Klin Wochenschr (1988) 66 (Suppl XI): 42–49

Klinische Wochenschrift

Incidence Rates of Fatal and Nonfatal Myocardial Infarction in Relation to the Lipoprotein Profile: First Prospective Results from the Göttingen Risk, Incidence, and Prevalence Study (GRIPS)

P. Cremer[1], H. Elster[2], B. Labrot[2], B. Kruse[1], R. Muche[1], and D. Seidel[1]

[1] Abteilung für Klinische Chemie der Universität Göttingen

[2] Abteilung Gesundheitsschutz VW-Werk, Baunatal

Summary. In a screening investigation in 1982, which included medical history, clinical examination, general laboratory investigation, and quantification of lipids, lipoproteins, and apoproteins A1 and B, 5020 male subjects aged 40 to 59 years took part. All subjects were free of any heart or vascular disease at the basic examination. Of them 40 suffered fatal or nonfatal myocardial infarction (MI) during the first 3-year observation period between January 1982 and December 1984 (incidence cases), the others remained free of heart or vascular diseases (reference group).

Comparison with the reference group revealed a strong relationship between MI-incidence rate and LDL cholesterol (correlation coefficient according to univariate regression analysis $r = +0.248$; P value according to Chi-square test $P < 0.001$). The relationship was less strong but significant for age ($r = +0.189$; $P < 0.001$), total serum cholesterol ($r = +0.197$; $P < 0.001$), and apoprotein B ($r = +0.195$; $P < 0.001$). Although statistically significant, the relationships to the MI-incidence rate were comparatively weak for HDL cholesterol ($r = -0.09$; $P < 0.01$), apo-A1 ($r = -0.09$; $P < 0.01$), systolic blood presssure ($r = +0.067$; $P < 0.05$), and blood glucose level ($r = +0.066$; $P < 0.05$). Body mass index, diastolic blood pressure, and plasma levels of uric acid, triglycerides, and VLDL did not exert relevant influences on the MI-incidence rate in our study population. The present results from the ongoing GRIPS incidence project indicate that LDL-cholesterol reveals a dose-response relationship with the incidence rate of MI and is the most powerful predictor of MI risk. This holds for all investigated age groups. LDL-cholesterol concentrations of 120 and 190 mg/dl seem to be suitable values for the discrimination of subjects at low and increased or high MI risk, respectively. The GRIPS project will be continued in order to reinforce these results of the first 3-year follow-up.

Key words: Myocardial infarction – Cholesterol – Triglycerides – LDL – VLDL – HDL – Hypertension – Smoking – Diabetes mellitus

Introduction

The prevention of atherosclerosis and its subsequent diseases, especially coronary heart disease and myocardial infarction, is predominantly based on the elimination of the so-called risk factors [1, 12, 30]. This is approached by an early recognition and consequent treatment of individuals with risk factors (individual strategy), and also by reduction of the prevalence of risk factors in the general population (population strategy) [1, 12, 13, 30].

On the basis of results from various epidemiological case control or incidence studies as well as intervention trials [1, 11–14, 22] hypercholesterolemia and hypertension are considered to be the major risk factors for coronary heart disease and myocardial infarction, among numerous other factors which have been discussed in the past as being

Abbreviations: Apo A1 = Apolipoprotein A1; Apo B = Apolipoprotein B; GRIPS = Göttingen risk, incidence, and prevalence study; HDL = High-density lipoproteins; LDL = Low-density lipoproteins; MI = Myocardial infarction; VLDL = Verly low density lipoproteins

potentially related to atherosclerosis [11]. Cigarette smoking in particular has been discussed controversially [1, 11–13, 21, 30]. Its role as risk factor for myocardial infarction may be different from its influence on the chronic atherosclerotic process. Similarly, the impact of overweight, sedentary lifestyle, diabetes mellitus, psychosocial stress, and other factors on atherogenesis remains unclear [1, 11–13, 15, 20, 30]. With regard to the atherogenic potential of the various plasma lipoprotein fractions or their constituents (i.e., cholesterol or apolipoproteins, etc.) differences in the techniques for measuring these compounds make it difficult, sometimes impossible to compare the results of the various studies. This is particularly true for LDL which, to our knowledge, has so far not been directly determined in any large prospective study.

