Non-HDL Cholesterol as a Predictor of Cardiovascular Disease in Type 2 Diabetes

The Strong Heart Study

WEIQUAN LU, MD
HELAINE E. RESNICK, PHD
KATHLEEN A. JABLONSKI, PHD
KRISTINA L. JONES, MPH
ARVIND K. JAIN, MS
WM. JAMES HOWARD, MD
DAVID C. ROBBINS, MD
BARBARA V. HOWARD, PHD

OBJECTIVE — To determine whether non-HDL cholesterol, a measure of total cholesterol minus HDL cholesterol, is a predictor of CVD in patients with diabetes.

RESEARCH DESIGN AND METHODS — The Strong Heart Study, a population-based study of CVD and its risk factors in 13 American Indian communities in three geographic areas in the U.S. The baseline examination, conducted between July 1989 and January 1992, consisted of a personal interview, a physical examination, and laboratory tests. Of the 4,549 women and men aged 45–74 years participating in the study, 2,108 had diabetes but no CVD at baseline. Data on fatal and nonfatal CVD were collected during the follow-up period through 31 December 1998 (average 9 years).

RESULTS — Multivariable analyses indicated that non-HDL cholesterol is a strong predictor of CVD in men and women with diabetes and is particularly indicative of coronary events. Hazard ratios for the highest tertile of non-HDL cholesterol in men and women with diabetes (2.23 and 1.80, respectively) were higher than those for either LDL cholesterol or triglycerides alone in both men and women and were higher than the ratio of total/HDL cholesterol in women. The utility of non-HDL cholesterol in predicting CVD extended over a wide range of triglyceride concentrations.

CONCLUSIONS — This study suggests that non-HDL cholesterol index may be particularly useful in predicting CVD risk in patients with diabetes.

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Cardiovascular disease (CVD) is currently the primary cause of morbidity and mortality in patients with diabetes (1–4). Because individuals with diabetes have greatly increased CVD risk compared with nondiabetic individuals (5–9), it is important to identify factors that may increase CVD risk in diabetic patients.

In type 2 diabetes, there is a characteristic dyslipidemia consisting of elevated triglycerides, decreased HDL cholesterol, and LDL particles of altered composition (10–12). Previous studies (5–9,13–15) indicate that, in addition to LDL cholesterol level, this dyslipidemia is an important CVD risk factor in individuals with diabetes. Although the CVD risk associated with individual lipoproteins has been examined, it would be valuable to have a measure that reflects the combined risk of all lipoprotein changes observed in diabetes. Some investigators (16–18) have recently suggested that a measure of non-HDL cholesterol, which reflects total cholesterol minus HDL cholesterol (i.e., all apolipoprotein B–containing atherogenic lipoproteins), might be a useful marker of this combined risk. A recent study conducted in a cohort containing both diabetic and nondiabetic individuals showed that non-HDL cholesterol was a somewhat better predictor of CVD than LDL cholesterol (19). Furthermore, the Adult Treatment Panel (ATP-III) of the National Cholesterol Education Program has recommended using non-HDL cholesterol in assessing CVD risk in patients with diabetes (20). However, there have been no population-based studies evaluating the utility of non-HDL cholesterol as a predictor of CVD in patients with diabetes.

The Strong Heart Study is a population-based study of CVD and its risk factors in American Indians. This population has a high prevalence of diabetes, and those with diabetes have a greatly increased risk of CVD (5). Using the data from this population, the purpose of this study is to evaluate the ability of non-HDL cholesterol and individual lipoprotein indicators to predict CVD in patients with diabetes.

RESEARCH DESIGN AND METHODS

— The study design, survey methods, and laboratory techniques of the Strong Heart Study have been reported previously in detail (21,22). The baseline examination included American

From the MedStar Research Institute and Washington Hospital Center, Washington, DC.
Address correspondence and reprint requests to Barbara V. Howard, PhD, President, MedStar Research Institute, 6495 New Hampshire Ave., Suite 201, Hyattsville, MD 20783. E-mail: barbara.v.howard@medstar.net.
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Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; HR, hazard ratio; IDL, intermediate-density lipoprotein; MI, myocardial infarction; SBP, systolic blood pressure.
The views expressed in this paper are those of the authors and do not necessarily reflect those of the Indian Health Service.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
See accompanying editorial on p. 240.

Table 1—*Selected CVD risk factors at 9-year follow-up in diabetic men and women with and without CVD at baseline: the Strong Heart Study*

