Lipoprotein(a) Was an Independent Predictor for Major Coronary Events in Treated Hypertensive Men

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Summary

Background and Hypothesis: Lipoprotein(a) may play a part in the development of coronary heart disease. The purpose of this prospective study was to evaluate lipoprotein(a) as a predictor of major coronary events (fatal and nonfatal myocardial infarction and sudden death).

Methods: This was a prospective study of 118 men, aged 56 to 77 years, with treated hypertension and at least one additional cardiovascular risk factor (hypercholesterolemia, diabetes mellitus, or smoking) were included in the study. Lipoprotein(a) was measured at entry and major coronary events were followed during follow-up.

Results: The mean observation time was 3.0 years. Fourteen patients had a major coronary event during the follow-up period. Subjects with coronary heart disease (previous myocardial infarction, angina pectoris, or major electrocardiographic changes) at entry ($n = 27$) had significantly higher lipoprotein(a) levels than subjects without ($n = 91$) known coronary heart disease ($p < 0.05$). Lipoprotein(a) was a significant predictor for major coronary events ($p = 0.033$). Furthermore, when coronary disease at entry was included into the Cox regression analysis, lipoprotein(a) was an independent predictor for major coronary events ($p = 0.044$).

Conclusions: Among treated hypertensive men, lipoprotein(a) was an independent predictor of major coronary events.

Key words: lipoprotein(a), hypertension, coronary artery disease

Introduction

Lipoprotein(a) contains two distinct components: an apolipoprotein B-containing lipoprotein particle that is structurally similar, but not identical, to low-density lipoprotein (LDL) and apolipoprotein(a), which is linked to apolipoprotein B. Lipoprotein(a) has been suggested to be a risk factor for atherosclerosis. The underlying pathogenic mechanism of lipoprotein(a) has not fully been elucidated; however, it is documented that lipoprotein(a) is present in the arterial wall at the sites of the atherosclerotic lesions.^{1, 2} Furthermore, lipoprotein(a) has been detected in larger amounts in lesions from patients with unstable angina pectoris than it was in lesions from patients with stable angina pectoris, suggesting lipoprotein(a) plays a role in the progression of atherosclerosis.³ There have been several prospective studies that have identified lipoprotein(a) as a coronary heart disease risk factor.^{4–6} However, other studies have failed to show a relationship between lipoprotein(a) levels and future coronary disease.^{7–9}

In patients with hypertension, the data regarding lipoprotein(a) is heterogeneous. Some studies report normal lipoprotein(a) levels in hypertensive patients,¹⁰ whereas others have documented elevated plasma levels of lipoprotein(a).¹¹ As previously reported, we have performed a cardiovascular risk factor intervention study in hypertensive men.¹² In this study, lipoprotein(a) was also measured. As the patients in this study were followed up for more than 3 years, we wanted to examine, in a hypothesis-seeking study, whether lipoprotein(a) predicted major coronary events (fatal and nonfatal myocardial infarction and sudden death).

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Material and Methods

Subjects

In all, 508 male patients with treated primary hypertension were included in a risk factor intervention study.¹² Apart from treated hypertension and male gender, the inclusion criteria for the intervention study were one or more of the following: hypercholesterolemia (serum cholesterol > 6.5 mmol/l), tobacco smoking (one or more cigarettes per day), or diabetes mellitus (fasting blood glucose > 7 mmol/l).¹³ The patients were representative of high-risk hypertensives in Gothenburg since the majority (over 90%) were recruited by screening a random third of all men in their respective age groups in Gothenburg.¹⁴ In the intervention study, mentioned above, the patients had been randomized either to a multiple risk factor treatment program or to conventional treatment. The intervention program was based upon a nonpharmacological and, if necessary, pharmacological regimen aiming at lowering hypercholesterolemia, and also a smoking cessation program.¹² From this group of 508 men, one third were randomly selected to take part in an ultrasound study of the carotid artery.¹⁵ Of these 164 patients, 118 were reexamined after 3 years of follow-up. During this reexamination, the lipoprotein(a) samples were drawn. Subsequently the patients were followed up for 3.0 ± 0.6 years. Thus, the present report is based upon the reexamination after 3 years and the ensuing follow-up period. All subjects gave informed consent after written and oral information, and the ethical committee of the Faculty of Medicine, Göteborg University, approved the study.