Based on this situation we initiated in 1979 the "Göttingen Risk, Incidence, and Prevalence Study" (GRIPS). GRIPS consists of several projects [6, 7, 22, 23] which intend to improve the possibilities of an early recognition of patients with increased risk for coronary sclerosis and myocardial infarction. They focus on the practicability, sensitivity, and specificity of modern clinical chemical analyses.

An important GRIPS project is the prospective incidence study, initiated in 1982 [7, 22, 23]. The first incidence data of this project, based on a 3-year observation period, are described in this communication.

Study Participants and Methods

Design of the Study

The basic examinations for the prospective GRIPS project were performed in the spring of 1982 and included 6029 German males aged 40–59 years, all subjects belonging to one company. They underwent a clinical examination and were given a standardized questionnaire concerning medical history (family and individual), social and psychosocial situation, lifestyle, and life habits. Furthermore, extensive laboratory investigations were performed with special interest in parameters of lipid metabolism.

In the spring of 1985 the participants were again contacted in order to record the incidence of deaths and diseases within the first 3 years of observation. A second follow-up examination is in progress at present. Further examinations are planned for 1989, 1991, and, hopefully, 1994.

Endpoints of the Study

For the present analyses definite fatal and nonfatal myocardial infarction were defined as primary endpoints of the study. Other vascular or heart diseases, including suspect myocardial infarction (fatal or nonfatal), as well as death by other causes were defined as additional (secondary) endpoints.

Definite nonfatal myocardial infarction was considered if an acute event of typical ischemic cardiac pain was combined with at least one of the following two criteria: characteristic ECG changes at the time of the event; typical enzyme activity pattern at the time of the event (CK activity increased to a value representing at least twice the upper reference limit of the local laboratory combined with a CKMB activity of more than 10 U/l and more than 6% of the total CK activity). Definite fatal myocardial infarction was considered in cases who died after hospitalization due to a definite nonfatal myocardial infarction as defined above, and furthermore in persons who suffered sudden death if a chronic coronary heart disease had been diagnosed previously by ECG or coronary angiography.

Study Participants

Of the 6029 subjects who took part in the basic examiniation 5878 answered the questionnaire of the first follow-up examination (97%). The following endpoints were registered:

1. Primary endpoints ($n = 51$): 10 cases of definite fatal myocardial infarction (including one case of sudden death) and 41 cases of definite nonfatal myocardial infarction
2. Secondary endpoints ($n = 208$): two cases of suspected nonfatal myocardial infarction, 36 deaths due to noncardiovascular causes, 170 instances of development of other vascular or heart diseases.

Cases with secondary endpoints as well as all participants ($n = 650$) who had suffered from any endpoint disease at the time of the basic examination in 1982 were excluded from the following analyses.

Thus, the definite study group consisted of 5020 subjects, among them 40 with definite myocardial infarction (incidence group) and 4980 subjects who remained free of any vascular of heart disease until December 1984 (reference group).

Definition of Investigated Attributes

Besides various continuous variables several discrete variables (attributes) were investigated in the study and defined as follows:

1. Positive family history of myocardial infarction: subjects with at least one first-degree relative who suffered MI before the age of 60
2. Hypertension: borderline (140–159 mmHg systolic or 90–94 mmHg diastolic) or high blood pressure (≥ 160 mmHg systolic or ≥ 95 mmHg diastolic) at the basic examination
3. Diabetes mellitus: increased blood glucose levels (≥ 120 mg/dl) at the basic examination
4. Smoking: regular consumption of ≥ 5 cigarettes/day at the basic examination and for at least 1 year prior to this
5. Alcohol consumption: regular = on at least 4 days/week; occasional = on 1–3 days/week; never = less than once/week
6. Sporting activities: regular = at least 3 h per week; occasional = less than 3 h but at least 0.5 h per week; never = less than 0.5 h per week
7. Overweight: body mass index (bmi) > 25 kg/m^2

