Diabetes mellitus and raised serum triglyceride concentration in treated hypertension—are they of prognostic importance? Observational study

Ola Samuelsson, Kjell Pennert, Ove Andersson, Göran Berglund, Thomas Hedner, Bengt Persson, Hans Wedel, Lars Wilhelmsen

Abstract

***Objective*—To analyse whether metabolic changes during long term treatment with antihypertensive drugs are associated with an increased risk of coronary heart disease.**

***Design*—Observational study.**

***Setting*—Gothenburg, Sweden.**

***Subjects*—686 middle aged hypertensive men, recruited after screening of a random population sample, and followed for 15 years during treatment with predominantly β adrenoceptor blockers or thiazide diuretics, or both. Coronary heart disease and diabetes mellitus were registered at yearly patient examinations. Entry characteristics, as well as within study serum concentrations of cholesterol and triglycerides and the development of diabetes mellitus, were related to the incidence of coronary heart disease in a time dependent Cox's regression analysis.**

***Main outcome variable*—Coronary heart disease morbidity.**

***Results*—Diabetes mellitus, raised serum cholesterol and triglyceride concentrations present at the beginning of the study were all significantly predictive of coronary heart disease in univariate analysis. The relative risk of diabetes mellitus and of a 1 mmol/l increase in the cholesterol and triglyceride concentrations was 2.12 (95% confidence interval 1.11 to 4.07), 1.21 (1.05 to 1.39), and 1.21 (1.03 to 1.43) respectively. However, when the within study metabolic variables were analysed, only the serum cholesterol concentration was significantly and independently associated with coronary heart disease (relative risk 1.07 (1.02 to 1.13)). Although the triglyceride concentrations increased slightly during the follow up, the within study serum triglyceride concentrations were not associated with the incidence of coronary heart disease (1.04 (0.96 to 1.10)). New diabetes mellitus—that is, onset during follow up—was not significantly associated with an increased risk for coronary heart disease (1.48 (0.37 to 6.00)).**

***Conclusions*—Metabolic disturbances such as diabetes mellitus and hyperlipidaemia presenting before the start of antihypertensive treatment have a prognostic impact in middle aged, treated hypertensive men. Moreover, while within study cholesterol concentration was an independent predictor of coronary heart disease, drug related diabetes mellitus and raised serum triglyceride concentrations that are associated with treatment do not seem to have any major impact on the coronary heart disease prognosis in this category of patients.**

Section of Nephrology, Department of Medicine, Sahlgrenska Hospital, S-413 45 Gothenburg, Sweden
Ola Samuelsson, *associate professor*

Section of Angiology, Department of Medicine, Sahlgrenska Hospital
Ove Andersson, *associate professor*
Bengt Persson, *associate professor*

Department of Clinical Pharmacology, Sahlgrenska Hospital
Thomas Hedner, *professor*

Clinical Data Care AB, Lund, Sweden
Kjell Pennert, *head of biostatistics*

Department of Medicine, Malmö General Hospital, University of Lund, Malmö, Sweden
Göran Berglund, *professor*

Department of Epidemiology and Biostatistics, Nordic School of Public Health, Gothenburg
Hans Wedel, *professor*

Department of Medicine, Östra Hospital, Gothenburg
Lars Wilhelmsen, *professor*

Correspondence to:
Dr Samuelsson.

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Introduction

Antihypertensive treatment with β adrenergic blockers or thiazide diuretics reduces overall morbidity of cardiovascular disease and stroke.[1-4] However, the outcome of intervention trials has been less encouraging for coronary heart disease.[3,4] Among several suggested underlying explanations for this is that treatment with β adrenergic blockers or with diuretic drugs produces adverse metabolic effects.[5-11] It has even been suggested that the metabolic changes observed during treatment with β blockers or thiazide diuretics may have such deleterious effects on coronary heart disease that these may obscure or even override the benefit of reduction in blood pressure and prevent an appreciable benefit from being perceived.[6]

To study the prognostic impact on coronary heart disease morbidity of metabolic changes that occur during long term antihypertensive treatment we analysed separately the predictive role of baseline serum concentrations of cholesterol and triglycerides and diabetes mellitus—that is, at the start of treatment—and the role of these metabolic variables during long term follow up.

