Lipoproteins and Cardiovascular Risk—from Genetics to CHD Prevention

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Dyslipidemia is said to be present when lipid or lipoprotein levels lie within a range which is known from epidemiological studies to be associated with secondary complications, in particular atherosclerosis of the coronary arteries, or when a lipid or lipoprotein grossly deviates from the norm as in abetalipoproteinemia, hypobetalipoproteinemia or the HDL deficiency syndromes. In most cases, dyslipidemia is due not to a single genetic or environmental factor, but to a combination of the effects of several genes of small effect (polygenes) and environment. In other cases, however, dyslipidemia is caused by a mutation in a single gene of large effect. In such cases, the extent and nature of the phenotype depends primarily on the identity of the gene involved, but is also modulated to an important degree by the nature of the mutation and the genetic and environmental background against which this mutation occurs. In addition, many cases of hyperlipidemia are secondary to other disorders such as hypothyroidism or renal dysfunction. Such disorders may also unmask or exacerbate a genetic lipoprotein disorder. Examples of the latter are the unmasking of type III hyperlipidemia by diabetes mellitus or the exacerbation of familial hypercholesterolemia by hypothyroidism. J Atheroscler Thromb, 1997; 4: 51-58.

Key words: Dyslipidemia, Lipoprotein, Coronary heart disease

Genetic Epidemiology of Dyslipidemia

Only a minor part of the genetic component of the population variance in lipid parameters can be explained by disorders in single genes of large effect. The bulk of variation is due to a number of genes (polygenes), each of which accounts for only a small part of overall genetic variance. The challenge of current genetics is to unravel these complex genetic effects. A strategic approaches to achieve this aim is outlined in Fig. 1. In this approach, candidate genes are first identified based on biochemical knowledge of so-called "intermediate" phenotypes (e.g. raised LDL cholesterol, homocysteine or fibrinogen levels). These genes are then screened for genetic variation and the phenotypic effects of the variant are assessed in vivo and in vitro. The technique of pool-screening is very useful in rapidly screening populations of interest for presence or enrichment of a rare mutations in genes of interest (1). Using this technique, a carrier can be detected in a pool consisting of DNA samples from several thousand individuals. By selecting appropriate populations (e.g. patients with premature myocardial infarction or very elderly individuals) an association of a particular DNA variant with coronary artery disease or decreased (or increased) life expectancy can be detected. Using this strategy, differences in the frequencies of a number of genes affecting lipid metabolism between a control population from the Münster Heart Study (PROCAM) and patients with coronary artery disease before the age of 60 years. For example, in the coronary artery disease patients, the Arg3500Gln mutation in apolipoprotein B, which is responsible for familial defective apolipoprotein B, was found to be three times as common, while the Argf58Cys polymorphism in apolipoprotein E (E-2 allele) was found to be slightly less common (odds ration 0.8) than in the Münster Heart Study controls [Dr. Harald Funke, unpublished observation].
Dyslipidemia and CHD Risk

For many years, epidemiological evidence has been accumulating of a link between high LDL cholesterol, low HDL cholesterol, and coronary heart disease (2-7). More recently, solid support for the causal nature of this link has been provided by large well-conducted trials showing that lowering LDL, both in patients with no history of angina pectoris (primary prevention) (8), and in patients with established CHD (secondary prevention) (9, 10), reduces the incidence of fresh coronary events including coronary death. In the 4S study (secondary prevention) (10), total mortality was also reduced significantly. In addition, evidence from angiographic trials has convincingly shown that LDL cholesterol lowering may hinder progression and perhaps even cause regression of coronary atherosclerosis (11-27). Evidence relating to the role of triglycerides in CHD has been more complex. In the MOnster Heart Study, however, there was clear evidence of increased CHD risk in persons with a combination of high triglyceride and low HDL cholesterol (28). In addition, it is not known whether the observed relationship between triglycerides and CHD is direct or indirect. Hypertriglyceridemia may contribute to CHD via a direct atherogenic effect of VLDL. Alternatively, hypertriglyceridemia may be associated with other atherogenic lipoprotein profiles such as low HDL cholesterol, the presence of small, dense LDL, or the presence of large apo E-enriched VLDL particles.

