

# Outcomes in treated hypertensive men

*- a follow-up during three decades*

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*To Mia  
and  
to my mother  
and  
in memory of my father.*



Illustration Charlotte Österström

*Men störst av dem är kärleken.*

FÖRSTA KORINTIERBREVET 13



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# Abstract

## Objectives

To analyse survival, cause specific mortality and cardiovascular morbidity in relation to cardiovascular risk factors, to investigate the prevalence of type 2 diabetes and the cardiovascular risk this constitutes and to study systolic blood pressure over time in treated hypertensive men during three decades of follow-up.

## Subjects and methods

754 hypertensive men were identified at a screening in Göteborg of a randomly selected group of 10000 men, 47-54 years old, and were treated and followed with annual check-ups at an outpatient clinic during three decades.

## Results

During 22-23 years 37 % of the hypertensive men died compared to 29 % of the non-hypertensive men. The impaired survival in hypertensive men escalated with time and was mainly due to a doubled incidence of death in ischemic heart disease; 20 % compared to 10 %. Smoking, S-cholesterol and target organ damage at entry and S-cholesterol during follow-up was related to a fatal or nonfatal myocardial infarction in the hypertensive men.

During 25-28 years 22 % of the hypertensive men had a fatal or nonfatal stroke compared to 13 % of the non-hypertensive men. Diabetes at entry and smoking at entry and during the study was significantly related to a first, fatal or nonfatal stroke in treated hypertensive men. The most prevalent cardiovascular complication was myocardial infarction that occurred in 33 % of the hypertensive men and in 22 % of the non-hypertensive subjects.

In the 725 hypertensive men with no diabetes at entry, 20.4 % (n=148) developed type 2 diabetes during 25 years. Body mass index, serum triglycerides and treatment with beta-blockers at entry were significantly

related to new-onset diabetes. New-onset diabetes implied a significant increased risk for stroke (HR: 1.67; CI: 1.1-2.6), myocardial infarction (HR: 1.66; CI: 1.1-2.5) and mortality (HR: 1.42; CI: 1.1-1.9).

Systolic blood pressure increased 22.5 mmHg after 30 years from achieved blood pressure at the third annual check-up, in a 33 % randomly selected subgroup of treated hypertensive men free from cardiovascular disease. Systolic blood pressure increased 7.6 mmHg 30 years after screening in the randomly selected 3 % subgroup of the non-hypertensive men without current anti-hypertensive medication and free from cardiovascular disease. The difference in systolic blood pressure increment between treated hypertensive men and normotensive men was 15.0 mmHg (95 % CI: 7.7-22.2 mmHg).

### **Conclusions**

Hypertensive men had an impaired survival and an excess of cardiovascular complications in spite of long-term treatment. They had an increased prevalence of diabetes and new-onset diabetes implied an increased risk of cardiovascular complications. In spite of treatment systolic blood pressure increased three times more than in non-hypertensive men.

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## List of Publications

- I Andersson OK, Almgren T, Persson B, Samuelsson O, Hedner T, Wilhelmsen L.  
Survival in treated hypertension: follow up study after two decades.  
*BMJ 1998;317:167-171.*
- II Almgren T, Persson B, Wilhelmsen L, Rosengren A, Andersson OK.  
Stroke and coronary heart disease in treated hypertension – a prospective cohort study over three decades.  
*J Intern Med 2005;257:496-502.*
- III Almgren T, Wilhelmsen L, Samuelsson O, Himmelmann A, Rosengren A, Andersson OK.  
Diabetes in treated hypertension is common and carries a high cardiovascular risk: results from a 28-year follow-up.  
*J Hypertens 2007;25:in press.*
- IV Almgren T, Himmelmann A, Herlitz H, Fägerlind M, Widgren BR, Wilhelmsen L, Andersson OK.  
Systolic blood pressure rise in spite of therapy. Thirty years of follow-up in hypertensive male patients without complications.  
*Submitted.*



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# Introduction

## Origins of preventive cardiology

### Cardiovascular risk factors

Cardiovascular disease is the dominating cause of mortality and morbidity and the leading cause of disability in modern societies (1-2). In the middle of the twentieth century elevated blood pressure, smoking habits and high serum cholesterol (3-6) were found to be important, independent risk factors for cardiovascular disease. When these risk factors were combined a distinct escalation of atherosclerotic complications was evident (3,5,6) In a recent world-wide case-control study in both sexes, the Interheart Study, it was demonstrated that nine potentially modifiable risk factors were significantly related to 90% and 94% of myocardial infarctions in men and women, respectively (7). Hence, there is consensus today that all known cardiovascular risk factors should be regarded as ingredients in a global risk factor profile and that patients with hypertension should be treated according to their risk for cardiovascular disease (8).

### Early primary preventive interventions

When these traditional cardiovascular risk factors had been identified, population based multifactorial intervention studies were initiated. One such example is the North Karelia Project, conducted in an area with the highest known coronary mortality in the world. In 1972 a national pilot programme was initiated to reduce the incidence of cardiovascular disease by intervention against important risk factors (9). In this program, the combined efforts of life style intervention, i.e., smoking cessation, reduced intake of unsaturated fat and increased physical activity together with improved control of hypertension has resulted in markedly improved survival and lowering of morbidity in coronary heart disease (10). Similar studies varying in sample size and objectives, in both sexes, were started in many other places all over the world, e.g., in Chicago, Copenhagen, Oslo and Rotterdam (11-14). In Göteborg, the long-term intervention study by Bengtsson and co-workers was probably the first ever to concentrate on cardiovascular risk factors in women (15).

The Multifactor Primary Prevention Study, another important contribution from Göteborg, was started in 1970 (16). The study was intended to test whether an intervention against smoking, hypercholesterolemia and hypertension in a population of middle-aged men could positively affect morbidity and mortality in cardiovascular disease. In part, The Multifactorial Primary Preventive Study was designed based on experiences by Tibblin and co-workers (17). They had examined 50-year old men in the first screening ever for cardiovascular risk factors in Sweden (17). The definition of hypertension by casual blood pressure assessments was a blood pressure at 175/115 mmHg or above. This cut-off level was derived based on the observation of hypertensive retinal changes above this blood pressure levels. The hypertensive patients in the present report were recruited from screening for The Multifactor Primary Prevention Study (16).

Strategies for health promotion and disease prevention may follow two main avenues, i.e., intervention in the population or intervention in individuals at high risk. The former strategy takes the form of general intervention in all individuals of the society by information, education, community organisation of health care and environmental control. The latter strategy focuses on intervention in high-risk individuals. It often requires screening procedures for identification of patients at risk as well as health care and medication for control of risk factors. The study of hypertensive patients treated in the Outpatient Hypertension Clinic of Sahlgrenska University Hospital is an observational study on the effects of multifactorial intervention in a group of men at high cardiovascular risk with arterial hypertension as the determinant for recruitment.

## **Treatment of hypertension – initial concepts**

### **Treatment or not?**

Treatment of hypertension in the early 1970s was not very common in Sweden or elsewhere in the world. The prevailing opinion was that patients eligible for drug treatment should be restricted. The clinical relevance of treatment, at least in milder forms of hypertension, was disputed. The definition of hypertension in need of treatment was that of very high blood pressure, often with signs of target organ damage. Recommendations or guidelines on therapy were not available at that time. Moreover, the scientific evidence in favour of drug therapy was scarce. In some small studies in malignant hypertension an improved survival in treated patients compared to historical controls had been demonstrated (18-20).

### **Randomised controlled trials**

The first randomised prospective trial and the scientific breakthrough in the treatment of hypertension was the Veterans Administration Cooperative Study. It was reported in 1967 for patients with the diastolic blood pressure above 115 mmHg (21). For the first time, it was shown beyond doubt that drug treatment of severe hypertension reduced mortality and morbidity in stroke and congestive heart failure. The efficacy to prevent coronary heart disease was not quite convincing.