Laboratory Methods

In the basic examination of this study a multitude of clinical chemistry parameters were measured. Special interest was focused on lipid metabolism. Therefore, besides total serum cholesterol and triglycerides, which were quantified by means of commercially available fully enzymatic procedures (Boehringer, Mannheim, FRG), the cholesterol levels of all major lipoprotein fractions were directly measured by various laboratory techniques: (a) quantitative lipoprotein electrophoresis [27]; (b) determination of HDL-cholesterol by precipitation techniques: precipitation with heparin-magnesium-chloride (Merck, Darmstadt, FRG) and by sodiumphosphotungstate precipitation (Boehringer, Mannheim, FRG); (d) determination of LDL- cholesterol by precipitation techniques: selective precipitation of LDL with heparin in an acidic medium [28] (Merck, Darmstadt, FRG). Apoproteins A1 and B were directly measured by kinetic immun-nephelometry [26, 29]. Since the precipitation and electrophoretic procedures of lipoprotein quantification gave almost identical results in this study as well as in previous investigations [5], only data from quantitative lipoprotein electrophoresis are discussed in this presentation.

At the time of blood drawing, participants were in a 5 to 6-h postprandial state for practical reasons. With respect to blood glucose levels 5 to 6 h after ingestion only minor changes have to be expected in normals. In fact the glucose levels in our population are almost identical to those seen in another epidemiological study, where blood was drawn after a 12 h fasting period [2]. In pilot studies [5, 31] serum levels of cholesterol, lipoproteins, and apoproteins, proved to be virtually identical in fasting and postprandial states, provided the analyses were performed using the above-mentioned laboratory techniques. Triglycerides are potentially the main problem in postprandial laboratory analyses. However, the following facts indicate that our results concerning triglycerides should not be relevantly influenced by the blood-drawing conditions of the study:

1. Pilot studies [31] revealed that in normals triglyceride values are only slightly increased 5 to 6 h after ingestion as compared to the fasting state.
2. The same pilot study [31] showed that the principal procedure to measure the lipoproteins in GRIPS (quantitative lipoprotein electrophoresis, which retains chylomicrons and their remnants at the origin) provides the possibility to calculate "fasting" triglyceride concentrations from the concentrations of β, pre-β-, and α-lipoproteins with high accuracy. The calculated triglyceride values found in our study population are in good agreement with the fasting triglyceride concentrations found in white American male subjects of the same age group [18] and are even lower than those described for another German epidemiologic study [2], where blood was drawn in a 12-h fasting state.

To have the postprandial and the calculated "fasting" triglyceride values may in fact be of importance in the evaluation of the role of these lipids in atherogenesis. For the present analyses we used the calculated "fasting" triglyceride values.

Statistical Methods

Associations between the various variables and the primary endpoints were evaluated after direct age adjustment of the incidence and the reference group. Differences in mean values were tested for significance using Student's *t*-test. Univariate logistic regression analyses according to Cox [4] for modelling incidence rates of primary endpoints to various variables were performed. The influences of the variables were tested for significance using the likelihood ratio test. Finally, we compared incidence rates of myocardial infarction in different subgroups of our population stratified for various attributes. To calculate age-adjusted odds ratios we used four fold tables separately in 5-year age groups. The statistical significance of the age-adjusted odds ratios was tested using the Mantel-Haenszel test.

Table 1. Relationship between age and the MI incidence rate: number of subjects and new events of myocardial infarction as well as incidence rate/1000 participants during a 3-year observation period (January 1982–December 1984) in 5-year age groups

Age group (years)	*n*	New events	MI incidence rates
40–44	1950	4	2.0
45–49	1450	12	8.3
50–54	1113	15	13.5
55-59	507	9	17.8
Total	5020	40	8.0

Results

Age proved to be a variable with a strong and consistent relationship to the incidence rate of myocardial infarction (MI) in our study. This becomes evident from significant differences in the mean values for age between the incidence and the reference group (51+/−5 vs 47+/−5 years; $p < 0.0001$) and additionally from high and significant regression coefficients between age and the MI-incidence rate ($r = 0.189$; $P < 0.001$). Furthermore, it becomes obvious (Table 1) that the 3-year MI-incidence rate is markedly increased with age from 2.0 new events in 40– to 44-year-old subjects up to 17.8 cases/1000 participants in persons aged 55 to 59 years. In order to exclude the influence of age on the MI-incidence rate as a possible confounding factor for the relationships between other variables and the MI risk, the following evaluations were performed after suitable direct age adjustment.

