Apolipoprotein B but not LDL Cholesterol Is Associated With Coronary Artery Calcification in Type 2 Diabetic Whites

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OBJECTIVE—Evidence favors apolipoprotein B (apoB) over LDL cholesterol as a predictor of cardiovascular events, but data are lacking on coronary artery calcification (CAC), especially in type 2 diabetes, where LDL cholesterol may underestimate atherosclerotic burden. We investigated the hypothesis that apoB is a superior marker of CAC relative to LDL cholesterol.

RESEARCH DESIGN AND METHODS—We performed cross-sectional analyses of white subjects in two community-based studies: the Penn Diabetes Heart Study ($N = 611$ type 2 diabetic subjects, 71.4% men) and the Study of Inherited Risk of Coronary Atherosclerosis ($N = 803$ nondiabetic subjects, 52.8% men) using multivariate analysis of apoB and LDL cholesterol stratified by diabetes status.

RESULTS—In type 2 diabetes, apoB was associated with CAC after adjusting for age, sex, and medications [Tobit regression ratio of increased CAC for 1-SD increase in apoB; 1.36 (95% CI 1.06–1.75), $P = 0.016$] whereas LDL cholesterol was not [1.09 (0.85–1.41)]. In nondiabetic subjects, both were associated with CAC [apoB 1.65 (1.38–1.96), $P < 0.001$; LDL cholesterol 1.56 (1.30–1.86), $P < 0.001$]. In combined analysis of diabetic and nondiabetic subjects, apoB provided value in predicting CAC scores beyond LDL cholesterol, total cholesterol, the total cholesterol/HDL cholesterol and triglyceride/HDL cholesterol ratios, and marginally beyond non-HDL cholesterol.

CONCLUSIONS—Plasma apoB, but not LDL cholesterol, levels were associated with CAC scores in type 2 diabetic whites. ApoB levels may be particularly useful in assessing atherosclerotic burden and cardiovascular risk in type 2 diabetes. ***Diabetes* 58: 1887–1892, 2009**

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Apolipoprotein B (apoB) may be more useful clinically than LDL cholesterol in coronary heart disease (CHD) because it captures greater information about atherogenic particles and is not influenced by heterogeneity of particle cholesterol content (1). Measurement of LDL cholesterol is relatively insensitive to the accumulation of small, dense LDL particles, which are believed to be highly atherogenic (1). This is reflected in the preponderance of evidence from prospective epidemiologic studies and statin trials favoring apoB over LDL cholesterol as a predictor of cardiovascular risk as well as residual risk on statin therapy (2–10).

Heterogeneity of LDL particle cholesterol content is increased in type 2 diabetes because insulin resistance drives VLDL cholesterol production, leading to depletion of LDL cholesterol via the action of cholesterol ester transfer protein (CETP) (11). CETP exchanges triglycerides for cholesterol on LDL particles, which are remodeled by lipases to produce cholesterol-poor, small, dense LDL particles (11,12). Because there is one apoB per LDL particle, regardless of density, apoB detects the presence of these atherogenic particles, in contrast to LDL cholesterol, and thus may be better suited to guide lipid-lowering therapy, particularly in insulin resistance and type 2 diabetes.

Data are lacking on the relationship of apoB to coronary artery calcification (CAC), a quantitative measure of subclinical atherosclerosis and predictor of CHD in diabetes (13) as well as in the general population (14,15). Therefore, we examined the relative association of plasma apoB and LDL cholesterol with CAC in two cross-sectional studies of individuals without known CHD, one recruited based on type 2 diabetes and the other based on family history of CHD. We hypothesized that apoB levels would be stronger predictors of CAC than LDL cholesterol levels, particularly in type 2 diabetic subjects. We also hypothesized that apoB might add incremental value to traditional cholesterol-based CHD risk parameters.

RESEARCH DESIGN AND METHODS

Study participants. Details of the Penn Diabetes Heart Study (PDHS) (16,17) and the Study of Inherited Risk of Coronary Atherosclerosis (SIRCA) (18–20) have been reported previously. In brief, both are contemporary, single-center, cross-sectional community-based studies of subjects without clinical evidence of CHD (defined as myocardial infarction, coronary revascularization, angiographic disease, or positive stress test) recruited at the University of Pennsylvania that used the same clinical research center, research staff, electron beam computed tomography scanner, and lipid laboratory. SIRCA subjects were recruited in 1995–2005 based on a family history of premature CHD. PDHS subjects were recruited in 2001–2007 based on type 2 diabetes.