Global Risk

An important step in recent years has been the development of the concept of global risk. Treatment decisions should almost never be based solely on lipid levels but must also take into account other risk factors. One of the most significant long term achievements of the Münster Heart Study has been the development of an algorithm for calculation of global risk in middle-aged men, which takes into account the independent risk factors age, systolic blood pressure, LDL cholesterol, HDL cholesterol, triglycerides, cigarette smoking, presence of diabetes mellitus, and family history of myocardial infarction (Table 1) (28).

Treatment Goals in Hyperlipidemia

In all three recent major intervention trials (4S, WOSCOPS, CARE), cholesterol lowering has been achieved by statins, drugs which lower LDL cholesterol and triglyceride and increase HDL cholesterol and which have become the drugs of choice for treatment of hypercholesterolemia. The availability of these drugs has allowed persistent lowering of LDL cholesterol of the order of 30% with commonly used doses. In the near future, statins of greater efficacy will be available which will allow even greater reductions in LDL cholesterol, effectively permitting titration to any desired level in most patients. This possibility has reopened the questions of treatment goals in LDL cholesterol lowering. Should absolute target LDL levels be defined, or is the important issue the extent by which LDL is lowered? Data from epidemiological studies including the Münster Heart Study indicates a log-linear relationship between the level of LDL cholesterol and CHD risk (Fig. 2). Thus, when relative risk of CHD is plotted against cholesterol, a straight line relationship is obtained (Fig. 3). However, the effect of lowering cholesterol on CHD risk depends on a person's global risk of CHD. Thus, as shown in Fig. 3, a person with a total cholesterol of 280 mg/dl but no other risk factors ("average risk") may have the same CHD risk as a person with a total cholesterol of 200 mg/dl but with other risk factors ("high risk"). In both cases, prolonged lowering of cholesterol by 40 mg/dl is associated with an approximate halving of CHD risk. Data from large scale intervention trials and indicate that this log-linear relationship between LDL cholesterol and CHD risk also applies to levels achieved by treatment (diet, drugs) and that 6 years of cholesterol reduction produces an approximate 30% reduction in CHD risk (8-10).

Since the relationship between statin dosage and cholesterol lowering is log-linear, a higher dose of statin (or a statin with higher efficacy) is necessary to reduce cholesterol in the high risk individual from for example 195 mg/dl to 155 mg/dl than to reduce cholesterol in the average risk individual from 310 mg/dl to 270 mg/dl (Fig. 3). In both cases this would be expected to produce an approximate halving in the absolute coronary risk. Thus different doses of statin may be required to produce the same degree of risk reduction, depending on global risk (including LDL cholesterol) at baseline. Studies in China and Japan indicate that the log-linear relationship between cholesterol and CHD risk is maintained down to values as low as 120 mg/dl and, probably, even 80 mg/dl (Fig. 4). Even at these extremely low levels, there is no evidence

<p>| Table 1. Coefficients of the multiple logistic function calculated in the Münster Heart Study |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
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<tbody>
<tr>
<td>Age in yrs</td>
<td>+0.1001</td>
</tr>
<tr>
<td>Systolic blood pressure in mmHg</td>
<td>+0.0118</td>
</tr>
<tr>
<td>LDL cholesterol in mg/dl</td>
<td>+0.0152</td>
</tr>
<tr>
<td>HDL cholesterol in mg/dl</td>
<td>-0.0450</td>
</tr>
<tr>
<td>In (triglycerides in mg/dl)</td>
<td>+0.3346</td>
</tr>
<tr>
<td>Cigarette smoking, 0 = no, 1 = yes</td>
<td>+0.0266</td>
</tr>
<tr>
<td>Diabetes mellitus, 0 = no, 1 = yes</td>
<td>+0.4016</td>
</tr>
<tr>
<td>Family history of myocardial infarction, 0 = no, 1 = yes</td>
<td>+0.4193</td>
</tr>
<tr>
<td>Angina pectoris, 0 = no, 1 = yes</td>
<td>+1.3190</td>
</tr>
<tr>
<td>Incidence of major coronary event in 8 years = 1/[1-exp(-y)] with y = -12.3199+ Σ (variable×coefficient)</td>
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of a threshold below which the relationship no longer holds. The relevance of these findings to clinical practice, however, remains to be determined.

