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Ten-year follow-up results from the Goettingen Risk, Incidence and Prevalence Study (GRIPS). I. Risk factors for myocardial infarction in a cohort of 5790 men

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Abstract

Besides the accepted major risk factors for myocardial infarction (MI), cholesterol, hypertension and smoking, several other variables such as lipoproteins, apolipoproteins, fibrinogen and family history of MI, have been considered, but their usefulness as predictors of MI is controversially discussed. The Göttingen Risk Incidence and Prevalence Study (GRIPS) aimed to evaluate the independent impact of the latter in comparison to the established risk factors. GRIPS is a prospective cohort study, which included 5790 men, aged 40–59.9 years, without cardiovascular disease at baseline. Multivariate logistic regression models for the estimation of the MI risk based on the 10-year follow-up data from 97.4% of the study participants established LDL cholesterol as the strongest predictor of MI. It was followed by family history of MI, Lp(a), age, smoking, systolic blood pressure, HDL cholesterol (inversely related) and plasma glucose ($P < 0.00l$). Apolipoprotein B as well as the ratios total/HDL cholesterol, LDL/HDL cholesterol and Apo B/AI were less effective predictors than LDL cholesterol and did not contribute independently to the estimation of MI risk. Similarly apoprotein AI was a weaker predictor of MI risk then HDL cholesterol. GRIPS is the first prospective cohort study which clearly justifies the key role of LDL cholesterol in preventive strategies. However, the data also give strong support for the additional consideration of other risk factors for a valid estimation of the MI risk for an individual subject. © 1997 Elsevier Science Ireland Ltd.

Keywords: Prospective cohort study; Coronary risk factors; Myocardial infarction; LDL cholesterol

1. Introduction

Plasma cholesterol, cigarette smoking and hypertension are established as the major cardiovascular risk factors [1]. Total cholesterol is primarily distributed among the lipoprotein classes HDL, LDL and VLDL. Determination of these should yield more reliable information on the individual risk of myocardial infarction (MI) and coronary heart disease (CHD) as compared to a serum cholesterol measurement alone [2]. Although the major apolipoprotein components of LDL and HDL, apo B and apo AI, have been claimed to be useful additional or better predictors of coronary risk than lipids or lipoproteins [3–5], this is still a controversial issue [6–8]. On the basis of pathophysiological findings [9,10], Lp(a) and plasma fibrinogen have also recently been considered as possible coronary risk factors. This is, however, only in part supported by prospective epidemiological data [11–17].

In order to conclusively estimate the impact of coronary risk factors, as well as their ranking and potentiating power, a prospective cohort study on a large homogeneous group of subjects with a long term fol-

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low-up, a high follow-up response (close to 100%) and measurement of a comprehensive spectrum of currently discussed risk factors is essential.

The Goettingen Risk Incidence and Prevalence Study (GRIPS) is a prospective cohort study, which meets these criteria. We therefore report the final data of this study on risk factors for acute coronary events (MI, sudden coronary death).

2. Subjects and methods

The design and organization of GRIPS have been reported elsewhere [18] and are therefore described only in brief.

2.1. General design

GRIPS is a prospective cohort study. The baseline investigation included 6002 men, aged 40–59.9 years. According to anamnestic data and non-invasive clinical examinations, 5790 of these subjects were free of atherosclerotic diseases (coronary heart disease, myocardial infarction, peripheral arterial vascular disease, stroke) at study entry. They represent the definitive study group, which includes 62 more individuals than the study population of the previously published 5-year follow-up analysis [18,19]. These 62 subjects had been excluded from the former analysis due to suspect cardiovascular diseases before baseline. However, these subjects had to be retrospectively classified as free of atherosclerotic diseases at study entry, since they revealed no symptoms of any previous or current cardiovascular problems after 10-years of follow-up. The total definitive study group was prospectively followed for 10 years in order to record causes of morbidity and mortality. The follow-up response rate was 97.4% (5639 subjects). In addition, a vital status was obtained for a further 140 subjects, who were still alive at the 10-year follow-up. A total of 11 subjects were lost to follow-up. Only the 5639 subjects with entire follow-up data were included in the present analysis.

2.2. Endpoints

Subjects who developed one of the following primary endpoints during the follow-up period, were classified as incidence cases of myocardial infarction (MI) ($n = 299$): definite sudden coronary death ($n = 25$), definite fatal MI ($n = 45$) or definite non-fatal MI ($n = 229$).

