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Original Article

Long-term survival in the randomized trial of drug treatment in mild to moderate hypertension of the Oslo study 1972–3

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ABSTRACT

Background: In the Oslo cardiovascular study of 1972–3 a 5-year randomized trial in mild to moderate hypertension was performed. Several changes in treatment practices have been recommended since that time. We followed the mortality patterns up to 40 years.
Methods: Invited to the Oslo study screening were 25,915 middle-aged men and 16,203 (63%) participated. Reexaminations were done to select suitable participants into the trial. Men had blood pressure 150–179/95–109 mm Hg and the active group (n = 406) was treated with thiazides, alpha-methyldopa and propranolol versus untreated controls (n = 379). Cox regression analysis was used for statistical analyses.
Results: There was no trend towards reduction in total mortality by treatment. A nominally significant increase in risk of death at first myocardial infarction was observed in the trial treatment group across the follow-up period, HR = 1.51 (1.01–2.25); (P = 0.042). The excess risk developed rapidly during the first 15 years, but the gap between the groups diminished to a large extent during the next 15 years, but the curves stayed at a certain distance for the last 10 years. Cerebrovascular death tended to be non-significantly reduced, HR = 0.85 (0.52–1.41).
Conclusions: Drug treatment of mild hypertensive men initiated in the 1970s did not reduce mortality at first MI or total mortality. However, during the period (late 1980s and whole 1990s), when large changes in hypertension treatment practices occurred into regimes with more use of combination therapies including metabolically neutral drugs at lower doses, beneficial effects on MI mortality could be observed.

1. Introduction

The Oslo study of cardiovascular disease (CVD) in 1972–3 was the first in a series of similar studies performed by the National Health Service in different counties of Norway [1]. In several counties screenings were repeated after some years and the data collected have provided much of the basic knowledge about cardiovascular disease (CVD) epidemiology in Norway [2–9].

One major purpose of the screening in Oslo was to recruit participants to two randomized controlled trials among supposedly healthy men with a high risk of developing CVD. The background was that myocardial infarction (MI) incidence and mortality had increased at all years from World War II and had reached epidemic proportions. Prevention and treatment of the major risk factors were regarded as cornerstones to stop the epidemic. One of the trials was a treatment trial of 785 mild to moderate hypertensive men who were randomized to drug treatment or no treatment. Drug treatment consisted mainly of hydrochlorothiazide 50 mg daily and in addition if necessary methyldopa twice daily was added. If side effects occurred propranolol up to 160 mg twice daily was given. The other was a combined diet and antismoking trial in men with high total serum cholesterol levels and 80% smokers. Both trials stopped at the end of the 1970s and detailed results have been reported [10,11]. In light of the drastic changes since the 1970s in dietary and smoking habits, the large exchange to modern and metabolically neutral antihypertensive drugs and the massive use of statins in secondary coronary prevention and other high-risk populations with a reduction of coronary mortality in middle aged men to less than a fourth, the long term mortality outcomes of the trials would be difficult to predict. We know of no randomized hypertension drug trial that has been followed with respect to cardiovascular and total mortality for up to 35 years after its close.

Thus, the purpose of this study was to report up to 40 years survival results with respect to death at first MI, cerebrovascular and all-cause mortality in the mild to moderate hypertension trial.

2. Material and methods

All men in Oslo born 1923–1932 were in 1972/73 invited to a screening examination for CVD. Of the 25,915 eligible 16,203 (63%) participated. They were asked to fill in a questionnaire about prevalent CVD

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and diabetes. Those without such diseases were called healthy men and in them two examinations followed to select suitable participants to two planned randomized trials [3]. In the mild to moderate hypertension trial men with blood pressure 150–179/95–109 mm Hg were included.

Men with a higher blood pressure than those included in the trial were referred to the general practice system. The trial has previously been followed up with respect to coronary morbidity and mortality up to 10 years [12]. The survivors (n = 12,764) in the screened population were invited to a second screening examination in year 2000. However, only 6014 men (45%) of the invited participated and among the trial groups only 144 (35.2%) and 134 (35.9%) attended in the active and control group respectively. The present study is extended as a survey only to December 31st 2011 with respect to mortality at first MI, cerebrovascular and total mortality. Thus, no morbidity data other than prevalence of some diseases at the year 2000 screening were available through the whole follow-up period. Statistics Norway added mortality data to the Oslo study data file according to permissions given by the Data Inspectorate and tax authorities, Department of Health and the project was approved by the regional ethics committee for medical research.

3. Statistical analysis

Rates per 1000 observation years and differences between rates with 95% confidence limits were calculated. Cox proportional hazards regression models were used and time to death, time to death at first MI or time to cerebrovascular death were dependent variables. Group codes were exposure factors. Hazard ratios were calculated with 95% confidence limits. The log rank test was used to test for differences between treatment groups with respect to survival. Kaplan–Meier curves were made by the STATA 13 software.

