LDL Cholesterol as a Strong Predictor of Coronary Heart Disease in Diabetic Individuals With Insulin Resistance and Low LDL

The Strong Heart Study


Abstract—Diabetes has been shown to increase the risk of coronary heart disease in all populations studied. However, there is a lack of information on the relative importance of diabetes-associated risk factors for cardiovascular disease (CVD), especially the role of lipid levels, because low density lipoprotein (LDL) cholesterol often is not elevated in diabetic individuals. The objective of this analysis was to evaluate CVD risk factors in a large cohort of diabetic individuals and to compare the importance of dyslipidemia (ie, elevated triglycerides and low levels of high density lipoprotein [HDL] cholesterol) and LDL cholesterol in determining CVD risk in diabetic individuals. The Strong Heart Study assesses coronary heart disease and its risk factors in American Indians in Arizona, Oklahoma, and South/North Dakota. The baseline clinical examinations (July 1989 to January 1992) consisted of a personal interview, physical examination, and drawing of blood samples for 4549 study participants (2034 with diabetes), 45 to 74 years of age. Follow-up averaged 4.8 years. Fatal and nonfatal CVD events were confirmed by standardized record review. Participants with diabetes, compared with those with normal glucose tolerance, had lower LDL cholesterol levels but significantly elevated triglyceride levels, lower HDL cholesterol levels, and smaller LDL particle size. Significant independent predictors of CVD in those with diabetes included age, albuminuria, LDL cholesterol, HDL cholesterol (inverse), fibrinogen, and percent body fat (inverse). A 10-mg/dL increase in LDL cholesterol was associated with a 12% increase in CVD risk. Thus, even at concentrations well below the National Cholesterol Education Program target of 130 mg/dL, LDL cholesterol is a strong independent predictor of coronary heart disease in individuals with diabetes, even when components of diabetic dyslipidemia are present. These results support recent recommendations for aggressive control of LDL cholesterol in diabetic individuals, with a target level of <100 mg/dL. (Arterioscler Thromb Vasc Biol. 2000;20:830-835.)

Key Words: low density lipoprotein cholesterol ■ coronary heart disease ■ diabetes mellitus ■ insulin resistance ■ Indians, North American

Macrovacular complications are the leading causes of morbidity and mortality in diabetic patients: >60% of diabetic patients die of cardiovascular diseases.1 In all populations studied, individuals with diabetes have a greatly increased risk of coronary heart disease (CHD) compared with nondiabetic individuals,2 and risk of cardiovascular disease (CVD) death in diabetic individuals may be as high as that in nondiabetic individuals with previous myocardial infarction.3 Despite this, there is insufficient information on the relative importance of CVD risk factors in persons with diabetes and strategies for risk factor reduction. Only a few population-based studies in the United States have followed individuals with diabetes. Post hoc analysis of the Multiple Risk Factor Intervention Trial (MRFIT) data set indicated that for men with diabetes, serum cholesterol level, systolic blood pressure, and cigarette smoking were significant predictors of CVD mortality.4 The Framingham Study evaluated both men and women with diabetes and found that smoking,5 hypertension,6 and elevated triglycerides6,7 were significant independent predictors of CVD. An analysis of diabetic individuals in the Rancho Bernardo cohort stressed the role of cigarette smoking in CVD deaths in older men and women.
with diabetes. In these studies, diabetes was diagnosed by self-report, and several diabetes-related measures, such as albuminuria, were not evaluated.

A question of particular importance is the relative role of various lipoprotein abnormalities in determining CVD risk in diabetic individuals. In many individuals with diabetes, LDL cholesterol is not elevated, but there is a characteristic dyslipidemia consisting of elevated triglycerides, decreased HDL cholesterol levels, and LDL particles of altered composition. Although 3 recent clinical trials of cholesterol lowering have shown that lowering LDL cholesterol in diabetic persons does reduce the incidence of CVD, the relative importance of LDL cholesterol, compared with the characteristic dyslipidemia, in determining CVD risk in diabetic individuals is still a subject of debate.

The present study examines CVD and its risk factors in diabetic American Indians in the Strong Heart Study. This cohort, which has a high prevalence rate of type 2 diabetes, insulin resistance, and the characteristic dyslipidemia of elevated triglycerides, low HDL cholesterol, and small dense LDL, is the largest cohort of individuals with diabetes under surveillance for CVD and its risk factors in the United States. LDL cholesterol concentrations in this population are lower than US means.

### Methods

The study design, survey methods, and laboratory techniques of the Strong Heart Study have been reported previously.