Since the present evaluations were specifically aimed to evaluate the risk factors for these acute coronary events, all subjects who developed one of the following secondary endpoints were excluded from the analysis and will be reported separately: definite chronic coronary heart disease (CHD) without MI ($n = 259$), definite stroke (fatal or non-fatal) ($n = 101$), definite peripheral arterial vascular disease (PAVD) ($n = 168$), carotid stenosis ($n = 14$), suspect MI, CHD, stroke or PAVD ($n = 34$) or death from non-cardiovascular causes ($n = 189$; 51% malignancies; 21% non-malignant diseases of lung, gastrointestinal organs or kidney; 15% accident or suicide; 8% infectious diseases; 5% other causes). A total of 1030 subjects developed at least one of the above mentioned 1084 primary or secondary study endpoints. The remaining 4609 subjects from the study group remained free of any endpoints during the 10-year observation period and were taken as a reference group.

Definite and suspect endpoints were defined according to the recommendations of other epidemiological studies [20–22] as described in detail elsewhere [18]. The diagnosis of endpoints was based on clinical symptoms, resting and exercise ECG, serum enzyme activity pattern, angiography and computer tomography. An independent panel of physicians, without knowledge of the baseline data, was responsible for the final endpoint evaluations.

2.3. Baseline variables

The major baseline parameters of GRIPS were as follows.

Anamnestic variables:
- date of birth
- history of diseases and medications
- family history of myocardial infarction (0 vs. ≥ 1 first degree relative with MI before the age of 65 years) (Table 2);
- smoking habits: smokers (subjects smoking daily at the time of baseline investigation) or non-smokers (ex-smokers were not distinguished from subjects who had never smoked as the information was not sufficiently reliable) (Table 2);
- alcohol consumption (0–1 days per week, 2–4 days per week, ≥ 5 days per week, referred to hereafter as never, occasionally, or regularly). Since the MI incidence was similar in subjects consuming alcohol occasionally or regularly, these subgroups were combined for the analysis (Table 2);
- leisure time sporting activities (less than once per week or at least once per week, referred to as rarely or regularly) (Table 2).

Clinical variables:
- Body mass index calculated as weight (kg)/height (m^2);
- Blood pressure (determined as mean of three measurements in sitting posture after at least 10 min of rest).

Laboratory variables, serum total cholesterol, triglycerides, LDL cholesterol, VLDL cholesterol, HDL cholesterol, apolipoprotein B, apolipoprotein AI, Lp(a), fibrinogen and plasma glucose.

2.4. Laboratory methods

The laboratory methods have been described in detail elsewhere [18,19]. In brief, cholesterol and triglycerides were measured by CHOD-PAP or GPO-PAP methods (Boehringer Mannheim, FRG), respectively, on a Hitachi 704 analyzer (Boehringer Mannheim, FRG). Lipoproteins were quantified by an analytical schedule [19] consisting of precipitation and electrophoretic techniques and if indicated ultracentrifugation. Fibrinogen and the apolipoproteins AI and B were measured by immunologic nephelometry using commercially distributed monospecific antisera and a nephelometer analyzer from Behring AG, FRG. The nephelometric methods were calibrated using commercially available standard materials from Behring AG, FRG. Calibration was based on the standard concentrations as declared by the manufacturer, since international standard preparations and procedures were not defined for these parameters at the time of measurement. Lp(a) was quantified as Lp(a) total mass by an ELISA technique (Immuno GmbH, FRG). The respective standard material was provided and declared by the same manufacturer. All procedures had high precision: the inter assay coefficients of variation ranged from $<2\%$ (cholesterol, LDL cholesterol, triglycerides) to $<3\%$ (apo Al, apo B, fibrinogen) or $<4\%$ (HDL cholesterol, Lp(a)), respectively.

2.5. Statistical methods

All statistical analyses were performed using SAS statistical software [23]. The difference of risk factors between the reference and the incidence group was tested with the two-tailed t-test for continuous variables except for Lp(a), for which the Kolmogorov-Smirnov test was used. For dichotomous variables the chi-square test was used and the relative risks were computed together with 95% confidence intervals. Relative risks for continuous variables were calculated by dividing the reference and the incidence group into five subgroups according to quintiles which were derived from the distribution of values in the total definitive study group. The relative risks, together with the respective 95% confidence intervals, were calculated, using as a baseline the highest (HDL cholesterol and apo AI) or the lowest quintile (other variables), respectively.

To study the joint relationship of potential risk factors to MI risk, and to calculate adjusted odds ratios, multivariate logistic regression analyses were carried out. The anamnestic variables, smoking habits, alcohol consumption, sporting activities and family history of MI, entered the analyses as described in 'Baseline variables' (Section 2.3). Quantitative factors were tested for a linear or log-linear trend in the relationship to the logistic transformation of MI-probability [24]. In this case the factor had to enter the model as continuous or logarithmic transformed continuous variable respectively. The selection of the final variant, continuous, logarithmic or categorized, was based on an analysis of deviances [24]. Modified forward and backward variable selection procedures were used, with a value of $P<0.01$ for the initial probability to enter and the partial significance to remain in the model in the presence of other variables. Maximum likelihood statistics was used for the selection process. As a last step, interactions between the variables remaining finally in the model were tested.

