How can we best prolong life? Benefits of coronary risk factor reduction in non-diabetic and diabetic subjects

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Abstract

Objective—To compare the theoretical benefits of different approaches to reduce risk factors for coronary heart disease in subjects at risk.

Design—The results of findings from meta-analyses of intervention studies on cause specific mortality and of observational studies on smokers and ex-smokers were applied to observational data on 10 year cause specific mortality derived from the multiple risk factor intervention trial. Lifetable analyses were used to estimate gains in life expectancy.

Subjects—Diabetic and non-diabetic men initially 35–57 years of age.

Main outcome measures—10 year mortality from coronary heart disease, 10 year total mortality, man years of intervention to prevent one death and one death from coronary heart disease, gain in life expectancy, and drug costs per year of additional life in diabetic and non-diabetic men of 45.

Results—In non-diabetic men a 10 year mortality from coronary heart disease of 14.4 per 1000 would be reduced by a mean of 0.58, 0.82, 2.64, and 2.74 per 1000 by antihypertensive treatment, lowering cholesterol concentration, taking aspirin, and stopping smoking respectively; a 10 year total mortality of 44.1 per 1000 would fall by a mean of 1.06, 5.16, and 8.65 per 1000 with antihypertensive and aspirin treatment and stopping smoking respectively and increased by a mean of 0.07 per 1000 with the lowering of cholesterol concentration. In diabetic men the reductions in mortality from coronary heart disease would be between three and five times greater, and total mortality would show mean reductions of 5.81, 0.56, 16.17, and 20.84 per 1000 respectively, with all interventions of significant benefit except the lowering of cholesterol concentration. Between 2400 and 3800 man years of pharmacological intervention were calculated as being necessary to prevent one death from coronary heart disease in a non-diabetic man, and between 800 and 1200 man years in a diabetic man. The loss of life expectancy associated with smoking and hypertension is greater than that accruing from hypercholesterolaemia, but stopping smoking would prolong life by a mean of around four years in a 45 year old non-diabetic man and three years in a diabetic man, whereas aspirin and antihypertensive treatment would provide approximately one year of additional life expectancy in both categories.

Conclusions—Studies to date have shown little impact of drugs that lower cholesterol concentration and blood pressure on either coronary heart disease or total mortality. Although new treatments for hypercholesterolaemia and hypertension might help prevent coronary heart disease, other approaches to reduce the burden of premature death are required.

Introduction

Tackling the burden of coronary heart disease needs both population strategies, based on reducing the overall levels of risk factors in populations, and interventional approaches for those at the upper end of the risk factor distribution.¹ Calculations of the efficacy of population approaches have estimated gains in life expectancy of between 0.4 and 1.1 years for different strategies applied to 35 year olds.² Such studies have estimated benefit by calculating mortality before and after statistical removal of the adverse effect of the risk factor,^{2,4} but in reality treated hypertensive subjects or ex-smokers remain at greater risk than normotensive subjects or those who have never smoked. To my knowledge, no estimates exist comparing the likely benefits of different targeted interventions in people at high risk.

Several recent meta-analyses have assessed the effects of treating hypertension⁵ and hypercholesterolaemia^{6–8} and of aspirin treatment⁹ on both cardiovascular and other causes of death. These analyses have provided estimates, with confidence intervals, of proportional changes in cause specific mortality resulting from the effects of the interventions. If these interventions are assumed to have similar effects in people at high risk in the general population measurement and comparison of the likely effects of different interventional approaches should be possible.

Diabetic subjects are at high risk of coronary heart disease and stroke, and risk factors, such as serum cholesterol concentration, blood pressure, and smoking, are also important in diabetes.^{10–12} Large intervention studies of risk factor reduction have not been done in diabetic subjects. Indeed, only one of the studies in which people with diabetes have been included, the hypertension detection and follow up program, has reported the effects of intervention separately in diabetic and non-diabetic participants¹³; similar proportional effects on outcome were found in the two groups. It might, therefore, be valid to use similar approaches to those outlined above to estimate the effects of intervention in a group at high risk of cardiovascular disease.

Detailed observations on cause specific 10 year mortality are available for 342 815 non-diabetic and 5163 diabetic men screened for the multiple risk factor intervention trial who were aged 35–57 and free of myocardial infarction at baseline. I used these data as the baseline for calculations comparing the benefits of four different approaches to reducing cardiovascular risk in the population: lowering cholesterol concentration and blood pressure, stopping smoking, and primary prevention with the antiplatelet drug aspirin.

