Published in final edited form as:

J Clin Lipidol. 2014 ; 8(6): 576–583. doi:10.1016/j.jacl.2014.08.008.

Plasma Triglycerides Predict Incident Albuminuria and Progression of Coronary Artery Calcification in Adults with Type 1 Diabetes: the Coronary Artery Calcification in Type 1 Diabetes Study

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Abstract

Background—Coronary artery disease and diabetic nephropathy, which are thought to share pathogenic mechanisms, remain the most common causes of mortality in type 1 diabetes (T1D). Data from basic and clinical studies indicate that hypertriglyceridemia plays an important role in the pathogenesis of vascular complications, but the role of triglycerides (TG) in the normal range remains unresolved in T1D.

Objective—We hypothesized that fasting TG would independently predict cardiorenal disease in adults with T1D and normal-to-low levels of TG.

Methods—Subjects (N=652) were 19–56 years old at baseline and reexamined 6-years later. Urinary albumin excretion was measured, and categorized as microalbuminuria or greater. Progression of coronary artery calcification (CACp), measured using electron beam CT, was defined as a change in the square root transformed CAC volume ≥ 2.5 . The association of low-density-lipoprotein-C (LDL-C), high-density-lipoprotein-C (HDL-C), apolipoprotein B, nonHDL-

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Duality of interest

Drs. Bjornstad, Maahs, Wadwa, Pyle, Rewers, Eckel and Snell-Bergeon have no conflict of interest to disclose.

Author Contributions

PB researched, wrote, contributed to discussion, and reviewed/edited the manuscript; DMM researched, contributed to discussion, and reviewed/edited the manuscript; MR designed the CACTI Study, researched, contributed to the discussion and reviewed/edited the manuscript; RJJ contributed to the discussion and reviewed/edited the manuscript; JKSB researched, contributed to the discussion, reviewed/edited the manuscript.

C, lnTG, ln(TG/HDL-C) ratio with CACp and incident albuminuria were examined in logistic regression. The models were adjusted for age, sex, T1D-duration, hemoglobin A1c, SBP, DBP, BP-medications, statins and smoking status. Integrated discrimination index and net-reclassification improvement were used to examine prediction performance.

Results—Incident albuminuria was independently associated with CACp. LnTG independently predicted both incident albuminuria (OR: 1.53, 1.02–2.30, $p=0.04$) and CACp (1.41, 1.11–1.80, $p=0.006$). The addition of lnTG to ABC risk factors (HbA1c, SBP, DBP and LDL-C) moderately improved discrimination and reclassification of CACp and incident albuminuria.

Conclusion—In adults with type 1 diabetes, fasting TG independently predicted cardiorenal disease over 6 years and improved reclassification of risk by conventional risk factors.

Keywords

Triglycerides; dyslipidemia; type 1 diabetes; microvascular complications; macrovascular complications; integrated discrimination index; net-reclassification improvement

Background

Cardiorenal complications cause the majority of deaths in type 1 diabetes [1, 2]. Diabetic nephropathy (DN) accounts for almost half of ESRD in the United States [1], and the risk of mortality from CAD is exceptionally high in type 1 diabetes and almost 4 fold greater than what is observed in those without diabetes [2]. CAD and DN have been proposed to be manifestations of the same underlying pathology and also exist as interrelated risk factors [3, 4]. The increased mesangial matrix, associated with DN is similar to the pathophysiology of atherosclerosis [3]. The shared pathogenic mechanisms imply common risk factors and therapeutic targets, including hypertension, glycemic control and dyslipidemia [5].