3. Results

The MI incidence patients revealed marked differences for several variables in mean or median values respectively (Table 1): Age, systolic blood pressure, diastolic blood pressure, fibrinogen, plasma glucose, cholesterol, LDL cholesterol, triglycerides, VLDL cholesterol, apolipoprotein B, and Lp(a) showed significantly higher values in incidence than in reference subjects, whereas HDL cholesterol and apo AI were significantly lower in subjects with than in those without MI. Accordingly, the MI incidence was consistently and significantly raised with increasing quintiles of age (data not shown), cholesterol, LDL cholesterol, apolipoprotein B, triglycerides, VLDL cholesterol, and fibrinogen (Fig. 1a–c,e,f,i) as well as with decreasing quintiles of apo AI (Fig. 1h). A significantly elevated hazard of MI was also found in the highest quintiles of Lp(a), body mass index, systolic blood pressure, and plasma glucose (Fig. 1d,k–m) and also in the lowest quintile of HDL cholesterol (Fig. 1g). Among the dichotomous variables 'hypertension' (according to WHO criteria), 'smoking' and 'family history of MI' were of major importance for the MI incidence, whereas 'alcohol consumption' and 'sporting activities' were only of minor impact (Table 2).

The performance in estimating MI risk for some parameters of lipid metabolism are compared in Fig. 2a,b by receiver operating characteristic (ROC) curves, which are generated by plotting sensitivity vs. specifity for all possible cut-off points used to identify an individual at increased risk. It is apparent that LDL cholesterol provided more sensitivity in predicting MI at all given levels of specificity (or vice versa) than total cholesterol which in turn was superior to apolipoprotein B. The ratios total/HDL cholesterol, LDL/HDL cholesterol and apo B/AI, did not have better

predictive value for MI risk as compared to total cholesterol. HDL cholesterol was superior to apo AI in predicting MI. However, both were much weaker predictors than the above mentioned variables.

For the majority of the tested variables the results of the univariate analysis were strongly supported by multivariate logistic regression analysis, which was performed to model the dependency of MI risk on these variables. Using forward or backward selection did not affect the variables remaining in the analysis. The final model (Table 3) included LDL cholesterol as logarithmic transformed continuous variable. Age, systolic blood pressure, and Lp(a) were included as continuous variables, whereas HDL cholesterol ($<$, ≥ 0.9 mmol/l; 35 mg/dl), smoking (yes/no), family history of MI (yes/no), and plasma glucose ($<$, ≥ 8.3 mmol/l, 150 mg/dl) were used as categorized variables. It is important to note that all tested models were virtually identical, with respect to the ranking and odds ratios of the variables. LDL cholesterol as the strongest predictor was followed by family history of MI, Lp(a), age, smoking, systolic blood pressure, HDL cholesterol (inversely related) and plasma glucose, all of which were included in the model on the basis of a significance level of $P < 0.01$ (Table 3). Fibrinogen failed to enter the final prediction model on the basis of a significance level of $P < 0.01$, but would have been included (ranking 9th, without influence on the ranks or the odds ratios of the more powerful predictors) by reducing the significance level to $P < 0.02$. Triglycerides and VLDL cholesterol totally failed to enter the final prediction model even on the basis of a significance level of $P < 0.05$. There were no significant interactions between the variables of the final prediction model.

Table 1
Comparison of MI incidence and reference group for continuous variables

Variable	MI incidence cases	Reference group	
	Mean	Mean	P-value[a]
Cholesterol (mmol/l)	6.35 (1.03)	5.54 (0.99)	<0.001
Triglycerides (mmol/l)	2.00 (0.85)	1.70 (0.87)	<0.001
LDL cholesterol (mmol/l)	4.47 (0.91)	3.67 (0.82)	<0.001
HDL cholesterol (mmol/l)	1.16 (0.3)	1.26 (0.31)	<0.001
VLDL cholesterol (mmol/l)	0.71 (0.42)	0.59 (0.43)	<0.001
Apo B (mg/dl)	136.9 (25.89)	118.0 (22.91)	<0.001
Apo AI (mg/dl)	119.5 (26.14)	126.7 (27.73)	<0.001
LDL/HDL cholesterol	4.15 (1.46)	3.09 (1.07)	<0.001
Total/HDL cholesterol	5.84 (1.75)	4.62 (1.32)	<0.001
Apo B/Apo AI	1.21 (0.38)	0.98 (0.3)	<0.001
Fibrinogen (mg/dl)	402.0 (87.8)	360.2 (83.53)	<0.001
Systolic BP (mmHg)	137.8 (17.91)	130.7 (14.84)	<0.001
Diastolic BP (mmHg)	88.85 (9.97)	85.39 (8.63)	<0.001
Plasma glucose (mmol/l)	6.11 (2.37)	5.62 (1.35)	<0.001
Body mass index (kg/m^2)	26.71 (3.24)	26.16 (2.96)	<0.01
Age (years)	49.63 (4.99)	47.22 (5.0)	<0.001
	Median	Median	P-value[b]
Lp(a) (mg/dl)	18 (<5–58)	9 (<5–41)	<0.001