Several epidemiological studies have shown a U or J-shaped relationship between total and LDL-cholesterol and all-cause mortality with an excess of deaths primarily among men with total cholesterol levels below a cut-off of approximately 200 mg/dl or LDL cholesterol levels below.
Münster Heart Study (PROCAM)

Expected number of coronary events per 1,000 men in 8 yrs

Fig. 2. Münster Heart Study (PROCAM), 8-year risk of a coronary event according to LDL cholesterol in middle-aged men with angina pectoris (246 events, 4501 men aged 40-65 years, results standardized to age 50 years). Statins produce a similar proportional lowering of LDL cholesterol (shown beneath X axis) irrespective of the baseline LDL cholesterol level (X axis). Thus the absolute reduction in LDL cholesterol is lower for a given baseline LDL cholesterol. In addition, because of the log-linear relationship between LDL cholesterol and CHD risk, the absolute difference in CHD risk associated with the same absolute difference in LDL-cholesterol is greater at higher baseline levels of LDL cholesterol. For these reasons, all other things (pre-existing CHD, other risk factors) being equal, a prolonged 30% difference in baseline LDL cholesterol of 175 mg/dl vs. 250 mg/dl is associated with almost 4 times as much benefit as a prolonged 30% difference of 125 mg/dl vs. 175 mg/dl.

Fig. 3. Diagram to indicate that similar proportional and absolute reductions in CHD risk are expected with the same absolute cholesterol reductions in individuals at the same absolute risk (33, 60).
a cut-off of approximately 130 mg/dl, in both community-based (5, 29-43) and occupational (44-53) cohorts. This finding is not universal, however, and was not detected in a number of studies performed in younger (54-57), and in healthy (58) or non-smoking (59) middle-aged cohorts. Data from the Münster Heart Study clearly shows that this increase in mortality at low cholesterol levels was seen in smokers only and was explained by an increase in death due to smoking-related cancers (Fig. 5). In the CARE study, no benefit was seen in lowering LDL cholesterols below 125 mg/dl at baseline. However, this result may reflect the play of chance in a retrospective analysis of a small subgroup. From a theoretical point of view there is no reason to expect a cutoff for any level of LDL cholesterol within this range. However, the benefits of treatment at low levels of cholesterol may become so small that they are outweighed by side-effects of treatment and by the large number of persons who have to be treated in order to prevent one event. Nevertheless, in persons at high risk, treatment of LDL cholesterols of 125 mg/dl may be indicated.

Treatment goals for LDL cholesterol in the secondary prevention of CHD: absolute levels or percentage lowering? Although an answer cannot be given which applies to every patient, a consensus view may be formulated:

(a) In patients at high global risk of CHD (including patients with established CHD), LDL cholesterol should be lowered as far as possible. If initial levels are markedly elevated this is likely to require combination therapy with diet and drugs.

(b) The benefits to be expected from lowering LDL cholesterol levels of below 125 mg/dl in patients with a history of MI may be small. However, patients with other risk factors in addition to a history of MI (e.g. diabetes, high blood pressure, overweight) may benefit to a worthwhile extent from LDL cholesterol lowering. More research is needed to conclusively answer this question and treatment decisions in such patients must currently be made on an individual basis.

(c) Since the important factor in determining a person’s chance of developing CHD is his or her global risk, and not just the LDL cholesterol level, every attempt should be made to modify other adverse variables by losing excess weight, giving up smoking, taking exercise etc. Moreover, since these risk factors interact in an approximately multiplicative rather than an additive fashion, small changes in a number or risk variable may produce a disproportionately large overall beneficial effect.

Fig. 4. No “threshold” below Western cholesterol normal range. Shanghai prospective study in low cholesterol population of 9000 urban Chinese followed for 8-13 years (61). Risk is plotted on a doubling (i.e. log) scale. The “usual” cholesterol was derived from the baseline cholesterol by correction for “regression dilution” bias.

Fig. 5. Age standardized total, cancer-related and CHD death according to quintiles of LDL cholesterol/HDL cholesterol ratio in male smokers (5a) and nonsmokers (5b) aged 35 to 65 years in the Münster Heart Study (PROCAM). Population = number of men on whom data were available as shown, total = total number of deaths, cancer = number of deaths due to cancer, CHD = number of deaths due to coronary heart disease.
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