	Men			Women		
Characteristics	CVD	Non-CVD	*P*	CVD	Non-CVD	*P*
Participants (*n*)	202	570		319	1017	
Age (years)	58 ± 8	56 ± 8	<0.0001	60 ± 8†	57 ± 8†	<0.0001
BMI (kg/m^2)	31 ± 7	32 ± 6	0.0433	32 ± 6	33 ± 6†	0.0058
Waist circumference (cm)	105 ± 14	107 ± 14	0.0492	110 ± 14†	111 ± 14†	0.1022
HbA_{1c} (%)	8.5 ± 2.5	7.9 ± 2.3	0.0015	9.0 ± 2.5	8.5 ± 2.5†	0.0094
SBP (mmHg)	133 ± 20	130 ± 18	0.0008	138 ± 24	128 ± 19	<0.0001
DBP (mmHg)	81 ± 10	81 ± 10	0.9044	76 ± 10†	75 ± 9†	0.3253
Hypertension (%)	38	31	0.1021	42	27	<0.0001
Current smoker (%)	37	33	0.3421	26†	22†	0.1448
Fasting plasma glucose (mg/dl)	200 ± 78	188 ± 72	0.0443	216 ± 85	204 ± 83†	0.0344
2-h plasma glucose (mg/dl)	300 ± 118	274 ± 113	0.0898	310 ± 104	299 ± 113†	0.3668
Insulin (μU/ml)*	19 (16–21)	19 (18–20)	0.8535	23 (21–24)	23 (22–24)†	0.115
Total cholesterol (mg/dl)	196 ± 47	184 ± 46	0.0019	205 ± 48	187 ± 39	<0.0001
HDL cholesterol (mg/dl)	39 ± 12	41 ± 12	0.0502	44 ± 11†	45 ± 11†	0.6238
LDL cholesterol (mg/dl)	109 ± 35	102 ± 31	0.0127	112 ± 37	102 ± 31	<0.0001
Triglycerides (mg/dl)*	151 (141–173)	136 (129–142)	0.0171	162 (150–173)	142 (137–146)	<0.0001
Ratio of albumin/creatinine*	86 (48–131)	26 (21–31)	<0.0001	79 (52–112)	32 (28–37)	<0.0001
Fibrinogen (mg/dl)	323 ± 82	300 ± 81	0.0003	348 ± 86†	326 ± 84†	<0.0001
Non-HDL cholesterol	157 ± 48	143 ± 47	0.0004	160 ± 49	143 ± 40	<0.0001
Ratio of total/HDL cholesterol	5.3 ± 1.7	4.8 ± 2.5	0.0027	4.9 ± 1.8†	4.4 ± 1.4†	<0.0001

Data are means ± SD or %. *Geometric mean values and 95% CI; †significant difference ($P < 0.05$) between diabetic men and women with CVD or between men and women without CVD.

Indians aged 45–74 years who were resident members of the following tribes between July 1989 and January 1992: the Akimel O'odham (Pima), Pee Posh (Maricopa), and Tohono-Oodham (Papago) tribes of central Arizona who live in the Gila River, Salt River, and Ak-Chin communities; the seven tribes of southwestern Oklahoma (Apache, Caddo, Comanche, Delaware, Fort Sill Apache, Kiowa, and Wichita); and the Oglala and Cheyenne River Sioux in South Dakota and the Spirit Lake Community in the Fort Totten area of North Dakota (23).

The baseline examination consisted of personal interviews, physical examinations, laboratory tests, and 12-lead resting electrocardiograms of 4,549 men and women. Participants were examined in the morning after at least a 12-h overnight fast. After informed consent was obtained, fasting blood samples were collected for measurement of lipid and lipoprotein levels. A 75-g oral glucose tolerance test was administered, and plasma glucose was measured 2 h after the glucose load (21). All laboratory tests were performed centrally. Standard assays were used to measure plasma glucose (24), cholesterol (24), triglyceride (24), lipid, and lipoprotein levels (25); fibrinogen determinations (26); HbA_{1c} (27), urinary albumin (28), and urinary creatinine levels (29); and LDL particle size (30).

Anthropometric measurements were made with the participant wearing lightweight clothing and no shoes (22). BMI was calculated as weight (in kilograms)/height (in meters) squared. Waist circumference was measured at the level of the umbilicus with the participant in the supine position (31). Participants were considered to have hypertension if systolic blood pressure (SBP) was ≥140 mmHg or diastolic blood pressure (DBP) was ≥90 mmHg or if they were taking antihypertensive medication.

Diabetes was determined by World Health Organization recommendations (32), i.e., treatment with insulin or oral hypoglycemic agents, fasting plasma glucose level ≥126 mg/dl, or 2-h plasma glucose level ≥200 mg/dl after a 75-g glucose tolerance test.

Of the 4,549 participants examined at baseline, for 4,168 patients, diabetes status had been determined, lipoprotein measurements were available, and no CVD was present. Of these individuals, 2,108 had diabetes but no CVD at baseline and were included in this analysis. Total deaths and fatal CVD occurring between baseline and 31 December 1998 were identified through death certificates and tribal and Indian Health Service hospital records and by direct contact of study personnel with the study participants and their families. The process used to confirm CVD deaths has been described previously (21). Primary CVD deaths included myocardial infarction (MI), sudden cardiac death, coronary heart disease (CHD), stroke, congestive heart failure, and other fatal CVD. For nonfatal CVD, medical histories or medical records were reviewed during the second and third examinations to ascertain nonfatal CVD events that had occurred during follow-up. The process used to confirm nonfatal CVD events has been described previously (21). The nonfatal CVD events used in this study were CHD, MI, stroke, and other CVD. All fatal and nonfatal events were reviewed by committee following standard criteria to classify CVD (33).