Patients and methods

STUDY POPULATION

A total of 686 hypertensive men aged 47-54 years were derived from screening a random population sample during 1970-4.[12,13] They were followed at the outpatient hypertension clinic at Sahlgrenska Hospital for 15 years.

During the first year of follow up 25 patients (3.6%) stopped attending the clinic, but thereafter the annual withdrawal rate was only 1.1%.[13] No patient was lost to follow up with regard to total or cause specific mortality.[13] All death certificates were collected for registration. Data on fatal and non-fatal coronary heart disease were updated from a myocardial infarction register.[13]

Yearly check up examinations were performed, and the incidence of diabetes mellitus and of coronary heart disease was registered. Coronary heart disease was defined as a non-fatal myocardial infarction or a fatal coronary event.[13] Myocardial infarction was defined as admission to hospital for a clinically diagnosed infarction and fulfilment of two or more of: (*a*) central chest pain, shock, syncope, or pulmonary oedema suggesting myocardial infarction; (*b*) typical changes in transaminase or lactate dehydrogenase enzymes; and (*c*) typical electrocardiographic changes with occurrence of pathological Q waves or localised ST variations. Fatal coronary heart disease was evidenced by a statement on the death certificate of myocardial infarction or sudden death.

Fasting blood samples were taken. Presence of albuminuria and glucosuria was recorded. Diabetes mellitus was defined as a fasting blood glucose concentration of >7.0 mmol/l.[14] Smoking habits were graded with a five point scale (1 = non-smoker, 2 = former smoker, 3 = 1-4 g/day tobacco, 4 = 15-24 g/day tobacco, 5 = ≥25 g/day tobacco).[13] For serum triglycerides concentration the analysis was based on the first seven years of follow up; owing to altered clinical routines at the outpatient clinic at that time they were not analysed after the eighth annual check up.

The average systolic/diastolic blood pressure at entry was 169/106 (SD 21/13) mm Hg. Treatment was adapted to each patient's needs, with a treatment goal of ≤160/95.[13]

The most commonly used drugs were β adrenoceptor blocking agents and thiazide diuretics, used alone or in combination with one another. The proportion of patients taking β blockers after one year was 472/646 (73%) and at

Table 1—*Partial regression coefficients, hazard ratios (95% confidence interval), and P values derived by updated covariate multiple Cox's regression analysis[17] for variables with predictive capacity for coronary heart disease morbidity*

Patient characteristics	Regression coefficient	Hazard ratio (95% confidence interval)	P value
Smoking status at entry*	0.39	1.48 (1.26 to 1.73)	<0.0001
End organ damage at entry†	0.82	2.27 (1.53 to 3.37)	<0.0001
Raised cholesterol during study‡	0.06	1.06 (1.01 to 1.12)	0.0302

*Scored on scale of 1-10 (see methods).
†According to World Health Organisation's criteria (see methods).
‡≥1 mmol/l increment.

the 5, 10, and 15 year check ups was 429/588 (73%), 389/525 (74%), and 319/442 (72%) respectively. The corresponding proportions of patients taking thiazide diuretics were 310 (48%), 282 (48%), 299 (57%), and 232 (52%) respectively. At the five year check up 34% (197) of the patients were receiving treatment with a single drug (equal proportions of patients were taking thiazide diurectics and β blockers), 30% (176) were taking both a β blocker and a thiazide diuretic, and the rest were taking other combinations of drugs, most of which included a β blocker or a thiazide diuretic. Hydralazine was the most frequently added drug when further treatment was necessary.[13] At the 10 year check up 29% (153) of the patients were taking only one drug (about two thirds of these were taking a β blocker and the rest a diuretic), 26% (137) were taking a combination of these two drugs, and 111 (21%) did not have either of these two drugs as the basis for treatment. During the last five years of follow up angiotensin converting enzyme inhibitors or calcium antagonists were rarely used alone, but were used in combination with either a thiazide diuretic or a β adrenoceptor blocker in a few patients.