In 1970 results from the Veterans Administration Cooperative Study for patients with diastolic blood pressure between 90 and 114 mmHg were presented (22). Clear benefits following treatment were obvious, in patients with diastolic blood pressure 105 mmHg or higher. However, the results were not significantly positive in favour of therapy in the treated subgroup with entry diastolic blood pressure of 90-104 mmHg. These results guided and restrained the diagnosis of hypertension in need of treatment for more than a decade. In 1973, The US National High Blood Pressure Program recommended individualisation with regard to drug therapy for patients with mean diastolic blood pressures of 90-104 mmHg given the indecisive data on efficacy of drug treatment in this stratum (23).

**Inclusion blood pressure to be accepted**

Evidence for the beneficial preventive effects of therapy in less severe forms of hypertension were presented in the Hypertension Detection and Follow-up Program in 1979 (24). The central finding in that study was a significant reduction in five-year all-cause mortality in the special care group. The patients in this group were offered organised follow-up and a strict program for drug therapy. In this group a majority of the patients had drug treatment over the five-year intervention period. They had about 5 mmHg lower diastolic blood pressure as compared to a group of patients allocated to usual care. Of importance for forthcoming guidelines, in patients with diastolic blood pressure 90-104 mmHg at entry evidence was obtained of improved survival with the special care regimen.

One year later, The Australian National Blood Pressure Study was presented (25). Patients were included if their diastolic blood pressure exceeded 95 mmHg in this prospective randomised double-blind study over five years. Significant and clinically relevant reduction of morbidity in hypertension related complications was observed. Following this, a diastolic blood pressure level of 95 mmHg was accepted for inclusion to therapy in most countries.

**Summary of treatment benefits in hypertension**

In 1985 the principal results of the Medical Research Council Working Party Trial were published (26). Patients with mild hypertension, i.e., diastolic blood pressure 90-109 mmHg, were included and treated in a randomised double-blind design with beta-blockers or diuretics or placebo. It was obvious that also in patients with mild hypertension stroke rate and all cardiovascular events were reduced on active treatment. However, no effect on the rate of coronary events could be shown by active treatment. Thus, at this time available data indicated that therapy in hypertension seemed to be effective in preventing stroke, congestive heart failure and renal disease, whereas in all studies an expected beneficial effect on coronary heart disease could not be demonstrated.

By the method of meta-analysis on all relevant studies it was demonstrated, in 1990 that drug treatment for hypertension also reduced the risk of coronary heart disease, although to a lesser degree than was anticipated (27). In the major randomised trials of antihypertensive drugs conducted at that time, the diastolic blood pressure was reduced by 5-6 mm Hg. Active treatment reduced stroke by 42%, suggesting that virtually all the epidemiologically blood pressure related expected strokes could be prevented. In contrast, coronary heart disease was reduced by only 14%, which was approximately half of what could be expected from epidemiology.

### **The outpatient hypertension clinic at Sahlgrenska.**

#### **Special-care units**

In the early days of management of hypertension target blood pressure levels to be achieved by therapy were not well defined. The results of therapy were also unpredictable and less effective compared to contemporary experience, primarily because of less effective and less tolerable drugs. The Hypertension Detection and Follow-up Program suggested clear benefits with regard to lower blood pressure, better compliance and outcome by special care units (24). The outpatient blood pressure clinic at Sahlgrenska Hospital was set up in 1970 to care for hypertensive patients from the ongoing prevention study (16). It was also a referral centre for patients with severe hypertension or blood pressure resistant to treatment. Life style intervention and drug therapy in primary prevention was then unknown and had limited acceptance in the general population. Thus, one of the basic concepts with the organisation was to ensure continuous follow-up and a structured program for diagnosis, evaluation, treatment and follow-up.

#### **Target diastolic blood pressure**

During the later part of the twentieth century results of prospective controlled trials accumulated. Gradually the lower blood pressure levels used for inclusion in these studies showed preventive effects and

became the target blood pressure levels for therapy in clinical practice. Hence, based on available results the diastolic blood pressure target for therapy was 95 mmHg when the outpatient blood pressure clinic at Sahlgrenska Hospital was organised. As a consequence of preliminary analyses of our own data indicating lower risk of cardiovascular and coronary complications the lower the achieved blood pressure and cholesterol levels (28) and based on international results and recommendations (29) the diastolic blood pressure target level (30) was changed to 90 mmHg in 1988. Further recommendations and guidelines were gradually incorporated in the clinical work (31, 32).

## **Clinical work-up**

At the first clinic visit at the outpatient blood pressure clinic at Sahlgrenska Hospital a detailed patient history was taken. Moreover, a physical examination, standard laboratory tests and ECG were performed. Extended evaluations, looking for secondary forms of hypertension, were performed when a patient had low potassium levels, increasing S-creatinine or proteinuria or did not respond adequately to therapy. Drug therapy was usually initiated after at least three assessments.

All hypertensive patients had at least one annual check up. The patient's history concerning cardiovascular disease morbidity was updated, and blood pressure measurements and laboratory data were obtained. In the common interest of the individual patient's health and the collection of data for the present study, patients who did not keep an appointment were immediately contacted and given a new one.

## **Life-style intervention**

In the present high-risk group of male patients the objectives were to reduce the incidence or delay the occurrence of cardiovascular disease through multifactorial intervention. Thus, all patients had recommendations regarding diet and physical exercise from their physician. Booklets on low-caloric, low-fat diets were distributed and



body weight was measured regularly. The cholesterol and triglyceride levels were determined. In diabetic patients professional nutritionists were used. Smoking cessation was strongly advised in the regular consultations. Smokers were also referred for group sessions with a psychologist with the purpose to improve motivation to stop smoking. Nicotine containing chewing gum was used to help smokers stop.

### **Drug therapy**

Initial treatment comprising a beta-adrenoceptor blocking agent or a thiazide diuretic was adapted for each patient's needs. If necessary these two drugs were combined to achieve the target blood pressure of <160/95 mmHg, and after a diastolic blood pressure <90 mmHg. If further drugs were needed to achieve the target blood pressure, a stepped care regimen was followed, without a strict protocol. Hence, hydralazine or other drugs, or both were added if necessary.

When dihydropyridine calcium antagonists became available in the late 1980s such drugs replaced hydralazine, due to their improved effect on blood pressure control and fewer side effects. ACE inhibitors were also used in therapy resistant cases but primarily in patients with diabetes or signs of renal disease, e.g., increasing creatinine level or proteinuria.

Patients with type 2 diabetes had diet instructions from the physician and from dieticians. The medical therapy metformin or sulphonylureas and if necessary insulin.

In hypercholesterolemia cholestyramin was used and only in those with severely elevated cholesterol levels and only after failure to achieve reduction in cholesterol level by dietary advice. It was only in the later part of the 1990s that statins were used to reduce elevated cholesterol levels.

**Outcomes in treated hypertension (Papers I-II)**

The possibility to draw conclusions regarding long-term treatment of hypertension has been limited from previous controlled trials due to their relatively short duration, about 5 years. Of interest, observations have suggested an even better therapeutic effect at later stages of treatment (33,34). Based on outcome data in three cohorts of men and women from the Framingham heart Study Sytkowski and co-workers showed that the 10-year risk of death from cardiovascular disease with long-term antihypertensive treatment was reduced by 60% as compared to no treatment (34). If that observation also was applicable for other populations, important information could be gained from other prospective studies of long duration. Such long-term follow-up would also allow the evaluation of patient characteristics of prognostic importance.

The present population based, prospective study with analyses up to 30 years of follow-up were aimed to analyse the long-term mortality and morbidity in treated hypertensive men compared with non-hypertensive men taking part in the same prevention program and to analyse the effects of treatment on metabolic adverse effects and blood pressure control.