Data for Lp(a) are given as median and percentiles (10–90%), data for the other variables are presented as mean values (standard deviations).
BP, blood-pressure.
[a] t-test.
[b] Kolmogorov-Smirnov test.

Based on the final prediction model, Fig. 3 shows the relationship of the 10-year MI risk to the LDL cholesterol concentrations:

(a) For subjects with a minor expression of all other relevant risk factors; age = median value of the total study group; HDL cholesterol ≥ 0.9 mmol/l (35 mg/dl); plasma glucose < 8.3 mmol/l (150 mg/dl); other continuous variables = lowest quintiles; categorized (yes/no) variables = no;

(b) For subjects with Lp(a) concentrations of 30 mg/dl (usually considered as a borderline value) as an additional risk factor; all other variables were defined as mentioned for (a);

(c) For subjects with a positive family history of MI as a particularly strong additional risk factor; all other variables were defined as mentioned for (a).

It becomes evident that at any LDL cholesterol level other risk factors such as Lp(a) or positive family history of MI potentiate the LDL induced MI risk. Thus, for example, the MI risk, which is associated with a relatively high LDL cholesterol concentration of 5.2 mmol/l (200 mg/dl) in the absence of other risk factors, is equivalent to the risk at LDL cholesterol levels of 4.4 mmol/l (170 mg/dl) in the presence of a borderline Lp(a) value, or to the risk at a relatively low LDL cholesterol level of 3.8 mmol/l (145 mg/dl) if combined with a positive family history of MI.

4. Discussion

Results obtained from multivariate logistic regression models might be considerably influenced by the manner in which the various variables are entered into the analyses. In the GRIPS evaluations, however, all tested variants of the multivariate prediction models showed only minor differences concerning the rank order of the selected risk factors or their odds ratios.

As in the 5-year evaluations [19] and in agreement with current strategies for the prevention of MI [25,26] the data from the 10-year GRIPS study confirmed LDL cholesterol as the most important risk factor. This