Data were analyzed using SAS statistical software (Version 8.1; SAS Institute, Cary, NC). Incidence rates for fatal and nonfatal CVD were calculated per 1,000 person-years. Person-years were calculated from the date of the baseline examination to the date of the fatal event, the

Table 2—*Adjusted HRs for overall CVD by tertiles of non-HDL cholesterol in diabetic American Indians: the Strong Heart Study*

	Men		Women	
Tertiles*	Case/person-year†	HR (95% CI)‡	Case/person-year§	HR (95% CI)‡
Non-HDL cholesterol (mg/dl)				
T-1	57/1,894	1	78/3,404	1
T-2	56/1,883	1.02 (0.69–1.52)	105/3,344	1.33 (0.96–1.83)
T-3	89/1,654	2.23 (1.41–3.43)	136/3,123	1.80 (1.32–2.46)
HDL cholesterol (mg/dl)				
T-1	89/1,789	1	106/3,314	1
T-2	64/1,862	0.76 (0.54–1.07)	121/3,509	1.02 (0.77–1.36)
T-3	49/1,780	0.59 (0.40–0.88)	92/3,048	0.97 (0.71–1.32)
LDL cholesterol (mg/dl)				
T-1	57/1,905	1	88/3,364	1
T-2	70/1,794	1.34 (0.89–1.92)	103/3,327	1.23 (0.91–1.68)
T-3	75/1,732	1.71 (1.17–2.48)	128/3,180	1.61 (1.19–2.17)
Triglycerides (mg/dl)				
T-1	56/1,875	1	78/3,428	1
T-2	68/1,798	1.40 (0.94–2.07)	110/3,324	1.36 (0.99–1.87)
T-3	78/1,758	1.39 (1.00–1.98)	131/3,119	1.61 (1.17–2.22)
Ratio of total/HDL cholesterol				
T-1	43/1,937	1	86/3,401	1
T-2	68/1,838	1.85 (1.23–2.79)	102/3,313	1.16 (0.85–1.59)
T-3	91/1,655	2.46 (1.65–3.68)	131/3,157	1.48 (1.09–2.00)
Total	202/5,431		319/9,871	

**Tertiles for diabetic men*: non-HDL, <127, 127–162, >162; HDL, 36, 36–44, >44; LDL, <91, 91–115, >115; triglyceride, <106, 106–175, >175; total/HDL ratio, <4.1, 4.1–5.3, >5.3. *Tertiles for diabetic women*: non-HDL, <127, 127–160, >160; HDL, <40, 40–49, >49; LDL, <90, 90–115, >115; triglyceride, <113, 113–176, >176; total/HDL ratio, <3.8, 3.8–4.9, >4.9. †Case/person-year: diabetic (n = 772) and nondiabetic (n = 913). §Case/person-year: diabetic (n = 1,336) and nondiabetic (n = 1,147). ‡Adjusted for age, BMI, smoking status, study center, systolic blood pressure, HbA_{1c}, fibrinogen, insulin, and ratio of albumin to creatine.

first nonfatal event, or 31 December 1998 in event-free individuals. Subsequent analyses focused on comparisons between diabetic individuals who did and did not develop CVD. ANOVA was used for continuous variables and the χ^2 test was used for categorical variables.

Cox multivariate regression models were used to calculate the hazard ratios (HRs) and 95% CIs for tertiles of baseline non-HDL cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and ratio of total to HDL cholesterol to evaluate their independent roles as predictors of fatal and nonfatal CVD by sex, adjusted for confounding variables. Cox models were also used to calculate HRs and 95% CIs for non-HDL cholesterol and other levels to assess the association with incidence of CHD, MI, stroke, and all CVD in patients with diabetes. Kaplan-Meier plots for the proportion of patients with diabetes in whom CVD developed over 9 years of follow-up were estimated using the product-limit method. Statistical significance was defined either as $P < 0.05$ or 95% CIs for HRs that did not include 1.0. Because of their severely skewed distributions, insulin, triglycerides, and ratio of albumin to creatinine were log-transformed for statistical analyses.

RESULTS — Univariate comparisons of baseline CVD risk factors in patients with diabetes in whom CVD did and did not develop during follow-up are shown in Table 1. Compared with those who did not develop CVD, men and women with diabetes in whom CVD developed were older and had higher HbA_{1c} and SBP. Baseline total cholesterol, LDL cholesterol, triglycerides, VLDL triglycerides, VLDL cholesterol, albumin/creatinine ratio, fibrinogen, non-HDL cholesterol, and total/HDL cholesterol ratio were all significantly higher in patients with diabetes in whom CVD developed than in those with no CVD.

During the 9-year follow-up, CVD developed in 521 of the 2,108 diabetic participants and 145 of the 2,060 nondiabetic participants. The incidence of fatal and nonfatal CVD was 34.1/1,000 person-years (37.2 in men and 32.3 in women) in diabetic subjects and 8.9 in nondiabetic subjects (18.3 in men and 2.0 in women). The highest and middle tertiles of the lipoprotein parameters were compared with the lowest tertile in relation to CVD risk after adjustment for age, BMI, smoking status, study center, SBP, HbA_{1c}, fibrinogen, insulin, and albumin/creatinine ratio (Table 2). Although lipoprotein parameters were all significant predictors of CVD risk in men and women with diabetes (except HDL cholesterol in women), non-HDL cholesterol seemed to be the stronger predictor (except for total/HDL cholesterol ratio in men), with an HR of 2.23 (95% CI 1.41–3.43) in men and an HR of 1.80 (1.32–2.46) in women. A Kaplan-Meier plot by tertiles of non-HDL cholesterol (Fig. 1) shows continuous effects of non-HDL cholesterol on CVD risk in patients with diabetes over the 9-year follow-up period, especially for those in the highest tertile of non-HDL cholesterol.

