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ORIGINAL ARTICLE

Cardiovascular morbidity and multifactorial primary prevention: Fifteen-year follow-up of the Helsinki Businessmen Study*

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Abstract

Objective: Mortality and morbidity in a long-term follow-up after a multifactorial primary prevention of cardiovascular diseases (CVD).

Design? The five-year randomized controlled multifactorial prevention trial for CVD was performed between 1974-1980. Evaluation of participants (including electrocardiograms) was performed at start, end of trial and five years post-trial. CVD morbidity and mortality follow-up, using ' the country-wide Hospital Discharge Register and Death Certificate Register, was continued up to the end of 1989.

Setting: Second Department of Medicine, University of Helsinki.

Participants: In all, 3490 business executives born during 1919-34participated in health check-ups in the late 1960s. In 1974,1222 of these men who were clinically healthy, but with CVD risk factors, were entered into the primary prevention trial; 612 randomized to an intervention group and 610 to a control group. In addition, 593 men, who volunteered for the study but were excluded because of low levels of CVD risk factors, were followed- up as a nonrandomized low-risk group.

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Key words: prevention, cholesterol, beta-blockers, cardiovascular diseases, risk factors.

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Interventions: During the five-year trial in 1974-1980 the subjects of the intervention group visited the investigators every fourth month. They were treated with intensive dietetic-hygienic measures and frequently with hypolipidemic (mainly clofibrate and/or probucol), and antihypertensive (mainly pindolol or propranolol and/or hydrochlorothiazi-de plus amiloride) drugs. The control group and the low-risk group were not treated by the investigators.

Main outcome measures: Coronary mortality, nonfatal clinical and silent myocardial infarction (Ml), coronary artery bypass grafting (CABG), fatal and nonfatal ischemic stroke, transient ischemic attack (TIA) leading to hospitali-zation, fatal and nonfatal hemorrhagic stroke (subarachnoid and intracerebral hemorrhage).

Results: The total number of fifteen-year coronary events was 75 in the intervention group, 49 in the control group ($p<0.05$ vs intervention) and 26 in the low-risk group ($p<0.05$ vs intervention and control). The respective numbers of coronary deaths were 34,14 and 6; of definite or probable MI 32, 30 and 17 (posttrial 16, 24 and 15); of CABG 5, 0 and 0 and of ischemic cerebrovoscular events 8, 20 ($p<0.05$ vs intervention) and 14. In multifactoriai analysis coronary events were positively associated with serum cholesterol (negatively with HDL-cholesterol), blood pressure and smoking in the intervention and control groups, and with serum triglycerides in the low-risk group. Basal alcohol consumption was a significant predictor of fewer coronary events in the intervention group but not in the control groups. In-trial pindolol treatment of the intervention group, but not the overall beta-blocker treatment, was associated with total (OR 197, 95% CI 103-3.78) and nonfatal coronary events

(or 2.51, 95% Cl 1.06-5.93) but not with coronary mortality or with post-trial total or nonfatal coronary events. Associations with other drug treatments tended to be protective only with diuretics.

Summary: Low traditional CHD risk factor levels are "ssociated with low coronary morbidity also in this popula-.^jn of middle-aged men. Total coronary events were more frequent, mainly due to coronary deaths, in the intervention group than in the control group. Nonfatal coronary events in the intervention group were significantly associated with the frequent in-trial use ofpindolol, a beta-blocker with intrinsic sympathomimetic activity. Stroke incidence was low in the intervention group.

Introduction

Several multifactorial primary prevention studies were started during the 1970's in order to efficiently control the development of cardiovascular diseases (CVD, for a recent review see 1). Many of these trials had quite meager or even disappointing results, often interpreted to be due to modest risk factor lowering. However, risk factor reduction was substantial in the Helsinki Businessmen Study (2, 3); yet, 15-year follow-up showed increased total, coronary id violent mortality in the intervention group as compa-red to the randomized control group (2, 4, 5). The results have evoked several speculations about causes (6-10), but even though the multidrug treatments of the trial were suspected, no clear-cut explanation could have been elucidated for the result. We have now extended the follow-up to include nonfatal coronary and cerebrovascular events during the 15-year follow-up. For comparison, the respective morbidity will be reported also for a non-randomized low-risk group of the same background population presented in the initial intervention trial (2,3).