**New-onset diabetes in treated hypertension (Paper III)**

Diabetes mellitus is strongly associated with atherosclerosis (35-39). In particular, hypertension with superimposed diabetes carries an even worse prognosis. It is well established that antihypertensive therapy reduces cardiovascular risk in non-diabetic and diabetic patients (27,40). However, thiazide diuretics and beta-blockers, especially in combination, also increase blood glucose levels and the risk to develop diabetes mellitus (41-45).

A therapeutic controversy appeared when consistent data from randomised interventional outcome studies indicated that other antihypertensive drug classes, i.e., ACE inhibitors, angiotensin-II-receptor antagonists and calcium antagonists, were associated with a

lower risk of new-onset diabetes (46-52). Hence, concerns were raised that potential adverse metabolic effects of diuretics and beta-blockers may partly offset the beneficial effects of blood pressure reduction on overall cardiovascular risk reduction. To ensure maximal cardiovascular protection to the hypertensive patient it is essential to clarify the cardiovascular risk associated with new-onset diabetes mellitus.

It is proposed from a report of the Systolic Hypertension in the Elderly Program that type 2 diabetes diagnosed during diuretic therapy in elderly patients with isolated systolic hypertension is rather mild and not associated with a significant increase in cardiovascular mortality (53). In a previous report from the present long-term follow-up it was suggested that new-onset diabetes mellitus during therapy with beta-blockers or thiazide diuretics did not seem to have any major impact on coronary heart disease (54). In contrast to that observation, it has recently been reported that new-onset diabetes mellitus during antihypertensive treatment with beta-blockers or thiazide diuretics was indeed related to an increased risk of cardiovascular events (55). Thus, it is obvious that the role of new-onset diabetes mellitus has not yet been fully elucidated. The scientific reliability in this matter is limited by the few data available and long-term studies are lacking. In this study (Paper III), we re-analyse extended long-term data. The results question and challenge our previous view that new-onset diabetes mellitus does not carry an increased cardiovascular risk.

### **Systolic blood pressure control in treated hypertension (Paper IV)**

Several large-scale observational studies have identified blood pressure as an important risk factor for stroke and myocardial infarction (1, 3-7). Importantly, high systolic blood pressure is an even stronger risk factor than elevated diastolic pressure for most hypertension related complications (56-58). The importance of systolic blood pressure rise for the continuously rising pulse pressure in normotensive subjects is well documented (59). Moreover, increased pulse pressure is an independent predictor of myocardial infarction, congestive heart

failure and cardiovascular death, in normotensive subjects as well as in hypertensive patients on antihypertensive drug therapy (60).

Increasing systolic blood pressure with age has been described as a consequence of increasing arterial stiffness. Such age-related arterial changes are caused by time related loss of elastic fibres and a transition towards collagen fibres in the arterial wall (61-62). Systolic hypertension is the most common form of hypertension and it constitutes 60-65% of all hypertensive diagnoses in the population. The importance of systolic hypertension is emphasized in recent guidelines for management of arterial hypertension (31-32). Prospective, randomised and placebo-controlled trials have clearly demonstrated the efficacy of pharmacological treatment with regard to reduction in hypertension related cardiovascular disease also in patients with systolic hypertension (42, 63).

The clinical characteristics of systolic hypertension are emphasized by two important observations. Among subjects with systolic hypertension a deteriorated prognosis is observed (56-58). Furthermore, systolic hypertension is often more difficult to control with pharmacological treatment than diastolic hypertension (64).

Clinical observations suggested that systolic blood pressure during ageing in our patients continuously increased although diastolic control was better preserved. To test this hypothesis we analysed randomised subgroups of treated hypertensive patients and referent subjects after 30 years follow-up (paper IV).

## Objectives

To analyse survival and cause specific mortality in hypertensive men and the relation of cardiovascular risk factors to ischemic heart disease during 22-23 years of follow up (Paper I)

To analyse cardiovascular morbidity in hypertensive men and the relation of cardiovascular risk factors to stroke during 25-28 years of follow up (Paper II).

To analyse predictive factors and prevalence of type 2 diabetes during life-long therapy for hypertension and the alleged additional cardiovascular risk this constitutes (Paper III).

To analyse systolic blood pressure over time in treated hypertensive patients during thirty years of follow-up (Paper IV)



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## Subjects and Methods

### Subjects

The Multifactor Primary Prevention Study started in Göteborg in 1970 (16). It was intended as an intervention trial against smoking, hypercholesterolaemia and hypertension, at predefined levels in an intervention group comprising 10000 men. The men constituted a random third of all men in the city who were born between 1915 and 1925. Men born in 1923 were excluded, since that cohort was already included in another long-term follow-up study in the city. Only men were studied in this early population based intervention study because of their higher incidence of coronary heart disease relative to women. There were two control groups of 10000 men each. Risk factor analyses were performed only in subgroups of the controls, and these data were not used in the present studies.

The first screening examination took place between 1970 and 1973 and a second examination was performed between 1974 and 1977. Those who fulfilled criteria for risk factor intervention at either examination were offered interventional measures. After 10 years of follow-up subsamples of intervention and control group were re-examined. Serum cholesterol, smoking and blood pressure had decreased. No significant differences in the pattern of risk factors or in outcome were detected between the intervention and control group. Any changes brought about by the intervention took place among the general population as well. Thus, the present study group, i.e., the intervention group from the The Multifactor Primary Prevention Study is considered to be representative of the background population in the city (16).

All subjects in the intervention group (n=9996) were sent a postal questionnaire and invitation to the first screening examination. The questionnaire included questions about family history of cardiovascular disease, smoking habits, physical activity and previous history or present symptoms of cardiovascular disease. A physician at the screening examination checked the answers and filed data.

Of all invited men, 75% (n=7455) attended the first screening examinations. They were performed on a normal working day, between 4 and 7 p.m. Blood pressure was measured after a 4-5 minute interview with the subject seated. A mercury manometer and a 12 x 35 cm rubber cuff placed on the right arm were used. Recordings of blood pressure were done to the nearest 2 mmHg and diastolic blood pressure was recorded as phase 5 of the Korotkoff sounds. After the blood pressure measurements a blood sample for determination of total serum cholesterol was taken.

At the first screening examination 1159 subjects had either antihypertensive treatment (n=361) or a blood pressure exceeding one or both cut off points for hypertension (n=798), i.e., a systolic blood pressure >175 mm Hg or a diastolic blood pressure >115 mmHg. The latter group was invited for a re-examination within two weeks; 324 of them had a blood pressure below the cut off points, 58 men did not attend the re-examination and 416 men had a blood pressure exceeding one or both cut off points. The cut-off points for hypertension, i.e., 175/115 mmHg at screening were comparable to 165/95 mmHg at resting conditions (65)

The group of men with a systolic blood pressure >175 mmHg or a diastolic blood pressure >115 mmHg on two occasions (n=416) and some of 361 patients already receiving antihypertensive treatment at screening (n=270), agreed to have treatment at a special, outpatient clinic originally designed for the care of such patients (30).

In the analyses of mortality and morbidity (Paper I) these men (n=686) constitute the group of treated hypertensive patients. All the remaining men participating in the first screening were included in the group of non-hypertensive referents (n=6810). Subjects with one blood pressure reading above cut off limits and one below at the first screening were followed annually. In some subjects (n=68) supine diastolic blood pressure increased above 95 mmHg during the following three years were included in the group (n=754) of treated



hypertensive patients (Paper II and III). In the study on blood pressure level in treated hypertensives (Paper IV) a 33% random subsample of surviving hypertensive men (n=170) were used. Only patients without a history or signs of coronary heart disease, congestive heart failure or cerebrovascular disease were eligible (n=59). Their diastolic blood pressures should be well treated (85-95 mmHg) during the 12 years following the third annual control. For comparison a 3% random subsample of the non-hypertensive men from the intervention group of the trial was identified and used as a reference group. They were invited and included if their history was free from cardiovascular disease and if they received no drug therapy (n=106). Subjects with newly detected and untreated hypertension (n=34) were not excluded.