Advances in the management of conventional risk factors over the past two decades however has improved the outcome of microvascular complications, while the prevalence of macrovascular complications is on the rise [6]. Lipids remain part of the conventional risk factors for DN [7] and atherosclerosis [8, 9]. Low-density lipoprotein cholesterol (LDL-C), the only lipid variable accounted for in the American Diabetes Association's ABC goals (A: hemoglobin A1c [HbA1c] <7.0%, B: Blood pressure (BP) <130/80 mmHg, C: LDL-C <100mg/dL) [10], did not predict progression of subclinical coronary atherosclerosis and incident albuminuria in adults with type 1 diabetes in the Coronary Artery Calcification in Type 1 Diabetes Study [11]. Data from adults with and without type 2 diabetes suggest that alternative lipid markers including triglycerides (TG) may be superior to LDL-C in predicting CAD and DN [12, 13]. There is good evidence that hypertriglyceridemia is an important risk factor of vascular complications in type 1 diabetes [8, 13], but to what extent TG contribute to vascular complications outside the hypertriglyceridemia range is less clear. We hypothesized that TG would independently predict both incident albuminuria and CACp in adults with type 1 diabetes and low-to-normal levels of TG over a 6-year period. Second, we hypothesized that the association between TG and cardiorenal complications would be stronger than the associations with alternative lipid indices including LDL-C, high-density lipoprotein cholesterol (HDL-C), nonHDL-C, apolipoprotein B and TG/HDL-C. Finally, we

hypothesized that the addition of TG to SBP, DBP, HbA1c and LDL-C (ABC risk factors) would improve the risk discrimination and classification of cardiorenal disease.

Methods

The CACTI Study enrolled 1416 subjects 19–56 years old, 652 with type 1 diabetes and 764 without diabetes, who were asymptomatic for cardiovascular disease (CVD) at the baseline visit in 2000–02 and then were re-examined 3 and 6 years later. Only the 652 participants with type 1 diabetes were included in this analysis. The flowchart of subject selection for this analysis is depicted in Figure 1. The study was approved by the Colorado Multiple Institutional Review Board and all participants provided informed consent.

We measured height and weight, and calculated BMI in kg/m². Resting systolic (SBP) and fifth-phase diastolic blood pressure (DBP) were measured three times while the patient was seated, and the second and third measurements were averaged. After an overnight fast, blood was collected, centrifuged, and separated. Plasma was stored at 4°C until assayed. Total plasma cholesterol and triglyceride levels were measured using standard enzymatic methods, HDL cholesterol was separated using dextran sulfate and measured by enzymatic methodology (Beckman Coulter), and LDL-C was calculated using the Friedewald formula at University of Colorado Denver CTRC Lab. NonHDL-C was calculated by subtracting HDL-C from total cholesterol, and the ratio of TG to HDL-C was calculated by dividing TG by HDL-C. ApoB was measured by Beckman Array Nephelometer (Beckman Coulter Inc., Brea, CA). High performance liquid chromatography was used to measure HbA1c (HPLC, BioRad variant).

Incident albuminuria

Albuminuria was defined as AER ≥ 20 $\mu\text{g}/\text{min}$ if timed urine samples were obtained, or ACR ≥ 30 mg/g for spot samples (if timed urine was not available). Overnight urine samples were collected and urine creatinine and albumin were measured (RIA, Diagnostic Products). At both visits, urinary albumin excretion rate (AER) and/or albumin/creatinine ratio (ACR) were measured. Of the 27 subjects who developed incident albuminuria all had AER calculated, and all but two (n=326/328) of those who did not develop incident albuminuria had AER calculated.

Progression of CAC

CAC measurements were obtained in duplicate using an ultrafast Imatron C-150XLP electron beam computed tomography scanner (Imatron, San Francisco, CA) and the two scores were averaged. The average of the two scores was used as the CAC score for that visit. Scans were repeated on follow-up, an average of 6.2 ± 0.6 years after the baseline exam. Presence of CAC was defined as a CAC score > 0 . Progression of CAC was defined as an increase in volume of CAC of ≥ 2.5 square root transformed units.