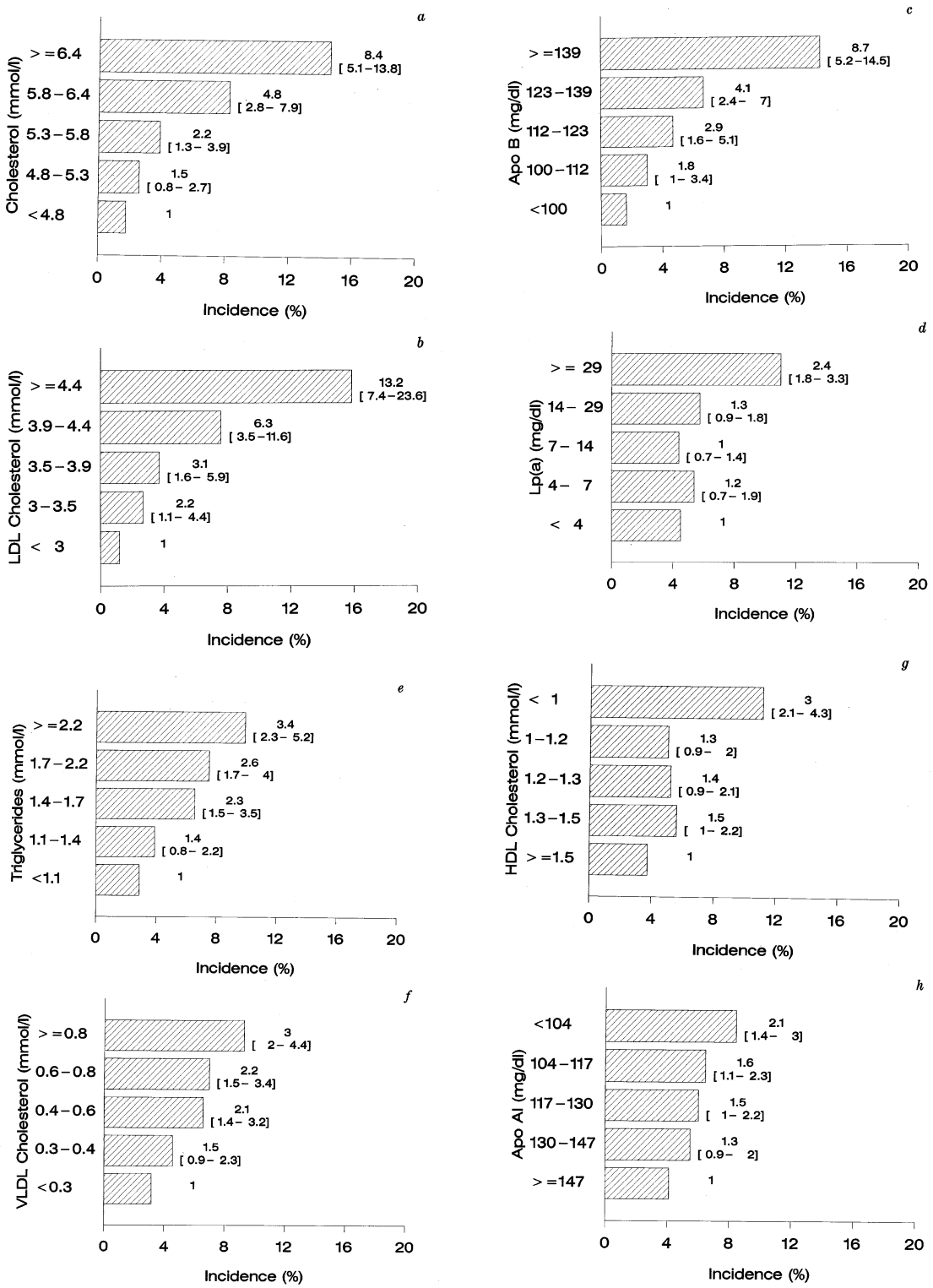

Fig. 1. MI incidence during 10 years of follow-up in quintiles of continuous variables as measured at baseline. The relative risks [95% confidence intervals] are given at the top of the respective column, and are defined for each variable as 1.0 for the highest (HDL cholesterol, apo AI) or the lowest quintile (other variables) repectively: (a) total cholesterol; (b) LDL cholesterol; (c) apolipoprotein B; (d) Lp(a); (e) triglycerides; (f) VLDL cholesterol; (g) HDL cholesterol; (h) apolipoprotein AI; (i) fibrinogen; (k) body mass index; (l) systolic blood pressure; (m) plasma glucose.

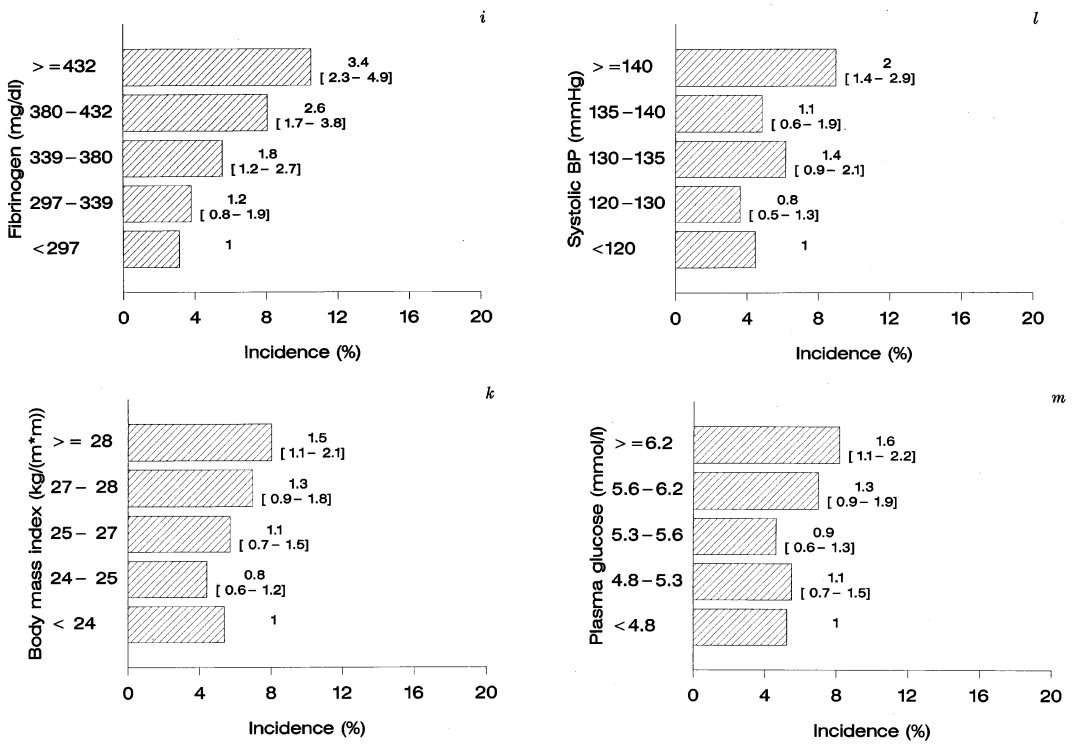

Fig. 1 (continued).