## Methods

At the first visit, a detailed patient history was taken and a physical examination, a 12-lead resting electrocardiogram, chest X-ray and standardised laboratory tests were performed. Blood pressure was measured after 5 minutes of supine rest and after standing for 1 minute. The blood pressure level was checked at least three times before introduction of therapy. The effect on blood pressure level and possible side effects of antihypertensive drug was evaluated before drugs were titrated further or changed. After these initial visits all hypertensive patients had at least one annual check up.

At the annual visits the patient's history concerning cardiovascular morbidity was updated and blood pressure measurement and laboratory test data, e.g., haemoglobin, electrolytes, creatinine, cholesterol and triglycerides were obtained. Urine tests for protein and glucose were performed. Blood glucose level was monitored only in patients with a suspected or confirmed diagnosis of diabetes mellitus. Smoking habits were registered at the annual check-ups and serum cholesterol concentrations were determined at a regularly standardised laboratory.

Patients who did not keep an appointment were given a new one. During the first year of follow-up 25 (3,6%) stopped attending the clinic, but

thereafter the annual withdrawal rate was less than 1%. No patient in the treated hypertensive group was lost to follow-up for the relevant end-points.

All patients had dietary advice to maintain or if needed reduce body weight. They were recommended low-fat diets and strongly advised to stop smoking. Regular exercise was advocated.

Initial treatment comprised of a beta-adrenoceptor blocking agent or a thiazide diuretic or a combination of the two drugs, to achieve the target blood pressure. Initially the target blood pressure was <160/95 mm Hg, but in 1988 the target blood pressure was revised to a diastolic blood pressure <90 mm Hg. If further drugs were needed to achieve the target blood pressure, a stepped care treatment schedule was followed, although without a strict protocol. Hence, hydralazine or other drugs were added. Following the introduction of vasoselective calcium antagonists these drugs soon replaced hydralazine. ACE inhibitors were adopted initially in therapy resistant patients, but later also in patients with proteinuria or diabetic renal disease. Patients with type 2 diabetes were given diet instructions from physicians and from dieticians. The drug treatment for control of hyperglycemia in diabetic patients was sulphonylureas or metformin. If necessary insulin could also be used. Cholestyramin was used to treat hypercholesterolemia

After 10 years, 64% (368/575) of all patients were receiving a beta-adrenoceptor blocking agent; 13% (74/575) took this drug alone as single drug treatment. After 15 years the corresponding frequencies for all beta-blocker use was 68% (311/457) of which 18% (81/457) were given the drug as monotherapy. Thiazides were used in 58% (n=334) of all patients after 10 years, with 6% (n=35) having this drug as single drug treatment. After 15 years the corresponding thiazide treatment was 62% (283/457), of which 8% (n=37) received the drug as monotherapy.

In the subgroup of patients who were investigated for systolic blood pressure control (paper IV), the treatment profile after 30 years of follow-

up was diuretics in 80%, beta-blocking drugs in 38%, vasoselective calcium antagonists in 77% and ACE inhibitors in 42% of the patients.

Data on mortality and cause specific morbidity were obtained from hospital files and the Swedish National Register on Deaths and the Swedish National Register on Hospital Admissions. Census data and local registers (both based on each individuals' 10-digit person number) were also compared for diagnosis of each specific death certificate with hospital records (n=261). An almost complete (99,8%) accordance between our coding and that of the other registers was found. Until 1987 we used codes according to the international classification of disease 8th revision (ICD-8). Five separate categories were used: ischaemic heart disease (ICD codes 410-414); cerebrovascular disease (430-440); other vascular disease (390-456) excluding the above; cancer (140-207 and 230-239); and all other causes (any other ICD code). When available the 9th revision (ICD-9) and corresponding codes were used. All statistical analyses on mortality and morbidity were performed according to "intention-to-treat" principles.

### **Statistical methods**

The data were analysed using PC-SAS version 6.12 (66, 67). Standard summary statistics were used to illustrate results.

Total and cause specific mortality and the incidence of first myocardial infarction and stroke in the treated hypertensive men were compared with such complications in the non-hypertensive men attending the same screening examination. Life table analyses of the cumulative survival and survival from coronary artery disease and absence from myocardial infarction and stroke were performed using the Kaplan-Meier estimates. The log rank test was used to test differences between curves.

Mean in study blood pressure and serum cholesterol measurements were defined as the mean of annual readings after 5, 10, and 15 years of follow-up or until the end of the follow-up period, or the time for drop-

out, or the last check up visit preceding a cardiovascular complication or death. Patients with a history of a clinically verified myocardial infarction or stroke before entry were excluded from analyses.

The Cox's proportional hazards model was used to test the multivariate correlations between both entry and mean in study variables and cardiovascular disease (68). Among entry characteristics blood pressure, S-cholesterol, smoking, left ventricular hypertrophy, and target organ damage (WHO), diabetes and body mass index, and triglycerides were used for analysis. When variables with updated measurements were tested (blood pressure, S-cholesterol, smoking, diabetes and triglycerides) the updated covariates proportional hazards model was used (68). This model is also known as Cox's time dependent regression model.

The survival and incidence of cardiovascular morbidity from the tenth annual check-up in diabetic patients at entry, in new-onset diabetes and in non-diabetic patients were performed using the Kaplan-Meier estimate.

Multivariate regression analysis with new-onset diabetes as the dependent variable was used to test the association with various clinical features at entry.

Intra-individual change in blood pressure was analysed by the non-parametric Wilcoxon rank-sign test. For comparison between groups the non-parametric Wilcoxon sum-sign test was used.

A p-value less than 0.05 was considered significant.

## Results

### Survival in treated hypertension: follow-up study after two decades (paper I).

Table 1 shows the patients' characteristics at entry to the study. Hypertensive patients were heavier, they had signs of hypertensive organ involvement, higher concentrations of serum cholesterol and a higher prevalence of diabetes.

**Table 1** Characteristics at screening of 686 hypertensive men and 6810 non-hypertensive men aged 47-55 years.

Characteristic	Hypertensive men (mean) (SD)	Non-hypertensive men (mean) (SD)
Age (years)	52.4 (2.3)	52.6 (2.1)
Screening blood pressure*		
Systolic (mmHg)	185.3 (19.1)	145.5 (11.3)
Diastolic (mmHg)	114.6 (12.3)	93.4 (8.7)
Serum cholesterol concentration (mmol/l)	6.6 (1.2)	6.4 (1.1)
Smoking score (1-5 points)	2.2 (1.1)	2.1 (1.0)
Body weight (kg)	83.3 (12.4)	76.9 (11.3)
Height (cm)	175.4 (6.2)	175.3 (5.9)
Target organ damage (%) <sup>‡</sup>		
1	77	-
2	9	-
3	11	-
Diabetes (%)	3.8	1.1

\*Sitting blood pressure without previous rest.

<sup>‡</sup>1=non-smoker; 2=ex-smoker; 3=1-14g tobacco per day; 4=15-24g tobacco per day; 5=>24g tobacco per day.

<sup>‡</sup>According to World Health Organisation staging.

Table 2 shows the risk factor changes. Blood pressures were reduced after the first year of follow-up, and a further reduction was observed after 5 years. After 10 and 15 years the mean blood pressure was 149/89 mm Hg and 145/89 mm Hg, respectively. Serum cholesterol concentrations were reduced and the proportion of smokers decreased from 34% at baseline to 17% after 15 years of follow-up.

**Table 2** Risk factor changes during clinical follow-up of 686 hypertensive men.

Follow up	No of men	Blood pressure (mmHg)	Heart rate (beats/min)	Serum cholesterol (mmol/l)	Smoking (%)
Baseline	686	169/106	80	6.6	34
Year:					
1st	654	158/97	72	6.5	30
5th	596	148/91	67	6.2	– <sup>†</sup>
10th	575	149/89	65	6.2	27
15th	457	145/89	66	6.1	17

<sup>\*</sup> After 5 minutes of supine rest.