Methods

The multiple risk factor intervention trial screened 347 978 men aged 35–57 who were free of myocardial

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infarction at baseline,^{12,14} with assessment of blood pressure while sitting, serum cholesterol concentration, and smoking state. Published data on six year mortality according to the value of baseline variables¹² have been supplemented by similar figures for 10 year mortality according to the quintile of baseline cholesterol concentration and systolic blood pressure and smoking state (O Vaccaro, 26th annual meeting of the European Diabetes Epidemiology Study Group, Lund, 1991). Causes of death were grouped as coronary heart disease; stroke; vascular (non-coronary and non-stroke); cancer; and non-vascular, non-cancer. Because of the possibility that lowering cholesterol concentration affects the risk of accidental death and suicide,^{7,15-17} these two causes of death were grouped and considered separately in calculations on the effects of lowering cholesterol concentration. At the 10 year follow up of the multiple risk factor intervention trial 15 486 non-diabetic men and 801 diabetic men had died, and I have used these figures, with no error assumed, as the baseline rate with which to calculate the theoretical benefits of interventions.

I assessed the proportionate effects of different interventions on each cause of death from meta-analyses of studies of lowering blood pressure⁵ and cholesterol concentration (R Collins, personal communication)^{6,7} and of the effects of aspirin (Antiplatelet Trialists' Collaboration, personal communication),⁹ the effects of lowering cholesterol concentration and of aspirin being updated from published figures. The mean reductions in blood pressure and cholesterol concentration in these studies were around 5.6 mm Hg and 0.6 mmol/l respectively. Because the proportionate effects of lowering cholesterol concentration and of aspirin treatment were not significantly different in primary and secondary prevention studies (R Collins and Antiplatelet Trialists' Collaboration, personal communications)^{8,9} I used the meta-analyses of all trials combined for the calculations presented in the tables, although calculations were also done using data from primary prevention studies alone. Because intervention studies on smoking have concerned only small numbers of subjects¹⁸ the effects of stopping smoking on different causes of death were calculated by comparing the observations on mortality in smokers and ex-smokers among the 89 691 men of the American veterans' study.¹⁹ For all interventions, I have assumed that the proportional effects of interventions on mortality are constant for the whole period of intervention, although the full benefits of reducing a risk factor might take several years to become apparent (R Collins, personal communication).²⁰

I estimated the effects of a theoretical intervention in men in the top fifth of the distribution of total cholesterol concentration (≥ 6.3 mmol/l) and of systolic blood pressure (≥ 142 mm Hg). The proportionate benefits of treating hypertension have been taken from a meta-analysis of studies of hypertension in which diastolic blood pressure was the criterion for treatment.⁵ In my analysis, however, systolic blood pressure was the criterion for intervention because of the recently shown efficacy of treating isolated systolic hypertension.²¹ Results are similar if diastolic blood pressure is used instead. The effects of stopping smoking were calculated by applying the proportionate differences in mortality between smokers and ex-smokers, although, if anything, this might produce bias against the benefits of stopping smoking because it includes people who stop smoking for health reasons. The benefits of aspirin treatment were calculated by assuming that all subjects were treated.

The change, and standard deviation in change, for each cause of death were calculated for 1000 diabetic and 1000 non-diabetic men, dichotomised in the case of cholesterol concentration and blood pressure as

Necessary assumptions for validity of estimates

Non-diabetic and diabetic subjects

- Meta-analyses reliably estimate effects of interventions
- Benefits and risks of interventions are similar in intervention studies and in treating populations
- Proportional effects of interventions on outcome are constant over time
- Newer agents have similar effects on cause specific mortality to drugs previously used in major studies
- Benefits and risks are similar in primary and secondary intervention trials (but data have been calculated for primary prevention studies alone)

Diabetic subjects

- Risk factor has same proportional effect on cause specific mortality as in non-diabetic subjects
- Intervention has same proportional effects on risk factor, and on cause specific mortality, as in non-diabetic subjects

being either in the top fifth or in the remaining group of the total population distribution, and in the case of smoking as being ex-smokers, non-smokers, or smokers. The absolute reduction or increase in numbers of deaths and the standard deviations were then used to calculate the theoretical 10 year mortality in the total population; 95% confidence intervals were derived from these standard deviations.