finding is based, for the first time, on directly measured LDL cholesterol serum levels in each subject by precise and accurate techniques. In accordance with recently published secondary intervention trials [27,28] our data confirm the opinion that LDL cholesterol levels in the lowest quintile (around 2.5 mmol; 100 mg/dl) are associated with a particularly low incidence of coronary events and should therefore be defined as target values in the preventive therapy of patients at an extremely high coronary risk, i.e. those with overt coronary heart disease.

With regard to Lp(a), the 10-year GRIPS results not only confirm our own 5-year findings but also support some other prospective studies, which revealed Lp(a) as a major additional risk factor [7,12,14,15]. The contradictory data from the Helsinki Heart [11] or the Physicians Health Study [13] may be due to interferences as discussed by Schaefer et al. [15]. Moreover the GRIPS results on Lp(a) as well as on LDL cholesterol are in accordance with a recent comprehensive hypothesis of atherogenesis [29].

The generally accepted recommendations to consider HDL cholesterol as a negative risk factor for MI [25,30] are supported by the GRIPS findings. There was, however, no overall association between HDL cholesterol and the MI incidence. Only subjects from the lowest (first) quintile of HDL cholesterol (< 1 mmol/l or 38 mg/dl respectively) revealed a significantly increased hazard of MI, whereas no relevant differences in the MI incidence were observed between subjects from the remaining four quintiles. Thus, particularly low HDL cholesterol levels proved to be an important risk factor, whereas no evidence was obtained from the GRIPS data for a relevant protective effect of particularly high HDL cholesterol values.

Total cholesterol, apolipoprotein B and the ratios LDL/HDL cholesterol, total/HDL cholesterol or apo B/AI proved to be weaker predictors of the MI risk than LDL cholesterol, as shown for example in the ROC curve (Fig. 2). In view also of their strong pathophysiologically explainable relationships to LDL cholesterol it is not surprising that they failed to enter the final estimation model for MI risk in either the 5-year or 10-year evaluation of GRIPS. This is obviously due to the strong relationships [19] of these variables to the stronger predictor LDL cholesterol. Likewise apo AI was excluded from the final prediction model because of its strong relationship to HDL cholesterol [19]. It is important to note that apo B and apo AI were less effective predictors of MI than LDL or HDL cholesterol respectively, a result which is in contrast to some earlier retrospective case control studies [3–5], but in good agreement with more recent prospective studies [6–8]. The various ratios did not provide better predictive information on the MI risk as compared to total cholesterol alone and were less predictive than

Table 2
Comparison of MI incidence and reference group for dichotomous variables by means of chi-square test

Trait	MI cases		Ref. group		RR	95% CI	*P*-value
	n	%	*n*	%			
Smoking (yes)	170	56.9	1597	34.6	2.3	1.9–2.9	<0.001
Alcohol (never)	51	17.1	481	10.4	1.7	1.3–2.3	<0.001
Sports (rarely)	199	66.6	2760	59.9	1.3	1.0–1.7	<0.05
Family history of MI (yes)	74	24.7	380	8.2	3.2	2.5–4.1	<0.001

RR, relative risk; CI. confidence interval; *n*, number of subjects.

LDL cholesterol. This supports the consideration [31,32] that the predictive value of LDL/HDL cholesterol or similar ratios depends on the absolute LDL cholesterol level of the respective individual and provides additional information on the MI risk especially in subjects with borderline, but not in those with definitely high or low LDL cholesterol levels.