### Study Population

The Strong Heart Study population included men and women aged 45 to 74 years (during the period from July 1989 through January 1992) who were resident members of the following tribes: Pima/Maricopa/Papago Indians of central Arizona who live in the Gila River, Salt River, and Ak-Chin Indian communities; the 7 tribes of Southwestern Oklahoma (Apache, Caddo, Comanche, Delaware, Fort Sill Apache, Kiowa, and Wichita); the Oglala and Cheyenne River Sioux in South Dakota; and the Spirit Lake Tribe in the Fort Totten area of North Dakota.

The Strong Heart Study cohort consists of 4549 American Indians aged 45 to 74 years who were seen at the first (phase I, 1989 to 1991) examination. Participation rates of all age-eligible tribal members were 72% in the Arizona center, 62% in the Oklahoma center, and 55% in the Dakota center. Reexamination rates for those alive at the second (phase II) examination averaged 88% (90%, 89%, and 85% in Arizona, Oklahoma, and South/North Dakota, respectively). The second examination was conducted between July 1993 and December 1995.

### Clinical Examination and Analysis of Samples

The baseline and follow-up clinical examinations consisted of a personal interview and a physical examination. Fasting blood samples were obtained for measurements of lipids and lipoproteins (total cholesterol and triglycerides; VLDL, LDL, and HDL cholesterol; and VLDL triglycerides), insulin, plasma creatinine, plasma fibrinogen, and glycated hemoglobin (HbA1c). A 75-g oral glucose tolerance test was performed as described previously. Measurement of lipoproteins (using the β quantification procedure), insulin, fibrinogen, HbA1c, albumin, and creatinine were as described previously. As were anthropometric measurements (weight, height, and waist and hip circumferences), estimations of percent body fat, and blood pressure measurements.

A 12-lead ECG was taken by use of a Marquette system (MAC-PC or MAC-12, Marquette Electronics) and analyzed by using the Minnesota codes. Questions administered during the interview assessed demographic information, family health history, lifestyle, and medical history, including the Rose Questionnaire for angina pectoris. Percentage of Indian heritage was computed from the reported degree of Indian heritage (to the nearest quarter) for each parent and grandparent.

### Definitions of Terms

Participants were classified as diabetic according to World Health Organization (WHO) criteria if they were taking insulin or oral antidiabetic medication or if they had a fasting glucose concentration ≥140 mg/dL (>7.8 mmol/L) or a 2-hour glucose concentration ≥200 mg/dL (>11.1 mmol/L) after a 75-g oral glucose tolerance test. In this analysis, the nondiabetic group encompassed only those with normal glucose tolerance (fasting and 2-hour glucose levels <140 mg/dL [<7.8 mmol/L]) and excluded those with impaired glucose tolerance (fasting glucose levels ≤140 mg/dL [<7.8 mmol/L] and 2-hour glucose levels 140 to 199 mg/dL [7.8 to 11.0 mmol/L]). Participants with unknown diabetic status by WHO criteria (n=245) were reclassified according to the American Diabetes Association (ADA) criteria for fasting glucose (nondiabetic ≤110 mg/dL, diabetic ≥126 mg/dL), and impaired glucose tolerance 110 to 125 mg/dL. This reduced the number of participants with indeterminate diabetic status from 245 to 28; these individuals were included with the nondiabetic group. Rates of diabetes determined by WHO and ADA criteria are similar in this population (E.T. Lee et al, unpublished observations, 1999) and analyses using ADA criteria gave similar conclusions.

Participants were considered hypertensive if they had a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg or if they were taking antihypertension medication. Urinary albumin excretion was estimated by the ratio of albumin (in milligrams) to creatinine (in grams); this ratio is highly correlated with the albumin excretion rate in a 24-hour urine collection.

Microalbuminuria was defined as a ratio of urinary albumin (in milligrams per milliliter) to creatinine (in grams per milliliter) of 30 to 299 mg/g, and macroalbuminuria was defined as a ratio >300 mg/g. Diabetes and hypertension therapy were assessed during the personal interview, and individuals were asked to bring all medications to the examination site.

### Fatal CVD

Deaths occurring among the original Strong Heart Study cohort between the date of the participants’ first examinations and December 1995 (n=522 [12%], 252 women and 270 men) were identified through tribal and Indian Health Service hospital records and via direct contact by study personnel with participants and their families during the recruitment period of the phase II examination. The process used to ascertain that each death was due to CVD has been described previously. Criteria for fatal CHD and stroke appear in Table I (Tables I and II appear online at http://ahajournals.org/cgi/content/full/20/3/830/DC1).