ABC control and medications

ADA's ABC goals were defined as (A; HbA1c $< 7.0\%$, B; BP $< 130/80$ mm Hg (irrespective of anti-hypertension medication use), C; LDL-C $< 100\text{mg}/\text{dL}$) [10]. Anti-hypertension

medication use was determined by a medication inventory as previously described [14] and all anti-hypertension medications (including beta-blockers, calcium channel blockers, diuretics, ACE inhibitor (ACEi) and/or angiotensin receptor blockers (ARB) were combined for these analyses. Statin use was also determined by a medication inventory.

Statistical Analysis

Analyses were performed in SAS (version 9.3 for Windows; SAS Institute, Cary, NC). Differences between men and women, CAC progressors and non-progressors, and subjects who developed incident albuminuria and those who did not were assessed using Chi-Square for categorical variables and t-test for continuous variables. Variables with skewed distributions were natural log-transformed in multivariable models. Logistic regression was performed to evaluate the associations between lipid variables, one at a time, at baseline and development of CAC progression and incident albuminuria. Subjects with albuminuria at baseline were excluded from the analyses for incident albuminuria.

In addition to including the lipid variables, one at a time, the following variables were included in the fully adjusted models: age, sex, diabetes duration, HbA1c, SBP, DBP, BP meds and statins. We further adjusted the multivariable models for BMI, waist circumference and CRP respectively to challenge the independence of the associations. We also compared age, sex and statin adjusted lipid profiles stratified by cardiorenal complications as adjusted least square means with ANOVA. Prediction metrics for incident albuminuria and CACp over 6-years were investigated with integrated discrimination index (IDI), category-free net reclassification improvement (NRI) and categorical NRI. Subjects without data at baseline and follow-up were excluded from the analyses. The C-statistic has been criticized for insensitivities to changes in clinical decisions yielded for information gained [15, 16]. Therefore, we utilized IDI, category-free and categorical NRI. NRI estimates correct changes in clinical classification across risk thresholds [16], and IDI uses probability differences instead of categories [16, 17]. We examined categorical NRI; estimating the ability of SUA to appropriately reclassify 6-year risk of experiencing CACp or incident albuminuria from a categorical model using risk cut-offs derived from the Framingham studies [18–21]. For incident albuminuria, the 6-year risk was reported as low (0–3%), intermediate (3–6%) and high (>6%). For CAC progression, the 6-year risk was reported as low (0–20%), intermediate (20–50%) and high (>50%). Significance was based on an α -level of 0.05.

Results

Baseline subject characteristics stratified by gender are shown in Table 1. Over 6-years 9.6% of men and 6.1% of women developed incident albuminuria and 52.5% of men and 34.0% of women experienced CACp. Lipid profiles stratified by cardiorenal complications are shown in Table 2 adjusted by age, sex and statins.

Incident albuminuria was independently associated with CACp (OR: 3.21, 95% CI: 1.22–8.46, $p=0.02$) after adjusting for age, sex, SBP, DBP, HbA1c, diabetes duration, BP meds, statins and ever smoking. In univariate analyses, lnTG (OR 1.74, 95% CI: 1.20–2.50,

$p=0.003$, per 0.46 [SD]), apoB (OR 1.49, 95% CI: 1.03–2.14, $p=0.03$, per 22.3 mg/dL [SD]), and $\ln(\text{TG}/\text{HDL-C})$ (OR 1.71, 95% CI: 1.19–2.46, $p=0.004$, per 0.61 [SD]) were associated with incident albuminuria. $\ln\text{TG}$ (OR: 1.40, 1.15–1.69, $p=0.0006$, per SD), HDL-C (OR: 0.78, 95% CI: 0.64–0.95, $p=0.01$, per 16.6 mg/dL [SD]), LDL-C (OR 1.26, 95% CI: 1.05–1.52, $p=0.01$, per 27.7 mg/dL [SD]), nonHDL-C (OR: 1.35, 95% CI: 1.12–1.62, $p=0.002$, per 31.5mg/dL [SD]), apoB (OR: 1.29, 95% CI: 1.07–1.55, $p=0.008$, per 1 SD) and $\ln(\text{TG}/\text{HDL-C})$ (OR 1.45, 95% CI: 1.20–1.76, $p=0.0001$, per 1 SD) were univariately associated with CACp. Statin use was also univariately associated with CACp (OR: 4.28, 95% CI: 2.48 – 7.38, $p<0.0001$) and incident albuminuria (OR: 2.65, 95% CI: 1.09–6.41, $p=0.03$).