<sup>†</sup> Data not available.

All cause mortality was significantly higher in the treated hypertensive men, after 22-23 years 37.4 % had died as compared to 29.2 % of the non-hypertensive men (Figure 1). The odds ratio (OR) and 95% confidence interval (CI) 1.6 (1.4 –2.1).

### Systolic blood pressure rise in spite of therapy. Thirty years of follow-up in hypertensive male patients without complications (paper IV)

Baseline characteristics in the hypertensive and the reference groups are given in table 9. Both systolic blood pressure and diastolic blood pressure were significantly higher in hypertensive men compared to referents. The hypertensive patients had higher body mass index, but there were fewer smokers than among the referents.

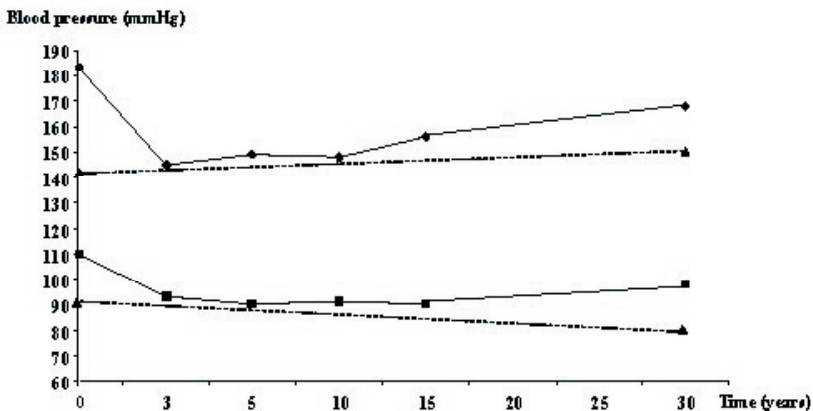
**Table 9** Baseline characteristics (mean  $\pm$ SD)

	Hypertensive patients N=59	Non-hypertensive referents N=106	p-value
Age (years)	51.4 $\pm$ 2.3	50.7 $\pm$ 2.7	0.07
Height (cm)	175.2 $\pm$ 6.2	176.6 $\pm$ 6.3	n.s.
Weight (kg)	80.8 $\pm$ 10.0	79.2 $\pm$ 9.5	0.18
BMI (kg/m <sup>2</sup> )	26.3 $\pm$ 3.4	25.4 $\pm$ 2.7	0.05
SBP (mmHg)	183.7 $\pm$ 19.7	142 $\pm$ 18.4	0.001
DBP (mmHg)	110.9 $\pm$ 10.3	90.3 $\pm$ 10.1	0.001
PP (mmHg)	52.0 $\pm$ 11.1	52.3 $\pm$ 12.9	n.s.
S-Chol (mmol/l)	6.49 $\pm$ 1.03	6.26 $\pm$ 1.12	n.s.
S-TG (mmol/l)	1.5 $\pm$ 0.9	n.a.	
Current smokers (%)	20	35	0.03

BMI=body mass index, SBP=systolic blood pressure, DBP=diastolic blood pressure, S-Chol=serum cholesterol, S-TG=serum triglycerides, PP=pulse pressure, n.a.=Not available

The hypertensive subsample (n=59) was also characterised regarding baseline variables compared to the rest of the hypertensive patients (n=695). This subsample had lower baseline systolic blood pressure (164 vs. 170 mmHg;  $p < 0.05$ ) and at the third annual control (145 vs. 151 mmHg;  $p < 0.05$ ) while the diastolic blood pressure was comparable. Furthermore, there were fewer smokers (22% vs. 48%;  $p < 0.01$ ), and less signs of retinal changes, fundus hypertonicus 1-3, (1.4 vs. 1.6;  $p < 0.05$ ) at the baseline examination. Type 2 diabetes did not develop in any case in the studied subsample, while it occurred in 23% in the rest of the hypertensive patients. Furthermore, in the subsample patients reported significantly higher leisure time physical activity. Thus, the surviving patients of this subsample were healthier than the rest of the hypertensive patients. The mortality in the entire group of treated hypertensive patients (n=754) after 30 years of follow-up was 72%.

After three years of active treatment, systolic blood pressure fell from  $184 \pm 20$  mmHg to  $145 \pm 11$  mmHg among the subsample of treated hypertensive subjects. Simultaneously, diastolic blood pressure was reduced from  $111 \pm 10$  mmHg to  $93 \pm 9$  mmHg (Figure 8).



**Figure 8** Systolic and diastolic blood pressure in treated hypertensive patients (solid line) and non-hypertensive subjects (broken line) during 30 years of follow-up.



The pulse pressure after three years treatment was  $52 \pm 11$  mmHg in the hypertensive patients. Drug therapy at the third annual visit was thiazide diuretics in 53%, beta-blockers in 54% and hydralazin in 24% of the patients and after ten years 55%, 70% and 33%, respectively. The treatment profile after 30 years of follow-up was diuretics in 80%, beta-blocking drugs in 38%, vasoselective calcium antagonists in 77% and ACE inhibitors in 42% of the patients.

At subsequent visits after the third annual control until the fifteenth annual control, the diastolic blood pressure was virtually unchanged, whereas the systolic blood pressure rose (Figure 8). At the annual control after 15 years of therapy the systolic blood pressure had significantly increased from  $145 \pm 11$  to  $158 \pm 10$  mmHg ( $p < 0.01$ ) in the treated hypertensive subsample. After 30 years of follow-up systolic blood pressure was  $168 \pm 15$  mmHg in the treated hypertensive subsample compared to  $150 \pm 17$  mmHg among the non-hypertensive referents (Table 10).

**Table 10** Characteristics at follow-up after 30 years (mean  $\pm$ SD).

	Hypertensive patients N=59	Non-hypertensive referents N=106	p-value
Age (years)	80.7 $\pm$ 1.7	80.0 $\pm$ 1.6	n. s.
Height (cm)	174 $\pm$ 5.9	175 $\pm$ 8.1	n. s.
Weight (kg)	77.4 $\pm$ 9.5	78.1 $\pm$ 10.	n. s.
BMI (kg/m <sup>2</sup> )	25.7 $\pm$ 3.1	25.3 $\pm$ 2.5	n. s.
SBP (mmHg)	168 $\pm$ 15	150 $\pm$ 17	P<0.001
DBP (mmHg)	98 $\pm$ 15	79 $\pm$ 9	P<0.05
PP (mmHg)	69.5 $\pm$ 18	71.1 $\pm$ 18	n. s.
Current smokers (%)	1.6	1.6	n. s.

*BMI=Body mass index, SBP=systolic blood pressure, DBP=diastolic blood pressure, PP=pulse pressure, n.s.=non significant*

Compared to the systolic blood pressure level after 3 years the systolic blood pressure increased by 22.5 mmHg (95% confidence interval (CI): 17.6-27.4 mmHg) in the hypertensive subsample during the follow-up period (Table 11). In the reference group, systolic blood pressure increased by 7.6 mmHg (95% CI: 2.8-12.3 mmHg). The difference in systolic blood pressure increase between the two groups was 15.0 mmHg (95% CI: 7.7-22.2 mmHg).

After the initial decline in diastolic blood pressure during the first 3 years of treatment in the hypertensive subsample, the diastolic blood pressure significantly increased after 30 years of follow-up (Figure 8). Compared

to the diastolic blood pressure level after three years the diastolic blood pressure increased by 5.1 mmHg (95% CI: 0.8-9.3 mmHg) from  $93 \pm 9$  to  $98 \pm 15$  mmHg during the follow-up period (Table 11). From baseline to follow-up the diastolic blood pressure level fell by 11.2 mmHg (95% CI: 8.8-13.5 mmHg) from  $90 \pm 10$  to  $79 \pm 9$  mmHg in the reference group.