### Nonfatal CVD

The intervening medical history or medical record of each member of the cohort was reviewed at the time of the second examination to ascertain nonfatal cardiovascular events that had occurred between the baseline and follow-up examinations. Records of those who did not participate in the second examination (n=498) were also reviewed. The process used for identifying nonfatal CVD events has been described previously. Criteria for nonfatal CHD and stroke appear in Table I (online).

### Data Analysis

Incidence rates for fatal and nonfatal events were calculated per 1000 person-years after elimination of individuals in the cohort who had definite CHD or stroke at baseline. Person-years were calculated from the date of the baseline examination to diagnosis, date of fatal event or first nonfatal event, or date of follow-up examination in event-free individuals. For analysis of total CVD, the first nonfatal or fatal event was used for each person. A stepwise Cox proportional hazards model was used for computing age- and center-adjusted hazard ratios and 95% CIs. All variables examined in the individual risk factor assessment, plus sex and center, were then used in the hazards model for examination of CVD risk factors. Stepwise Cox regression analysis, with entry and retention criteria of 5%, was used to compute hazard ratios for the multivariate analysis.
Results

The baseline examination of the Strong Heart Study included 4549 men and women between the ages of 45 and 74 years, including 2145 (47%) with diabetes, 1678 (37%) with normal glucose tolerance, 698 (15%) with impaired glucose tolerance, and 28 (1%) with indeterminate status. Overall, 51% of the women and 42% of the men had diabetes. Of the 4549 individuals, 171 (68 men and 43 women with diabetes, 10 men and 5 women with impaired glucose tolerance, 39 men and 5 women with normal glucose tolerance, and 1 man of indeterminate status) had definite CHD or stroke as evidenced by their baseline examination or medical history review and were eliminated from the analysis of incident events. The population at risk for CVD mortality and morbidity thus totaled 4378 and was composed of 2034 individuals with diabetes (35% men and 65% women), 1634 individuals with normal glucose tolerance (47% men and 53% women), and 27 individuals with indeterminate status who were free of definite disease at baseline. Those with impaired glucose tolerance were excluded from the data presentation because there were too few end points to examine this group separately. Those with indeterminate status were included in the nondiabetic group. The diabetic and, to a lesser extent, the nondiabetic cohorts have insulin resistance, as suggested by fasting hyperinsulinemia, central obesity, and the characteristic dyslipidemia of elevated triglycerides and low HDL cholesterol (Table II [online]). Mean LDL cholesterol levels were lower than the US means, and those with diabetes, compared with individuals with normal glucose tolerance, had lower LDL cholesterol levels (109±33 versus 118±32 mg/dL, respectively). In individuals with diabetes, triglyceride levels were significantly higher, HDL cholesterol levels were lower, and mean LDL size was smaller.

The average length of follow-up for the total population at risk was 4.8 years (range 0.02 to 6.6 years). In nondiabetic and diabetic groups, men had significantly higher mortality rates for CHD than did women (Figure 1). Mortality rates for stroke were somewhat higher in diabetic men than in diabetic women but were similar in nondiabetic men and women. Numbers of stroke cases are low; thus, the confidence intervals for these estimates are wide. The relative risk for fatal CHD in diabetic compared with nondiabetic women was almost twice that of diabetic compared with nondiabetic men (5.1 versus 3.1). Rates for fatal stroke were similar in diabetic men and women compared with their nondiabetic counterparts, but the number of events was low. Incidence rates for nonfatal CVD (Figure 1) showed similar patterns, although the relative risks associated with diabetes were less marked than those associated with fatal events. Rates for nonfatal CHD in both the diabetic and nondiabetic groups were higher in men than in women, and rates for nonfatal stroke were higher in nondiabetic men than in women. The relative risk for nonfatal CVD events in diabetic compared with nondiabetic individuals was, again, higher in women than in men (3.2 versus 1.7). Composite rates for CVD (morbidity plus mortality, Figure 1) were much higher in diabetic men and women than in nondiabetic men and women, with relative risks of total CVD in those with diabetes being greater in women (3.1) than in men (1.9). Event rates, however, were still higher in diabetic men than in diabetic women. Events were more likely to be fatal in persons with diabetes.