In multivariable logistic regression models adjusting for age, sex, diabetes duration, HbA1c, SBP, DBP, BP medications, statins and ever smoking, only $\ln\text{TG}$ independently predicted both incident albuminuria (OR 1.53, 95% CI: 1.02–2.30, $p=0.04$, per SD) and CACp (OR 1.41, 95% CI: 1.11–1.80, $p=0.006$, per SD) (Figure 2). In contrast, neither LDL-C, apoB, HDL-C, nonHDL-C nor $\ln(\text{TG}/\text{HDL-C})$ predicted both incident albuminuria or progression of CAC in fully adjusted models (Figure 2). There were no significant interactions between statin use and the lipid variables for incident albuminuria or CACp respectively. For that reason, we did not stratify our analysis by statin use but rather included statin use as a covariate in our multivariable models. As a sensitivity analyses we reran the models in subjects not taking statins and obtained similar results for CACp, with only $\ln\text{TG}$ (OR: 1.31, 95% CI 1.01–1.70, $p=0.04$, per 1 SD) and HDL-C (OR: 0.63, 95% CI 0.48–0.83, $p=0.001$, per 1 SD) showing a significant association with CACp in fully adjusted models. For incident albuminuria, there were only 19 observations when excluding statin use providing insufficient sample size for the multivariable models

To further test the independence between $\ln\text{TG}$ with CACp and incident albuminuria we further adjusted for variables of adiposity, insulin resistance and inflammation; BMI, waist circumference and CRP, one at a time, in the multivariable models. The associations between $\ln\text{TG}$ and CACp remained significant after further adjustments for BMI (OR: 1.40, 95% CI: 1.09–1.80, $p=0.008$ per 1 SD), waist circumference (OR: 1.35, 95% CI: 1.05–1.73, $p=0.02$, per 1 SD) and CRP (OR: 1.42, 95% CI: 1.11–1.82, $p=0.005$, per 1 SD). The association between $\ln\text{TG}$ and incident albuminuria became attenuated by adjusting for BMI (OR: 1.52, 95% CI: 0.99–2.34, $p=0.058$, per 1 SD) and waist circumference (OR: 1.44, 95% CI: 0.95–2.20, $p=0.09$, per 1 SD), but remained significant after adjusting for CRP (OR: 1.53, 95% CI: 1.01–2.30, $p=0.04$, per 1 SD).

The addition of $\ln\text{TG}$ to the conventional ‘ABC’ risk factors improved the discrimination slope of CACp prediction, and risk reclassification of incident albuminuria and CACp (Table 3).

Discussion

In adults with type 1 diabetes and normal-to-low levels of TG, fasting TG at baseline independently predicted higher odds of both CACp and incident albuminuria, while LDL-C, HDL-C, nonHDL-C and apoB did not. Furthermore, the addition of $\ln\text{TG}$ improved risk discrimination and reclassification of ‘ABC’ models predicting CACp and incident

albuminuria. A major challenge in preventing cardiorenal complications of type 1 diabetes is the difficulty in accurately identifying high risk patients with preclinical disease.

Incident albuminuria and CACp indicate preclinical cardiorenal disease in type 1 diabetes. Albuminuria remains the definition for the earliest stage of DN in type 1 diabetes per ADA Standards of Medical Care in Diabetes 2014 [10]. Moreover, albuminuria has been shown to independently predict CVD and mortality in adults with and without type 1 diabetes [22]. CAC is a marker of coronary artery plaque burden and an established measure of subclinical atherosclerosis. Progression of CAC predicts coronary events in type 1 diabetes [11].