Compared to the third annual follow-up the pulse pressure increased by 17.5 mmHg (95% CI: 12.7-22.3 mmHg) during the follow-up period in the treated hypertensive subsample (Table 11). Compared to baseline the pulse pressure increased by 18.7 mmHg (95% CI: 15.7-21.7 mmHg) after 30 years in the referents. At the end of follow-up the pulse pressure was  $69 \pm 18$  in the treated hypertensive patients and  $71 \pm 18$  among the referents (Table 10).

**Table 11** Changes in blood pressure after 30 years from 3:rd annual check-up in treated hypertensives, from baseline in non-hypertensive referents. (Mean, 95% confidence interval)

	<b>Hypertensive patients N=59</b>	<b>Normotensive referents N =106</b>	<b>p-value</b>
<b>ΔBP mmHg</b>	22.5 (CI: 17.6-27.4)	7.6 (CI: 2.8-12.3)	<0.005
<b>ΔDBP mmHg</b>	5.1 (CI: 0.8-9.3)	-11.2 (CI: -8.8 - -13.5)	<0.005
<b>PP mmHg</b>	17.5 (CI: 12.6-22.4)	18.7 (CI: 14.9-22.5)	n.s.

*SBP=Change in systolic blood pressure,  
DBP=Change in diastolic blood pressure,  
PP=Change in pulse pressure,  
CI=95% confidence interval,  
n.s.=non significant*

In an analysis all the treated hypertensive men were grouped in quartiles according to achieved systolic blood pressure at the 15:th annual control. The risk to develop a first stroke was significantly increased risk (28.4%) in the quartile with systolic blood pressure above 168 mmHg. In the lower quartiles, i.e., below 168 mmHg or below 152 mmHg or below 142 mmHg the risk of a first stroke was 14.9%, 14.8% and 16.3%, respectively, for the next 10-13 years of follow-up. No relationship was noticed regarding achieved diastolic blood pressure and subsequent risk of stroke or achieved blood pressure at this point and coronary heart disease.

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## Discussion

The scientific evidence derived from randomised controlled clinical trials as compared to observational studies is not the same. Both study designs have their pros and cons. Beyond doubt several large-scale randomised controlled intervention trials have proven the benefits of blood pressure reduction in patients with hypertension (27,42,63).

This prospective population based observational study differs from the controlled trials of antihypertensive treatment as it has a much longer duration of 22-30 years. The presented morbidity and mortality rates are the results of continuous effort of multiple primary preventive intervention. It should be kept in mind that knowledge as well as therapeutic alternatives have changed dramatically during the three decade follow-up period. In particular, means and methods for therapy of dyslipidemia and counselling for smoking were ineffective for most of the observation period.

The principal observation in the present study was that hypertensive men treated for about 20 years had an increased mortality compared with non-hypertensive men (Figure 1). This was predominantly observed during the latter part of follow-up and was apparent despite a considerable reduction in blood pressure. Also, in the further follow-up of morbidity rates the same pattern is obvious. During 25–28 years the treated hypertensive men had an almost doubled risk for stroke compared with non-hypertensive men (Figure 3). Myocardial infarction was the most prevalent complication in these patients and the risk of coronary heart disease was increased by about 50% compared with that of the non-hypertensive referent group.

There are several possible explanations for the high long-term cardiovascular mortality and morbidity in the hypertensive men. To what extent this was a consequence of failure to reduce blood pressure to normal is difficult to evaluate. Hence, both systolic and diastolic blood pressures were reduced by 15-20%. If a diastolic blood pressure

reduction of about 6 mm Hg results in a 42% reduction of stroke and a 14% reduction of expected coronary heart disease over about 5 years (27), it is conceivable that the blood pressure control achieved in the present study would also be beneficial. However, the reduction in blood pressure did not bring all the patients to strict normotension, and a majority of the treated patients remained in the right part of the total blood pressure distribution curve. Interestingly, the incidence of stroke was not related to achieved blood pressure (Figure 4).

The higher total mortality rate in treated hypertensive men was due to cardiovascular complications (Figure 2), while mortality from non-cardiovascular causes was lower among treated hypertensive men compared with non-hypertensive men. Thus, a carefully structured interventional programme with defined blood pressure targets, regular follow-up, and a limited drop-out rate does not therefore allow a complete normalisation of cardiovascular risk.

On the basis of the difference in risk factor profile at entry between hypertensive and normotensive men, a certain proportion of hypertensive patients probably already had advanced atherosclerosis and hypertensive target organ damage at the start of follow-up. The outcome was therefore not unexpected. The strong association between target organ damage at entry to the study (Table 3) and the incidence of ischemic heart disease underlines the importance to prognosis of cardiovascular abnormalities present before treatment.

With the exception of target organ damage and smoking at entry to the study, the strongest association with ischemic heart disease in treated hypertensive men was baseline cholesterol level and achieved cholesterol concentrations (Table 3). However, the available programme of lifestyle modifications to control hyperlipidemia was not very effective. Only the lipid lowering agent cholestyramine was available for the major duration of follow-up, and it was only prescribed to patients with serum cholesterol concentrations  $>7.0$  mmol/l. The modest reduction of serum cholesterol concentration to about 6.2 mmol/l seems therefore

suboptimal for a substantial positive effect on coronary atherosclerosis. More recent pharmacologic principles with the use of statins have a superior preventive effect (69,70).

It has been suggested that antihypertensive treatment with beta-blockers and thiazide diuretics may increase cardiovascular risk because of induced impairment of metabolism of lipids and glucose (41-45). These drugs were used as first line treatment in the present study because they were available when treatment was started in the early 1970s. The impact of a high incidence of new-onset diabetes suggest that unfavourable therapy may partly explain the impaired prognosis in treated hypertension. This will be further discussed.

The major risk factor for stroke, whether haemorrhagic or ischemic, is high blood pressure (18-27). The systolic and diastolic components of the blood pressure predict cardiovascular complications and increased systolic blood pressure is especially related to the risk of stroke (42,63,71,72). Interventional studies have clearly demonstrated the favourable effect of treating isolated systolic hypertension (42,63). Moreover, there are some evidence suggesting that the lower the achieved blood pressure the better the prognosis (73,74). Randomized trials on this issue are few and most are limited to diabetic patients. The meta-analysis of these trials suggests about 20% better benefits of more intensive blood pressure lowering (74), but does not indicate whether this also applies to non-diabetic individuals.

In the present study an improved prognosis with lower achieved blood pressure could not be demonstrated (Figure 4). The risk to develop stroke was evenly distributed from the lowest to the highest achieved mean systolic and diastolic blood pressure. However, treated patients were not randomized to different levels of achieved blood pressure and therefore firm conclusions from that observation are dubious. It was also observed, that the risk of stroke was not related to the change in systolic or diastolic blood pressure (Figure 5). Consequently, a more aggressive blood pressure reduction is not harmful.

A J-shaped relationship between achieved blood pressure and the risk of stroke in treated hypertensive patients has been reported (75). In the Rotterdam Study, spontaneously occurring low blood pressure was beneficial but in treated patients with diastolic blood pressure below 65 mmHg a significantly increased stroke incidence than in the higher strata of achieved blood pressure was seen. This observation may be at variance with the results of the present study where it was safe to achieve a blood pressure of 136/87 mmHg or lower. However, the observation of an increased morbidity in the lowest blood pressure strata does not give the exact cut-off level for a plausible increased risk for stroke with low blood pressure. In randomized controlled studies such as the Systolic Hypertension in The Elderly Program (42) and the Systolic Hypertension in Europe (63) data on optimal achieved blood pressure are not available. In the Hypertension Optimal Treatment Study the risk of stroke shows a trend towards improved risk in the lower diastolic blood pressure stratum. The lowest risk was in the group with diastolic blood pressure below 80 mmHg and an average systolic blood pressure below 142 mmHg (73). The study was not powered to study this relationship below a blood pressure of <130/75 mmHg. Therefore, it is neither confirmed nor excluded the possibility of a J-shaped relation. With the presented results and limited data on what is optimal target blood pressure there may be concerns about the scientific grounds for actual guidelines regarding target pressure in the treatment of hypertension (31).

