HIGH DENSITY LIPOPROTEINS AND ATHEROSCLEROSIS II

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Proceedings of the Second International Symposium on High Density Lipoproteins and Atherosclerosis held in Leeds Castle, Maidstone, England on October 6–8, 1988.

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FOREWORD

In 1977 the first Workshop on High Density Lipoproteins and Atherosclerosis was held at Argenteuil, Waterloo, Belgium, under the auspices of the Foundation Cardiologique Princesse Liliane. At this meeting epidemiologists, biochemists, cell biologists and cardiologists from several countries met to discuss the emerging evidence for a function of high density lipoprotein (HDL) in reverse cholesterol transport and protection against atherogenesis. This was then a young and developing research area, but one with exciting prospects for the prevention of coronary disease. Since then enormous progress has been made. The epidemiologic basis for the association of low HDL cholesterol levels with increased coronary disease risk in several populations is now solid, and clinical trials have begun to provide evidence that drug-induced increases in HDL can contribute substantially to the avoidance of coronary disease. New biochemical approaches are clarifying the role of HDL in reverse cholesterol transport, and the metabolic determinants of HDL cholesterol concentration. And molecular geneticists are exploring the nature of its association with atherosclerosis by the powerful techniques at their disposal. These developments and others were discussed at the Second International Workshop on High Density Lipoproteins and Atherosclerosis, when forty-five scientists, from ten countries and representing all pertinent disciplines, met to present their most recent findings. It was a stimulating and productive event. The papers that were delivered are summarized in this volume.

Norman E. Miller, M.D., D.Sc.

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RECENT EPIDEMIOLOGY OF HDL

High density lipoproteins and atherosclerosis II. N.E. Miller.

HDL AND CORONARY HEART DISEASE: A COMPARISON OF RECENT EPIDEMIOLOGIC AND CLINICAL TRIAL RESULTS

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INTRODUCTION

Although the hypothesis that high density lipoprotein (HDL) may play a protective role in the development of atherosclerotic coronary heart disease (CHD) was first suggested more than 35 years ago, it is only in the past decade that we have begun to gain a real understanding of the biochemistry and metabolism of HDL, its genetic and environmental determinants, and its association with prevalence and future incidence of CHD manifestations. The present article will focus on the findings of prospective epidemiologic studies that have addressed the HDL-CHD relationship,[1-12] with particular attention to a standardized analysis of four large American studies.[1] The relationship of cholestyramine-associated increases in HDL cholesterol and subsequent CHD incidence in the Lipid Research Clinics (LRC) Coronary Primary Prevention Trial (CPPT)[4] will also be discussed.

EPIDEMIOLOGIC STUDIES

The relationship of HDL cholesterol levels and subsequent CHD incidence has been studied prospectively in North America, Northern Europe and Israel (Table 1). Seven of the 12 studies listed reported significant inverse associations. Among three studies reporting non-significant inverse trends, the HDL-CHD association in the British Regional Heart Study (BRHS) was significant in univariate analysis, but not after adjustment for other risk factors.[6] HDL cholesterol levels were completely unrelated to CHD incidence only in the Swedish study (which was small and possibly confounded by use of lipid-lowering drugs)[9] and in the USSR[11]. The USSR study was also noteworthy in that a significant positive association of HDL-cholesterol levels and non-cardiovascular mortality was observed; thus, high HDL cholesterol levels appeared to have a net detrimental effect on all-cause mortality[11]. Among seven other studies in which non-cardiovascular deaths were analyzed, only the Minnesota cohort showed a similar (non-significant) trend, which was offset by an opposing trend for cardiovascular mortality.[3]

The failure of the inverse association of HDL cholesterol and CHD incidence in the BRHS to withstand covariance adjustment, a phenomenon not seen in other studies, prompted us to re-examine the experience of four large