Materials and Methods

Study population and intervention methods

The details of the Helsinki Businessmen Study have been described in previous reports (2-5). Participants had to be free of vascular disease but have at least one of the following risk factors: 1) serum cholesterol level £ 7.0 mmol/liter; 2) serum triglycerides level > 1.7 mmol/liter; 3) systolic blood pressure > 160 mm Hg; 4) diastolic blood pressure > 95 mmHg; 5) smoking > 10 cigarettes/day; 6) relative body weight 120% or higher; 7) one-hour glucose

tolerance (1 g/kg body weight of glucose orally) > 9.0 mmol/liter. In addition to the randomized high-risk control and intervention groups of 610 and 612 men, respectively, we also identified in 1974-75 a group of 593 men who volunteered for the trial, but were excluded because of low level of risk factors. This group has been referred to as the low-risk group.

The members of the intervention group visited the investigators every fourth month during the 5-year intervention period, while the control group and the low risk group were in usual health care. Drug treatment (mainly beta-blockers propranolol or pindolol and/or diuretics hydroch-lorothiazide chloride alone or combined with amiloride for hypertension; probucol and clofibrate for hyperlipidemias) was used, if target levels were not reached by hygienic measures (smoking cessation, physical exercise, diet instructions, weight reduction) alone. Diet instructions advised reduced intake of calories, saturated fat, cholesterol, alcohol and sugar, and increased intake of polyunsatu-rated fats, fish, chicken, veal and vegetables. At end-trial most of the individual risk factors were reduced in the intervention group so that the total coronary heart disease (CHD) risk score was substantially smaller in the intervention group than in the control group (2). However, the levels of the low-risk group were not reached (2).

At the end-trial all participants were informed of their laboratory results and were advised to continue the health check-ups and possible treatments in usual health care. Probucol therapy was discontinued because the drug is not registered in Finland.

Post-trial follow-up

The first and second post-trial follow-up evaluations including only mortality were performed in 1985-86 and 1990. They have been described in detail in the respective reports (4,5). The risk factor levels and use of drugs in the three groups were studied in 1985-86 using questionnaires and routine laboratory methods (11) and the results are summarized in Table 1.

For the present report the cases of nonfatal myocardial infarction (covering ICD-9 codes 410-412) and ischemic and hemorrhagic cerebrovascular events (ICD-9 codes 430-438) up to December 31, 1989 were collected from the country-wide Hospital Discharge Register. This includes the personal 10-digit code, unique for every citizen in Finland; the hospital code; diagnosis number and the treatment period. Thus, the hospital-made diagnoses of myocardial infarction (MI), transient ischemic attacks (TIA) or stroke can be reliably identified using this register. More

TABLE 1
Risk factor levels in the study groups (number of men evaluated in parenthesis) at 5-year post-trial evaluation

Value	Intervention group (n=454)	Control group n=456)	Low-risk group (n=489)
Age at entry (1974), yr	48 (4)	48 (4)	47 (4)
Relative body weight, %	115 (0.6)"	**117** (0.6)	109 (0.5)
Blood pressure, mmHg	141 (0.8)	142 (0.8)	137 (0.8)**
Systolic Diastollc	89 (0.4)	89 (0.5)	86 (0.4)'*
Serum cholesterol, mmol/E			
Total	6.6 (0.06)	6.6 (0.06)	6.2 (0.05)"
LDL HDL	4.5 (0.05)	4.5 (0.06)	4.25 (0.05)*
	1.38(0.02)	1.33(0.02)	1.5 (0.02)*
Serum triglycerides, mmol/l	1.7 (0.05)	1.6 (0.04)	1.2 (0.03)"
Fasting blood glucose, mmol/l	5.1 (0.08)	5.0 (0.05)	47 (0.04)**
Smokers, %	22	20	11"
Alcohol consumption, g/week	130 **(7)**	131 **(7)**	96 (5)**
Coffee consumption, cups/d	3.8 (0.1)	3.9 **(0.1)**	3.3 **(0.1)"**
Exercise, h/week	3.8 (0.2)	3.7 (0.2)	3.9 (0.2)
Medication, %	Coronary		**6**
Antihypertensive	Heart	**27**	**7**
Hypolipidemic	failure	**2**	
Antidiabetic		**4**	

