

# Arteriosclerosis, Thrombosis, and Vascular Biology

JOURNAL OF THE AMERICAN HEART ASSOCIATION



## **LDL Cholesterol as a Strong Predictor of Coronary Heart Disease in Diabetic Individuals With Insulin Resistance and Low LDL : The Strong Heart Study**

Barbara V. Howard, David C. Robbins, Maurice L. Sievers, Elisa T. Lee, Dorothy Rhoades, Richard B. Devereux, Linda D. Cowan, R. Stuart Gray, Thomas K. Welty, Oscar T. Go and Wm. James Howard

*Arterioscler Thromb Vasc Biol* 2000;20:830-835

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 2000 American Heart Association. All rights reserved. Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://atvb.ahajournals.org/cgi/content/full/20/3/830>

Data Supplement (unedited) at:

<http://atvb.ahajournals.org/cgi/content/full/20/3/830/DC1>

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at

<http://atvb.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:

[journalpermissions@lww.com](mailto:journalpermissions@lww.com)

Reprints: Information about reprints can be found online at

<http://www.lww.com/reprints>

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

## The Strong Heart Study

Barbara V. Howard, David C. Robbins, Maurice L. Sievers, Elisa T. Lee, Dorothy Rhoades, Richard B. Devereux, Linda D. Cowan, R. Stuart Gray, Thomas K. Welty, Oscar T. Go, Wm. James Howard

**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

Macrovascular complications are the leading causes of morbidity and mortality in diabetic patients; >60% of diabetic patients die of cardiovascular diseases.<sup>1</sup> In all populations studied, individuals with diabetes have a greatly increased risk of coronary heart disease (CHD) compared with nondiabetic individuals,<sup>2</sup> and risk of cardiovascular disease (CVD) death in diabetic individuals may be as high as that in nondiabetic individuals with previous myocardial infarction.<sup>3</sup> 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.<sup>4</sup> The Framingham Study evaluated both men and women with diabetes and found that smoking,<sup>5</sup> hypertension,<sup>5</sup> and elevated triglycerides<sup>6,7</sup> 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

Received July 1, 1999; revision accepted October 15, 1999.

From MedStar Research Institute and Washington Hospital Center (B.V.H., D.C.R., W.J.H.), Washington, DC; the Center for American Indian Health Research (E.T.L., O.T.G.), University of Oklahoma Health Sciences Center, Oklahoma City; the Department of Biostatistics and Epidemiology (L.D.C.), University of Oklahoma, Oklahoma City; Cornell University (R.B.D.), College of Medicine, Ithaca, NY; West Lothian NHS Trust (R.S.G.), St. John's Hospital at Howden, Scotland, UK; the Native Elder Research Center (D.R.), University of Colorado Health Sciences Center, Denver; the Aberdeen Area Tribal Chairmen's Health Board (T.K.W.), Rapid City, SD; and the National Institutes of Health (M.L.S.), Phoenix, Ariz.

The views expressed in this article are those of the authors and do not necessarily reflect those of the Indian Health Service.

Correspondence to Barbara V. Howard, PhD, MedStar Research Institute, 108 Irving St, NW, Washington, DC 20010. E-mail bvhl@mhg.edu

© 2000 American Heart Association, Inc.

*Arterioscler Thromb Vasc Biol.* is available at <http://www.atvbaha.org>

with diabetes.<sup>8</sup> 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,<sup>9</sup> 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,<sup>10–12</sup> 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.<sup>13</sup>

## Methods

The study design, survey methods, and laboratory techniques of the Strong Heart Study have been reported previously.<sup>14,15</sup>

### 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.<sup>16</sup> 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 (HbA<sub>1c</sub>). A 75-g oral glucose tolerance test was performed as described previously.<sup>14</sup> Measurements of lipoproteins (using the  $\beta$  quantification procedure), insulin, fibrinogen, HbA<sub>1c</sub>, albumin, and creatinine were as described previously,<sup>17–22</sup> as were anthropometric measurements (weight, height, and waist and hip circumferences), estimations of percent body fat, and blood pressure measurements.<sup>15</sup>