The increases in median life expectancy were calculated by life table methods, using actuarial data showing that a British non-diabetic man of 45 would have a median additional life expectancy of 29.9 years.²² The value q_x , representing the probability of dying in each year, for men of each age from 45 years was obtained from these life tables.²² This value was then multiplied by the ratio of 10 year total mortality in a stratum of risk (or that calculated with an intervention) divided by the 10 year mortality observed in the multiple risk factor intervention trial for non-diabetic men (44.1 per 1000; O Vaccaro, 26th annual meeting of the European Diabetes Epidemiology Study Group, Lund, 1991) (see tables I and II). These calculations assume that the proportionate changes in total mortality for each intervention operate in each year of follow up. The calculations of years of treatment per additional year of life were derived by dividing the estimated life expectancy for a man of 45 with a particular intervention by the gain in life expectancy resulting from that intervention. Cost was estimated from the prices listed in the *British National Formulary*.²³

Necessary assumptions

Assumptions are outlined in the box. Differences in compliance during clinical studies and in real life might overestimate the possible benefits of clinical trials. However, the full effects of reducing a risk factor on mortality from coronary heart disease may become apparent only after several years of intervention.²⁰ Newer drugs might achieve greater reductions in cholesterol concentration, and perhaps blood pressure, with consequently greater possible benefits, although this remains to be proved.

Two other assumptions are necessary to be able to estimate likely benefits in diabetic subjects. Firstly, each risk factor is assumed to have the same proportionate effects in diabetic and non-diabetic subjects, although data from the multiple risk factor intervention trial suggest that the odds ratios for serum

cholesterol concentration and blood pressure are lower in diabetic than in non-diabetic subjects.¹² If the adverse effects of a risk factor are less in diabetic subjects the proportionate benefits of lowering that risk factor may be less than I have used in these calculations. The other necessary assumption is that there are no disease specific benefits or hazards of particular interventions in the diabetic group. Anti-hypertensive treatment might be more beneficial in diabetic subjects with proteinuria,²⁴ or the presence of asymptomatic coronary heart disease might increase the risks of reducing blood pressure in diabetic patients because of the putative J shaped curve.^{25,26} Diuretic treatment may also be associated with increased mortality from cardiovascular disease in diabetic patients.²⁷

Results

Table I shows the approach used in this study. From the observations of cause specific mortality by baseline characteristics in the 347 978 non-diabetic subjects of the multiple risk factor intervention trial and the prevalence of hypertension in these subjects (section A) (O Vaccaro, 26th annual meeting of the European Diabetes Epidemiology Study Group, Lund, 1991), the number of deaths was calculated in each stratum for each cause (section B). In section C the findings of the meta-analysis on the efficacy of antihypertensive treatment according to cause of death are given.⁵ If these proportionate changes in mortality are applied to the calculated numbers of deaths in the hypertensive

stratum of subjects the expected numbers of deaths with treatment (section D) and the reductions in the numbers of deaths (section E) can be derived. In the hypertensive group treatment results in a mean reduction of 11.1% in deaths from coronary heart disease (0.58 of 5.2) and an overall reduction of 8.0% in deaths (1.06 of 13.2), but this corresponds to only a mean reduction of 4% in deaths from coronary heart disease (0.58 of 14.4) and reduction of 2.4% in overall mortality (1.06 of 44.1) for the population as a whole. If these reductions are achieved as a result of treating 194 hypertensive men for 10 years 3345 (95% confidence interval 1564 to ∞) man years of antihypertensive treatment would be needed to prevent one death from coronary heart disease, 6929 (5389 to 10 778) to prevent one stroke death, and 1830 (862 to ∞) to prevent one death (table II). Because the confidence intervals of effect on mortality encompass zero the duration of treatment per death prevented reaches infinity.