The mean values of other investigated continuous variables in the incidence and reference group (Table 2) indicate that pronounced differences were found for total serum cholesterol. This is confirmed by univariate regression analyses which reveal a strong and statistically significant correlation for this variable to the MI-incidence rate. Comparatively weak and inconsistent, but positive relationships to the MI risk are also evident for serum triglycerides (measured postprandial concentrations as well as calculated fasting values), systolic blood pressure and blood glucose level, whereas body mass index, diastolic blood pressure, and the serum level of uric acid do not seem to exert any influence (Table 2).

These results are confirmed by the incidence rates of MI (MI cases per 1000 participants during the 3-year observation period) in subgroups with and without various attributes (Table 3). Obviously total serum cholesterol again exerts pronounced influence: According to the age-adjusted odds ratio subjects with cholesterol levels equal to or above 245 mg/dl had a 3.5-fold increased MI risk as compared to persons below this value. A similar 3.2-fold increase of MI risk is evident for persons with a positive family history of MI. Comparatively weak but significant increases of the MI risk (odds ratios around 2.0) were found for hypertensive vs normotensive persons, for smokers vs nonsmokers, and for hypertriglyceridemic vs normotriglyceridemic subjects (according to measured postprandial concentrations as well as calculated fasting values). Persons with a regular physical activity reduce their risk approximately by one-half as compared to those preferring a more sedentary lifestyle. An even more pronounced decrease in MI risk was found for persons who drink alcohol at least occasionally as compared to subjects who drink alcohol almost never. No significant differences in MI-incidence rates were seen between diabetics vs nondiabetics and between overweight persons vs those with normal weight.

In accordance with pathophysiological concepts, we found an even more pronounced relationship to the MI risk for LDL-bound choles-

Table 2. Age-adjusted mean values and standard deviations of continuous variables in persons who suffered myocardial infarction during a 3-year observation period (MI+) and those who remained free of heart or vascular diseases (MI-0). Regression coefficients are derived from univariate logistic regression analyses according to Cox [4]

Variable	Mean (SD)		*P* value (*t*-test)	Univariate regression analysis	
	MI+ ($n = 4980$)	MI-0 ($n = 40$)		Regression coefficient	*P* value
Body mass index (kg/m^2)	26 (3)	26 (3)	NS	–	NS
RR systolic (mmHg)	135 (18)	131 (15)	NS	0.067	*
RR diastolic (mmHg)	87 (8)	86 (9)	NS	–	NS
Glucose (mg/dl)	111 (32)	102 (29)	*	0.066	*
Uric acid (mg/dl)	5.8 (5)	5.9 (6)	NS	–	NS
Cholesterol (mg/dl)	261 (39)	226 (40)	***	0.197	***
Triglycerides (mg/dl)	173 (74)	150 (79)	*	0.034	NS

NS = not significant; * = $P < 0.05$; ** = $P < 0.01$; *** = $P = 0.001$

Table 3. Age-adjusted incidence rates of myocardial infarction (incidence cases per 1000 participants during 3 years of observation) in subjects with (AB+) or without (AB−) various attributes. The age-adjusted odds ratios indicate the relative increase or decrease of MI risk in AB+ as compared to AB− subjects

Attribute (AB) (*n*: AB−/AB+)	MI incidence rates in AB− subjects	MI incidence rates in AB+ subjects	Age-adjusted odds ratio	*P* value
Family history MI (*n*: 4571/449)	7.0	17.8	3.2	**
Hypertension (*n*: 2545/2475)	6.8	12.6	2.1	*
Diabetes mellitus (*n*: 3869/1151)	7.0	11.3	1.5	NS
Overweight (*n*: 1726/3294)	4.6	9.7	1.6	NS
Smoking (*n*: 3243/1777)	6.1	11.3	1.9	*
Alcohol+ (*n*: 563/4457)	16.0	7.0	0.4	*
Sports+ (*n*: 3037/1983)	10.2	4.5	0.5	NS
Cholesterol ≥245 mg/dl (*n*: 3552/1468)	4.5	16.4	3.5	***
Triglycerides ≥200 mg/dl (*n*: 4016/1004)	6.4	14.0	2.3	*