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.<sup>23</sup> Questions administered during the interview assessed demographic information, family health history, lifestyle, and medical history, including the Rose Questionnaire for angina

pectoris.<sup>24</sup> 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<sup>25</sup> 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  $\leq 110$  mg/dL, diabetic  $\geq 126$  mg/dL, and impaired glucose tolerance 110 to 125 mg/dL).<sup>26</sup> 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  $\geq 140$  mm Hg or a diastolic blood pressure  $\geq 90$  mm Hg<sup>27</sup> 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.<sup>28</sup>

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  $\geq 300$  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.<sup>29</sup> Criteria for fatal CHD and stroke appear in Table I (Tables I and II appear online at <http://atvb.ahajournals.org/cgi/content/full/20/3/830/DC1>).<sup>29</sup>

### 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.<sup>29</sup> Criteria for nonfatal CHD and stroke appear in Table I (online).<sup>29</sup>

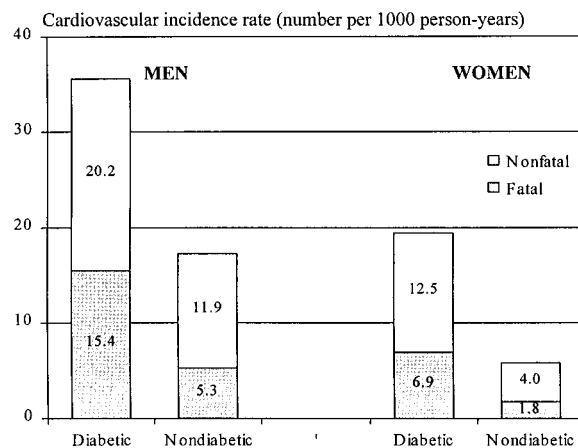
### Data Analysis

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,<sup>13,30</sup> and those with diabetes, compared with individuals with normal glucose tolerance, had lower LDL cholesterol levels ( $109 \pm 33$  versus  $118 \pm 32$  mg/dL, respectively). In individuals with diabetes, triglyceride levels were significantly higher, HDL cholesterol levels were lower, and mean LDL size was smaller.<sup>31</sup>

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). Downloaded from <http://atvb.ahajournals.org/> by on November 29, 2009



**Figure 1.** Incidence rates of CVD by diabetic status: the Strong Heart Study. Overall incidence rates per 1000 person-years were as follows: for diabetic men, 31.8; for nondiabetic men, 16.4; for diabetic women, 17.9; and for nondiabetic women, 5.8. Person-years were calculated to whichever fatal or nonfatal event occurred for each individual. For fatal CVD, rates with 95% CIs were 15.4 (CI 11.2 to 19.6) in diabetic men, 5.3 (CI 3.0 to 7.6) in nondiabetic men, 6.9 (CI 4.9 to 8.9) in diabetic women, and 1.8 (CI 0.6 to 3.1) in nondiabetic women. The relative risks for fatal CHD, stroke, and total fatal CVD were 3.1 (CI 1.8 to 5.3), 2.3 (CI 0.6 to 9.2), and 2.9 (CI 1.8 to 4.9) in diabetic men and 5.1 (CI 2.0 to 12.9), 1.5 (CI 0.4 to 5.9), and 3.8 (CI 1.8 to 8.0), respectively, in diabetic women. For nonfatal CVD, rates with 95% CIs were 20.2 (CI 15.2 to 25.1) in diabetic men, 11.9 (CI 8.4 to 15.4) in nondiabetic men, 12.5 (CI 9.8 to 15.2) in diabetic women, and 4.0 (CI 2.1 to 5.8) in nondiabetic women. The relative risks for nonfatal CHD, nonfatal stroke, and total nonfatal CVD were 1.8 (CI 1.2 to 2.8), 1.7 (CI 0.7 to 4.2), and 1.7 (CI 1.2 to 2.5) in diabetic men and 3.3 (CI 1.8 to 6.0), 3.4 (CI 1.2 to 10.0), and 3.2 (CI 1.9 to 5.3), respectively, in diabetic women.