STATISTICAL ANALYSIS

The Cox's proportional hazard model[15] was used to test the associations between variables in patient characteristics and the incidence of coronary heart disease. We used both the variables at entry previously shown to be associated with coronary heart disease in this patient series[13] (smoking habit, serum concentrations of cholesterol and triglycerides, diastolic blood pressure, diabetes mellitus, and stage II or III end organ damage according to the World Health Organisation's criteria) and the follow up variables (serum concentrations of cholesterol and triglycerides, diastolic blood pressure, and development of diabetes mellitus). When a variable with updated measurements was tested, an updated covariates proportional hazards model was used.[16] This model is also known as Cox's time dependent regression model.

All the variables significantly associated (P<0.05) with coronary heart disease in the univariate analysis were entered in a multivariate analysis. In all univariate as well as multivariate analyses of associations between metabolic changes during follow up—that is, "within study" variables of serum concentrations of cholesterol and triglycerides, new cases of diabetes mellitus, and coronary heart disease morbidity—the 27 patients with diabetes mellitus at entry were not included.

The updated covariates proportional hazards model was also used to estimate the relative risk for coronary heart disease associated with a given change in a risk factor. All relative risks cited are hazard ratios. All analyses were perfomed with PC-SAS, version 6.08.[17]

Results

During 15 years of follow up, 133 of the 686 (19.4%) patients had a non-fatal myocardial infarction or died of coronary heart disease.

The mean serum cholesterol concentration at entry was 6.6 (SD 1.1) mmol/l and decreased to 6.2 (1.2) mmol/l (P<0.001) at 15 years. The serum concentration of triglycerides increased from 1.7 (0.9) mmol/l to 2.1 (1.6) mmol/l (P<0.001) at seven years (see methods). At the start of the study the prevalence of diabetes mellitus was 3.9% (n = 27). Ninety one new cases of diabetes mellitus were diagnosed during follow up, an average yearly incidence of 1.3 %.

SERUM LIPIDS AS CORONARY RISK FACTORS

Figure 1 shows the relative risk of coronary heart disease associated with serum concentrations of cholesterol and triglycerides. The serum cholesterol concentration both at entry and during the study was significantly associated with coronary heart disease in univariate analyses. The relative risk of coronary heart disease associated with a 1 mmol/l increment in the concentration at entry was 1.21 (95% confidence interval 1.05 to 1.39)—that is, a 21% increase in risk. The corresponding risk for the same increase in the within study concentration was 1.07 (1.02 to 1.13).

The serum triglyceride concentration at entry was also significantly associated with coronary heart disease in univariate analysis, with a relative risk associated with a 1 mmol/l increment of 1.21 (1.03 to 1.43). However, the risk of a 1 mmol/l increment in the within study serum triglyceride concentration was not significant 1.04 (0.96 to 1.10).

In the multivariate analysis also (table 1) the within study serum cholesterol concentration—like smoking and signs or symptoms of end organ damage (at entry of study)—was independently associated with the incidence of coronary heart disease. The within study diastolic blood pressure was not significantly associated with coronary heart disease in the updated covariated model. As all the analyses of within study variables excluded diabetes mellitus at entry, this baseline variable was not included in the

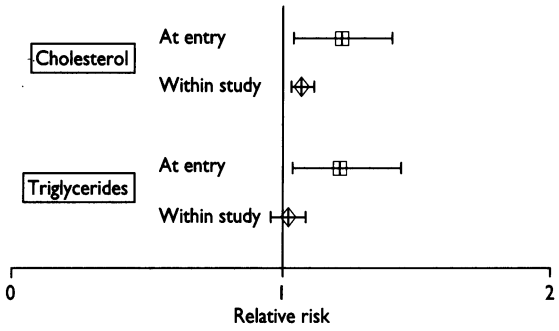

Fig 1—*Relative risk of coronary heart disease, with corresponding 95% confidence interval, associated with increment of 1 mmol/l in serum cholesterol and triglyceride concentrations measured at entry and during follow up in 686 treated hypertensive men followed for 15 years*