NS = not significant; * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$

terol than for total cholesterol: LDL-cholesterol (LDL-C) showed a similar strong relationship to the MI-incidence rate in univariate regression analyses and more pronounced differences in the mean values of incidence and reference subjects (Table 4). HDL-bound cholesterol seems to be a component which might be inversely associated with the MI risk. It reveals higher mean values in the reference as compared to the incidence group and a negative regression coefficient with the MI-incidence rate (Table 4). However, these data are less impressive than those for LDL-cholesterol. No significant differences in mean values and no relationship to the MI-incidence rate according to univariate regression analyses can be seen for VLDL-cholesterol (Table 4).

Apo-A1, the main protein component of HDL reveals very similar relationships to the MI risk as its corresponding lipoprotein HDL. Apo-B, the main protein of LDL, but also present in VLDL, is positively related to he MI risk. This correlation however is weaker than that for LDL-cholesterol (Table 4).

Using threshold values for lipid, lipoprotein, and apoprotein parameters which are derived from a previous GRIPS case control project [22] we found pronounced differences for the MI-incidence rate between subjects with normal and pathological levels of these various variables (Table 5). This is especially true for LDL-cholesterol: the odds ratio indicates that subjects with LDL-cholesterol levels equal to or above 170 mg/dl have an almost six fold increased MI risk as compared to persons with LDL-cholestrol below this value. Decreased HDL-cholesterol levels below 35 mg/dl are associated with a 2.8 fold increase in MI risk. Despite the fact that VLDL-cholesterol revealed no significant univariate relationship to the MI-incidence rate, subjects with serum levels above 30 mg/dl seem to be at a 2.3-fold increased MI risk as compared to persons with lower VLDL-cholesterol concentrations. Apo-B and Apo-A1

Table 4. Age-adjusted mean values and standard deviations of lipid, lipoprotein, and apoprotein parameters (mg/dl) in persons who suffered myocardial infarction during a 3-year observation period (MI+) and those who remained free of heart or vascular diseases (MI-0). Regression coefficients are derived from univariate logistic regression analyses according to Cox [4]

Variable	Mean (SD) MI+	Mean (SD) MI-0	*P* value (*t*-test)	Univariate Regression analysis Regression coefficient	*P* value
Total cholesterol	261 (39)	226 (40)	***	0.197	***
Triglycerides	173 (74)	150 (79)	*	0.034	NS
LDL-cholesterol	178 (30)	144 (33)	***	0.248	***
VLDL-cholesterol	27 (15)	24 (17)	NS	0.026	NS
HDL-cholesterol	46 (9)	49 (12)	*	−0.09	*
Apo B	125 (21)	108 (21)	***	0.195	***
Apo A1	105 (20)	114 (25)	*	−0.09	*
LDL/HDL-cholesterol	4.1 (1.1)	3.2 (1.1)	***	0.238	***
Apo B/A1	1.2 (0.3)	1.0 (0.3)	***	0.155	***

NS = not significant; * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$

Table 5. Age-adjusted incidence rats of myocardial infarction (incidence cases per 1000 participants during 3 years of observation) in subjects with (AB+) or without (AB−) pathologic values of lipid, lipoprotein, and apoprotein parameters. The age-adjusted odds ratios indicate the relative increase of MI risk in AB+ as compared to AB− subjects