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The values are mean (SD)
* p<0.05 vs. control group, ** p<0.01 vs. other groups

detailed patient records were obtained from the respective hospital. However, it was not possible to obtain serial elec-trocardiograms (ECG) of all cases but the records invariably contained ECG decryptions (made by a physician) and enzyme data relevant to MI. The records were rewieved and the diagnosis was finally established by a cardiologist (Dr. Matti Romo) blinded the treatment status. Concerning nonfatal myocardial infarctions we have used the following criterra:

A) definite myocardia] infarction: at least two of the fol lowing: typical chest pain, diagnostic ECG changes, eleva ted enzymes;

B) probable myocardial infarction: clinical suspicion of myocardial infarction but only one the aforementioned cri teria was fulfilled.

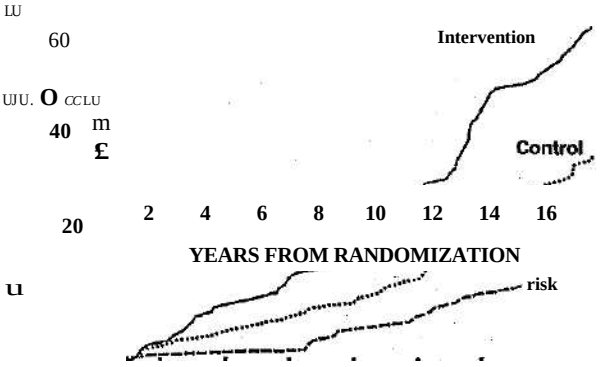
The criteria for nonfatal ischemic stroke included unequivocal findings or focal or global neurological deficit with sudden onset, which lasted for more than 24 hours. If the duration was less than 24 hours the diagnosis of TIA was established. The cases of hemorrhagic (intracerebral) stroke and subarachnoid hemorrhage were diagnosed using lumbar puncture and/or computerized tomography. One man in the intervention group and four men in the low-risk control group experienced both a nonfatai MI and ischemic cerebrovascular event during the follow-up. In separate analyses these individuals were counted both as coronary and cere-brovascular cases. In two subjects (one in the high-risk control group and one in the intervention group) MI was associated with a pre-diagnosed and metastasized malignant disease; the subjects were not classified as coronary cases.

The ECGs obtained in 1985-86 were coded according to the Minnesota code by an independent physician (Dr. Nan Li). The occurrence of a new (compared to pre-trial) major (code 1:1 or 1:2) or minor Q/QS item (code 1:3) without other diagnosis of MI was defined as a silent MI. "ibsequently, these were pooled with the silent Mis diagnosed at end-trial ECG evaluation (2).

Statistical method

Standard BMDP statistical software (12) was used for analyses. Differences in means and proportions between the groups were tested using t-test and chi-square tests. The odds ratios for different risk factors were computed -using Cox proportional hazards models as described in previous publications (2-5). In the Cox models log values of triglicerides and alcohol consumptions were used. However, in the low-risk group triglycerides were used as a dichotomous variable with a cutpoint of 1 mmol/1, which halved the distribution. In order to increase the power for the Cox models of coronary heart disease, the definite and probable nonfatal events (clinical and silent) were combined with fatal coronary events. When examining the contribution of different drug treatments, the treatment duration of >4 months (time between intervention visits) was chosen as the cutpoint. Treatment durations of 6 and 12 months

FIGURE 1
Cumulative clinical coronary heart disease events (fatal and nonfatal myocardial infarction and coronary artery bypass grafting) in the intervention, control and low-risk groups during the 15-year follow-up. P=0.001 (Breslow) for the difference between the groups



were also tested, but the results were consistent with the first alternative, which is therefore reported. In earlier reports beta-blocker users were analyzed as one group. We have now divided the users according to the type of beta-blocker (mainly pindolol or propranolol).

Results

Post-trial risk factors and treatments

Table 1 shows that the risk factor levels and drug treat-

ments were largely similar in the intervention and control groups at 5-year post-trial evaluation. In the low-risk group most values had increased since baseline, but have still remained significantly below the two other groups and the drug treatment was infrequent.