Measurements

Resting blood pressure was measured phonographically (Korotkoff sounds recorded on electrocardiogram [ECG] paper) in the right arm after supine rest in connection with the ultrasound examination as previously described. Body mass index was measured according to recommended principles. Smoking was assessed by a questionnaire. Established criteria for myocardial infarction and angina pectoris were used.¹² A 12-lead resting ECG was recorded and coded according to the revised Minnesota code.¹⁶ A major finding according to the Minnesota code was defined as definite Q- or QS-item (1:1 or 1:2), definite ST- or T- wave item (4:1–2, 5:1–2), left bundle-branch block (7:1), or a wide QRS complex above 0.12 s (7:4). Venous blood was drawn after an overnight fast and after 5 min of supine rest for determination of serum levels of triglycerides total and high-density lipoprotein (HDL) cholesterol using established methods.¹² Low-density lipoprotein (LDL) cholesterol was calculated according the formula by Friedewald. The serum concentration of lipoprotein(a) was determined by RIA (Pharmacia Biotech, Uppsala, Sweden).

Follow-Up

No patient was lost to follow-up. Major coronary events were defined as a nonfatal myocardial infarction or a coro-

nary death. Two doctors who did not participate in the study and who were blinded to the patients' identity or laboratory measurements independently coded all events. They had access to copies of hospital records, autopsy records, and death certificates.

Statistical Analysis

Results are presented as means $\pm$ standard deviation. Mann-Whitney tests were used to compare continuous variables. To investigate the association at entry between the concentration of lipoprotein(a) and potential cardiovascular risk factors at entry, Spearman correlation analyses were performed. Relative risk and 95% confidence interval were calculated with the Cox regression model. Relative risk was calculated as the risk when the variable in focus was increased with one unit $[(x+1)/x]$. As lipoprotein(a) showed a skewed distribution, logarithmic transformation was performed before performing the regression analyses. Only two-sided tests were performed, and $p < 0.05$ was regarded as statistically significant.

Results

Baseline Characteristics

The characteristics at the start of the follow-up period are given in Table I. Subjects with coronary heart disease (previous myocardial infarction, angina pectoris, or major ECG changes) at baseline ($n = 27$) had significantly higher lipoprotein(a) levels than subjects without ($n = 91$) known coronary heart disease ($p < 0.05$). The other factors in Table I were not significantly associated with lipoprotein(a) concentration.

TABLE I Characteristics of treated hypertensive men at baseline ($n = 118$)

Variable	Mean (SD)
Age (years)	69.3 (4.8)
Body mass index (kg/m ²)	26.7 (3.5)
Blood pressure (mmHg)	
Systolic	154 (20)
Diastolic	80 (10)
Cholesterol (mmol/l)	6.1 (1.0)
LDL cholesterol (mmol/l)	4.1 (0.9)
HDL cholesterol (mmol/l)	1.2 (0.3)
Lipoprotein(a) median, (ranges, U/l)	159 (0.9–2253)
Triglycerides (mmol/l)	1.9 (1.0)
Hypercholesterolemia, no. (%)	90 (76)
Current smoking, no. (%)	31 (26)
Diabetes mellitus, no. (%)	30 (25)
Coronary artery disease and/or ECG major changes	27 (23)

Abbreviations: SD = standard deviation, LDL = low-density lipoprotein, HDL = high-density lipoprotein, ECG = echocardiographic.

Prediction of the Risk of Major Coronary Events

There were 14 major coronary events (10 nonfatal myocardial infarction and 4 acute coronary sudden death/fatal myocardial infarction) during follow-up. Lipoprotein(a) was a significant predictor for major coronary events ($p = 0.033$) (Table II). Also, when coronary disease at baseline was included into the Cox regression analysis, lipoprotein(a) was an independent predictor for major coronary events ($p = 0.044$) (Table II). The inclusion of other potential coronary risk factors (age, systolic blood pressure, cholesterol, diabetes mellitus, smoking, and being in the group included in the underlying risk factor intervention study) did not change the significance level (Table II).

