addition, antihypertensive treatment is often associated with side-effects,[12-14] which may reduce patient compliance.

The renin-angiotensin-aldosterone system (RAAS) seems to have an important role in blood-pressure regulation; therefore, interference with this system seems a logical approach in the management of hypertension.

Enalapril is a highly specific, long-acting, non-sulphydryl angiotensin-converting enzyme (ACE) inhibitor.[15] Earlier studies have shown its antihypertensive effect, safety, and acceptability.[16,17]

The aim of this study was to compare antihypertensive efficacy, safety, and tolerance of enalapril with that of atenolol and hydrochlorothiazide in patients with mild to moderate hypertension in general practice.

Methods

Study Design

76 general practitioners and consultants in internal medicine participated in the study. At each centre the office assistant ensured patient compliance, dispensed and monitored the test-medication, and assisted in the administration of the trial.