Exclusion criteria included clinical CHD, elevated creatinine, and, in SIRCA, the presence of diabetes. This report focuses on unrelated, white subjects (diabetic participants $n = 611$, nondiabetic participants $n = 803$).

Evaluated parameters. Participants were evaluated at the General Clinical Research Center at the University of Pennsylvania Medical Center after a 12-h overnight fast. ApoB and plasma lipids were measured in Penn's Center for Disease Control–certified lipid laboratory. Standard lipid panels and apoB were measured enzymatically (Cobas Fara II; Roche Diagnostic Systems, Somervile, NJ) in lipoprotein fractions after ultracentrifugation (β-quantification technique) in PDHS (21) and in whole serum in SIRCA in a Penn's Center for Disease Control–certified lipid laboratory (21). Analyses use LDL cholesterol calculated by the Friedewald formula; direct LDL cholesterol measurement was available for diabetic subjects and produced essentially identical results (data not shown). For apoB and C-peptide response (high sensitivity), immunoturbidimetric assays were used (16,19). Laboratory test results were generated by personnel blinded to the clinical characteristics and CAC scores of research subjects. Clinical parameters, including blood pressure and waist circumference, were assessed as previously reported (16,18). Framingham risk scores, using calculated LDL cholesterol (similar results using total cholesterol), were determined as described by Wilson et al. (22). Subjects were classified as having the metabolic syndrome using the revised National Cholesterol Education Program definition (glucose cut point 100 mg/dl) (23). Global CAC scores were quantified as described (18) according to the method of Agatston et al. (24) by electron beam tomography.

Statistical analysis. Data are reported as median (interquartile range [IQR]) or mean ± SD for continuous variables and as proportions for categorical variables. The crude association of apoB and LDL cholesterol with lipid, metabolic, and inflammatory parameters was examined by Spearman correlation. Multivariable analysis of CAC scores was performed using Tobit conditional regression of natural log (CAC+1). Tobit conditional regression is particularly suited to the unusual distribution of CAC data (many zero scores but also a marked right skew) (18,25). It combines two regression approaches: first, a logistic regression of the presence of CAC (any CAC present versus CAC zero score) and second, a linear regression (of log-transformed CAC) when CAC is present. This provides a single estimate for the relationship of risk factors with CAC data. We present Tobit ratios for CAC score increment for a 1-SD increase in a lipid parameter, which allows a similarly scaled comparison of different lipid parameters. A Tobit ratio of 1.30 means that there is a 30% increase in the CAC score for every SD increase in a lipid parameter. We also performed secondary logistic regression analysis of the presence of any CAC.

Our modeling is based on the assumption that current lipoprotein measures reflect prior levels and exposures that contributed to atherosclerosis over time. The association of apoB, LDL cholesterol, and non-HDL cholesterol levels with CAC was assessed in incremental models with increasing numbers of confounding risk factors: Model 1 was adjusted for age, sex, and medications; model 2 was additionally adjusted for atherosclerotic risk factors including hypertension, tobacco use, alcohol use, exercise, family history of premature CHD, C-reactive protein, and metabolic syndrome; whereas for apoB, model 3 was further adjusted for total cholesterol. Interaction of apoB and LDL cholesterol with type 2 diabetes was tested by likelihood ratio testing, and stratified results are presented when appropriate. Finally, we applied likelihood ratio testing in nested models to assess the incremental value of apoB over cholesterol parameters and clinical risk assessments (Framingham risk score, metabolic syndrome), and vice versa, in predicting CAC scores. Statistical analyses were performed using Stata 10.0 software (Stata, College Station, TX).

RESULTS

Characteristics of study samples. Table 1 summarizes study sample characteristics stratified by type 2 diabetes status. Diabetic subjects were older, predominantly male, more obese, and had lower total and LDL cholesterol as well as apoB levels ($P < 0.001$ for all), likely reflecting greater use of statin therapy. Fifteen percent of those with diabetes were on insulin, and median A1C was 6.8%. As expected, National Cholesterol Education Panel–defined metabolic syndrome was present in over 75% of type 2 diabetic and ~25% of nondiabetic patients. The correlation of apoB with LDL cholesterol was similar in diabetic ($r^2 = 0.67$) and nondiabetic ($r^2 = 0.64$) subjects. Spearman correlations revealed associations of apoB and LDL cholesterol with other CHD risk parameters that were broadly similar across diabetes status (Table 2).