Coronary morbidity

The numbers of total coronary events during the fifteen-year follow-up are demonstrated in Figure 1 and Table 2. In

TABLE 2
Coronary heart disease (CHD) and cerebrovascular events in the study groups 1974-1989. In-trial (1974-1980) events in parenthesis

Events	Group		
	Intervention n=612	**Control** n=610	**Low-risk** n=593
Fatal CHD	34* (4)	14 **(1)**	6 (0)
Nonfatal Ml	27 (10)	26 **(5)**	14 (2) 3
Definitive	5 (2)	4 **(2)**	(0)
Probable			
CABG only	5 (0)	**0** **(D**	0 (0)
ECG only {up to 1985)	4 (3)	**5** **(1)**	3 (0)
Total coronary	75" (19)	**49** **0)**	26"(2)
Cerebrovascular ischemic stroke	(0)	**155** **(8)(2)**	8 (1) 6
TIA Total ischemic	(0)	**20** **(10)**	(0)
	(0)		14 (1)
Hemorrhagic stroke	1 (0)	**1** **(0)**	1 (0) 1
Intracerebral	3 (0)	**1** **(0)**	(0)
Subarachnoid			
Total coronary or ischemic cerebrovascular patients	82 (19)	**69** **(19)**	36"(3)

• p<0.05 vs. control group, ** p<Q,Q5 vs. other groups Ml denotes myccardial infarction, CABG denotes coronary artery bypass grafting, TIA denotes hospitalized transient Ischemia attack.

the intervention group, the total number of coronary morbidity (75 cases) was higher than in the control group (49 cases). The difference was mainly due to coronary deaths, 34 vs. 14 cases, while the numbers of the definite non fatal events (definite MIs+silent Mis) were similar, 31 vs. 31 cases. In fact, during the post-trial ten-year period the respecti--ve nonfatal figures are 16 and 24. In addition, five men had been coronary bypassed without MI in the intervention and none in the control groups. The lowest morbidity figures (26 cases) were found in the low-risk group, including 6

coronary deaths (all post-trial) and 20 nonfatal (18 post-trial) events.

Risk factors, treatments and coronary morbidity A closer analysis of in-trial beta-blocker users (192 overall, 135 at the end-trial) showed that 63% used only pindo-lol and 29% propanolol in the intervention group. Of these men 14 used both pindolol and propranolol (not concomi-tantly). Only 8 men (4%) used other beta-blockers. In the control group 38% of beta-blocker users (23 out of 61) were on pindolol, 16% on propranolol and 46% on other beta-blockers.

In a univariate within-group analysis (Table 3) the 15-year incidence of total CHD events were significantly positively associated with the in-trial clofibrate and pindolol ise and were higher than in the whole intervention group. The men without medications, in turn, had the lowest incidence. The respective analysis with Cox proportional hazards models (Table 4) revealed that of the initial risk factors serum cholesterol level and-smoking (plus systolic blood pressure in the intervention group) were significant predictors of total coronary events in both high-risk groups. Reported alcohol consumption (log value) was significantly associated with coronary only in the intervention group (OR 0.41,95% CI 0.26-0.65). Interestingly, only serum triglyceride level was significantly positively associated with coronary events in the low-risk group.

The initial HDL cholesterol levels were unknown because their determination from frozen serum samples turned out to be unreliable (3). As the effect of HDL-cholesterol on multivariate analyses may be of interest we substituted pre-trial HDL-cholesterol by the levels determined in the 1985-86, a time point no more affected by the probucol treatment. When controlled for other initial risk factors shown in Table 4, this surrogate HDL-cholesterol was a significant additional predictor of coronary events in the three groups. The ORs were 0.29 (95% CI 0.10-0.80), 0.26 (95% CI 0.07-0.98) and 0.12 (95% CI 0.02-0.99) in the intervention, control and low risk groups, respectively.

The inclusion of different in-trial drug treatments of the intervention group into the Cox model with the initial risk factors is shown in Table 4. The total use of beta-blockers or propranolol alone was not significantly associated with fifteen-year coronary events (OR 1.73, 95% CI 0.89-3.35 and 1.14, 0.51-2.54, respectively). However, the association of pindolol was significant with total coronary events (OR 1.97, 95% CI 1.03-3.78) and total nonfatal coronary events (OR 2.51, 95% CI 1.06-5.93) but non significant with coronary

TABLE 3 Univariate associations of in-trial treatments and 15-year CHD events* in the intervention and control groups