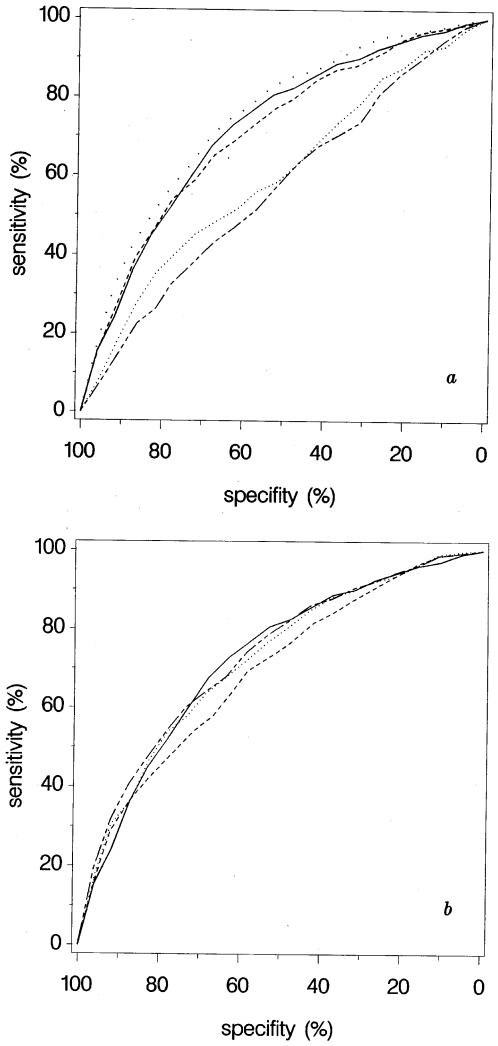

Fig. 2. Receiver operating characteristic curves for predicting MI risk by several parameters of lipid metabolism:(a) total cholesterol (——), LDL cholesterol (· · ·), apoprotein B (- - -), HDL cholesterol (· · · · ·), apoprotein AI (– · · – · · –); (b) total cholesterol (——), total/HDL cholesterol (· · · ·), LDL/HDL cholesterol (– · · – · · –), apo B/AI (- - -).

Triglycerides and VLDL cholesterol revealed a considerable impact on the MI risk only in the univariate analyses. Both variables did not significantly contribute to the improvement of the multivariate prediction model. This finding is in accordance with other reports [30,33,34] and may be due to the fact that the distribution of triglycerides among the various lipoprotein fractions is not sufficiently elucidated by the laboratory methods commonly used in epidemiologic studies.

In contrast to the 5-year evaluation of GRIPS [19], fibrinogen was no longer a major risk factor of MI after the 10-year follow-up period. In the 5-year analyses smoking had been excluded from the prediction model as an independent risk factor for MI if fibrinogen was incorporated into the multivariate analyses, as observed earlier by the Framingham Study Group [17], whereas in the present analysis the opposite was found. Smoking proved to be a strong independent risk factor and thus excluded fibrinogen, at least for a $P < 0.01$ level of significance, from the prediction model. The importance of fibrinogen as a predictor of MI decreased substantially with an increasing interval between time of measurement and the appearance of MI. Thus, fibrinogen had a higher predictive power in healthy subjects at baseline who developed a MI during the first 5 years and probably suffered from clinically still inapparent but already existing coronary lesions at study entry. In contrast, it was of minor relevance in those who suffered a MI 5 or more years later and probably had no or at least less advanced lesions at study entry. Considering also the high biological variance of fibrinogen plasma levels, this may indicate that fibrinogen promotes pathophysiological mechanisms of acute coronary events in patients with advanced coronary lesions rather than the chronic process of coronary sclerosis itself. This hypothesis is supported by recent experimental data [35]. Moreover it is in agreement with our own findings on subjects who developed chronic coronary heart disease but no acute coronary event during the GRIPS 10-year follow-up. In these subjects fibrinogen did not show any influence as a risk

Table 3
Ranking of risk factors for the estimation of MI risk evaluated by means of multivariate logistic regression analysis

Variable	Risk factor exposition	Odds ratio	Coefficient	Standard error	Chi-square	*P*-value
LDL cholesterol	+20%	2	4.005	0.323	153	0.0001
Family history of MI	Yes	3.4	1.238	0.165	57	0.0001
Lp(a)	+30 mg/dl	2	0.023	0.003	57	0.0001
Age	+8 years	2	0.09	0.013	49	0.0001
Smoking	Yes	2.5	0.904	0.133	46	0.0001
Systolic BP	+33 mmHg	2	0.021	0.004	27	0.0001
HDL cholesterol	<0.9 mmol/l	2.2	0.804	0.165	24	0.0001
Plasma glucose	≥8.3 mmol/l	2.8	1.033	0.267	15	0.0001
Constant			−16.647	0.952		

factor, in either the 5 or the 10-year follow-up evaluations (unpublished GRIPS data). Our interpretation is also supported by recent findings from the ECAT study, in which fibrinogen proved to be of particular importance as a risk factor for acute coronary events in patients with angiographically proven coronary sclerosis [36]. It is, however, important to note that fibrinogen remains a strong and independent predictor of MI in our multivariate logistic regression models as long as smoking is not incorporated into the analyses. Thus, the former interpretation of our data [19] and other studies [16,17] remains true, suggesting that the impact of smoking on MI risk and in particular its short-term influence, is largely due to raised plasma fibrinogen levels. In contrast to fibrinogen, the influence of smoking on MI incidence appeared to increase with time. This finding may confirm the suggestion [1] that smoking, besides its short-term effect, which promotes acute coronary events, also has an additional long-term impact, independent of fibrinogen, on stimulating the chronic atherosclerotic process.