TABLE 1
Characteristics of the study sample

	Type 2 diabetic subjects	Nondiabetic subjects
n	611	803
Age (years)	60 (54–68)	48 (42–54)
Male (%)	71.4	52.8
Total cholesterol (mg/dl)	174 (152–198)	205 (177–228)
HDL cholesterol (mg/dl)	45 (37–53)	48 (39–59)
Triglycerides (mg/dl)	134 (92–197)	117 (87–159)
LDL cholesterol (mg/dl)	97 (79–119)	126 (103–148)
ApoB (mg/dl)	82 (71–94)	98 (84–114)
Medications		
Statin (%)	57.4	13.9
Niacin (%)	5.6	3.0
Fibrate (%)	10.0	1.1
Insulin (%)	14.9	N/A
Metformin (%)	63.8	N/A
Thiazolidinediones (%)	27.3	N/A
Sulfonylureas (%)	40.3	N/A
Ten-year Framingham risk (%)	13 (8–20)	5 (3–8)
Current smoking (%)	8.4	11.3
Alcohol use (%)	58.4	67.8
Blood pressure (mmHg)		
Systolic	131 (122–140)	126 (117–136)
Diastolic	75 (71–81)	77 (72–84)
BMI (kg/m^2)	32 (28–36)	27 (24–30)
Waist circumference (cm)	107 (98–117)	89 (81–99)
Metabolic syndrome (%)	76.6	25.8
C-reactive protein (mg/dl)	1.6 (0.8–3.4)	1.2 (0.5–2.6)
CAC		
Mean score (±SD)	424 ± 795	87 ± 266
Median (IQR)	89 (1–456)	3 (0–45)
>0 (%)	75.3	68.9
≥100 (%)	49.1	16.4
≥400 (%)	26.8	5.4

Data are median (IQR) or percent, unless otherwise noted.

Plasma levels of apoB, but not of LDL cholesterol, are associated with CAC in diabetic participants. In type 2 diabetic whites (Table 3, left columns), apoB [Tobit ratio for 1-SD increase, 1.36 (95% CI 1.06–1.75), $P = 0.016$], but

TABLE 2
Spearman correlations of lipid, metabolic, and inflammatory variables with plasma apoB and LDL cholesterol

	Type 2 diabetic subjects ($n = 611$)		Nondiabetic subjects ($n = 803$)	
	ApoB	LDL cholesterol	ApoB	LDL cholesterol
Total cholesterol	0.78‡	0.90‡	0.77‡	0.90‡
HDL cholesterol	−0.21‡	0.02	−0.21‡	−0.03
Triglycerides	0.47‡	0.15‡	0.51‡	0.18†
Glucose	0.20‡	0.07	0.12‡	0.02
Waist circumference	0.08*	−0.004	0.25‡	0.13‡
BMI	0.07	−0.05	0.23‡	0.13‡
Framingham risk	0.43‡	0.41‡	0.50‡	0.38‡
Blood pressure				
Systolic	0.05	−0.01	0.20‡	0.14‡
Diastolic	0.14‡	0.05	0.20‡	0.12‡
C-reactive protein	0.17‡	0.05	0.25‡	0.12‡

*$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$.

TABLE 3
Association of plasma levels of apoB and cholesterol parameters with CAC

Variables adjusted for	Type 2 diabetic subjects (n = 611)	Nondiabetic subjects (n = 803)
	*Tobit ratio (95% CI)	*Tobit ratio (95% CI)
ApoB		
Age, sex, medications	*1.36 (1.06–1.75)	1.65 (1.38–1.96)
Age, sex, medications, risk factors	1.37 (1.05–1.79)	1.50 (1.25–1.80)
LDL cholesterol		
Age, sex, medications	1.09 (0.85–1.41)	1.56 (1.30–1.86)
Age, sex, medications, risk factors	1.13 (0.87–1.47)	1.51 (1.27–1.81)
Non-HDL cholesterol		
Age, sex, medications	1.30 (1.01–1.68)	1.68 (1.41–2.00)
Age, sex, medications, risk factors	1.28 (0.99–1.67)	1.54 (1.29–1.85)