Attribute (AB) (n: AB−/AB+)	in subjects	Age-adjusted MI incidence rates Age-adjusted AB−	AB+	odds ratio	P value
Total cholesterol (n: 3552/1468)	≥245 mg/dl	4.5	16.4	3.5	***
Triglycerides (n: 4016/1004)	≥200 mg/dl	6.4	14.0	2.3	*
LDL-cholesterol (n: 4028/992)	≥170 mg/dl	4.0	24.2	5.7	***
VLDL-cholesterol (n: 3825/1195)	≥ 30 mg/dl	6.3	13.5	2.3	*
HDL-cholesterol (n: 4415/605)	< 35 mg/dl	6.6	17.8	2.8	**
Apo B (n: 4367/383)	≥140 mg/dl	6.0	31.3	5.2	***
Apo A1 (n: 3061/1959)	<105 mg/dl	6.4	10.3	1.5	NS
LDL/HDL-cholesterol (n: 4066/952)	≥4.0	5.2	20.0	3.8	***
Apo B/A1 (n: 3347/1517)	≥1.1	4.6	15.8	3.8	***

NS = not significant; * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$

Table 6. Number of MI incidence cases and MI incidence rates (incidence cases per 1000 participants during 3 years of observation) in various subgroups stratified for LDL-cholesterol

LDL-cholesterol (mg/dl)	n	Age-adjusted MI incidence rates
<120	1129	0.9
120–139	1245	5.6
140–159	1148	5.2
160–169	476	4.2
170–189	587	17.0
190–199	146	27.4
≥200	289	34.6

Table 7. Discrimination between persons who developed myocardial infarction (MI+) and those who remained healthy (MI-0) during a 3-year observation period (1982–1984) according to various screening levels of LDL-cholesterol (mg/dl): sensitivity (%), specificity (%), and positive predictive values (%)

LDL-cholesterol screening levels (SL)	Sensitivity (MI+ > SL)	Specificity (MI-0 < SL)	Positive predictive value
120	98	23	1.0
140	80	48	1.2
170	60	80	2.4
180	43	87	2.6
190	35	92	3.5

again show similar but substantially weaker associations with the MI risk as compared to their corresponding lipoproteins, LDL or HDL, respectively.

In this study LDL-cholesterol was not only most strongly associated with the MI-incidence rate, but it also revealed a dose-response relationship with this disease (Table 6). It is evident that MI risk is negligible at LDL-cholesterol values below 120 mg/dl. If LDL-cholesterol exceeds 120 mg/dl the 3-year incidence rate increases to about five new events per 1000 subjects and remains rather constant upt to the range of 170 mg/dl. If LDL-cholesterol exceeds 170 mg/dl the MI-incidence rate rises three fold to 17/1000. A further two fold increase up to approximately 30/1000 is evident in persons with LDL-cholesterol levels equal to or above 190 mg/dl. From this level onwards the MI-incidence rate rises continuously with the LDL-cholesterol values.

With regard to practical purposes it is of major importance to focus on sensitivity, specificity, and the positive predictive value of a parameter. In the present study this can be achieved by assuming various LDL-cholesterol concentrations as screening levels for the discrimination between persons who developed MI and those who remained healthy during the 3-year observation period (Table 7). A screening level of 120 mg/dl LDL-cholesterol provides excellent sensitivity (98%) but poor specificity (23%) and only a low positive predictive value (1%; Table 6). Using 170 mg/dl as a screening level decreases sensitivity to 60% but increases specificity to 80% and reveals a positive predictive value of 2.4%. A screening level of 190 mg/dl provides a rather poor sensitivity (35%) but excellent specificity (92%) and a positive predictive value of 3.5% which is markedly increased as compared to that obtained at the lower threshold values. If HDL-cholesterol (screening level 35 mg/dl) is used comparatively to discriminate incidence and reference subjects a specificity of 88%, a sensitivity of 28%, and a positive predictive value of 1.8% are obtained.

Table 8. Incidence rates of myocardial infarction (incidence cases per 1000 participants during 3 years of observation) in various subgroups stratified by LDL-cholesterol. The data are given separately for smokers and nonsmokers

LDL-cholesterol (mg/dl)	Nonsmokers		Smokers	
	n	MI rate	*n*	MI rate
<140	1586	3.8	788	2.5
140–169	1058	3.8	562	7.1
170–189	368	8.2	219	32.0
≥190	231	30.3	204	34.3

Discussion

The first results from the GRIPS incidence project as described here reveal a predominant relationship between LDL-cholesterol and MI risk. This was much more pronounced then that of other investigated variables and independent of age. According to the present data one might speculate that LDL-cholesterol values of 120 and 190 mg/dl merit special interest with regard to the discrimination of persons at various levels of MI risk: LDL-cholesterol concentrations below 120 mg/dl seem to indicate low, while values above 190 mg/dl seem to indicate high MI risk. LDL-concentrations between 120 and 190 mg/dl indicate a critical concentration. In this range of LDL-cholesterol, other potential risk factors which are rather weak predictors in the total population (such as hypertension, diabetes, smoking, or low HDL-cholesterol) might be of increased "additive" importance for the individual MI risk [21].