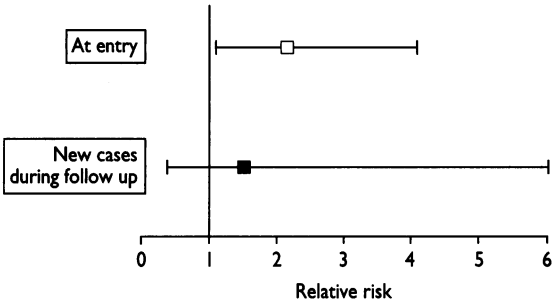

Fig 2—*Relative risk of coronary heart disease, with corresponding 95% confidence interval, associated with diabetes mellitus at entry and occurring during follow up in 686 treated hypertensive men followed for 15 years*

multivariate analysis, even though it was significantly associated with coronary heart disease in the univariate analysis (see figures).

DIABETES MELLITUS AS CORONARY RISK FACTOR

Diabetes mellitus present at entry was significantly associated with a higher incidence of coronary heart disease. These patients (n = 27) had double the coronary risk of non-diabetic patients (relative risk 2.12 (1.11 to 4.07)) (fig 2). After exclusion of these 27 patients the hypertensive subjects who developed clinically overt diabetes mellitus during follow up did not have a significantly higher risk of coronary heart disease than non-diabetic hypertensive patients. The relative risk of coronary heart disease associated with diabetes mellitus occurring during the study was 1.48 (0.37 to 6.0).

Discussion

The results of the present study challenge the view that metabolic changes that are related to drugs have a major impact on the cardiovascular prognosis in treated hypertension. This has been an issue of intense debate[1 2 4-11 18-22] ever since major hypertension trials showed the reduction in coronary heart disease morbidity to be lower than expected.[3]

The present study population is representative of an important population at risk—that is, middle aged hypertensive men.[13] It represents a higher yield (9% of all screened subjects) than the yield for the large intervention studies where screening data have been reported.[23-25] Furthermore the length of follow up of these treated hypertensive patients (15 years) may be long enough to assure an eventual impact on morbidity of changes in the pattern of risk factors. As the incubation period of coronary heart disease is substantial[26] an extended observation period is necessary if the effects of small absolute changes in metabolic variables on long term morbidity are to be evaluated. The extended follow up of two major intervention trials[27 28] shows that at least 8-10 years may be needed to demonstrate a beneficial effect of antihypertensive treatment on coronary heart disease. Thus, it was considered that the 15 year observation period in this study could be used to observe important effects on morbidity due to metabolic changes occurring during treatment with antihypertensive drugs.

In the past 10 years the use of the proportional hazards regression model has become widespread in medical research. Such analysis, however, does not usually use all information available as models using merely baseline data estimate the effect on the hazard of a unit difference in a covariate at time zero only. It has recently also been pointed out that these types of regression models may easily be used inappropriately, resulting in the wrong conclusions.[29] In clinical practice individual data are routinely collected at frequent time points after entry to a study but are rarely examined in relation to survival. Yet a clinical question of major importance is that of prognosis, and a means of updating prognosis on the basis of the latest observation on a patient would be of great value. The updated covariates proportional hazards regression model provides such a means and examines the effect of changes in a covariate after entry.[16 29] In the updated covariates model the regression coefficient represents the effect on the hazard of a unit difference in a covariate at entry or at any time after entry. This means that the relative risks, or hazard ratios, obtained from baseline data are constant in time, and in an updated covariates model the estimated relative risks change in time as the values of the covariates change.