4. Results

Table 1 shows some risk factors at screening in year 1972–73 by treatment group. They were fairly balanced as could be expected by design and demonstrate a population with normal bodyweight and mild to moderate blood pressure levels. The daily smoking proportion was just above the average as compared to the whole screened population (data not given). When these men were invited to a new screening in year 2000 many had died and many declined to participate once more, but Table 2 gives an indication that groups were still fairly balanced on major coronary risk factors. In this selected group the level of systolic blood pressure was still high, but also glucose stayed somewhat elevated. Table 3 demonstrates small differences between proportions of men with experienced diabetes, MI or stroke by treatment group and so do the use of antihypertensive or cholesterol lowering drugs.

The hypertension trial treatment group had a nominally significant increased risk of death at first MI as compared to controls (HR = 1.51; 95% CI: 1.01–2.25; P = 0.042), Fig. 1. The risk difference developed proportionally the first 15 years. In the next 15 years from late 1980s to beginning of year 2000s the gap narrowed. During the last 10 years curves went more parallel. Cerebrovascular death was non-significantly reduced, HR = 0.87 (0.52–1.43), but number of such deaths was only 61. Total mortality was similar between the two treatment groups throughout the follow-up period, Fig. 2.

Table 1
Mean (SD) of some risk factors at screening in 1972–73 and in year 2000 by treatment group.*

	Treatment group (n = 406)	Control group (n = 379)
Screening 1972–73		
Systolic blood pressure (mm Hg)	163.8 (11.6)	162.9 (10.4)
Diastolic blood pressure (mm Hg)	100.3 (10.1)	101.2 (9.1)
Bodyweight (kg)	81.7 (11.5)	82.1 (11.2)
Daily smoking (N, % yes)	200 (52.8)	197 (48.5)
Screening year 2000		
Attendants (N, %)	144 (35.4)	134 (34.5)
Systolic blood pressure (mm Hg)	157.6 (20.2)	158.4 (19.7)
Diastolic blood pressure (mm Hg)	86.5 (11.2)	84.6 (10.0)
Bodyweight (kg)	82.4 (12.3)	82.7 (13.0)
Total serum cholesterol (mmol/L)	5.72 (1.11)	5.74 (1.16)
Triglycerides (mmol/L)	1.87 (0.84)	1.79 (0.96)
High density cholesterol (mmol/L)	1.41 (0.40)	1.42 (0.42)
Serum glucose (mmol/L)	6.08 (1.64)	2.70 (6.56)
Daily smoking (n, %)	21 (15.3)	16 (11.1)
Previous smoking (n, %)	70 (51.1)	91 (63.2)
Never smoking (n, %)	46 (33.6)	37 (25.7)

* Number of valid measurements may vary due to some incompleteness in some variables.

5. Discussion

This study showed an excess MI mortality risk, a slight and non-significant decrease in cerebrovascular death and equal total mortality by active treatment as compared to control. Unfortunately, the negative development of death at first MI continued in the hypertension trial participants up to 40 years of follow-up. The trend at close out of the trial was also confirmed at 10 years follow-up [12]. However, after about 15 years of follow-up, the gap between the curves seemed to shrink for the next 15 years, but continued later on without fully catching up the lower risk in the control group. The interpretation of this finding is difficult since no regular clinical follow-up was made on these men. Our data only stems from a mortality survey follow-up at end of 2011. In year 2000 the re-screened population among the survivors had a low (45%) participation frequency and this was even lower in the trial participants due to their higher mortality. Among these the prevalence of drug treatment was 80.9% in the active and 82.4% in the control group men. Also other conventional risk factors were fairly equal in this selected subgroup at that time. This gives an indication that both groups were equally treated at that time and is thus consistent with the parallel MI survival curves observed during the last 10 years of follow-up. It is unknown to what degree old treatment modalities used in the hypertension trial have been exchanged with effective and more metabolically neutral antihypertensive drugs, since no such effort was made systematically. In Norway there was generally a great exchange of new drugs such as ACE inhibitors, angiotensin II blockers or calcium antagonists with more combination therapy each prescribed at lower doses during late 1980s and through the 1990s due to anticipated favorable results in large clinical trials. This is documented by prescription statistics during these years [13]. There was a high use of thiazides into the beginning of the 1980s, but then more calcium channel blockers were prescribed together with less use of thiazides that was almost not used in the period 1990 to about 2005, when new statements about the use of thiazides as basic choice of drug were issued from the Government Health Department but again abandoned in 2010. From about 1995 use of ACE and AII inhibitors increased rapidly and at the end of the follow-up period defined daily dose per 100,000 inhabitants per day of all hypertensive use (covering somewhat more diagnoses than pure hypertension) more than doubled in the population as compared

Table 2
Disease prevalence and drug use at year 2000 by attending men per treatment group.

Diseases and drug use	Treatment group (n = 144)	Control group (n = 134)
Diabetes	22 (15.3)	14 (10.4)
Myocardial infarction	24 (16.9)	27 (20.1)
Cerebral stroke	12 (8.5)	15 (11.3)
Use of antihypertensive drugs	115 (80.4)	112 (82.4)
Use of cholesterol lowering drugs	45 (33.3)	39 (30.5)