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, HbA<sub>1c</sub>, 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**

Risk Factor	Women		Men	
	HR	95% CI	HR	95% CI
LDL cholesterol, <sup>a</sup> mg/dL	2.43	1.53–3.86	2.86	1.74–4.71
HDL cholesterol, <sup>b</sup> mg/dL	0.71	0.43–1.16	0.66	0.37–1.17
Triglycerides, <sup>c</sup> mg/dL	1.58	1.28–1.95	1.06	0.89–1.26
Hypertension, Y/N	2.06	1.39–3.04	1.41	0.94–2.12
Current smoking, Y/N	1.00	0.64–1.57	1.49	1.00–2.23
Insulin, <sup>d</sup> μU/mL	1.03	0.78–1.36	1.21	0.95–1.55
Albuminuria				
Micro vs normal	1.58	0.96–2.59	1.47	0.89–2.43
Macro vs normal	3.68	2.29–5.93	3.28	2.02–5.32
Percent body fat, <sup>e</sup>	0.52	0.33–0.83	0.53	0.32–0.89
Waist circumference, <sup>f</sup> cm	0.72	0.44–1.19	0.58	0.34–0.99
Fibrinogen, <sup>g</sup> mg/dL	2.28	1.50–3.47	2.23	1.38–3.61
Indian heritage, <sup>h</sup> Y/N	0.79	0.50–1.26	1.12	0.66–1.88
HbA <sub>1c</sub> , <sup>i</sup> %	2.06	1.26–3.39	1.85	1.13–3.01
Diabetes duration, <sup>j</sup> y	1.91	1.29–2.84	2.21	1.37–3.57
LDL size, <sup>k</sup> Å	0.59	0.37–0.96	1.00	0.60–1.66

HR indicates hazard rate ratio.

Mean of the upper quartile group vs mean of the lowest quartile group: <sup>a</sup>153 vs 71 mg/dL in women, 149 vs 68 mg/dL in men; <sup>b</sup>60 vs 33 mg/dL in women, 58 vs 28 mg/dL in men; <sup>c</sup>333 vs 78 mg/dL in women, 391 vs 68 mg/dL in men; <sup>d</sup>58.43 vs 11.05 μU/mL in women, 49.80 vs 8.03 μU/mL in men; <sup>e</sup>50% vs 33% in women, 38% vs 22% in men; <sup>f</sup>129 vs 94 in women, 124 vs 91 in men; <sup>g</sup>442 vs 238 mg/dL in women, 419 vs 215 mg/dL in men; <sup>h</sup>self-reported; <sup>i</sup>12% vs 6% in women, 11% vs 5% in men; <sup>j</sup>24 vs 0.16 y in women, 21 vs 0 y in men; and <sup>k</sup>268 vs 246 in women, 268 vs 245 in men.

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

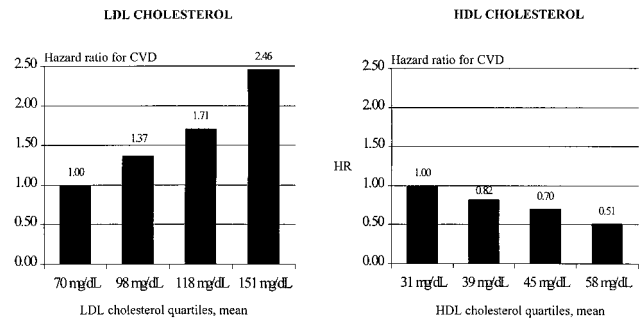
Crude incidence rates of CVD, per 1000 person-years, in diabetic individuals with LDL cholesterol ≥100 mg/dL were 38.8 for men and 18.3 for women; with LDL cholesterol <100 mg/dL, rates were 20.2 for men and 14.6 for women.