METABOLIC VARIABLES AND CORONARY RISK

Serum cholesterol concentration was clearly an important cardiovascular risk factor both at the start of the study and during antihypertensive intervention. This is in agreement with other reports.[24 30-32] It is now also well documented that β adrenergic blockers and thiazide diuretics have only marginal effects on serum cholesterol concentration during long term treatment.[4 22] In our study the concentration even decreased during follow up. In spite of this reduction the within study cholesterol concentration remained a significant coronary risk factor, although the risk associated with a given increment in the plasma concentration seemed to decrease to some extent. The difference in the relative risk ratios between cholesterol concentration at entry and the within study concentration may be due to random variation but may also indicate that the within study concentration is a more precise measurement of the long term exposure. Therefore, it will yield a better estimate of the risk associated with raised cholesterol concentration during antihypertensive treatment.

The atherosclerotic process is a complex dysfunction of a dynamic balance of many components.[33 34] Despite raised concentrations of low density lipoprotein cholesterol observed during treatment with β blockers, animal studies have shown that β blockers can reduce the degree of atherosclerosis.[20] Furthermore, secondary prevention studies of diabetic patients with a myocardial infarction have shown that the β blockers provide a considerable degree of cardioprotective benefit.[35] Thus, the role of drug induced changes in the serum lipoprotein profile in the interplay with other atherogenic factors seems to be very difficult to define.

Considerable attention has been focused on the association of hypertension and insulin resistance.[9 36 37] We still do not know, however, what represents the "chicken" or the "egg" in this metabolic syndrome.[38-41] Hyperinsulinaemia and hyperglycaemia have been incriminated as contributors to atherogenesis in hypertensive subjects,[42 43] although data do not seem to be consistent and convincing.[44] It is commonly claimed that β blockers and thiazide diuretics aggravate the degree of insulin resistance, trigger diabetes mellitus, and induce a rise in the serum concentration of triglycerides.[45-48] However, the occurrences of diabetes mellitus or slightly raised serum concentrations of triglycerides during treatment with antihypertensive drugs do not a priori translate to an increase in coronary risk. It may be that metabolic changes triggered by drugs do not alter (in any direction) putative and possibly even more important and fundamental underlying defects that may be the cause of both the insulin resistance and the pathogenic events leading to atherosclerosis.[37 43 49] This line of argument gains some support from the present data on diabetes mellitus and serum triglyceride concentrations, both being control components of the metabolic syndrome.

The risk of diabetes mellitus being present at entry before treatment was of the same magnitude as in other observational studies.[50-53] The same was true for the predictive role of raised serum concentration of triglycerides at entry to follow up.[54] The outcome of the present analyses, however, does not support the idea that the development of diabetes mellitus and raised serum concentrations of triglycerides—possibly triggered by the β blockers or thiazide diuretics—is of any substantial importance for the development of coronary heart disease. Thus, the role of drug associated diabetes mellitus as a coronary risk factor may have been greatly exaggerated. The confidence interval of the relative risk associated with newly developed diabetes mellitus, however, was rather wide, and the non-significant finding on coronary heart disease may have been a type II error. Also, the diabetogenic effects by β blockers could well be counteracted by other cardioprotective actions of these drugs.[35] We are obviously still awaiting clarification of the eventual prognostic relevance of drug induced metabolic changes.[55 56]

As already stated, this study was a retrospective analysis in this patient population. We are eagerly awaiting the out-

Key messages

- Hypertension is common in middle aged and elderly people and is one of the major risk factors for cardiovascular disease
- The issue of "newer" versus "older" antihypertensive agents is an important one in the treatment of hypertension
- This study shows that diabetes mellitus and raised serum triglyceride concentrations occurring during long term treatment of middle aged hypertensive men taking β blockers or thiazide diuretics, or both, have no major impact on the prognosis for coronary heart disease
- Until the outcome of controlled trials comparing "metabolically neutral" drugs with β blockers and thiazide diuretics, β blockers or thiazide diuretics, either alone or combined, should continue to be used as major first line drugs in the treatment of hypertension

come of current hypertension trials[57-59] comparing "metabolically neutral" antihypertensive agents with conventional first line treatment.[2 4 60] Until such data are available we must still question, however, whether drug related metabolic changes carry any major prognostic importance in treated hypertensive patients. It would therefore seem reasonable to continue to recommend β adrenergic blockers and thiazide diuretics as major first line drugs in the treatment of primary hypertension.

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