Treatment**	No. of r Interven
Probucol	2
Clofibrate	2
All betablocker	1
Pindolol	121
Propranolol	
Diuretics	1
Diet or drug < 4 mo	1
Any intervention	6

* Includes fatal CHD, nonfatat and silent myocardial I
trial drug treatment £ 4 months * Drug at end-trial

TABLE4
Odds ratios (OR with 95% confidence interval) of 15-year coronary morbidity for initial risk factors and alcohol consumption without (model A) and with in trial treatment procedures (Model B)

Risk factor or treatment (change)*	Morbidity due to coronary heart disease							
	Intervention, n=75				Control, n=49		Low-risk group, n=26	
	Model A		Model B		Model A		Model A	
	OR	95% CI	OR	95% CI	OR	95% Ci	OR	95% CI
Age (1 year)	1.00	0.95-1.06	0.98	0.93-1.04	1.13	1.05-1.22"	**1.10**	0.98-1.24
Obesity (1 kg/m^1)	1.03	0.94-1.12	1.03	0.95-1.13	1.15	1.03-1.28*	**1.19**	0.92-1.54
Systolic blood pressure (10 mmHg)	1.14	1.01-1.29*	**1.15**	0.99-1.33	1.16	0.99-1.36	**1.02**	0.99-1.23
Serum cholesterol (1 mmol/i)	1.40	1.15-1.70*	1.48	1.17-1.88"	1.50	1.17-1.93*	**0.56**	0.30-1.03
Serum trigiycerides {mmol/l, log value)	1.02	0.31-3.38	0.71	0.19-2.62	0.57	0.12-2.82	2.58	1.49-4.44*
(Serum NDL-cholesterol (1 mmol/1)#	0.29	0.10-0.80*	0.29	0.10-0.85"	0.26	0.07-0.98*	0.12	0.02-0.99*)
One-hour glucose (1 mmol/l)	1.05	0.95-1.16	1.06	0.96-1.18	0.92	0.80-1.06	**1.17**	0.85-1.60
Smoking (> 10 cig./day)	1.52	0.92-2.50	1.69	1.01-2.83*	1.57	0.80-3.10	2.43	0.92-6.38
Alcohol (g/week, log value)	0.41	0.26-0.65*	0.60	0.45-0.81*	1.16	0.72-1.87	1.08	0.54-2.18
Probucol			0.71	0.40-1.26				
Clofibrate			1.34	0.78-2.30				
Beta-blocker			1.73	0.89-3.35				
Pindolol			1.97 .	1.03-3.78*				
Propranolol			1.14	0.51-2.54				
Oiuretics			0.52	0.26-1.03				
"-tJiet or drug < 4 mo			0.61	0.28-1.33				

* p<0.05 *Log transformed values for serum trigiycerides (dichotomous in low-risk group, >1.0 mmol/l) and alcohol use. Smoking (> 10 cigarettes in Intervention and control groups, any smoking in tow-risk group) and treatments are dichotomous variables (drug use > 4 months during intervention period). The diet group includes subjects with no drug treatment, or drugs less than 4 months during the intervention period. # Five-year post-trial values

deaths (OR 1.36, 95% CI 0.48-3.83) or with post-trial total (OR 1.01,95% CI 0.45-2.28) or nonfatal (OR 0.88,95% CI 0.28-2.75) coronary events. The association for pindolol was strongest for the in-trial total coronary events during 1974-80 (OR 4.97, 95% CI 1.63-1511). Other in-trial treatments were insignificantly associated with the fifteen-year or post-trial events, even though probucol and diuretics were associated with significantly reduced in-trial events (2,3).

Cerebrovascular morbidity

During the intervention period (2) there were 8,0 and 0 cases of cerebrovascular ischemic events in the control, intervention and low-risk group ($p < 0.01$), respectively. During the ten subsequent post-trial years respective new events were 8, 12 and 14 (Table 2). Thus, during the 15-

year follow-up the cumulative number of hospitalized ischemic cerebrovascular events (virtually all nonfatal) was lowest in the intervention group (Fig. 2). The numbers of hemorrhagic strokes were low and similar in all three groups. The Cox proportional hazards model for the combined three groups using various risk factors as covariates revealed that the ischemic cerebrovascular events were associated only with initial serum cholesterol (OR 1.43, 95% CI 1.06-1.93). Separate group analyses should be interpreted cautiously because of relatively small number of events, but they showed that cholesterol was the only significant predictor in the intervention group (OR 2.33,95% CI 1.18-4.60), and smoking in the control group (OR 3.18,95% CI 1.23-8.27). The ORs for systolic ox diastolic blood pressure ranged from 1.42 to 1.09 but all Cls included unity.