Dyslipidemia along with hypertension and hyperglycemia are major contributory factors for cardiorenal complications in type 1 diabetes [23]. The classical dyslipidemia of type 1 diabetes as described by Fredrickson (elevated TG and small dense LDL-C and low HDL-C) however is rarely seen in contemporary cohorts of type 1 diabetes [24]. In fact, adults with type 1 diabetes have lipid profiles typically comparable to or better than nondiabetic control subjects [24]. Adults with type 1 diabetes are still at significantly greater risk of nephropathy and CAD than their non-diabetic counterparts [1, 2], and despite the relative improvement in diabetic dyslipidemia, lipids remain risk factors for DN and CAD in adults with type 1 diabetes [9]. Lipoprotein subfraction cholesterol distribution has been proposed to be more atherogenic in those with type 1 diabetes [25]. Possible mechanisms include differences in lipoprotein particle size, LDL-C oxidation, COX2 expression, inflammatory response to lipids and increased transvascular and macrophage lipid transport in patients with type 1 diabetes [26].

Clinical and basic research strongly indicate that hypertriglyceridemia worsens microvascular and macrovascular disease [13], but the role of low-to-normal levels of TG remains unresolved. In the Women's Health study, non-fasting TG levels were associated with incident cardiovascular events, independent of conventional risk factors, other lipids and markers of insulin resistance [27]. Furthermore, the Diabetes Control and Complications Trial Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) studies reported an association between proteinuria and TG-rich lipoproteins [7].

Although the exact mechanisms underlying the association between TG and cardiorenal complications in type 1 diabetes are not completely understood, there are increasing data supporting an important role of TG-related lipoproteins in the pathogenesis [8, 13]. TGs have been proposed to mediate atherogenicity by many pathways; enhancement of inflammation and oxidative stress, induction of cell adhesion molecule expression, direct effects of TG-rich lipoproteins on the endothelium and glomeruli, and toxic effects of free fatty acids [13]. TG may also induce vascular injury through activation of TGF- β pathway by inducing the production of reactive oxygen species (ROS), which results in damage to the endothelium, glomeruli and glomerular glycocalyx [13].

Despite convincing data of a link between TG and vascular complications - the extent to which TG mediates DN and CAD is not without controversy and debate. High TG-related lipoproteins are often associated with other risk factors that may contribute to vascular complications, including visceral obesity, insulin resistance and hypertension [28].

However, in our cohort the associations between TG and CACp remained significant after adjustments for markers of insulin resistance and visceral obesity including waist circumference and BMI. Furthermore, in type 1 diabetes, TG has been shown to correlate with poor glycemic control and hyperglycemia [29], but the relationship between TG and cardiorenal complications were independent of HbA1c in our cohort. The TG/HDL-C ratio, which has been linked with insulin resistance and proposed to be a better predictor of the atherogenic small, dense LDL than LDL-C [30] performed no better than TG and HDL-C combined in predicting CACp and incident albuminuria in our cohort.

The ADA recommends TG concentrations below 150mg/dL [10]. Despite only 11% of our subjects having a TG concentration equal to or greater than 150mg/dL, baseline TG remained an independent and strong predictor of cardiorenal complications over 6 years in the entire cohort after adjusting for conventional risk factors. This suggests that TG is an important risk factor in type 1 diabetes even with low to normal levels of TG. Reduction of more than 50% in TG can be attained by intense lifestyle changes including weight loss, reduction in added sugars and fructose, increasing unsaturated fat intake and aerobic exercise [8]. Statins, niacin and ezetimibe all lower TG, but not to the extent of fibrates [8]. The fenofibrate intervention and event lowering in diabetes (FIELD) study demonstrated a treatment-associated reduction in microvascular complications, especially diabetic retinopathy and progression of albuminuria [31], and cardiovascular disease [32]. Conversely, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial there was no difference in cardiovascular event rates between adults with type 2 diabetes in the fenofibrate and the placebo groups who were not dyslipidemic [33]. Further clinical trials are needed to establish the benefits of fenofibrate and TG lowering in type 1 diabetes.