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

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

Variables are listed in descending order of importance.

\*Nonsignificant covariates in the analysis included sex, hypertension, waist circumference, triglycerides, LDL size, HbA<sub>1c</sub>, total cigarettes (pack/y), microalbuminuria (Y/N), and diabetes duration. Downloaded from [atvb.ahajournals.org](http://atvb.ahajournals.org) by on November 29, 2009



**Figure 2.** Hazard ratios (HR) for fatal and nonfatal diabetes-associated CVD by quartile for LDL and HDL cholesterol for diabetic men and women, calculated from results in Table 2. The y axis is logarithmic scale.

**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.<sup>32</sup>

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.<sup>33</sup> 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.<sup>9,34</sup> Thus, it has been proposed that in diabetes, the dyslipidemia, rather than elevated LDL cholesterol, is the predominant lipoprotein determinant of atherosclerosis.<sup>35</sup> 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 MRFIT and Framingham,<sup>36</sup> and from studies in other

populations, eg, North Finland<sup>37</sup> and Paris.<sup>38</sup> 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.<sup>36–38</sup>

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.<sup>39–42</sup>

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/m<sup>2</sup>.<sup>43</sup> 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 from any of the US populations.

do not have clinical evidence of CVD—a recommendation suggested by the ADA.<sup>26</sup> 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.

## Acknowledgments

This study was conducted by cooperative agreement grants (U01-HL-41642, U01-HL-41652, and UL01-HL-41654) from the National Heart, Lung, and Blood Institute. The authors acknowledge the assistance and cooperation of the Ak-Chin Tohono O'odham (Papago)/Pima, Apache, Caddo, Cheyenne River Sioux, Comanche, Delaware, Spirit Lake Community, Fort Sill Apache, Gila River, Pima/Maricopa, Kiowa, Oglala Sioux, Salt River Pima/Maricopa, and Wichita Indian communities, without whose support this study would not have been possible. The authors also wish to thank the Indian Health Service hospitals and clinics at each center and Betty Jarvis, Taqueer Ali, and Marcia O'Leary, directors of the Strong Heart Study clinics and their staffs; the physicians who performed the morbidity and mortality reviews: James Galloway, Everett Rhoades, Richard Rodeheffer, Sabeeh Jaffrey, Cheryl Pegus, Kamran Rafiq, Boureima Sambo, and Arvo Oopik, who died in a plane crash on February 22, 1994, while serving American Indian patients; and William Moore, Jeunliang Yeh, and Carl Schaeffer, who monitored the surveillance. We also gratefully acknowledge the editorial assistance of Ellen Shair.

## References

1. World Health Organization. Prevention of diabetes mellitus. In: *WHO Technical Report Series #844*. Geneva, Switzerland: World Health Organization; 1994.
2. Wingard DL, Barrett-Connor E. Heart disease and diabetes. In: National Diabetes Data Group, ed. *Diabetes in America*. 2nd ed. Bethesda, Md: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. NIH publication No. 95-1468, 1995:429–448.
3. Haffner SM, Lehto S, Ronnema T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339:229–234.
4. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*. 1993;16:434–444.
5. Kannel WB, Higgins M. Smoking and hypertension as predictors of cardiovascular risk in population studies. *J Hypertens*. 1990;8(suppl 8):S3–S8.
6. Castelli WP. The triglyceride issue: a view from Framingham. *Am Heart J*. 1986;112:432–437.
7. Castelli WP. Epidemiology of triglycerides: a view from Framingham. *Am J Cardiol*. 1992;70:3H–9H.
8. Suarez L, Barrett-Connor E. Interaction between cigarette smoking and diabetes mellitus in the prediction of death attributed to cardiovascular disease. *Am J Epidemiol*. 1984;120:670–675.
9. Cowie CC, Howard BV, Harris MI. Serum lipoproteins in African Americans and Whites with non-insulin-dependent diabetes in the US population. *Circulation*. 1994;90:1185–1193.
10. Pyorala K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. *Diabetes Care*. 1997;20:614–620.
11. Sacks FM, Pfeffer AM, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JMO, Wun C-C, Davis BR, Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med*. 1996;335:1001–1009.
12. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Krayer W, Gotto AM Jr. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279:1615–1622.
13. Robbins DC, Welty TK, Wang WY, Lee ET, Howard BV. Plasma lipids and lipoprotein concentrations among American Indians: comparison with the US population. *Curr Opin Lipidol*. 1996;7:188–195.