Major risk factors for fatal and nonfatal CVD in men and women with diabetes were individually evaluated in Cox models adjusting only for age and center (Table 1). In diabetic women and men, LDL cholesterol, albuminuria, percent body fat (inverse), fibrinogen, HbA1c, and diabetes duration were CVD risk factors. Triglycerides and hypertension were risk factors in diabetic women only, and waist circumference (inverse) was a risk factor in diabetic men only.

A multivariable analysis (Table 2) was conducted only for the diabetic group because the number of events in the nondiabetic group was small. The significant independent predictors of total CVD in diabetic individuals were lower percent body fat, higher LDL cholesterol levels, older age, macroalbuminuria, lower HDL cholesterol levels, residence in South/North Dakota compared with the other centers, and fibrinogen. The coefficients for diabetes indicate that in this cohort, a 10-mg/dL increase in LDL cholesterol corresponded to a 12% increase in CVD risk, and a 10-mg/dL decrease in HDL cholesterol was associated with a 22% increase in CVD risk.

The effects of increasing levels of LDL cholesterol and decreasing levels of HDL cholesterol on risk of CVD events in diabetic men and women, adjusted for all other covariates (listed in Table 2), are shown in Figure 2. There appears to be a linear increase in CVD risk in diabetic individuals with
TABLE 1. Age- and Center-Adjusted Cox Hazard Rate Ratios for Fatal and Nonfatal CVD for Each Major Risk Factor in Diabetic Women and Men

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>2.43 (1.53–3.86)</td>
<td>2.86 (1.74–4.71)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>0.71 (0.43–1.16)</td>
<td>0.66 (0.37–1.17)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>1.58 (1.28–1.95)</td>
<td>1.06 (0.89–1.26)</td>
</tr>
<tr>
<td>Hypertension, Y/N</td>
<td>2.06 (1.39–3.04)</td>
<td>1.41 (0.94–2.12)</td>
</tr>
<tr>
<td>Current smoking, Y/N</td>
<td>1.00 (0.64–1.57)</td>
<td>1.49 (1.00–2.23)</td>
</tr>
<tr>
<td>Insulin, μU/mL</td>
<td>1.03 (0.78–1.36)</td>
<td>1.21 (0.95–1.55)</td>
</tr>
</tbody>
</table>

Factors in Diabetic Individuals

TABLE 2. Cox Multivariate Regression Analysis of CVD Risk Factors in Diabetic Individuals

<table>
<thead>
<tr>
<th>Variables*</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body fat, %</td>
<td>−0.06</td>
<td>0.092</td>
<td>0.0001</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>0.01</td>
<td>0.0023</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.05</td>
<td>0.0101</td>
<td>0.0001</td>
</tr>
<tr>
<td>Macroalbuminuria, Y/N</td>
<td>0.58</td>
<td>0.1936</td>
<td>0.0028</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>−0.03</td>
<td>0.0081</td>
<td>0.0020</td>
</tr>
<tr>
<td>Arizona center, Y/N</td>
<td>−0.72</td>
<td>0.1986</td>
<td>0.0003</td>
</tr>
<tr>
<td>Oklahoma center, Y/N</td>
<td>−0.56</td>
<td>0.2047</td>
<td>0.0065</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>0.0022</td>
<td>0.0009</td>
<td>0.0202</td>
</tr>
</tbody>
</table>

HR indicates hazard rate ratio.

Increasing LDL cholesterol, beginning with the first quartile of LDL cholesterol (mean 70 mg/dL). The inverse relation of HDL cholesterol continued to a fourth quartile mean of 58 mg/dL.

Crude incidence rates of CVD, per 1000 person-years, in diabetic individuals with LDL cholesterol ≥100 mg/dL were 38.8 for men and 18.3 for women. With LDL cholesterol <100 mg/dL, rates were 20.2 for men and 14.6 for women.

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*Non-significant covariates in the analysis included sex, hypertension, waist circumference, triglycerides, LDL size, HbA1c, total cigarettes (pack/y), microalbuminuria (Y/N), and diabetes duration.