Analyses of CVD subclasses were conducted in men and women combined. Increasing non-HDL cholesterol concentrations had significant, curvilinear relationships with CVD and CHD risk ($P < 0.001$) (Fig. 2). Compared with the refer-

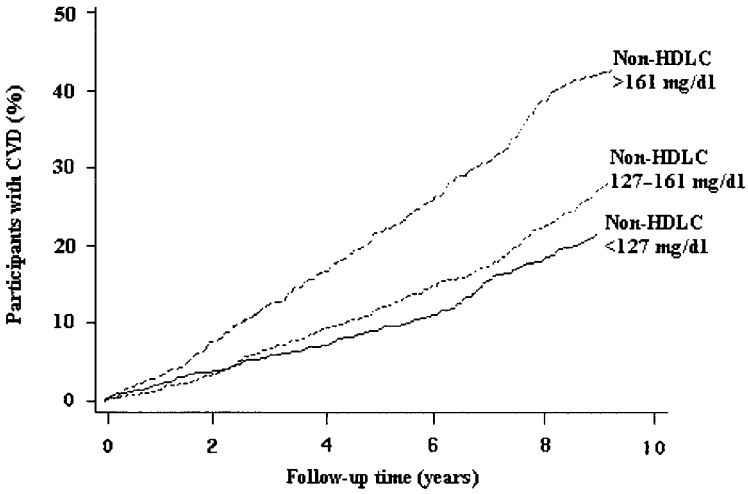

Figure 1—*Kaplan-Meier plot for CVD incidence by tertiles of non-HDL cholesterol: the Strong Heart Study.*

ence tertile, after adjustment for covariates (Table 3), non-HDL cholesterol was associated with a higher HR for MI than any of the lipid parameters and was higher than all but total/HDL ratio for CHD. However, there was overlap in the CIs.

Finally, we also compared the predictive value of non-HDL cholesterol for CHD and CVD in participants with triglyceride levels >150 and <150 mg/dl. The predictive value of non-HDL cholesterol was not greater in those with fasting triglyceride levels >150 mg/dl (Table 4). Similar results were observed for those with triglyceride levels ≥200 mg/dl, but the number of events was not adequate for stable estimates (data not shown).

CONCLUSIONS — The Adult Treatment Panel III of the National Cholesterol Education Program recently recommended that non-HDL cholesterol be used as a secondary target of therapy in people with triglyceride levels >200 mg/dl, especially those with diabetes or the metabolic syndrome (20). There are several advantages to the non-HDL cholesterol measurement. First, it makes no assumption about the relationship between VLDL cholesterol and triglycerides; in patients with diabetes, this relationship can be altered, leading to falsely low LDL values as calculated by the Friedewald formula, especially in conjunction with elevated triglyceride levels. Second, non-HDL cholesterol includes an assessment of all apolipoprotein B–containing lipoproteins considered to be atherogenic, i.e., VLDL, intermediate-density lipoprotein (IDL), and LDL, and even lipoprotein(a). Finally, non-HDL cholesterol has several practical advantages in a clinical setting, including the ability to be assessed in patients with triglyceride levels >400 mg/dl and in patients who are not fasting (34–41).

Diabetes is associated with greatly increased CVD. Although many factors play a role in the accelerated atherosclerosis observed in diabetes, lipoprotein abnormalities are key contributors. LDL, the main cholesterol-bearing lipoprotein, is a major determinant of atherosclerosis in patients with diabetes. Whereas average LDL concentrations in patients with diabetes may not be higher than those of their nondiabetic counterparts, changes in LDL particle composition, such as density, oxidation potential, and glycation, render even normal LDL levels highly atherogenic (10,42). Other lipoprotein abnormalities in patients with diabetes include changes in triglyceride-rich lipoproteins (43,44). VLDL remnants and IDL accumulate as a result of altered lipoprotein metabolism; both types of particles have been shown to be highly atherogenic. Also, remnant triglyceride–rich lipoproteins can be taken up by macrophages, leading to increased foam cell formation and accelerated atherosclerosis in patients with elevated triglyceride levels (16). Elevated VLDL is also associated with increases in prothrombotic and procoagulant factors. Because of the many lipoprotein abnormalities in diabetes, an easily measured composite indicator may be useful to clinicians who treat patients with diabetes.

The Strong Heart Study cohort is an ideal population to assess the utility of non-HDL cholesterol in predicting CVD in patients with diabetes. This population includes a large number of individuals with type 2 diabetes who have been under continued surveillance since 1989. Our data show that in both men and women with diabetes, non-HDL cholesterol is a strong predictor of CVD; although the CIs were overlapping, HRs are higher than those for either LDL cholesterol or triglycerides alone. When compared with the ratio of total/HDL cholesterol, a compos-

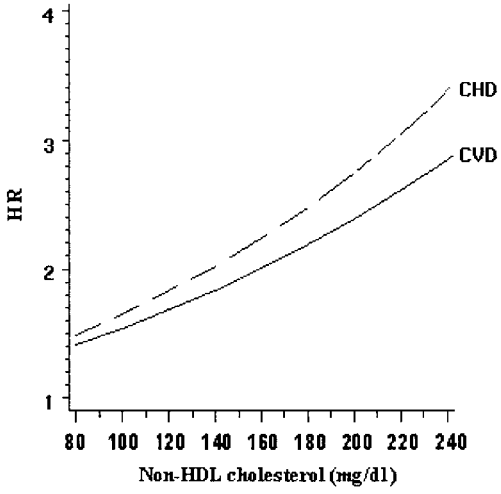

Figure 2—*Effect of non-HDL cholesterol on CVD and CHD, adjusted for sex, age, BMI, smoking status, study center, systolic blood pressure, HbA_{1c}, fibrinogen, insulin, and albumin to creatinine ratio: the Strong Heart Study.*