TABLE 1

PROSPECTIVE EPIDEMIOLOGIC STUDIES OF HDL CHOLESTEROL

Study (Ref).	Cardiovascular Disease	Non-Cardiovascular Mortality
North America		
Framingham[1,2]	Significant inverse trend.	No trend.
Minnesota[3]	Inverse trend (p = .08).	Positive trend (p = .15).
LRC Follow-Up[1]	Significant inverse trend.	No trend.
LRC-CPPT[1,4]	Significant inverse trend.	No trend.
MRFIT[1,5]	Significant inverse trend.	No trend.
Great Britain		
BRHS[6]	Inverse trend (p = .0004; .21 after covariance adjustment).	Not reported.
Scandinavia		
Tromso[7]	Significant inverse trend.	Not reported.
Oslo[8]	Significant inverse trend.	Not reported.
Sweden[9]	No trend.	Not reported.
Finland[10]	Weak inverse trend (p = .27).	No trend.
USSR		
LRC Follow-Up[11]	No trend.	Significant positive trend.
Israel		
Israeli IHD[12]	Significant inverse trend.	No trend.

American cohorts: the Framingham Heart Study (FHS), the LRC Mortality Follow-Up Study (LRCF), and the control groups of two randomized trials, the CPPT and the Multiple Risk Factor Intervention Trial (MRFIT). Although these cohorts differed in many important respects (e.g., FHS subjects were all at least 49 years old, CPPT and MRFIT included only middle-aged men at high risk for CHD), the studies used similar methods for data collection and HDL cholesterol determination, and their statistical analysis could be standardized.[1]

We first classified each of the four male and two female cohorts according to HDL cholesterol levels as high (≥50 mg/dl [1.30 mM]), intermediate, or low (<40 mg/dl [1.04 mM]), and calculated the annual CHD incidence rate for subjects in each category (Figure 1). Within each cohort, CHD incidence tended to be highest in the low-HDL and lowest in the high-HDL subgroup. Note that CHD incidence rates should not be compared across studies without considering the differing risk factor profiles of each cohort. Similar trends (not shown) were observed for cardiovascular mortality.[1]

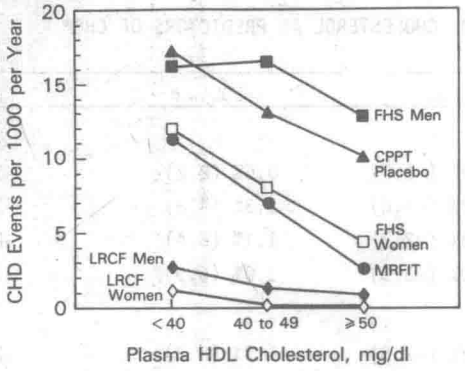

Fig. 1. Annual CHD incidence rates in low (<40 mg/dl), intermediate, and high- (≥50 mg/dl) HDL subgroups of six epidemiologic cohorts. The rates in LRCF men and women include only CHD deaths, since nonfatal events were not ascertained.

The trends seen in this simple univariate analysis were then quantified and adjusted for age, systolic blood pressure, cigarette smoking, body mass index, and LDL cholesterol by proportional hazards analysis.[1] The regression coefficients, each expressed as a percent increment (or decrement) in CHD risk corresponding to a 1 mg/dl (0.026 mM) increment in HDL cholesterol level, and their associated Z scores are given in Table 2. A hypothetical 1 mg/dl increment in HDL-C was associated with a CHD risk decrement of 1.9 to 4.2% in men and 3.2 to 3.7% in women. The coefficients for five of the six cohorts were statistically significant ($-Z > 1.96$). The lack of statistical significance in LRCF women (the lone exception) probably reflects inadequate statistical power (only 6 CHD deaths); their regression coefficient became statistically significant when other cardiovascular deaths were included in the analysis. Despite the differences among cohorts, the 95% confidence intervals of the regression coefficients all included the interval corresponding to a 1.9 to 2.9% decrement in CHD risk per 1 mg/dl increment in HDL cholesterol.[1]

It is interesting to compare the coefficients relating HDL and LDL cholesterol levels to CHD incidence in these same four studies (Table 2). A 1 mg/dl increment in HDL cholesterol was associated with the same decrement in CHD risk as a 2-4 mg/dl decrement in LDL cholesterol. Both associations were statistically significant in every cohort except LRCF women. However, the statistical evidence supporting the LDL-CHD relationship was slightly more compelling than that supporting the HDL-CHD relationship (i.e., the Z scores were generally somewhat larger).