14. Lee ET, Welty TK, Fabsitz R, Cowan LD, Lee N-A, Oopik AJ, Cucchiara AJ, Savage PJ, Howard BV. The Strong Heart Study: a study of cardiovascular disease in American Indians: design and methods. *Am J Epidemiol.* 1990;132:1141-1155.
15. Howard BV, Welty TK, Fabsitz RR, Cowan LD, Oopik AJ, Le NA, Yeh J, Savage PJ, Lee ET. Risk factors for coronary heart disease in diabetic and nondiabetic Native Americans: the Strong Heart Study. *Diabetes.* 1992;41(suppl 2):4-11.
16. Stoddart M, Jarvis B, Blake B, Fabsitz RR, Welty TK, Lee ET, Howard BV. Recruitment of American Indians in epidemiologic research: the Strong Heart Study. *Harvard J Minority Public Health.* In press.
17. Lipid Research Clinics Program. *Manual of Laboratory Operations.* Vol. 1. Washington, DC: Department of Health, Education, and Welfare (DHEW publication No. 75-628); May 1994.
18. Morgan C, Lazarow A. Immunoassay of insulin: two antibody system: plasma insulin levels in normal, subdiabetic and diabetic rats. *Diabetes.* 1963;12:115-126.
19. von Clauss A. Gerinnungsphysiologische Schnellmethode zur Bestimmung des Fibrinogens. *Acta Haematol.* 1957;17:237-246.
20. Little RR, England JD, Wiedmeyer HM, McKenzie EM, Mitra R, Erhart PM, Durham JB, Goldstein DE. Interlaboratory standardization of glycosylated hemoglobin determinations. *Clin Chem.* 1986;32:358-360.
21. Vasquez B, Flock EV, Savage PJ, Nagulesparan M, Bennion LJ, Baird HR, Bennett PH. Sustained reduction of proteinuria in type 2 (non-insulin dependent) diabetes following diet-induced reduction of hyperglycemia. *Diabetologia.* 1984;26:127-133.
22. Chasson AL, Grady HJ, Stanley MA. Determination of creatinine by means of automatic chemical analysis. *Tech Bull Regist Med Technol.* 1960;30:207-212.
23. Prineas RJ, Crow RS, Blackburn H. *The Minnesota Code Manual of Electrocardiographic Findings.* Littleton, Mass: John Wright PSC; 1982.
24. Rose GA, Blackburn H. Cardiovascular survey methods. 2nd ed. Geneva, Switzerland: World Health Organization; 1982. Monograph series No. 56G.
25. WHO Expert Committee on Diabetes Mellitus. *Second Report.* Geneva, Switzerland: World Health Organization; 1980. Technical report series 646.
26. American Diabetes Association. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: clinical practice recommendations. 1998. *Diabetes Care.* 1998;21(suppl 1):S5-S19.
27. National Heart, Lung, and Blood Institute. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNCV). *Arch Intern Med.* 1993;153:154-183.
28. Bennett PH, Nelson RG, Knowler WC, Hardy SA, Williams GW, Pettitt DJ, Saad MF, Mitch WB, Myers BD. Urine albumin/creatinine ratio estimates albumin excretion and predicts nephropathy in type II (non-insulin dependent) diabetes. *Diabetologia.* 1990;33(Suppl):A147. Abstract.