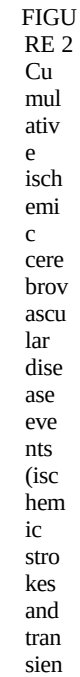


FIGURE 2 Cumulative ischemic cerebrovascular disease events (ischemic strokes and transient ischemic attacks) in the intervention, control and low-risk groups during the 15-year follow-up. P=0.0478 (Breslow) for the difference between the groups

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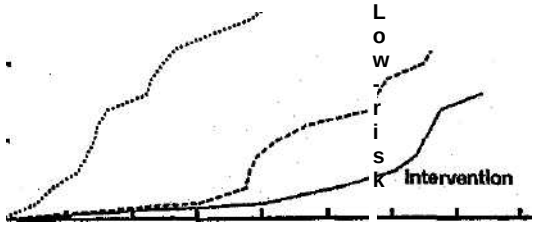

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Discussion

These extended 15-year follow-up results of the Helsinki Businessmen Study show that the unexpectedly high incidence of coronary events in the intervention group reported earlier for fatal events (5) remains after inclusion of the nonfatal coronary events. However, the difference between the groups is detectable mainly in the fatal events, less so in nonfatal events; in fact, post-trial non-fatal Mis were lower in the intervention group than in Che control group. The low-risk group continues to have the lowest rate of coronary events.

The earlier trend of ischemic stroke incidence has likewise remained; the intervention group has the lowest rate of hospitalized cerebrovascular events among all three groups. Actually, if the coronary and cerebrovascular ischemic events are combined, there is no significant difference between the intervention and control groups; low-risk group still has the lowest incidence.

Combined with the majority of evidence from decades of risk factor studies, as well as data from other multifactorial prevention trials (1), the favourable result in the low-risk group — concerning both coronary and coronary + cerebrovascular events — clearly supports the harmful role of traditional cardiovascular risk factors also in this selected population of middle-aged men. The important question

around this trial is whether the negative result in the treated group might be associated with the drug treatments used during the intervention period. The investigation is made complex by the multidrug treatments and frequent shifts of medications during the intervention. The trial results can narrowly be attributed only to the combination of multifactorial prevention methods used. Consequently, it is quite possible that no single factor is responsible for the negative result. In the following we will concentrate on three alternative explanations using within-groups analyses, namely, treatment of hypolipidemias, especially hypercholesterolemia, b) treatment of hypertension and c) type of intervention generally.

After the publication of the 15-year mortality results (5) several comments by scientists and lay press alike have advocated cholesterol lowering as the principal reason for the negative outcome in the intervention groups (10). This interpretation is not possible in the light of contemporary evidence of cholesterol lowering and CHD (13-19); neither does the totality of data from our trial support it. Initial serum cholesterol was a clearly significant risk factor and the treatment of hypercholesterolemia (mainly type IIA, 28% of the men) by probucol was associated with fewer CHD events (2,3,20). This association was strongest during the in-trial period, when probucol was used, diminishing thereafter (2-5, 20). The results with clofibrate in men with hypertriglyceridemi

a (types IIB or IV, 38% of the men) do not necessarily contradict this, because the use of hypolipi-demic drug was selective in our trial. The association between clofibrate and coronary events was significantly only in univariate analysis, but not in multivariate analyses. The low CDH event rate in the probucol-treated men was associated with 13-15% fall in serum cholesterol, irrespective of other treatments, and included a significant fall in HDL-cholesterol (3). In the ciofibrate-treated men cholesterol reduction was only 3% when antihypersensive drugs were used concomitantly (3,21). Excluding noncardiac events, clofibrate has generally been found favorable as regards coronary events in several trials on hypercholesterolemia (22-25).

We think that careful consideration should be given to the frequent treatment of mild to moderate hypertension in our trial. This is important, because — in contrast to the treatment of hypercholesterolemia — the impact on CHD in large antihypertensive prevention trials has not been unequivocal (26).