Table 3—*Adjusted HRs for CVD by tertiles of non-HDL cholesterol in American Indians with diabetes: the Strong Heart Study*

		CHD		MI		Stroke		CVD	
Strata	No.	Case/ person-year	HR (95% CI)	Case/ person-year	HR (95% CI)	Case/ person-year	HR (95% CI)	Case/ person-year	HR (95% CI)
Non-HDL cholesterol									
<127 mg/dl	706	42/5,703	1	417/5,806	1	24/5,780	1	135/5,297	1
127–161 mg/dl	714	65/5,674	1.37 (0.92–2.05)	26/5,801	1.60 (0.83–3.11)	29/5,769	0.85 (0.47–1.54)	160/5,276	1.21 (0.95–1.56)
>161 mg/dl	688	125/5,191	2.75 (1.91–3.97)	48/5,485	3.17 (1.72–5.84)	35/5,536	0.99 (0.56–1.74)	226/4,728	1.94 (1.53–2.46)
HDL cholesterol									
<39 mg/dl	777	111/5,895	1	44/6,124	1	32/5,802	1	210/5,415	1
39–47 mg/dl	684	70/5,428	0.75 (0.55–1.03)	26/5,608	0.67 (0.40–1.12)	35/5,603	1.24 (0.73–2.10)	166/5,024	0.84 (0.68–1.05)
>47 mg/dl	647	51/5,245	0.57 (0.39–0.82)	21/5,360	0.59 (0.34–1.04)	21/5,681	0.92 (0.49–1.69)	145/4,862	0.80 (0.63–1.02)
LDL cholesterol									
<91 mg/dl	728	57/5,834	1	23/5,961	1	30/5,922	1	146/5,433	1
91–115 mg/dl	683	72/5,382	1.29 (0.90–1.85)	27/5,556	1.28 (0.71–2.30)	21/5,588	0.66 (0.36–1.19)	172/4,956	1.28 (1.02–1.62)
>115 mg/dl	697	103/5,352	1.90 (1.35–2.67)	41/5,575	1.96 (1.14–3.37)	37/5,576	1.03 (0.61–1.75)	203/4,912	1.61 (1.29–2.02)
Triglycerides									
<111 mg/dl	714	45/5,733	1	18/5,829	1	24/6,178	1	131/5,347	1
111–175 mg/dl	691	76/5,425	1.98 (1.34–2.94)	29/5,617	1.56 (0.83–2.93)	30/5,550	1.28 (0.71–2.33)	179/5,017	1.44 (1.13–1.83)
>175 mg/dl	703	111/5,410	2.12 (1.44–3.11)	44/5,646	2.04 (1.12–3.69)	34/5,358	0.80 (0.43–1.50)	211/4,937	1.42 (1.11–1.81)
Total/HDL cholesterol ratio									
<3.9	702	39/5,753	1	19/5,814	1	21/5,802	1	128/5,362	1
3.9–5.0	704	83/5,517	2.11 (1.37–3.08)	27/5,722	1.69 (0.90–3.19)	34/5,681	1.27 (0.70–2.30)	181/5,090	1.50 (1.18–1.92)
>5.0	702	110/5,298	3.06 (2.03–4.59)	45/5,556	2.20 (1.21–3.98)	33/5,602	1.20 (0.64–2.23)	212/4,849	1.81 (1.41–2.31)
Total	2,108	232/16,568		91/17,092		88/17,085		521/15,301	

*Adjusted for sex, age, BMI, smoking status, study center, SBP, HbA_{1c}, fibrinogen, insulin, and albumin to creatinine ratio.

ite indicator suggested by the Framingham study (45), non-HDL cholesterol had a higher HR in women (1.80 vs. 1.48) but was slightly lower in men (2.23 vs. 2.46).

This report is the first population-based comparison of the utility of non-HDL cholesterol and individual lipoprotein parameters in predicting CVD in patients with diabetes. In the Systolic Hypertension in the Elderly Program (SHEP), a study of elderly, primarily white, nondiabetic individuals, non-HDL cholesterol was assessed along with serum cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol as a predictor of cardiovascular events in 4,736 participants. During an average 4.5 years of follow-up, non-HDL cholesterol was shown to be a predictor of cardiovascular events in multivariate analysis in the total population. Non-HDL cholesterol and LDL cholesterol had similar HRs in individuals with triglyceride levels >400 mg/dl; however, non-HDL cholesterol, but not LDL cholesterol, was an independent predictor of CVD when triglycerides were included in the model (46). In the Gubbio study (47), a sample of 2,963 men and women aged 35–74 with no major CVD was examined in 1983. Risk factors were measured and 6-year incidence was computed for CHD and all cardiovascular events. Multivariate models showed that the relative risk for a difference of 40 mg/dl in non-HDL cholesterol ranged from 1.15 to 1.27. Findings from the Lipid Research Clinics Program Follow-Up Study, in which a total of 4,462 men and women were followed for 19 years, showed that non-HDL cholesterol emerged as a somewhat better predictor of CVD mortality than LDL (19). Our findings of the utility of non-HDL cholesterol as a predictor of CVD in a large cohort of patients with diabetes are of particular interest considering the dyslipidemia that is common in diabetes.