Results of Tobit conditional regression are presented as the ratio of increase in CAC score for 1-SD increase in apoB (17.84 mg/dl in diabetic subjects; 22.83 mg/dl in nondiabetic subjects), LDL cholesterol (31.63 mg/dl in diabetic subjects; 35.08 mg/dl in nondiabetic subjects), or non-HDL cholesterol (36.91 mg/dl in diabetic subjects; 38.79 mg/dl in nondiabetic subjects). *Tobit ratio of 1.36 means that for every 17.84 mg/dl (1-SD) increase in apoB, there is a 36% increase in the CAC score. Medications included statins, niacin, fibrates, insulin, metformin, thiazolidinediones, sulfonylureas, and hormone replacement therapy. Risk factors included hypertension, tobacco use, alcohol use, exercise, family history of premature cardiovascular disease, C-reactive protein, and metabolic syndrome.

not LDL cholesterol [1.09 (0.85–1.41)], was associated with CAC after adjusting for age, sex, and lipid-lowering and diabetes medications. In nondiabetic patients (Table 3, right columns), both apoB [1.65 (1.38–1.96), $P < 0.001$] and LDL cholesterol [1.56 (1.30–1.86), $P < 0.001$] were associated with CAC in this simple model. After further adjusting for multiple cardiovascular risk factors, this pattern of CAC association persisted (Table 3). Even after adjusting for total cholesterol, apoB continued to have a strong association with CAC in diabetic subjects [1.83 (1.17–2.85)], whereas in nondiabetic subjects, this was attenuated [1.22 (0.90–1.65)]. In combined analysis of diabetic and nondiabetic subjects, interaction analysis suggested a consistent CAC association for apoB (diabetes interaction $P = 0.25$), but a difference by diabetes status in the relationship of LDL cholesterol with CAC (interaction $P = 0.02$). Results of logistic regression of the presence of CAC were similar to that for Tobit modeling (see Appendix Table 1, available online at http://diabetes.diabetesjournals.org/cgi/content/full/db08-1794/DC1). To explore the effect of greater statin use in the diabetic versus nondiabetic samples, we performed a secondary analysis excluding statin users. These analyses yielded analogous findings to the full sample for the pattern of apoB, LDL cholesterol, and other lipid relationships with CAC (Appendix Table 2 in the online appendix).

In diabetic participants, plasma levels of non-HDL cholesterol had stronger CAC association than LDL cholesterol but less than that for apoB. In contrast, non-HDL cholesterol had almost identical CAC association as apoB in nondiabetic whites (Table 3; Appendix Tables 1 and 2 in the online appendix).

Incremental value of apoB levels over cholesterol-based risk parameters. We combined data across diabetic and nondiabetic subjects and assessed the incremental value of apoB over cholesterol parameters (Table 4, *top rows*). ApoB added value in predicting CAC scores when added to LDL cholesterol and total cholesterol. In fact, it also added value to the total cholesterol/HDL cholesterol and triglyceride/HDL cholesterol ratios and marginally to non-HDL cholesterol. In contrast, adding LDL cholesterol, total cholesterol, and non-HDL cholesterol to apoB failed to provide additional value (Table 4, *bottom rows*). As expected, because they contain HDL data, the total cholesterol/HDL cholesterol and triglyceride/HDL cholesterol ratios added value to apoB in predicting CAC score. Notably, apoB provided incremental value in predicting CAC beyond Framingham risk scores, suggesting utility beyond current approaches in clinical practice. In secondary analyses, stratified by diabetes status, apoB also added value to LDL cholesterol in those with and without type 2 diabetes (Appendix Table 3). ApoB's additive value to non-HDL cholesterol and HDL cholesterol containing parameters was attenuated, however, likely because of reduced power in the smaller strata.

TABLE 4
Relative value of apoB and cholesterol parameters in predicting CAC scores in diabetic and nondiabetic subjects

	All subjects (n = 1,414)	
	χ^2	P value
ApoB added to		
LDL cholesterol	15.26	<0.001
Total cholesterol	16.65	<0.001
Non-HDL cholesterol	3.2	0.07
HDL cholesterol	24.37	<0.001
Triglyceride/HDL cholesterol ratio	17.31	<0.001
Total cholesterol/HDL cholesterol ratio	4.32	0.04
Framingham risk score and metabolic syndrome	16.09	<0.001
Cholesterol parameter(s) added to apoB		
LDL cholesterol	0.29	0.59
Total cholesterol	0.54	0.46
Non-HDL cholesterol	1.54	0.21
HDL cholesterol	9.25	0.002
Triglyceride/HDL cholesterol ratio	12.39	<0.001
Total cholesterol/HDL cholesterol ratio	10.79	0.001

Likelihood ratio testing was applied in nested Tobit models to assess the incremental value of apoB over cholesterol parameters, and vice versa, in predicting CAC scores. All models included age, sex, medications, and diabetes status.