Identical approaches are applied to mortality data on diabetic and non-diabetic subjects in table II. Although my chosen cut off point for systolic blood pressure, 142 mm Hg, represents the top quintile in the subjects of the multiple risk factor intervention trial as a whole, some 36% of diabetic subjects have higher blood pressures compared with 19% of non-diabetic subjects. By the nature of the exercise, the same proportionate changes apply to each individual cause of death, but in the diabetic subjects the mean reduction in overall mortality with antihypertensive treatment calculates as 4.4% (5.81 of 131.5), compared with 2.4% (1.06 of 44.1) in the non-diabetic subjects,

TABLE I—Calculated effects of antihypertensive treatment for patients with systolic blood pressure ≥ 142 mm Hg on cause specific mortality in 1000 men aged 35-57 without diabetes or history of myocardial infarction*

	Age adjusted mortality per 1000 from:				
	Coronary heart disease	Stroke	Other vascular	Non-vascular	Total
(A) Mortality data					
Systolic pressure (mm Hg):					
< 142 (n=806)	11.4	1.0	2.5	23.4	38.3
≥ 142 (n=194)	26.9	3.2	6.3	32.0	68.4
(B) Observed No of deaths (no treatment)					
Systolic pressure (mm Hg):					
< 142 (n=806)	9.2	0.8	2.0	18.9	30.9
≥ 142 (n=194)	5.2	0.6	1.2	6.2	13.2
Total (n=1000)	14.4	1.4	3.2	25.1	44.1
(C) Effect of treatment in meta-analysis ⁵					
Odds ratio for mortality in treated v untreated subjects	0.89	0.55	0.88	0.99	
95% Confidence interval	0.76 to 1.04	0.42 to 0.70	0.66 to 1.18	0.86 to 1.14	
(D) Expected No of deaths with treatment of 194 subjects with systolic pressure ≥ 142 mm Hg					
Systolic pressure (mm Hg):					
< 142 mm Hg (n=806)	9.2	0.8	2.0	18.9	30.9
≥ 142 mm Hg (n=194)	4.6	0.3	1.1	6.1	12.1
95% Confidence interval	4.0 to 5.4	0.3 to 0.4	0.8 to 1.4	5.3 to 7.1	10.9 to 13.3
Total (n=1000)	13.8	1.1	3.1	25.0	43.1
95% Confidence interval	13.2 to 14.6	1.0 to 1.2	2.8 to 3.5	24.2 to 25.9	41.9 to 44.3
(E) Reductions in deaths with 10 years' treatment of 194 hypertensive subjects					
	0.58	0.28	0.14	0.06	1.06
95% Confidence interval	-0.20 to 1.24	0.18 to 0.36	-0.23 to 0.41	-0.78 to 0.89	-0.13 to 2.25

*From multiple risk factor intervention trial (O Vaccaro, 26th annual meeting of the European Diabetes Epidemiology Study Group, Lund, 1991).⁵

TABLE II—Calculated effects of antihypertensive treatment for patients with systolic pressure ≥ 142 mm Hg on cause specific mortality in 1000 non-diabetic and diabetic men aged 35-57 without myocardial infarction*

	Non-diabetic subjects (19.4%)†					Diabetic subjects (35.7%)†				
	Coronary heart disease	Stroke	Other vascular	Non-vascular	Total	Coronary heart disease	Stroke	Other vascular	Non-vascular	Total
Deaths per 1000 without treatment	14.4	1.4	3.2	25.1	44.1	54.2	6.2	10.3	60.8	131.5
Reduction in deaths with treatment	0.58	0.28	0.14	0.06	1.06	3.03	1.83	0.67	0.28	5.81
95% Confidence interval	-0.20 to 1.24	0.18 to 0.36	-0.23 to 0.41	-0.78 to 0.89	-0.13 to 2.25	-1.04 to 6.49	1.20 to 2.32	-1.08 to 1.97	-3.98 to 3.96	0.03 to 11.59
Patient years of treatment to prevent one death	3345	6929	13 857	32 333	1830	1178	1951	5328	12 750	615
95% Confidence interval	1564 to ∞	5389 to 10 778	4128 to ∞	2156 to ∞	862 to ∞	550 to ∞	1539 to 2975	1566 to ∞	901 to ∞	308 to 119 000

*From multiple risk factor intervention trial (O Vaccaro, 26th annual meeting of the European Diabetes Epidemiology Study Group, Lund, 1991).⁵

†With systolic pressure ≥ 142 mm Hg.

because of the higher prevalence of hypertension and the greater proportion of deaths from coronary heart disease and stroke. As a consequence, although the confidence intervals are wide, only one third of the man years of treatment are necessary to prevent one death from coronary heart disease, one death from stroke, or one overall death compared with non-diabetic subjects. Nevertheless, over 600 years of treatment are necessary to prevent one death, with a lower limit of the 95% confidence interval of 308 years of treatment.