TABLE 2

COMPARISON OF HDL AND LDL CHOLESTEROL AS PREDICTORS OF CHD*

Study	HDL	LDL	Ratio
Men			
FHS	-1.9% (-2.2)	0.6% (2.2)	-3.5
LRCF**	-4.2% (-3.6)	1.3% (4.8)	-3.3
CPPT	-2.3% (-2.8)	1.1% (5.4)	-2.2
MRFIT	-2.0% (-3.9)	1.0% (6.9)	-2.1
Women			
FHS	-3.2% (-2.5)	1.2% (3.3)	-2.7
LRCF**	-3.7% (-1.2)	1.0% (1.2)	-3.9

* Regression coefficients are expressed as % risk increment per 1 mg/dl (.026 mM) increment in HDL cholesterol level. Z-scores (the ratio of each coefficient and its standard error) are shown in parentheses.

** Results for CHD mortality are presented, since nonfatal CHD cases were not ascertained.

TABLE 3

ALTERNATIVE ESTIMATES OF REGRESSION COEFFICIENT RELATING HDL CHOLESTEROL AND CHD INCIDENCE IN MEN*

Study	Cholesterol Covariates				
	None	LDL	LDL, VLDL	NHDL	Total
FHS	-1.9	-1.9	-1.9	-1.6	-2.0
LRCF**	-2.7	-3.6	-3.4	-2.7	-3.3
CPPT	-3.0	-2.3	-2.1	-1.8	-2.8
MRFIT	-1.7	-2.0	-1.6	-1.1	-2.0
BRHS	——	——	——	-1.0	-2.0

* Regression coefficients are expressed as % risk increment per 1 mg/dl (.026 mM) Increment in HDL cholesterol level. All except those in the "None" column have been adjusted for age, cigarette smoking, systolic blood pressure and body mass index.

** Results for cardiovascular mortality are presented, since nonfatal CHD cases were not ascertained.

Since the BRHS investigators did not determine LDL cholesterol levels (blood samples were not drawn in the fasting state), their covariance adjustment substituted "non-HDL" (i.e., total minus HDL) for LDL cholesterol; the remaining covariates were unchanged. We explored the effects of this and other substitutions for LDL cholesterol in our analysis of the four American studies (Table 3).

When compared with the unadjusted model, adjustment for LDL cholesterol had little effect on the HDL-CHD association; it was strengthened in LRCF, weakened in CPPT, and essentially unchanged in FHS and MRFIT. Incorporating an additional term for VLDL cholesterol had no further effect. However, combining LDL and VLDL cholesterol into a single term, non-HDL (NHDL) cholesterol, consistently weakened the estimate of the HDL-CHD association. This effect was not observed in the algebraically equivalent model incorporating total cholesterol as a covariate. The total-cholesterol-adjusted regression coefficient for HDL in BRHS men was identical to that in FHS and MRFIT men and only slightly weaker than that in CPPT men. Moreover, its value (a 2% decrement in CHD risk per 1 mg/dl increment in HDL cholesterol) was consistent with the unadjusted and LDL-cholesterol-adjusted coefficients in American men. Thus, the apparent inconsistency of the British and American results appears to reflect not a qualitative difference between British and American men, but a difference in statistical models.

INTERVENTION DATA —— THE CPPT

Although there has not yet been a randomized trial of the specific hypothesis that raising low HDL cholesterol levels will reduce CHD risk, post hoc analysis of the active treatment groups of clinical trials using cholesterol-lowering agents with concomitant HDL-raising effects has yielded suggestive results. We used the proportional hazards model to relate baseline levels and changes (two-year averages) in HDL cholesterol to subsequent incidence of CHD during 7.4 years of treatment with cholestyramine (or placebo) in the CPPT.[4] The relationship of baseline cholesterol levels and CHD incidence was nearly twice as strong in the cholestyramine as in the placebo group; a 1 mg/dl increment in HDL cholesterol was associated with a 5.5% decrement in CHD risk ($p < .001$). In addition, each 1 mg/dl increase in HDL cholesterol during cholestyramine treatment was associated with a 4.4% decrease in CHD risk ($p < .05$). When the relationship of CHD risk to net post-treatment HDL cholesterol levels (i.e., baseline plus change) was analyzed, the difference in regression

coefficients between drug (-5.8%) and placebo (-3.2%) groups approached statistical significance (p = .06).