DISCUSSION

We report that apoB, but not LDL cholesterol, was associated with CAC scores in type 2 diabetic whites. This was true despite relatively high correlations of these two lipid parameters in diabetic subjects. In contrast, both apoB and LDL cholesterol were equally associated with CAC in nondiabetic patients. Although non-HDL cholesterol was superior to LDL cholesterol, we found that apoB added incremental value to total cholesterol and LDL cholesterol and even tended to add to non-HDL cholesterol in CAC prediction, whereas the reverse was not true. Overall, these findings support the concept that apoB levels may be stronger predictors of atherosclerotic burden than LDL cholesterol and other cholesterol parameters in type 2 diabetes.

Robust evidence from large primary and secondary prevention clinical trials established the standard practice of LDL cholesterol lowering for CHD prevention (26). Contemporary data have refined our interventions toward more aggressive therapeutic targets (27), yet the majority of CHD events are not prevented. One potential means of improving outcomes is through more precise estimation of atherogenic lipoprotein parameters, beyond cholesterol content, that more fully capture CHD risk.

ApoB, a measure of LDL particle number (LDL-P), as well as total atherogenic particle number, may represent such a parameter. In most (2–10), but not all (28–30), prior reports, including several large, prospective epidemiological studies and clinical trials, apoB surpassed LDL cholesterol and other cholesterol parameters, as a predictor of new and recurrent CHD events and marker of residual risk on therapy. Concordantly, apoB is the top performer in our study, relative to LDL cholesterol, and even to non-HDL cholesterol, which, unlike apoB, loses significance in the diabetic group after adjustment for age, sex, medications, and risk factors (Table 3, $P = 0.07$). Although our sample was relatively small, large clinical studies also favor apoB over non-HDL cholesterol. Notably, when Pischon et al. (4) compared apoB head to head against LDL cholesterol and non-HDL cholesterol in a nested case-control study of 18,225 asymptomatic men in the Health Professionals Follow-up Study, apoB emerged the leading predictor of incident CHD. Although, non-HDL cholesterol was equal to apoB in CHD prediction in type 2 diabetes (31) and healthy women (28), the majority of clinical evidence, contemporary expert reviews, and consensus statements (1,5,32,33) as well measurement characteristics (5) favor apoB over non-HDL cholesterol. However, debate continues as to the optimal choice and application in clinic (33).

The INTERHEART study (34) extended the generalizability of apoB's utility in CHD risk prediction across a 30,000-person, ethnically diverse population, spanning every major continent. INTERHEART, along with other reports, support value in the apoB/apoA1 ratio, though data are mixed on whether apoA1 is superior, or even equal, to HDL cholesterol, as discussed in a recent review by Sniderman and Marcovina (32). Consistent with these findings, we found that plasma apoB, but not LDL cholesterol levels, were independently associated with CAC scores in type 2 diabetes. In fact, other than HDL cholesterol parameters, no cholesterol data added value to apoB. HDL cholesterol captures separate, anti-atherogenic effects (35), but may also provide information because of its inverse association with insulin resistance and positive correlation with LDL particle size (36). Our findings further support apoB's superiority over LDL cholesterol, as well as other cholesterol-based measures, and break new ground in relating apoB to subclinical coronary atherosclerosis, particularly in type 2 diabetes.

Among the laboratory methods that currently exist for determination of LDL-P, apoB is the most mature and cost-effective. It is broadly equivalent to LDL-P because each LDL particle, independent of density, contains exactly one apoB and the vast majority (≥90%) of apoB is carried on LDL particles (32). In this way, apoB is not affected by heterogeneity of particle cholesterol content. Such heterogeneity is greater in type 2 diabetes because insulin resistance drives VLDL cholesterol production that depletes LDL particles of their cholesterol content via CETP, producing cholesterol-poor small, dense LDL particles (11). Remarkably, the remainder of apoB is carried on chylomicrons, VLDL cholesterol, intermediate-density lipoprotein, and lipoprotein(a) and thus also captures information on residual non-LDL atherogenic particles. ApoB measurement is standardized (37) and automated, yielding cost, time, and precision advantages over other modalities. It is available in most large commercial laboratories and does not require a fasting state. Thus, apoB has several measurement-related advantages as a marker of lipid risk.