In table III the efficacy of four different approaches for reducing coronary heart disease and total mortality are compared. The reduction in coronary heart disease and in total deaths for each intervention are calculated as in tables I and II. Antihypertensive treatment and lowering of cholesterol concentration produce only around one quarter or one third of the benefit of stopping smoking or aspirin treatment on deaths from coronary heart disease, either in non-diabetic or diabetic subjects, although confidence intervals are wide. There are, however, major differences in the calculated effects on total mortality, with aspirin and smoking cessation producing larger benefits than antihypertensive treatment or lowering cholesterol concentration, neither of which, because of the wide confidence intervals, achieves significance in the non-diabetic population. Indeed, the calculated mean effect of lowering cholesterol concentration in non-diabetic subjects is an increase in total deaths, the most beneficial limit of the 95% confidence interval being 0.78 less deaths, a 1.8% reduction. In diabetic subjects, however, the benefits of antihypertensive treatment, but not lowering cholesterol concentration, just achieve significance at the 5% level (table III).

Figure 1 shows the man years of intervention to prevent one death from coronary heart disease, one death from stroke, and one death overall in non-diabetic and diabetic subjects aged 35-57. Because of the different proportions eligible for each intervention the ranking order of benefit is different from that in table III, but for each pharmacological intervention a mean of between 2400 and 3800 man years of treatment in non-diabetic subjects, and between 800 and 1200 man years of treatment in diabetic subjects are needed to prevent one death from coronary heart disease. Antihypertensive treatment is by far the most effective treatment for preventing deaths from stroke in both groups. The duration of treatment necessary for preventing one death from any cause shows that aspirin and antihypertensive treatment are of similar benefit in both diabetic and non-diabetic subjects. Although confidence intervals are wide, treatment to lower cholesterol concentration seems to be less effective, and the confidence intervals including infinity imply uncertainty as to whether cholesterol lowering would reduce total mortality in either group. In both groups

FIG 1—Patient years of treatment (95% confidence intervals) needed to prevent one death from coronary heart disease death, one death from stroke, and one death in 1000 non-diabetic and 1000 diabetic patients according to data from men aged 35-57 without myocardial infarction at baseline in multiple risk factor intervention trial (R Collins and Antiplatelet Trialists' Collaboration, personal communications; O Vaccaro, 26th annual meeting of the European Diabetes Epidemiology Study Group, Lund, 1991).¹⁰

stopping smoking is substantially better than any other intervention.

Data from meta-analysis of primary prevention trial of lowering cholesterol concentration alone (R Collins personal communication) show little effect on the number of man years of treatment to prevent death from coronary heart disease (3053 v 2439 years), but data from primary prevention trials for aspirin (Antiplatelet Trialists' Collaboration, personal communication) somewhat reduces its calculated benefits (5555

TABLE III—Calculated effects of different interventions on coronary heart disease and total mortality in 1000 non-diabetic and 1000 diabetic men aged 35-57 without myocardial infarction*

	% With criterion for treatment	Non-diabetic men		% With criterion for treatment	Diabetic men	
		Coronary heart disease deaths	Total deaths		Coronary heart disease deaths	Total deaths
Deaths per 1000 without treatment		14.4	44.1		54.2	131.5
Reductions in death with:						
Antihypertensive treatment (systolic ≥ 142 mm Hg)	19.4	0.58	1.06	35.7	3.03	5.81
95% Confidence interval		-0.20 to 1.24	-0.13 to 2.25		-1.04 to 6.49	0.03 to 11.59
Cholesterol lowering treatment (from ≥ 6.3 mmol/l)	20.0	0.82	-0.07	20.8	2.59	0.56
95% Confidence interval		0.51 to 1.14	-0.92 to 0.78		1.60 to 3.58	-3.80 to 4.88
Aspirin	100	2.64	5.16	100	9.70	16.17
95% Confidence interval		1.76 to 3.53	2.22 to 8.10		6.47 to 12.90	9.66 to 22.68
Stopping smoking	36.4	2.74	8.65	36.4	7.88	20.84
95% Confidence interval		2.54 to 2.93	8.22 to 9.08		7.31 to 8.43	19.76 to 21.92