There are limitations of this study worth mentioning, including the limited number of subjects with incident albuminuria. The use of CAC as a marker of CAD rather than traditional end points such as coronary artery stenosis, myocardial infarction, or death is another important limitation of this study. However, CAC is accepted as a quantifiable, reliable, noninvasive marker of the extent of coronary atherosclerosis, and CACp progression predicts both fatal and nonfatal coronary events [34]. We also acknowledge that albuminuria as a proxy for DN is not without some controversy, but it remains the earliest form of DN recognized by ADA [10], and furthermore there is robust evidence linking albuminuria with CVD and mortality in adults with and without type 1 diabetes [22]. We adjusted for a variety of important confounding variables, but cannot rule out the presence of unknown risk factors that may have biased or confounded the present analyses. Results from this study may not be generalizable to significantly younger or older subjects with type 1 diabetes or to cohorts with optimal ABC control, however our data on ABC control is comparable to data recently published from NHANES [35].

Conclusion

Cardiorenal complications remain the most devastating complications of type 1 diabetes. In our prospective cohort of adults with type 1 diabetes and low-to-normal levels of TGs, fasting TG at baseline was the only lipid marker to independently predict both CACp and incident albuminuria over 6 years. Although the independence of TG as a causal mediator of

cardiorenal disease remains controversial, TG levels appear to provide unique information about risk, independent of conventional risk factors in type 1 diabetes.

Acknowledgements

Support for this study was provided by NHLBI grant R01 HL61753, HL79611, and HL113029, JDRF grant 17-2013-313, and DERC Clinical Investigation Core P30 DK57516. The study was performed at the Adult CTRC at UCD support by NIH-M01-RR00051, at the Barbara Davis Center for Childhood Diabetes and at Colorado Heart Imaging Center in Denver, CO. Dr. Snell-Bergeon was supported by an American Diabetes Association Junior Faculty Award (1-10-JF-50).

Drs. Petter Bjornstad, Janet K. Snell-Bergeon and Laura Pyle are guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

List of abbreviations

TG	triglycerides
TRL	triglyceride-rich lipoproteins
CVD	cardiovascular disease
CAD	coronary artery disease
DN	diabetic nephropathy
BMI	body mass index
BP	blood pressure
SBP	systolic blood pressure
DBP	diastolic blood pressure
HbA1c	hemoglobin A1c
ACEi	angiotensin-converting-enzyme inhibitor
ARB	angiotensin receptor blocker
ABC	HbA1c, blood pressure and LDL-cholesterol
CAC	coronary artery calcification
CACp	coronary artery calcification progression
CACTI	coronary artery calcification trial in type 1 diabetes
FIELD	fenofibrate intervention and event lowering in diabetes
ACCORD	action to control cardiovascular risk in diabetes
NHANES	national health and nutrition examination survey
DCCT/EDIC	Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications
FinnDiane	the Finnish diabetic nephropathy study
ADA	American diabetes association

AHA	American heart association
ACC	American college of cardiology
HDL-C	high-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol
NonHDL-C	non high-density lipoprotein cholesterol
ApoB	apolipoprotein B
TG/HDL-C	triglyceride to high-density lipoprotein cholesterol ratio
TGF-β	transforming growth factor beta
COX-2	cyclooxygenase-2
AGE	advanced glycation end-product
ROS	reactive oxygen species
Hs-CRP	high-sensitivity c-reactive protein
OR	odds ratios
SD	standard deviation
SE	standard error
95% CI	95% confidence interval
C-statistics	concordance statistics
AUC	area under the curve
IDI	integrated discrimination improvement
NRI	net reclassification improvement

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Highlights

- We examined the associations between lipids and cardiorenal disease in type 1 diabetes.
- Adults with type 1 diabetes had low-to-normal levels of triglycerides.
- Only triglycerides were independently associated with cardiorenal disease.
- Triglycerides improved discrimination and classification of cardiorenal disease.