Especially after the MRFIT (30) and MAPHY (31) studies, the use of diuretics for hypertension became criticised; their possible effects on lipids, glucose tolerance and potassium levels were frequently emphasized. These fears seem

to have been exaggerated because the recent trials at least in elderly hypertensive persons have repeatedly shown favorable outcomes for both stroke and coronary heart disease (32-34). The low OR in diuretics-treated men in our trial is in keeping with this, possibly because we almost xclusively used potassium-sparing preparations. - In contrast to diuretics the in-trial beta-blocker treatment was significantly associated with fatal plus nonfatal coronary events during the intervention period (2) and to some extent in the five-year post-trial study (20). However, the association was insignificant with fatal coronary events even in the long-term post-trial follow-up (4, 5). The present new findings show that the in-trial use of pindolol with intrinsic sympathbmimetic activity (ISA) was significantly positively associated with fatal plus nonfatal coronary events over the fifteen-year follow-up period. However, the role of pindolol is more complicated because its in-trial use was not related to nonfatal events, mainly to myocardial infarctions, it can be speculated that the harmful effect of the drug was not related to arrhythmias, but more likely to thrombosis and/or progression of atheroslerosis. Evidence has been accumulated that beta-blockers with ISA may confer less benefit in the prevention of CHD (27). Other types of beta-blockers seem to be favourable in primary orevention especially shortly after myocardial infarction 29). Thus, the chemical characteristics of beta-blockers may make important clinical differences; possible mechanisms have been recently reviewed (28).

A highly interesting, but at the moment only speculative area, is the possible psychologically detrimental effects of any intervention methods. These mechanisms may be associated with intervention causing stress and accelerated atherosclerosis; for instance coronary constriction can be mentally induced (35). Equally important may be the abrupt end of the intervention period (7). In addition to drug treatments, our intervention group was submitted to frequent and aggressive health education in order to lower the risk factor levels as efficiently as possible. The setting clearly differs from ordinary double-blind drug trials, where both the control and the intervention groups feel to be similarly treated. We have a limited set of psychological data in questionnaires filled in by the participants at the start and the end of the intervention period and a study is now in progress to analyze these data.

In summary, the present fifteen-year follow-up results of the Helsinki Businessmen Study show significant differences between the intervention and control groups after inclusion of nonfatal coronary and cerebrovascular events. The use of pindolol was significantly associated with total and nonfatal coronary events, but its use does not explain the excess coronary deaths in the intervention group. As stated earlier (1, 5) and now supported by the favourable results from the low-risk group, we strongly feel that the results of our trial do not question either the importance of traditional risk factors in the development of cardiovascular diseases, or the value of multifactorial prevention as such. We rather think that these results should stimulate more research on the mechanisms of intervention and improved methods to optimally lower cardiovascular risk factors.

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References

1. Miettinen TA, Strandberg TE (1992) Implications from recent results of long term multifactorial primary prevention of cardio vascular diseases. Ann Med 24:85-89
2. Miettinen TA, Huttunen JK, Naukkarinen V, Strandberg T, Mattila S, Kumlin T et al (1985) Multifactorial primary preven tion of cardiovascular diseases in middle-aged men. JAMA 254: 2097-2102
3. Miettinen TA, Huttunen JK, Naukkarinen V, Starndberg T, Vanhanen H (1986) Long-term use of probucol in the multifacto rial primary prevention of vascular disease. Am J Cardiol 57: 49H-54H
4. Naukkarinen VA, Strandberg TE, Vanhanen HT, Salomaa VV, Sarna SJ, Miettinen TA (1989) Mortality rates after multifacto rial primary prevention of cardiovascular diseases. Ann Med 21: 441-446
5. Strandberg TE, Salomaa W, Naukkarinen VA, Vanhanen HT, Sama SJ, Miettinen TA (1991) Long-term mortality after 5-year multifactorial primary prevention of cardiovacsular diseases in middle-aged men, JAMA 266:1255-1229
6. Paul 0, Hennekens CH (1991) The latest report from Finland: a lesson in expectations. JAMA 266:1267-1268
7. Anonymous (1991) Should clinical trials carry a health warning? (Editorial) Lancet 338:1495-1496
8. Psaty BM_f Siscovick DS (1992) Long-term mortality after a car diovascular risk reduction program ACP Journal Club 116:1