*Data from multiple risk factor intervention trial (R Collins and Antiplatelet Trialists' Collaboration, personal communications; O Vaccaro, 26th annual meeting of the European Diabetes Epidemiology Study Group, Lund, 1991).¹⁰

TABLE IV—Estimated gains in life expectancy from risk factor reduction in a man of 45 with or without diabetes and without myocardial infarction*

	Non-diabetic man		Diabetic man	
	Life expectancy (years)	Loss with risk factor or gain with intervention (95% confidence interval) (years)	Life expectancy (years)	Loss with risk factor or gain with intervention (95% confidence interval) (years)
Mean	29.85		20.30	
Aspirin treatment	31.01	1.16 (0.43 to 1.88)	21.49	1.19 (0.71 to 1.74)
Smoking:				
Non-smoker	32.59		21.86	
Smoker	25.06	-7.53	17.58	-4.28
Ex-smoker	28.90	3.84 (3.68 to 4.04)	20.97	3.39 (3.18 to 3.63)
Cholesterol (mmol/l):				
< 6.3	30.35		20.88	
≥ 6.3	27.87	-2.48	18.10	-2.78
Lowering ≥ 6.3	27.86	-0.01 (-0.78 to 0.66)	18.24	0.14 (-0.92 to 1.28)
Systolic blood pressure (mm Hg):				
< 142	30.90		22.03	
≥ 142	25.50	-5.40	17.19	-4.84
Lowering ≥ 142	26.33	9.83 (-0.07 to 1.79)	17.92	0.73 (0.01 to 1.61)

*Screened at baseline of multiple risk factor intervention trial (R Collins and Antiplatelet Trialists' Collaboration, personal communications; O Vaccaro, 26th annual meeting of the European Diabetes Epidemiology Study Group, Lund, 1991).^{1,12}

3788 years to prevent one death from coronary heart disease and 3861 v 1938 years to prevent one death overall). If treatment is applied to the top two fifths of the distributions of blood pressure and serum cholesterol concentration the total reduction in deaths from coronary heart disease is roughly doubled, at the expense of treating around twice the number of subjects, so that the man years of treatment for each death from coronary heart disease prevented remains similar, as does the figure for total deaths (data not shown).

Death cannot be prevented, only postponed. If all interventions continue to produce the same proportionate benefit in mortality throughout life the benefits can be recalculated in terms of additional years of life expectancy.

The additional years of life expectancy for a man of 45 with or without diabetes, with or without different coronary heart disease risk factors, and with or without treatment for these risk factors is shown in table IV. The estimated losses of life expectancy are greater for smoking and for hypertension than for hypercholesterolaemia. The gains with treatment are around one year with aspirin and antihypertensive agents but are somewhat less for cholesterol lowering treatment, although confidence intervals are wide. Figure 2 shows the calculated drug costs per additional year of life expectancy. Once again, when an intervention is calculated to produce a shortening of life expectancy, the drug cost per year gained is calculated as infinite. Despite their not having been tested in large mortality outcome studies, an angiotensin converting enzyme inhibitor, calcium channel blocker, and hydroxymethylglutaryl coenzyme A reductase inhibitor have been included in these calculations but without any attempt to differentiate proportional benefits on life expectancy or degrees of risk factor lowering. The costs of persuading people to stop smoking are not included because of the difficulty in estimating them, but, clearly, such costs are substantial.

The possible maximum benefits of a targeted approach to reduce risk factors can similarly be calculated as the change in the numbers of deaths from coronary heart disease achieved by applying all approaches simultaneously to those who are at risk. If all non-diabetic subjects with a systolic blood pressure greater than or equal to 120 mm Hg and a cholesterol concentration greater than or equal to 5.2 mmol/l were treated as in the overviews, and all smokers stopped smoking, the 10 year mortality from coronary heart disease in the population would fall from 14.4 per 1000 to 10.5 per 1000, a reduction of 27%. This compares with a 10 year mortality from coronary heart disease of 3.9 per 1000 in those whose initial screening values

were below these cut off levels without treatment (O Vaccaro, 26th annual meeting of the European Diabetes Epidemiology Study Group, Lund, 1991). The corresponding figures for diabetic subjects are a fall from 54.2 per 1000 to 39.2 per 1000, compared with a mortality of 22.4 per 1000 in those with low risk values at screening. Thus, even at the expense of a pharmacological intervention for 89% of the non-diabetic and 93% of the diabetic population, only just over one third of the excess risk of coronary heart disease mortality attributed to these three risk factors is reversible using the treatments so far studied in major intervention trials.