Tobacco smoking is a strong risk factor for cerebrovascular disease and high blood pressure adds to the risk in normotensive and hypertensive individuals. In the Multiple Risk Factor Intervention Trial where 350 977 men were screened for cardiovascular risk factors smoking was highly predictive of future stroke with the same strength as for coronary heart disease (76). In the Medical Research Council Hypertension Trial (26) smoking proved to be a highly significant risk factor for stroke as well as coronary events in both sexes and regardless of therapy. Also, in the Multifactor Primary Prevention Study smoking was the most important risk factor together with the diagnosis of hypertension (77).



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In the present subsample of hypertensive patients under long-term treatment the importance of smoking as a significant risk factor for stroke was confirmed (Table 5). The patients received continuous counseling to motivate smoking cessation, but life-style changes are difficult to accomplish. Hence, the major change in the ratio of smokers to nonsmokers during the first 15 years of follow-up is to a great extent due to the higher mortality amongst smoking hypertensive men.

When analyses were performed on long-term adverse effects after almost three decades it was found that new-onset diabetes mellitus was common and it significantly increased mortality and morbidity in stroke and coronary heart disease (Table 8). In a previous report from the present study it was concluded that metabolic changes induced by beta-blockers and thiazide diuretics did not seem to have any major impact on coronary heart disease in treated middle-aged hypertensive men (54). Obviously, this conclusion now needs to be revised. As already pointed out in the previous report the confidence interval of the relative risk associated with new-onset diabetes mellitus was wide, and that the non-significant increase in risk that was observed may have been due to lack of statistical power. The earlier analysis was based on fewer coronary events during 15 years of follow-up compared to the present analyses based on more events occurring during almost three decades of treatment.

In the present analyses we were also able to analyse the impact of new-onset diabetes mellitus on stroke morbidity and total mortality. For both outcome variables subjects who developed diabetes mellitus during this type of antihypertensive drug therapy had a significantly and independently higher risk than non-diabetic subjects (Table 8).

The major strength of the present report is the extended follow-up period. It was stated already in 1996 "as the incubation period of coronary heart disease is substantial an extended observation period is necessary if the effects of small absolute changes in metabolic variables on long term morbidity are to be evaluated" (54). Thus, the results should

be interpreted against the background that our patients were closely followed for a long time, and that there was a very low drop-out rate. Furthermore, the patients were recruited from a random population sample, and thus representative of an important population at risk, i.e. middle-aged hypertensive men. Considering the epidemiologic selection of the patient sample and its rather appreciable size and long duration of follow-up, the results are reliable and representative for the general population of hypertensive men in this age group.

In the extended analysis of the Systolic Hypertension in the Elderly Program, with 14.3 years of follow-up, new-onset diabetes in the patients treated with diuretics was not associated with increased mortality while new-onset diabetes in the patients treated with placebo was (78). Thus, the outcome in the follow-up of the randomised trial in elderly patients with isolated systolic hypertension was similar to the observation in the previous report in middle-aged men, after 15 years of follow-up (54). Another weakness of the report in the elderly, is that the patients were not closely followed with regard to morbidity after the randomised part of the trial was stopped. Mortality status in the extended follow-up analysis was assessed from the National Death Index. Another limitation is the lack of information about therapy during the extended follow-up.

It should be stressed that the great majority of the patients in our study was treated with low-dose thiazide diuretics and beta-adrenergic blocking drugs as first line therapy for most of the follow-up period. Today we have strong indications that antihypertensive treatment based on beta-blockers and a thiazide diuretic is associated with a rather high risk to develop clinical diabetes mellitus (45-52). In the ALPINE study, newly diagnosed patients with primary hypertension were randomised to a low dose diuretic, mostly combined with a beta-blocker, or to an angiotensin-II-receptor antagonist, mostly combined with a calcium channel blocker for one year (45). It was clearly shown that the former combination was associated with an aggravated metabolic profile, whereas the latter was metabolically neutral. Moreover, the incidence of new-onset diabetes mellitus was significantly higher in the patients on this treatment.

New-onset diabetes is reported as a secondary outcome in several prospective end-point studies (46-52), but in none of these has it been associated with increased risk of cardiovascular disease. The actual studies, however, have been of short duration, as compared to the present study, making a substantial increase in diabetes related complications during a few years observation an unrealistic expectation. Furthermore, the prospective end-point studies were not designed to study the effect of new-onset diabetes with relation to cardiovascular complications. However, some studies of reasonably long duration are presently available. Hence, Dunder et al. report that during treatment of hypertension for about 17 years with beta-blockers or diuretics the sole predictive factor for myocardial infarction was the increase in blood glucose (38). Also, indirect results from the 18-year follow-up of 11 645 subjects treated in the Multiple Risk Factor Intervention Trial (36), in which the special intervention group received diuretic therapy, show that new-onset diabetes is associated with significantly greater mortality rates. One recent study evaluated the prognostic implication of new-onset diabetes with a systematic approach (55). In the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) Study 795 previously untreated hypertensive patients were treated with diuretics or beta-blockers or their combination. The patients were followed for a median period of 6 years. The relative risk of cardiovascular events was significantly increased in patients with new-onset diabetes and in previously known diabetics as compared to patients who remained free of diabetes. In regression analysis, blood glucose and the exposure to diuretic therapy during follow-up were the only independent predictors of new-onset diabetes. Again, a rather short observation period and low end-point rate reduces the statistical power of the study.

Increasing cardiovascular risk with drug-induced diabetes is of obvious importance if this complication is frequent. In the present study the incidence of new-onset diabetes was high. More than one out of five patients had developed diabetes in the final stage of follow-up. The prevalence of diabetes in this group of patients clearly exceeds what is known from previous reports (78-81). When compared to male general

populations of corresponding age from the same city (78) and from a rural population in Sweden (79) the prevalence is almost doubled (Figure 6). In comparison with populations in Norway (80) and the Netherlands (81) the prevalence in the present study is more than 80% higher.

Predictive factors for new-onset diabetes were high body weight, increased triglycerides and therapy with beta-blocking drugs (Table 7). Similar findings have been reported earlier (44) and confirm other reports (43). Hence, medication with beta-blockers was related to onset of diabetes while thiazide diuretics, calcium channel antagonists and ACE-inhibitors were not in the Atherosclerosis Risk in Communities Study (43).

In the present study beta-adrenergic blocking drugs seemed to be especially related to the development of new-onset diabetes and the combination of betablockers and thiazide diuretics also carried an increased risk. However, it was not a randomised with respect to drug therapy and confounding factors, in particular selection bias cannot be ruled out. In the early 1970s, at the time of initiation of the study diuretics were regarded to be more diabetogenic than beta-blockers and this fact may have influenced the treating physicians to choose beta-blockers rather than diuretics to patients with a greater risk for development of diabetes.

Results from the first study to primarily address the problem with new-onset diabetes and associated cardiovascular complications were recently published (82). The Diabetes Reduction Assessment with ramipril and rosiglitazone Medication included 5269 subjects free from cardiovascular disease but with impaired glucose tolerance. In a double blind, randomised prospective study using a 2-by-2 factorial design these subjects received ramipril or placebo as well as rosiglitazone or placebo during 3 years. Interestingly, the use of ramipril did not significantly reduce the incidence of diabetes or death but a significant regression towards normal glucose levels was observed. The incidence of new-onset diabetes was high while mortality in the study was considerably

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lower than in the present long-term study.