Discussion

To our knowledge, this is the first prospective study demonstrating that lipoprotein(a) was an independent predictor of major coronary events in a group of hypertensive men.

The clinical significance of lipoprotein(a) has been confirmed in several studies. However, retrospective case-control studies cannot distinguish a causative role for lipoprotein(a) from the possibility that lipoprotein(a) may be a marker of atherosclerosis or that lipoprotein(a) may increase as a consequence of atherosclerosis. The results from previous prospective studies have been heterogeneous. Some studies have identified lipoprotein(a) as a coronary heart disease risk factor,⁴⁻⁶ whereas other studies have failed to show a relationship between lipoprotein(a) levels and future coronary disease.⁷⁻⁹ The reasons for the discordant results are unclear. Several explanations have been proposed for this obvious contradiction, for example, differences in study design, varying between prospective population-based studies and case-control studies.

Because of the metabolic and structural complexity of lipoprotein(a), the application of rigorous and standardized protocols is required.¹⁷ The atherogenic properties of lipoprotein(a) are linked to those of LDL,¹⁸ therefore the potential of lipoprotein(a) for causing cardiovascular disease may be more substantial in hypercholesterolemic subjects.¹⁹ In the present study, 76% were originally recruited to the study because of hypercholesterolemia, which may have made these patients vulnerable for elevated lipoprotein(a) concentrations. Lipoprotein(a) may have a different atherogenic potential in different ethnic groups, and the follow-up periods have differed between previous studies, which is also a possible explanation for the previous heterogeneous results regarding the relevance of lipoprotein(a).

There are also studies suggesting significant relationships between lipoprotein(a) concentrations and other atherosclerotic diseases such as peripheral atherosclerosis²⁰ and carotid atherosclerosis.²¹ These observations strengthen the hypothesis that lipoprotein(a) is involved in atherosclerotic disease.

In the present study, we found a significantly higher concentration of lipoprotein(a) among subjects with coronary heart disease than among patients without coronary heart disease, a finding in line with previous observations. However,

TABLE II The logarithm of lipoprotein(a) as a predictor for major coronary events in hypertensive men ($n = 118$)

	RR	95% CI	p Value
Log lipoprotein(a)	3.02	1.09–8.57	0.033
Adjusted for coronary disease at entry	2.97	1.03–8.37	0.044
Adjusted for coronary disease at entry, age, blood pressure, smoking, cholesterol, group and diabetes mellitus	2.84	1.06–7.63	0.038

Abbreviations: RR = relative risk, CI = confidence interval.

lipoprotein(a) was a predictor of major coronary events independent of coronary heart disease at entry.

Our findings have to be considered from some methodological aspects. Studies of the mechanisms underlying the atherosclerotic process and the associated clinical manifestations have to be based upon large populations or samples in which the cardiovascular risk is high and in which such diseases are prevalent. In the present study, high-risk patients were included by selecting hypertensive men with at least one further established cardiovascular risk factor: one third smoked, more than half of them were included because of hypercholesterolemia, and one fourth had diabetes mellitus. Another limitation of the study is the rather small study group.

It should also be emphasized that this study population was not a randomly selected sample of hypertensive men, even though most of the patients originally were recruited by screening a random third of all men in their respective age groups in Göteborg.¹⁴ Therefore, these men were representative of high-risk hypertensive patients in Göteborg, but the results may not be generally indicative for the entire hypertensive population.

It may be difficult to compare the results of the present study with those of previous studies. On one hand, the previous studies usually excluded subjects with any sign of cardiovascular disease and had longer follow-up periods. On the other hand, we included older hypertensive men at high risk with additional cardiovascular risk factors and with a high prevalence of concomitant cardiovascular disease at entry.

Conclusion

We observed that lipoprotein(a) was a predictor of major coronary events, independent of cholesterol levels, previous coronary heart disease, and other potential cardiovascular risk factors in a group of hypertensive men at high cardiovascular risk.

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