Our analyses provide strong supportive evidence that non-HDL cholesterol may be particularly useful in treating patients with diabetes. However, this analysis is restricted to American Indians, who have the highest rate of diabetes of any ethnic group in the U.S. (5). Ethnic differences in CVD risk factors and cultural/lifestyle practices require that our findings be confirmed in other diabetic populations. Importantly, because there were few cases of CVD in the nondiabetic

members of this cohort, it was not possible to adequately assess the utility of non-HDL cholesterol in individuals with the metabolic syndrome but without frank diabetes. This important question remains to be answered.

An important issue for interpretation of these results is the impact of the variance of a lipoprotein measure on its utility as a predictor of CVD. The intra-individual variation in triglyceride concentrations is much higher than that of HDL or LDL cholesterol. Therefore, it is not clear whether the diminished significance of triglycerides as a predictor is simply due to the fact that an accurate integrated measure of average triglyceride concentrations over a longer period of time cannot be obtained from a single fasting sample. Non-HDL cholesterol would be subjected to some of the same considerations. Although more stable than total triglyceride because a large component is LDL cholesterol, non-HDL cholesterol is also a reflection of VLDL and IDL cholesterol, which fluctuate widely in individuals from day to day, depending on dietary patterns and other metabolic variables. Use of non-HDL cholesterol in the nonfasting state, although feasible, would enhance this variability. Therefore, it is possible that this measure could be of even greater use if an integrated value that reflected days or weeks of combined VLDL, IDL, and LDL cholesterol concentrations could be developed.

In summary, our results show that non-HDL cholesterol is a significant predictor of CVD in diabetic men and women. Because diabetic patients are at high risk for CVD morbidity and mortality, adequate risk assessment and management is imperative. The simple non-HDL cholesterol measurement, which can be conducted in the nonfasting state and can be determined regardless of triglyceride concentration, may be of particular clinical utility. The Adult Treatment Panel (ATP-III) of the National Cholesterol Education Program recommended a therapeutic goal for non-HDL cholesterol of 30 mg/dl higher than the goal for LDL cholesterol; therefore, in patients with diabetes, the goal would be a non-HDL cholesterol target of <130 mg/dl.

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Table 4—*Adjusted HRs (upper versus lower tertile) for CVD and CHD in diabetic individuals with triglyceride levels greater than, less than, or equal to 150 mg/dl: the Strong Heart Study*

	CHD		CVD		Triglycerides
Lipoproteins	>150	≤150	>150	≤150	>150	≤150
Non-HDL cholesterol (mg/dl)	1.78 (1.13–2.80)	2.79 (1.53–5.10)	1.52 (1.12–2.07)	1.80 (1.27–2.54)	>181 vs. <151	>147 vs. <115
HDL cholesterol (mg/dl)	0.75 (0.48–1.19)	0.49 (0.27–0.89)	0.99 (0.72–1.36)	0.67 (0.46–0.96)	>43 vs. <35	>50 vs. <41
LDL cholesterol (mg/dl)	1.86 (1.21–2.88)	2.28 (1.31–3.98)	1.58 (1.16–2.16)	1.66 (1.17–2.34)	>119 vs. <93	>113 vs. <89
Triglycerides (mg/dl)	1.05 (0.68–1.63)	1.51 (0.89–2.56)	1.02 (0.75–1.39)	1.29 (0.93–1.79)	>260 vs. <191	>117 vs. <88
Ratio of total/HDL cholesterol	1.74 (1.11–2.75)	3.69 (1.97–6.93)	1.26 (0.92–1.72)	1.99 (1.40–2.81)	>6.0 vs. <4.8	>4.4 vs. <3.5

*Adjusted for sex, age, BMI smoking status, study center, SBP, HbA_{1c}, fibrinogen, insulin, and albumin to creatinine ratio.

References

1. 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* 16:434–444, 1993
2. Pyorala K, Laakso M, Uustitupa M: Diabetes and atherosclerosis: an epidemiology view. *Diabetes Metab Rev* 3:463–524, 1987
3. Department of Health and Human Services: Indian Health Service: HIS chart series book. Washington, DC, U.S. Govt. Printing Office, 1984
4. Sievers ML, Nelson RG, Knowler WC, Bennett PH: Impact of NIDDM on mortality and causes of death in Pima Indians. *Diabetes Care* 15:1541–1549, 1992
5. Howard BV, Lee ET, Cowan LD, Devereux RB, Galloway JM, Go OT, Howard WJ, Rhoades ER, Robbins DC, Sievers ML, Welty TK: The rising tide of cardiovascular disease in American Indians: the Strong Heart Study. *Circulation* 99:2389–2395, 1999
6. 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* 142: 254–268, 1995
7. Howard BV: Risk factors for cardiovascular disease in individuals with diabetes: the Strong Heart Study. *Acta Diabetol* 33: 180–184, 1996
8. Howard BV, Lee ET, Fabsitz RR, Robbins DC, Yeh JL, Cowan LD, Welty TK: Diabetes and coronary heart disease in American Indians: the Strong heart Study. *Diabetes* 45:S6–S13, 1996
9. Howard BV, Robbins DC, Cowan LD, Lee ET, Go OT, Welty TK: Adverse effects of diabetes on multiple cardiovascular disease risk factors in women: the Strong Heart Study. *Diabetes Care* 21:1258–