Figure 1. Flowchart of Subject Selection

CAC = coronary artery calcification, AER = albumin excretion rate, ACR = albumin creatinine ratio

OR represents the odds of developing CACp or albuminuria per 1-SD increase in the independent variable (e.g. for ln (TG) - per 1 SD of natural log transformed TG)

* Adjusted for age, sex, duration, HbA1c, SBP, DBP, BP meds, statins and ever smoked

Figure 2. Fully adjusted multivariable logistic regression models

CACp = coronary artery calcification progression, OR = odds ratios, CI = confidence interval, SD = standard deviation, HbA1c = hemoglobin A1c, SBP = systolic blood pressure, DBP = diastolic blood pressure, BP meds = blood pressure medications, Ln = natural log, LDL-C = Low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, TG = triglycerides, apoB = apolipoprotein B, nonHDL-C = non high-density lipoprotein cholesterol and TG/HDL-C = ratio of triglycerides to high-density lipoprotein cholesterol.

Table 1

CACTI Type 1 Diabetes Study Population

	Men (n=298)	Women (n=354)	p-value
Age (years)	37 ± 9	36 ± 9	0.07
Diabetes duration (years)	24 ± 9	23 ± 9	0.29
HbA1c (%)	8.0 ± 1.2	8.0 ± 1.3	0.90
HbA1c (mmol/mol)	64.0 ± 10.8	64.0 ± 11.9	0.90
LDL-C (mg/dL)	104 ± 30	98 ± 28	0.007
HDL-C (mg/dL)	51 ± 14	60 ± 17	<0.0001
BMI (kg/m ²)	26.5 ± 3.9	26.0 ± 4.7	0.09
Waist circumference (cm)	90.3 ± 11.7	80.8 ± 12.0	<0.0001
AER (µg/min)	7.4 (4.5–23.8)	5.8 (3.8–11.8)	<0.0001
Systolic BP (mm Hg)	121 ± 14	114 ± 14	<0.0001
Diastolic BP (mm Hg)	80 ± 9	75 ± 8	<0.0001
TG (mg/dL)	80 (61–113)	77 (61–104)	0.23
TG/HDL-C (mg/mg)	1.6 (1.1–2.6)	1.3 (0.9–1.9)	<0.0001
NonHDL-C (mg/dL)	123 ± 33	116 ± 32	0.007
ApoB (mg/dL)	94 ± 25	89 ± 23	0.003
On antihypertensive medications (%)	41%	35%	0.09
On statins (%)	21%	13%	0.004
Ever smoker (% yes)	18%	22%	0.21
Any CAC at baseline (% yes)	49	28	<0.0001
Albuminuria at baseline (% yes)	27	17	0.004

Data are means ± SD, % or median (25th – 75th %)

LDL-C = Low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, TG = triglycerides, apoB = apolipoprotein B, nonHDL-C = non high-density lipoprotein cholesterol, TG/HDL-C = ratio of triglycerides to high-density lipoprotein cholesterol, BMI = body mass index, BP = blood pressure, CAC = coronary artery calcification, AER = albumin excretion rate and HbA1c = hemoglobin A1c.

Table 2

Lipids adjusted for age, sex and statins stratified by cardiorenal complication

	Incident albuminuria		CAC progression		p-value
	No (n=328)	Yes (n=27)	Non-progressors (n=272)	Progressors (n=201)	
LDL-C (mg/dL)	98 (95–101)	99 (89–110)	97 (94–101)	101 (97–105)	0.17
HDL-C (mg/dL)	56 (55–58)	54 (48–60)	58 (56–60)	53 (51–55)	0.003
*TG (mg/dL)	76 (72–80)	97 (82–114)	75 (71–79)	88 (82–94)	0.0007
ApoB (mg/dL)	88 (86–91)	96 (86–104)	88 (85–91)	91 (88–95)	0.13
NonHDL-C (mg/dL)	115 (111–118)	122 (110–134)	114 (110–118)	120 (115–125)	0.03
*TG/HDL-C (mg/dL)	1.4 (1.3–1.5)	1.9 (1.5–2.3)	1.3 (1.2–1.4)	1.7 (1.6–1.9)	0.0001

Data are least-squares means adjusted for age, sex and statins expressed as mean (95% CI).