The implications of these results are illustrated graphically in Figure 2. The overall relative CHD risk of the cholestyramine (versus placebo) group in the CPPT was 0.81 —— i.e., a 19% risk reduction for the average participant with an HDL cholesterol level of 44.4 mg/dl at entry (B). However, because of the differing slopes of the curves relating baseline levels of HDL cholesterol to CHD risk in the two treatment groups, cholestyramine treated men with HDL cholesterol levels of 53.2 mg/dl (mean plus one standard deviation) at entry (C) experienced a 36% risk reduction, while men with HDL cholesterol levels of 35.6 mg/dl (mean minus one standard deviation) at entry (A) showed a 1% increase in CHD risk, relative to men with the same baseline HDL cholesterol levels who received placebo.

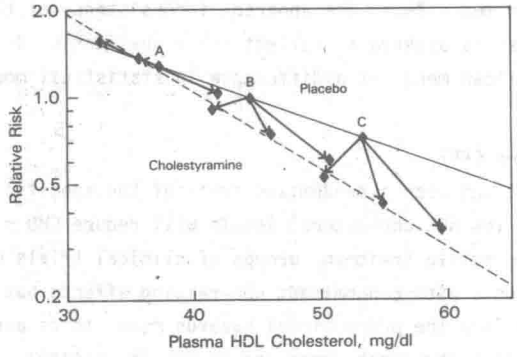

Fig. 2. Relationship of CHD risk to HDL cholesterol levels at entry and after treatment in the CPPT. Risk is plotted on a logarithmic scale and expressed relative to that of the average placebo-treated man. The solid and dashed lines represent the relationship of baseline HDL cholesterol levels to CHD risk in the placebo and cholestyramine groups. Points A, B, and C on the placebo curve represent hypothetical participants with HDL cholesterol levels one standard deviation (8.8 mg/dl) apart entering treatment. The arrows emanating from each of these three points represent the change in CHD risk when cholestyramine treatment is accompanied by a change in HDL cholesterol of -3.0, +1.6, and +6.2 mg/dl (values corresponding to the mean $\pm$ one standard deviation of the distribution of HDL cholesterol change).

These outcomes, which pertain to men experiencing the average HDL cholesterol increase (1.6 mg/dl) associated with cholestyramine treatment, were subject to modification by greater or lesser HDL changes. For example, among men with average (44.4 mg/dl) entry levels of HDL cholesterol (B), the CHD risk of those experiencing a 6.2 mg/dl increase in HDL cholesterol (i.e., the mean increase plus one standard deviation) fell by 34%, as compared with 1% in those experiencing a 3.0 mg/dl decrease in HDL cholesterol (i.e., the mean increase minus one standard deviation). Moreover, the effects of low (A) or high (C) entry levels of HDL cholesterol were mitigated or enhanced by changes in these levels during treatment. Men whose HDL cholesterol levels increased from 35.6 to 41.8 mg/dl during cholestyramine treatment experienced an 18% risk reduction, while those whose levels fell from 35.6 to 32.5 mg/dl experienced a 24% risk increase versus men in the placebo group with the same baseline levels. Men whose HDL cholesterol levels increased from 53.2 to 59.4 mg/dl during cholestyramine treatment experienced a 48% risk reduction, while those whose levels fell from 53.2 to 50.1 mg/dl experienced a 21% risk reduction.

CONCLUSIONS

During the past decade, epidemiologists have accumulated a mostly cohesive body of prospective observational evidence supporting an inverse relationship of HDL cholesterol levels and CHD incidence rates in industrialized countries. While this evidence is not as extensive as that supporting the cholesterol hypothesis, CHD incidence rates are predicted almost as well by low HDL as by high LDL cholesterol levels in studies that have examined both. A 1 mg/dl increment in HDL cholesterol is associated with the same CHD risk decrement as a 2-4 mg/dl decrement in LDL cholesterol. However, the benefit of raising low HDL (unlike lowering high LDL) cholesterol levels has not yet been confirmed by randomized trials. Thus, specific clinical interventions to raise low HDL cholesterol levels cannot yet be recommended with confidence.

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