Discussion

Analyses of the data from the Strong Heart Study provide an opportunity to examine CVD and its risk factors in a large population-based sample of well-characterized type 2 diabetic individuals. Previous results from the longitudinal surveillance have shown high rates of CVD in this cohort, largely attributable to diabetes.32

There has been a recent focus on the characteristic dyslipidemia of type 2 diabetes, which includes elevated triglycerides, low HDL cholesterol, and a preponderance of small dense LDL particles.33 These characteristics were highly prevalent in diabetic participants in this cohort, whereas LDL cholesterol levels were lower than in nondiabetic participants. These lipid findings are common among individuals with diabetes of all races in the United States. Mexican Americans and African Americans with diabetes have lower levels of LDL cholesterol than do those without diabetes.9,34 Thus, it has been proposed that in diabetes, the dyslipidemia, rather than elevated LDL cholesterol, is the predominant lipoprotein determinant of atherosclerosis.35 The present analysis, however, suggests that LDL cholesterol concentrations are important, even when they are considerably below the National Cholesterol Education Program (NCEP) target of 130 mg/dL. In this analysis, which examined individuals free of CVD at baseline, LDL cholesterol was a strong independent predictor of CHD, even when components of the dyslipidemia syndrome were considered. The hazard ratio indicates that a 10-mg/dL increase in LDL cholesterol levels would lead to a 12% increase in CVD risk, and the response appeared graded and linear between LDL cholesterol quartile averages of 70 to 151 mg/dL, for diabetic participants of both sexes. Incidence rates for CVD in diabetic men and women were higher in those with LDL cholesterol levels >100 mg/dL compared with those with levels <100 mg/dL.

Triglycerides were a significant univariate predictor of cardiovascular events in diabetic women, but in the multivariate model, neither triglycerides nor LDL size was a significant independent predictor of CVD. HDL cholesterol had a strong inverse effect in the multivariate model, with a 10-mg/dL decrease in HDL cholesterol associated with a 22% increase in CVD risk.

The observation that LDL cholesterol is a significant determinant of CVD in people with diabetes is consistent with findings from studies of whites in the United States, such as MRFIT1 and Framingham,36 and from studies in other
populations, eg, North Finland and Paris. In all these studies, however, average LDL cholesterol concentrations were much higher than those of the current cohort. The HDL cholesterol data in the present study are also consistent with data in other studies of diabetes in which HDL cholesterol was shown to be a predictor of CVD.

Other risk factors in diabetic individuals in this cohort relate almost entirely to their diabetes. Albuminuria was a strong independent risk factor. Several prospective studies examining risk factors for CVD among individuals with diabetes have observed a relation between albuminuria and CVD.

Hypertension, although more prevalent in individuals with diabetes in this cohort, was not a significant independent predictor of CVD in diabetes. Hypertension was a significant univariate risk factor, and if albuminuria is removed from the model, hypertension is a significant independent predictor (data not shown). The data further suggest that the increasing blood pressure with advanced diabetes is also a marker for advanced microvascular disease.

As with the analyses of the total Strong Heart Study cohort, obesity is a negative predictor of CVD in those with diabetes. Body fat distribution, determined by using waist measurement, showed no independent relation to CVD in either diabetic women or men. The latter may be explained by the observation that among obese American Indians in the cohort, body fat almost always is centrally distributed, with the waist-to-hip ratio averaging 0.97 in men and 0.94 in women. On the other hand, it is very difficult to understand the inverse relation of obesity and CHD. It is possible that this reflects the fact that individuals with long duration of diabetes, particularly those with renal disease (who are at high risk for CVD), lose weight and that this is not completely accounted for in the multivariate analysis. Another possibility is that congestive heart failure, which is more prevalent in obese individuals, was not included in the incident events. In Pima Indians, there was no association of obesity and mortality except in those with a body mass index >40 kg/m². Whether there may be ethnic differences in the impact of obesity on CVD requires further investigation.

A question may be raised concerning the applicability of the present findings to other populations. American Indians, who are plagued with high rates of type 2 diabetes, resemble many other ethnic groups in the United States and worldwide that also have high rates of diabetes, insulin resistance, and obesity. There has been no evidence that the microangiographic/macroangiographic sequelae in American Indians differ qualitatively from those seen in other US populations with type 2 diabetes. Thus, this population-based sample with complete ascertainment of follow-up data likely provides answers that are of general applicability to people with type 2 diabetes in the United States.

In conclusion, the results of this analysis provide data that can provide valuable insights into the relative importance of risk factors for CVD in diabetes. The key risk factors for diabetic patients in the present study were albuminuria and LDL and HDL cholesterol. The data provide strong evidence that LDL cholesterol concentrations are important, even when they are considerably below the current NCEP targets, and support the goal of lowering LDL cholesterol to <100 mg/dL (<2.6 mmol/L) in all individuals with diabetes even if they do not have clear evidence of CVD—a recommendation supported by the ADA. In the absence of clinical trial data, it would be reasonable to suggest that aggressive control of LDL cholesterol, control of hypertension, and prevention of proteinuria are appropriate therapeutic goals for diabetic patients.

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References


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