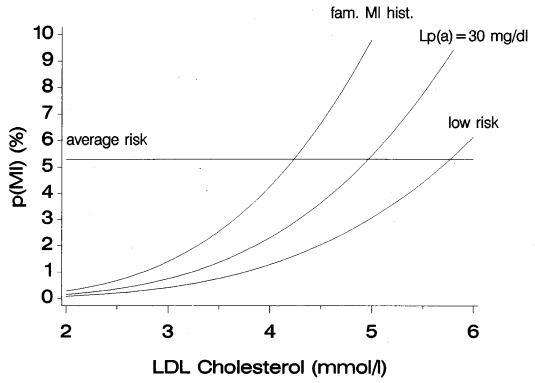

Fig. 3. Ten-year probability of MI according to LDL cholesterol concentrations in subgroups stratified as follows.Low risk: subjects with minor expression of additional risk factors age = median value of the total study group; HDL cholesterol ≥0.9 mmol/l; plasma glucose <8.3 mmol/l; other continuous risk factors = lowest quintile,; categorized risk factors = no.Lp(a) = 30 mg/dl: Lp(a) concentrations assumed as 30 mg/dl. All other risk factors as defined for 'low risk'. Fam. MI hist.: family history of MI assumed as positive. All other risk factors as defined for 'low risk'. Average risk: average 10-year risk of MI for the GRIPS study population.

Besides smoking, hypertension and hyperglycemia also proved to be strong and independent risk factors after 10 years but not after 5 years of follow-up [19]. However, in comparison to increased LDL cholesterol levels they seem to be less powerful risk factors for MI. High plasma levels of LDL cholesterol promote the occurrence of acute coronary events at rather young ages, possibly because they not only induce the early development of atherosclerotic changes in coronary arteries [29,37] but also unfavourably influence the endothelium-dependent coronary vasomotion [38,39]. In contrast, hypertension and hyperglycemia may need more time to exert an impact on the development of acute coronary death and MI, thereby indicating a merely chronic influence of both conditions on the atherosclerotic process.

The validity of these data is not influenced by the subjects who were excluded from the present evaluations because of secondary endpoints or refusal to participate in the follow-up. The latter subjects ($n = 151$) were very similar to MI patients with respect to age, alcohol and cigarette consumption and sporting activities and to reference subjects for all other baseline variables. Since major diseases during follow-up could be excluded for all of them (besides 11 who were completely lost to follow-up) they were tentatively assigned to the reference group without major influence on the results. Subjects who suffered non cardiovascular death during follow-up ($n = 189$) as a secondary endpoint were similar to the MI group not only for age, as expected, but also for smoking, fibrinogen, plasma glucose, alcohol consumption as well as sporting activities and to the reference group for the other baseline variables. These findings are not surprising, at least for smoking as well as consecutively for fibrinogen since the major cause of non cardiovascular death in this study group was cancer, in particular lung cancer. Subjects with secondary CVD endpoints (stroke, PAVD, chronic CHD without acute events; $n = 488$) as a whole were very similar to the MI subjects for all baseline variables. Each of these subgroups however, revealed specific characteristics, which need to be described in detail separately.

Including subjects with either secondary cardiovascular or non-cardiovascular endpoints appropriately into the univariate or multivariate evaluations did not substantially influence the outcome.

Baseline values and results for lipids, blood pressure and plasma glucose are not substantially influenced by baseline medications since only a minor proportion of the study group was on, antihyperlipidemic (1.6%), antihypertensive (7.1%) or antidiabetic (1.2%) drugs at study entry.

Taken together, the GRIPS data support the strategies of the NIH and the National Cholesterol Education Program of USA [25,30] and our own recommendations [18,26] for the identification and preventive treatment of subjects at increased MI risk. These strategies focus on LDL cholesterol as the key predictor of MI and the primary target of risk-lowering therapies, although a superior predictive power of this parameter in direct comparison to other risk factors has never before been clearly demonstrated by prospective epidemiological data. Our results for the first time justify the outstanding role of LDL cholesterol in current preventive strategies. Furthermore guidelines for the prevention of MI and CHD additionally take into account the fact that the individual LDL-induced MI risk is strongly augmented, if other risk factors are also present. This opinion is confirmed by the GRIPS data. In particular, not only a positive family history of MI, increased serum levels of Lp(a) and cigarette smoking, but also hypertension, low HDL cholesterol levels, hyperglycemia, and possibly hyperfibrinogenemia have to be considered as clinically relevant additional risk factors for MI. The presence and persistence of these risk factors in an individual justifies the definition of lower threshold and target values for the primary risk factor LDL cholesterol [18,25,26].

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