A major aim of our future GRIPS evaluations will be to test this "additive risk factor" hypothesis. Preliminary data along this line (Table 8) may indicate the potential additive risk for smoking. Smokers and nonsmokers with LDL-cholesterol levels below 140 mg/dl have an equally low MI risk, while for LDL-cholesterol levels between 140 and 190 mg/dl smokers obviously have a 2 to 4-fold higher MI risk as compared to nonsmokers. Beyond 190 mg/dl LDL-cholesterol, the risk of smokers and nonsmokers again becomes similar, i.e., equally high.

Taken together the present 3-year follow-up data of the GRIPS incidence project indicate that LDL-cholesterol merits special interest as an important variable in a future diagnostic schedule for early recognition of persons at highrisk. Other variables, however, also have to be taken into consideration for such a diagnostic scheme, either as independent or as additive, LDL-accelerating or inhibiting factors.

Our findings with regard to the close relationship of LDL-cholesterol to MI risk are in good agreement with our present pathophysiological knowledge of the impact of lipid metabolism in atherogenesis [3, 9, 19] and with results from other incidence studies and more important with intervention trials [13, 14]. However, there are also contradictory epidemiological data or interpretations [2, 10, 16] suggesting that HDL-cholesterol might be as good as or even better than LDL-cholesterol in predicting MI risk. Such discrepancies might be due to the fact, that in most epidemiologic studies LDL-cholesterol if quantified at all was calculated using the so-called Friedewald formula [8]. This procedure has proved to be rather poor in precision and accuracy as compared to a direct measurement of LDL-cholesterol [5, 25], which was used in the GRIPS study.

Because our data presented here are based only on 40 new events of myocardial infarction in 3 years, it is too early to make any definite statement or to claim general validity other than to underline the great importance of the analytical technology used in epidemiological studies. Results from the future GRIPS follow-up examinations will be based on an increased number of incidence cases and thereby provide stronger and more reliable results.

The GRIPS study is supported by the Bundesministerium für Forschung und Technologie of the Federal Republic of Germany, the Forschungsrat Rauchen und Gesundheit, and the Verband der Lebensversicherungsunternehmen Deutschlands e.V.

References

1. American Heart Association (1985) 1986 Heart Facts. Am Heart Assoc, Dallas, USA
2. Assmann G, Schulte H. (1986) Procam Trial. Panscientia, Zürich
3. Brown MS, Goldstein JL (1986) A receptor mediated pathway for cholesterol homeostasis. Science 232:34–47
4. Cox DR (1970) Analysis of binary data. Methuen, London
5. Cremer P, Seidel D, Wieland H (1985) Quantitative Lipoproteinelektrophorese: Ihre routinemäßige Anwendung im Vergleich mit anderen Verfahren zur differenzierten Untersuchung des Fettstoffwechsels. Lab Med 9:39–51
6. Cremer P, Kreuzer H, Seidel D (1986) Lipoproteine als Risikoindikatoren der koronaren Herzkrankheit bei Frauen. Med Klinik 81:693–701
7. Cremer P, Wieland H, Seidel D (1988) Göttinger Risiko-, Inzidenz- und Prävalenzstudie (GRIPS): Aufbau und bisherige Ergebnisse. Münch Med Wochenschr 130:268–275
8. Friedewald WF, Levy RI, Fredrickson DS (1972) Estimation of LDL-cholesterol concentration without use of the preparative ultracentrifuge. Clin Chem 8:499–502
9. Goldstein JL, Brown MS (1977) Atherosclerosis: the low-density lipoprotein receptor hypothesis. Metabolism 26:1257–1268