1265, 1998
10. Reaven GM: Non-insulin-dependent diabetes mellitus, abnormal lipoprotein metabolism, and atherosclerosis. *Metabolism* 36 (Suppl. 1):1–8, 1987
11. Barrett-Connor E, Grundy SM: Holdbrook JJ: Plasma lipids and diabetes mellitus in an adult community. *Am J Epidemiol* 115:657–663, 1982
12. Wilson PW, Kannel WB, Anderson KM: Lipids glucose tolerance and vascular disease: the Framingham Study. *Monogr Atheroscler* 13:1–11, 1985
13. Castelli WP, Garrison RJ, Wilson PWF, Abbott RD, Kalousdian S, Kannel WB: Incidence of coronary heart disease and lipoprotein cholesterol levels: the Framingham Study. *JAMA* 256:2835–2838, 1986
14. Pedersen TR, Olsson AG, Feargeman O, Kjekshus J, Wedel H, Wilhelmsen L, Haghfelt T, Thorgeirsson G, Pyorala K, Miettinen T, Christophersen B, Tobert JA, Musliner TA, Cook TJ: Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). *Circulation* 97:1453–1460, 1998
15. Barbagallo CM, Averna MR, Amato S, Marino G, Labisi M, Rao AC, Barbagallo M, Cupidi GF, Notarbartolo A: Apolipoprotein profile in type II diabetic patients with and without coronary heart disease. *Acta Diabetol Latina* 27:371–377, 1990
16. Havel RJ, Rapaport E: Management of primary hyperlipidemia. *N Engl J Med* 332: 1491–1498, 1995
17. Frost PH, Havel RJ: Rationale for use of non-high-density lipoprotein cholesterol rather than low-density lipoprotein cholesterol as a tool for lipoprotein cholesterol screening and assessment of risk and therapy. *Am J Cardiol* 81:26B–31B, 1998
18. Garg A, Grundy SM: Management of dyslipidemia in NIDDM. *Diabetes Care* 13: 153–169, 1990
19. Cui Y, Blumenthal RS, Flaws JA, Whiteman MK, Langenberg P, Bachorik PS, Bush TL: Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. *Arch Intern Med* 161:1413–1419, 2001
20. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adult (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001
21. Lee ET, Welty TK, Fabsitz RR, Cowan LD, Le NA, 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* 132:1141–1155, 1990
22. Howard BV, Welty TK, Fabsitz RR, Cowan LD, Oopik AJ, Le NA, Yeh JL, Savage PJ, Lee ET: Risk factors for coronary heart disease in diabetic and nondiabetic Native Americans: the Strong Heart Study. *Diabetes* 41 (Suppl. 2):4–11, 1992
23. 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. *J Natl Center Am Indian Alaska Native Ment Health Res* 9:20–37, 2000
24. Robbins DC, Welty TK, Wang WY, Lee ET, Howard BV: Plasma lipids and lipoprotein concentrations among American Indians: comparison with U.S. population. *Curr Opin Lipidol* 7:188–196, 1996
25. Department of Health, Education, and Welfare: Lipid Research Clinics Program: manual of laboratory operations. Vol. 1. Washington, DC, U.S. Govt. Printing Office, 1994 (DHEW publ. no. 75–628)
26. von Clauss A: Gerinnungsphysiologische scnellmethods zur bestimmung des fibrinogens. *Acta Haematol* 17:237–246, 1957
27. Little RR, England JD, Wiedmeyer HM: Interlaboratory standardization of glycated hemoglobin determinations. *Clin Chem* 32:358–360, 1986
28. 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* 26:127–133, 1984
29. Chasson AL, Grady HJ, Stanley MA: Determination of creatinine by means of automatic chemical analysis. *Tech Bull Regist Med Technol* 30:207–212, 1960
30. Krauss RM, Burke DJ: Identification of multiple subclasses of plasma low density lipoproteins in normal humans. *J Lipid Res* 23:97–104, 1982
31. Department of Health and Human Services: Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Washington, DC, U.S. Govt. Printing Office, 1993 (NIH publ. no. 93–1088)
32. Alberti KGMM, Zimmet PZ, for the WHO Consultation: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 15:539–553, 1998
33. 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 45–75 years, 1984–1988: the Strong Heart Study. *Am J Epidemiol* 147:995–1008, 1998
34. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
35. Expert Panel (Adult Treatment Panel II): Detection, evaluation, and treatment of high blood cholesterol in adults. *Circulation* 89:1329–1445, 1994
36. Winkleby MA, Robinson TN, Sundquist J, Kraemer HC: Ethnic variation in cardiovascular disease risk factors among children and young adults: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. *JAMA* 281:1006–1013, 1999
37. Winkleby MA, Kraemer HC, Ahn DK, Varady AN: Ethnic and socioeconomic differences in cardiovascular disease risk factors: findings for women from the Third National Health and Nutrition Examination Survey, 1988–1994. *JAMA* 280:356–362, 1998
38. Lehto S, Ronnemaa T, Haffner SM, Pyorala K, Kallio V, Laakso M: Dyslipidemia and hyperglycemia predict coronary heart disease events in middle-aged patients with NIDDM. *Diabetes* 46:1354–1359, 1997
39. Gardner CD, Fortmann SP, Krauss RM: Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women. *JAMA* 276:875–881, 1996
40. Haffner SM: Management of dyslipidemia in adults with diabetes. *Diabetes Care* 21: 160–178, 1998
41. Gardner CD, Winkleby MA, Fortmann SP: Population frequency distribution of non-high-density lipoprotein cholesterol (Third National Health and Nutrition Examination Survey [NHANES III], 1988–1994). *Am J Cardiol* 86:299–304, 2000
42. Niskanen L, Turpeinen A, Penttila I, Uusitupa MI. Hyperglycemia and compositional lipoprotein abnormalities as predictors of cardiovascular mortality in type 2 diabetes: a 15-year follow-up from the time of diagnosis. *Diabetes Care* 21: 1861–1869, 1998
43. Austin MA: Plasma triglyceride as a risk factor for cardiovascular disease. *Can J Cardiol* 14 (Suppl. B):14B–17B, 1998
44. Hokanson JE, Austin MA: Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Disc Risk* 3:213–219, 1996
45. Kannel WB: The Framingham Study: its