Nuclear magnetic resonance (NMR) is an alternative means of measuring LDL-P; however, its clinical utility is currently limited because it is expensive and not widely available across laboratories. Nevertheless, reports on its predictive power in CHD are revealing. NMR-measured LDL-P improved cardiovascular risk estimation over LDL cholesterol in several cross-sectional (38) and prospective studies (39–43). Cross-sectional studies of healthy individuals showed that LDL-P was associated with CAC in postmenopausal women (44) and carotid intima-media thickness in the 5,538-person Multi-Ethnic Study of Atherosclerosis study (38). Prospectively, LDL-P predicted incident CHD in healthy (39,41,43) and at-risk (42) populations, as well as progression of CHD (40). In a nested case-control analysis of 2,888 subjects from the European Prospective Investigation Into Cancer and Nutrition-Norfolk, LDL-P outperformed LDL cholesterol as a predictor of future coronary artery disease beyond the Framingham risk score, but not triglycerides and HDL cholesterol (43). Although NMR has the capacity to estimate LDL particle size as well as particle number (43), there is limited evidence that NMR-estimated lipid data add value beyond the more simple measurement of apoB (33,41,42).

Patients with type 2 diabetes tend to have increased circulating LDL particles but normal concentrations of LDL cholesterol because their particles have low cholesterol content (45). Despite elevated triglycerides and low HDL cholesterol, this normal LDL cholesterol has led to underappreciation of the risk associated with dyslipidemia in diabetes. Indeed, in type 2 diabetic subjects, apoB and non-HDL cholesterol were favored over LDL cholesterol as predictors of CHD risk in the Health Professional's Follow-Up Study (31). Our data also shows apoB and non-HDL cholesterol capture information beyond LDL cholesterol in type 2 diabetes. We go further, in agreement with the recent Casale Monferrato Study (46) and Collaborative Atorvastatin Diabetes Study (47), in suggesting utility of apoB measurement over cholesterol parameters, including non-HDL cholesterol. Casale Monferrato looked at 11-year CHD mortality in 1,565 Mediterranean subjects with type 2 diabetes and found apoB predicted outcome independent of non-HDL cholesterol. CARDS followed

2,627 type 2 diabetic participants for 108 primary CHD end points over 3.9 years. ApoB carried a very similar hazard ratio to non-HDL cholesterol [adjusted hazard ratio (95% CI) for 1-SD increment: 1.20 (1.04–1.38) vs. 1.17 (1.02–1.34), respectively], but apoB was the stronger predictor (χ^2 6.61; $P = 0.01$ vs. χ^2 4.71; $P = 0.03$). In receiver operating characteristic analysis, the area under the curve for apoB versus non-HDL cholesterol was significantly greater ($P = 0.01$). Overall, our data support others' in suggesting that apoB is likely to be an enhanced measure of subclinical coronary atherosclerosis and lipid-associated CHD risk beyond traditional lipid risk factors in type 2 diabetes.

Our study has several limitations. Analyses were cross-sectional; thus, causal and longitudinal relationships were not addressed. ApoB's stronger association with CAC might reflect less variability in its measurement, especially over time, relative to LDL cholesterol. However, we cannot differentiate this possibility from a true stronger apoB association with CAC in our cross-sectional study. We also did not examine clinical outcomes, although our data are consistent with large clinical outcomes studies. Moreover, given lipid (48) and CAC (49) variability by race, our findings cannot be generalized beyond whites. In addition, CAC is an estimate (14,50) and not a direct measure of coronary atherosclerosis; thus, it may fail to detect some coronary atherosclerotic plaques. Despite this limitation, CAC scores are clinically relevant because they are strong, independent predictors of CHD (14,15), including in diabetic subjects (13). In our study, there was also extensive and differential statin use between diabetic and nondiabetic participants. Although this could confound the results, it represents real-world practice. In fact, we found that apoB predicted CAC even after controlling for differences in statin use and in subgroup analysis of nonstatin users.

Ours is the first study to show that plasma apoB, but not LDL cholesterol, levels are associated with CAC beyond traditional risk factors in type 2 diabetic whites. LDL cholesterol and cholesterol-related parameters did not add value to apoB. These results for subclinical coronary atherosclerosis agree with clinical outcomes data supporting apoB as a predictor of cardiovascular events. Our findings are broadly consistent with a recent joint consensus statement from the American Diabetes Association and American College of Cardiology that recommends incorporating apoB in managing patients with cardiometabolic risk (33). We advance previous apoB literature by addressing its relationship to subclinical coronary atherosclerosis in type 2 diabetic patients free of clinical CHD and we provide data that apoB may warrant greater use in risk assessment beyond LDL cholesterol in these asymptomatic individuals at higher cardiometabolic risk.

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