10. Gordon T, Gastelli WP, Hjortland MC, Kannel WB, Dawber TR (1977) High density lipoprotein as a protective factor against coronary heart disease. Am J Med 62:707–714
11. Hopkins PN, WIlliams RR (1981) Survey of 246 suggested coronary risk factors. Atherosclerosis 40:1–52
12. Kannel WB, Schatzkin A (1984) Risk factor analysis. Progr Cardiovasc Dis 26:309–332
13. Kannel WB, Doyle JT, Ostfeld AM, Jenkins D, Kuller L, Podell R, Stamler J (1984) Optimal resources for primary prevention of atherosclerotic diseases. Circulation 29:157A–205A
14. Lipid Research Clinics Program (1984) The lipid research clinics coronary primary prevention trial results. JAMA 251:351–374
15. Manuck SB, Kaplan JR, Matthews KA (1986) Behavioral antecedents of coronary heart disease and atherosclerosis. Arteriosclerosis 6:2–14
16. Miller NE, Fjorde OH, Thelle DS, Mjos OD (1977) The Tromsø Heart Study. High density lipoprotein and coronary heart disease: a prospective case control Study. Lancet I:965–967
17. Pocock SJ, Shaper AG; Philips AN, Walker M, Whithehead TP (1986) High density lipoprotein cholesterol is not a major risk factor for ischemic heart disease in British men. Br Med J 292:515–519
18. Rifkind BM, Segal P (1983) Lipid Research Clinics Program reference values for hyperlipidemia and hypolipidemia. JAMA 250:1869–1872
19. Ross R (1986) The pathogenesis of artherosclerosis – an update. N Engl J Med 34:488–500
20. Ruderman NB, Haudenschild CH (1984) Diabetes as an atherogenic factor. Progr Cardiovasc Dis 26:373–411
21. Seidel D (1986) Rauchen als Risikofaktor? Verh Dtsch Ges Inn Med 92:320–324
22. Seidel D, Cremer P (1986) Guidelines for the clinical evaluation of lipoprotein profiles. A first report from the Göttingen Risk, Incidence and Prevalence Study. In: Gotto AM, Paoletti R (eds) Atherosclerosis Reviews, vol 14. Raven Press, New York, pp 61–90
23. Seidel D, Cremer P, Elster H. Weise M, Wieland H (1984) Influence of smoking on the plasma lipoprotein profile. Klin Wochenschr (Suppl II) 62:18–27
24. Seidel D, Cremer P, Thiery J (1985) Plasmalipoproteine und Artherosklerose. Internistische Welt 8:114–124; 159–165
25. Seidel D, Armstrong VW, Cremer P (1987) Die Bestimmung des LDL- bzw. β-Cholesterin im Serum: Klinische Bedeutung und methodische Möglichkeiten. Internist 28:606–614
26. Weinstock N, Bartholome M, Seidel D (1982) Determiniation of apolipoprotein A1 by kinetic nephelometry. Biochim Biophys Acta 663:279–288
27. Wieland H, Seidel D (1983) Quantitative lipoprotein electrophoresis. In: Lewis LA (ed) Handbook of electrophoresis, vol 3. CRC Press, Boca Raton, pp 83–102
28. Wieland H, Seidel D (1983) A simple and specific technique for precipitation of lowdensity liproproteins. J Lip Res 24:904–909
29. Wieland H, Cremer P, Seidel D (1983) Determination of apolipoprotein B by kinetic (rate) nephelometry. J Lip Res 23:893–902
30. WHO Expert Committee (1981) Prevention of coronary heart disease. In. WHO (ed) Technical Report Series, no 647. WHO, Genf
31. Zach M (1987) Möglichkeiten der Lipid-, Lipoprotein- und Apoproteinanalytik im Postprandialstadium. Dissertation, Georg-August-Universität, Göttingen

Received: October 26, 1987
Returned for revision: Jannuary 12, 1988
Accepted: March 12, 1988

Dr. P. Cremer
Abteilung für Klinische Chemie
Universität Göttingen
Robert-Koch-Str. 40
D-3400 Göttingen