50-year legacy and future promise. *J Atheroscler Thromb* 6:60–66, 2000
46. Frost PH, Davis BR, Burlando AJ, Curb JD, Guthrie GP Jr, Isaacsohn JL, Wassertheil-Smoller S, Wilson AC, Stamler J: Serum lipids and incidence of coronary heart disease: findings from the Systolic Hypertension in the Elderly Program (SHEP). *Circulation* 94:2381–2388, 1996
47. Menotti A, Lanti M, Puddu PE, Mancini M, Zanchetti A, Cirillo M, Vagnarelli OT: First risk functions for prediction of coronary and cardiovascular disease incidence in the Gubbio Population Study. *Italian Heart J* 1:394–399, 2000 Med Technol 30:207–212, 1960
30. Krauss RM, Burke DJ: Identification of multiple subclasses of plasma low density lipoproteins in normal humans. *J Lipid Res* 23:97–104, 1982
31. Department of Health and Human Services: Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Washington, DC, U.S. Govt. Printing Office, 1993 (NIH publ. no. 93–1088)
32. Alberti KGMM, Zimmet PZ, for the WHO Consultation: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 15:539–553, 1998
33. 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 45–75 years, 1984–1988: the Strong Heart Study. *Am J Epidemiol* 147:995–1008, 1998
34. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
35. Expert Panel (Adult Treatment Panel II): Detection, evaluation, and treatment of high blood cholesterol in adults. *Circulation* 89:1329–1445, 1994
36. Winkleby MA, Robinson TN, Sundquist J, Kraemer HC: Ethnic variation in cardiovascular disease risk factors among children and young adults: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. *JAMA* 281:1006–1013, 1999
37. Winkleby MA, Kraemer HC, Ahn DK, Varady AN: Ethnic and socioeconomic differences in cardiovascular disease risk factors: findings for women from the Third National Health and Nutrition Examination Survey, 1988–1994. *JAMA* 280:356–362, 1998
38. Lehto S, Ronnemaa T, Haffner SM, Pyorala K, Kallio V, Laakso M: Dyslipidemia and hyperglycemia predict coronary heart disease events in middle-aged patients with NIDDM. *Diabetes* 46:1354–1359, 1997
39. Gardner CD, Fortmann SP, Krauss RM: Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women. *JAMA* 276:875–881, 1996
40. Haffner SM: Management of dyslipidemia in adults with diabetes. *Diabetes Care* 21: 160–178, 1998
41. Gardner CD, Winkleby MA, Fortmann SP: Population frequency distribution of non-high-density lipoprotein cholesterol (Third National Health and Nutrition Examination Survey [NHANES III], 1988–1994). *Am J Cardiol* 86:299–304, 2000
42. Niskanen L, Turpeinen A, Penttila I, Uusitupa MI. Hyperglycemia and compositional lipoprotein abnormalities as predictors of cardiovascular mortality in type 2 diabetes: a 15-year follow-up from the time of diagnosis. *Diabetes Care* 21: 1861–1869, 1998
43. Austin MA: Plasma triglyceride as a risk factor for cardiovascular disease. *Can J Cardiol* 14 (Suppl. B):14B–17B, 1998
44. Hokanson JE, Austin MA: Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Disc Risk* 3:213–219, 1996
45. Kannel WB: The Framingham Study: its 50-year legacy and future promise. *J Atheroscler Thromb* 6:60–66, 2000
46. Frost PH, Davis BR, Burlando AJ, Curb JD, Guthrie GP Jr, Isaacsohn JL, Wassertheil-Smoller S, Wilson AC, Stamler J: Serum lipids and incidence of coronary heart disease: findings from the Systolic Hypertension in the Elderly Program (SHEP). *Circulation* 94:2381–2388, 1996
47. Menotti A, Lanti M, Puddu PE, Mancini M, Zanchetti A, Cirillo M, Vagnarelli OT: First risk functions for prediction of coronary and cardiovascular disease incidence in the Gubbio Population Study. *Italian Heart J* 1:394–399, 2000