Discussion

I calculated the benefits of risk factor interventions by using the observations on the actual effects of these interventions, rather than by assuming full reversibility, as is implicit in methods which calculate benefit by removing the adverse effect of the risk factor on mortality.^{2,4} The main assumption used in this approach is the validity of data derived from meta-analyses. Thompson and Pocock have analysed the problems of meta-analysis, including the criteria by which individual studies are included, and the validity of combining studies using different patient characteristics and study design; they conclude that it "may be unrealistic to imagine that it will produce simple statistical answers to complex clinical problems."²⁸ It is, nevertheless, a means of measuring the probable size of a treatment effect. The calculations on smoking used observational data, but recent evidence suggests that these benefits may have been underestimated.²⁹

The main assumptions which might be questioned are the validity of expecting benefits observed in clinical trials to be found in everyday clinical practice when asymptomatic risk factors are treated over 10 or more years. Conversely, newer agents might better

FIG 2—Estimated drug costs (95% confidence intervals) for one year of additional life expectancy for a non-diabetic or diabetic man of 45 screened for the multiple risk factor intervention trial study and without myocardial infarction at baseline (R Collins and Antiplatelet Trialists' Collaboration, personal communications).^{1,12,22}

reduce risk factors than those currently available, perhaps without deleterious effects on other risk factors such as insulin resistance or lipid concentrations. There are, nevertheless, hazards in extrapolating the effects on outcome from the effects on risk factors. The point needs re-emphasising that thiazides and β blockers for hypertension prevent around twice as many strokes as myocardial infarctions^{5,30} so that any gains of newer agents in terms of risk factors for coronary heart disease need proving for total mortality. The absolute benefits calculated for diabetic subjects may have been overestimated if, as seems probable, the odds ratios for any level of risk factor are smaller in a diabetic than a non-diabetic population.¹² Nevertheless, the absolute benefits of reducing risk factors in diabetes could be tested only in a randomised prospective intervention study.³¹

I have not calculated morbidity as the data have not permitted calculations of the possible benefits of non-fatal myocardial infarction or strokes. The Medical Research Council mild hypertension study showed that 850 person-years of treatment of mild hypertension is needed to prevent one non-fatal stroke,³² and this figure would probably be around 250-300 person years of treatment for a mildly hypertensive diabetic patient. Given that the physical, psychological, and social impacts of non-fatal strokes are usually much greater than those of non-fatal myocardial infarctions, these figures should be considered alongside those in table IV and figure 1 when the possible benefits of the different interventions are considered.

The poor efficacy of all pharmacological interventions is the consequence of three main considerations of the role of risk factors. Firstly, although the risks of coronary heart disease are increased by raised levels of any risk factor, most deaths occur in subjects at low level of risk: people in the top 15% of the distribution of a risk score for coronary heart disease risk provided only 32% of cases.³³ Secondly, the absolute degree of risk in middle age, even for men with a combination of risk factors, is comparatively low. A man of 45 with both hypercholesterolaemia and diabetes has an 83.5% chance of surviving for the next 10 years, and a 92.5% chance of not dying of coronary heart disease in those 10 years. Finally, the lack of reversibility of risk with lowering of a risk factor⁵ may relate to damage already done but could also imply that the risk factor is an epiphenomenon indicating the presence of the underlying true pathogenic mechanism. If a high cholesterol concentration is merely a marker of, say, free radical damage, or blood pressure of intrauterine environment³⁴ less benefit would come from intervention than might be expected.

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Correction

Intraocular foreign body missed by radiography

An editorial error occurred in this lesson of the week by Andrena M McElvanney and Alistair R Fielder (17 April, pp 1060-1). The second sentence of the second paragraph should have read: "Ferrous ions destroy retinal photoreceptors and pigment epithelial cells (siderosis), and copper induces chalcosis."

Diagnosis and treatment of malaria in Britain

An authors' error resulted in an incorrect telephone number being given in the appendix to this regular review by Malcolm Molyneux and Ray Fox (1 May, pp 1175-80). The correct number for the Liverpool School of Tropical Medicine is 051 708 9393.