* TG and TG/HDL-C analyzed in natural log scale and reported as geometric mean (95% CI).

LDL-C = Low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, TG = triglycerides, apoB = apolipoprotein B, nonHDL-C = non high-density lipoprotein cholesterol and TG/HDL-C = ratio of triglycerides to high-density lipoprotein cholesterol.

Table 3

A Prediction performance analyses for lnTG, ln(TG/HDL-C) and lnTG + HDL-C			
Model 1 (HbA1c, SBP, DBP and LDL-C) vs. model 2 (model 1 + lipid variable(s))			
Lipid variable(s)	IDI ($\pm$ SE)	Category-free NRI ($\pm$ SE)	Categorical NRI ($\pm$ SE)
<i>CAC progression (n=199)</i>			Low risk: <20% Intermediate risk: 20–50% High risk: >50%
Ln TG	0.008$\pm$0.004 (p=0.048)	19.2$\pm$9.3% (p=0.041)	5.4$\pm$2.7% (p=0.045)
<i>Events correctly reclassified</i>	N/A	1%	4%
<i>Non-events correctly reclassified</i>	N/A	19%	2%
Ln (TG/HDL-C)	0.017$\pm$0.006 (p=0.005)	28.4$\pm$9.3% (p=0.002)	11.1$\pm$3.6% (p=0.002)
<i>Events correctly reclassified</i>	N/A	8%	7%
<i>Non-events correctly reclassified</i>	N/A	21%	4%
Ln TG + HDL-C	0.022$\pm$0.007 (p=0.002)	30.8$\pm$9.2% (p=0.001)	11.8$\pm$3.9% (p=0.003)
<i>Events correctly reclassified</i>	N/A	17%	7%
<i>Non-events correctly reclassified</i>	N/A	14%	5%

B Prediction performance analyses for lnTG, ln(TG/HDL-C) and lnTG + HDL-C			
Model 1 (HbA1c, SBP, DBP and LDL-C) vs. model 2 (model 1 + lipid variable(s))			
Lipid variable(s)	IDI ($\pm$ SE)	Category-free NRI ($\pm$ SE)	Categorical NRI ($\pm$ SE)
<i>Incident albuminuria (n=27)</i>			Low risk: <3% Intermediate risk: 3–6% High risk: >6%
Ln TG	0.020$\pm$0.013 (p=0.13)	29.2$\pm$20% (p=0.14)	19.7$\pm$8.1% (p=0.01)
<i>Events correctly reclassified</i>	N/A	4%	0%
<i>Non-events correctly reclassified</i>	N/A	26%	20%
Ln (TG/HDL-C)	0.021$\pm$0.013 (p=0.10)	23.7$\pm$20.0% (p=0.24)	19.4$\pm$8.1% (p=0.02)
<i>Events correctly reclassified</i>	N/A	–4%	0%
<i>Non-events correctly reclassified</i>	N/A	27%	19%
Ln TG + HDL-C	0.022$\pm$0.014 (p=0.11)	30.4$\pm$20.0% (p=0.13)	20.6$\pm$8.1% (p=0.01)
<i>Events correctly reclassified</i>	N/A	4%	1%
<i>Non-events correctly reclassified</i>	N/A	27%	20%

Ln = natural log, IDI = integrated discrimination improvement, NRI = net reclassification improvement, HDL-C = high-density lipoprotein cholesterol, TG = triglycerides and TG/HDL-C = ratio of triglycerides to high-density lipoprotein cholesterol.