29. Lee ET, Cowan LD, Howard WJ, Sievers M, Welty TK, Wang W, Yeh JL, Rhoades ER, Devereux RB, Fabsitz RR, Go O, Howard BV. All-cause mortality and cardiovascular disease mortality in three American Indian populations, aged 45-74 years, 1984-1988: the Strong Heart Study. *Am J Epidemiol.* 1998;147:995-1008.
30. Welty TK, Lee ET, Yeh J, Cowan LD, Go O, Fabsitz RR, Le NA, Oopik AJ, Robbins DC, Howard BV. Cardiovascular disease risk factors among American Indians. the Strong Heart Study. *Am J Epidemiol.* 1995;142:269-287.
31. Howard BV, Cowan LD, Go O, Welty TK, Robbins DC, Lee ET. Adverse effects of diabetes on multiple cardiovascular disease risk factors in women: the Strong Heart Study. *Diabetes Care.* 1998;21:1258-1265.
32. Howard BV, Lee ET, Cowan LD, Fabsitz RR, Howard WJ, Oopik AJ, Robbins DC, Savage PJ, Yeh JL, Welty TK. Coronary heart disease prevalence and its relation to risk factors in American Indians: the Strong Heart Study. *Am J Epidemiol.* 1995;142:254-268.
33. Howard BV. Pathogenesis of diabetic dyslipidemia. *Diabetes Rev.* 1995;3:423-432.
34. Mitchell BD, Haffner SM, Hazuda HP, Patterson JK, Stern MP. Diabetes and coronary heart disease risk in Mexican Americans. *Ann Epidemiol.* 1992;2:101-106.
35. Reaven GM. Non-insulin-dependent diabetes mellitus, abnormal lipoprotein metabolism, and atherosclerosis. *Metabolism.* 1987;36(suppl 1):1-8.
36. Gordon T, Kannel WB, Castelli WP, Dauber TR. Lipoproteins, cardiovascular disease, and death: the Framingham Study. *Arch Int Med.* 1981;141:1128-1131.
37. Austin MA, Mykkanen L, Kuusisto J, Edwards KL, Nelson C, Haffner SM, Pyorala K, Laakso M. Prospective study of small LDLs as a risk factor for non-insulin dependent diabetes mellitus in elderly men and women. *Circulation.* 1995;92:1770-1778.
38. Fontbonne AM, Eschwege EM. Insulin and cardiovascular disease: Paris Prospective Study. *Diabetes Care.* 1991;14:461-469.
39. Borch-Johnsen K, Kreiner S. Proteinuria: value as a predictor of cardiovascular mortality in insulin-dependent diabetes mellitus. *Br Med J.* 1987;294:1651.
40. Parving HH, Gall MA, Nielsen FS. Dyslipidaemia and cardiovascular disease in non-insulin-dependent diabetic patients with and without diabetic nephropathy. *J Intern Med.* 1994;736(suppl):89-94.
41. Savage S, Estacio RO, Jeffers B, Schrier RW. Urinary albumin excretion as a predictor of diabetic retinopathy, neuropathy, and cardiovascular disease in NIDDM. *Diabetes Care.* 1996;19:1243-1248.
42. Nelson RG, Pettitt DJ, Carraher MJ, Baird HR, Knowler WC. Effect of proteinuria on mortality in NIDDM. *Diabetes.* 1988;37:1449-1508.
43. Fagot-Campagna A, Hanson RL, Narayan KM, Sievers ML, Pettitt DJ, Nelson RG, Knowler WC. Serum cholesterol and mortality rates in a Native American population with low cholesterol concentrations: a U-shaped association. *Circulation.* 1997;96:1408-1415.