Clinical observations over time indicated that systolic blood pressure was difficult to control also with the use of effective antihypertensive drugs (83). When addressing this question systematically, a significant increase in systolic blood pressure in a random subsample of hypertensive patients with well-controlled diastolic pressure during the first 15-years of follow-up was observed. In the present subsample of surviving treated hypertensives the systolic blood pressure had increased further after 30 years. The observed increase in systolic blood pressure was three times higher among these patients compared to normotensive referents. Suboptimal effect of therapy is most conceivably the main explanation for the lack of good long-term systolic blood pressure control, since the systolic blood pressure level after the first 3 years of treatment was almost the same in the group of treated hypertensive patients as in the normotensive reference group. It should be underlined, that there was no documented evidence for a specific systolic blood pressure goal prior to the presentation of the SHEP (42) and Syst-Eur results (63) in 1991 and 1997, respectively. In fact, it was only after that a paradigm shift occurred and more emphasize was put on systolic blood pressure control in treatment guidelines (8,31,84,85). To further support our hypothesis of insufficient treatment in the present study is the observation of a concomitant increase in diastolic blood pressure, although to a lesser extent.

The hypertensive patients in this study did not have severe or secondary forms of hypertension. In fact, only 20% showed signs of target organ damage (86). Hence, the observed rise in systolic blood pressure should probably be considered as a shortcoming in long-term management regarding life-style intervention and drug treatment. Alternatively, hypertensive patients may well be susceptible to arterial remodelling and an increase of systolic blood pressure regardless of therapy. Regarding management, patients were instructed to avoid dietary sodium although this is difficult to implement. Data on sodium excretion from a subsample of patients in our clinic indicate a consumption of about 180 mmol per

24 hours (87). Further counselling regarding lifestyle modifications included smoking habits and fat consumption. Regarding drug therapy thiazide diuretics are well documented as effective in systolic hypertension and so are ACE inhibitors (88,89). Hence, thiazides were the first choice of drugs throughout the study while ACE inhibitors and calcium antagonists were available only in the latter half of the follow-up. Interestingly, the systolic blood pressure showed a tendency to increase already after fifteen years (Table 4, Figure 8) and subsequent add-on therapy with calcium antagonists and ACE inhibitors as substitute for hydralazin and other drugs did not prevent further increase of systolic blood pressure.

The subsample of hypertensive patients in the present study were survivors over three decades of treatment and follow-up. They were free from cardiovascular complications and diabetes and may represent an interesting type of patients where also possible cardiovascular protective factors should be considered. In this regard there was no family history in favour of such a hypothesis. The one interesting observation was that leisure time physical activity was significantly higher compared to the rest of the hypertensive patients. Physical exercise is known to improve insulin sensitivity and lipids and to lower blood pressure. In the initial part of the follow-up this subsample of patients also had somewhat lower systolic blood pressure. Although a superior risk factor profile and more active exercise habits may well be part of the explanation for longevity and good health in this group of patients they still had an amazing increase in systolic blood pressure in spite of therapy.

The accelerated rise in systolic blood pressure seen with ageing is primarily due to an increased peripheral vascular resistance during the early years but due to an increased large arterial stiffness during the late part of development (59,62). In the elderly, the increasing pulse pressure seems to indicate large artery stiffness. Diastolic blood pressure apparently loses its ability to reflect the increase in vascular resistance with age and large artery stiffness rather than small vessel resistance becomes the dominant hemodynamic factor in both normotensive and

hypertensive subjects. Systolic blood pressure is an important component of cardiovascular disease risk especially regarding stroke (95-96). In the present study it was also demonstrated that systolic blood pressure after 15 years was a predictor of future stroke. It should also be kept in mind that the increased stroke risk in the highest quartile of systolic blood pressure may underestimate the rise with time of systolic blood pressure in the treated patients.

In the normotensive subjects systolic blood pressure also rose, but to a lesser extent. However, at variance with the hypertensive patients there was a decline in diastolic blood pressure. Thus, pulse pressure rose in both the hypertensive patients and normotensive subjects and at the end of the follow-up period pulse pressure was the same in both groups. Ageing is known to increase arterial stiffness. In the Framingham Heart Study age-related changes in blood pressure in both normotensive and untreated hypertensive subjects during 30 years of follow-up has been described (59). A linear rise in systolic blood pressure from age 30 through 84 years and a concurrent increase in diastolic blood pressure up to age 50 years was demonstrated. Subjects with initially higher systolic blood pressure increased the most. After age 50 to 60 years, diastolic blood pressure declined and consequently pulse pressure increased steeply with advancing age. The results from the present study also show an increase in pulse pressure. The decline in diastolic blood pressure in the normotensive reference group was in agreement with the report by Franklin et al. (59). Interestingly, hypertensive patients show a different hemodynamic or vascular development with both signs of large artery stiffening and arteriolar hypertrophy.

Systolic blood pressure is difficult to treat (64). This is an obvious fact observed also in the present study. In most of the intervention trials conducted in hypertensive subjects diastolic blood pressure has often been well controlled, whereas the systolic blood pressure goal has been far less often reached (64). Thus, the prevalence of systolic hypertension in subjects treated in antihypertensive drug trials is often high. In one recent Italian report in 2775 hypertensive patients seen by specialist

physicians, optimal blood pressure control was shown in less than half of the patients (97), and the rate of controlled values was much greater for diastolic than for systolic blood pressure. Similar observations have been described from northern Sweden in a representative population sample (95). Furthermore, in the Framingham Heart Study cohort Lloyd-Jones et al. found good systolic blood pressure control in less than half of the subjects, whereas good diastolic blood pressure was achieved by 90% of all treated hypertensives (96). Interestingly, increasing age, overweight, and left ventricular hypertrophy were related to inadequate systolic control. Thus, the duration and severity of hypertension may be factors of importance for lack of good systolic blood pressure control.

Several lessons may be learnt from the present study. First, and perhaps most importantly, it is possible to treat, follow and evaluate hypertensive patients for as long as three decades. The data derived from such a long observation period add important knowledge to the vast field of hypertension research.

Of importance, some of the results may be surprising in the light of what has been learnt from the major intervention trials. However, the results do not oppose the conclusions that can be drawn from the major intervention trials. Instead, the results of the present long-term follow-up reflect what happens in real life when the evidence from hypertension research is applied in clinical practice.

Second, as the follow-up period is extended for as long as thirty years, previous conclusions need to be revised. This is in agreement with the change in guidelines and clinical practice that needs to occur as important findings from well designed and conducted studies accumulate. In particular, the revised conclusions regarding new-onset diabetes during treatment and its risk should be kept in mind in the care taking of patients with hypertension in the future. Moreover, the observation regarding systolic blood pressure rise despite treatment may be underlined. Third, not all answers are given by the present study. The results reflect outcomes, in a representative cohort followed for the



past three decades. However, since treatment strategies have changed during this long follow-up period it is not known if the same outcome would occur in middle-aged men treated for thirty years from today.

Conceivably, current knowledge with regard to target blood pressure level and choice of first-line antihypertensive drugs, injurious effects of new-onset diabetes in treated hypertensives and harmful effects of systolic blood pressure rise may improve outcomes in thirty years from now.



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## Conclusions

All cause mortality was increased and mortality from ischemic heart disease was doubled in treated hypertensive men compared to non-hypertensive men during 22-23 years of observation. Smoking, target organ damage and S-cholesterol at screening and S-cholesterol during the study was related to the incidence of ischemic heart disease. (Paper I)

Treated hypertensive men had 50 % more of myocardial infarctions and an almost doubled incidence of stroke compared to non-hypertensive men during 25-28 years of follow up. Smoking and diabetes at entry and smoking during the study was related to the incidence of stroke. (Paper II)

New-onset diabetes is a common complication during long-term treatment of hypertension in men and was related to obesity, elevated triglycerides and the use of beta-blockers. New-onset diabetes was associated with increased risk of stroke, myocardial infarction and mortality. The mean duration to a cardiovascular complication was 9 years after diagnosis of diabetes. (Paper III)

Systolic blood pressure increased during 30 years of therapy in treated hypertensive patients, whereas diastolic blood pressure was more responsive to therapy. The systolic blood pressure rise was about three times greater than in an age matched normotensive reference group from the same population. (Paper IV)



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