Association Between Plasma Triglycerides and HDL-Cholesterol and Microvascular Kidney Disease and Retinopathy in Type 2 Diabetes: A Global Case-Control Study in 13 Countries

Running title: Sacks et al.; Plasma lipids in diabetic microvascular disease

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Abstract

Background—Microvascular renal and retinal diseases are common major complications of type 2 diabetes. The relation between plasma lipids and microvascular disease is not well established.

Methods and Results—The cases were 2535 patients with type 2 diabetes with average duration 14 years, 1891 having kidney disease and 1218 retinopathy. The cases were matched for diabetes duration, age, sex, and LDL-cholesterol to 3683 controls with type 2 diabetes who did not have kidney disease or retinopathy. The study was conducted in 24 sites in 13 countries. The primary analysis included kidney disease and retinopathy cases. Matched analysis was performed using site-specific conditional logistic regression in multivariable models that adjusted for hemoglobinA1C, hypertension, and statin treatment. Mean LDL-cholesterol concentration was 2.3mmol/L. The microvascular disease odds ratio (OR) increased by a factor of 1.16 (95% CI: 1.11,1.22) for every 0.5mmol/L (approximately 1 quintile) increase in triglycerides; or decreased by a factor of 0.92 (0.88, 0.96) for every 0.2mmol/L (approximately 1 quintile) increase in HDL-cholesterol. For kidney disease, the OR increased by 1.23 (1.16,1.31) with triglycerides and decreased by 0.86 (0.82, 0.91) with HDL-cholesterol. Retinopathy was associated with triglycerides and HDL-cholesterol in matched analysis but not significantly after additional adjustment.

Conclusions—Diabetic kidney disease is associated worldwide with higher levels of plasma triglycerides and lower levels of HDL-cholesterol among patients with good control of LDL-cholesterol. Retinopathy was less robustly associated with these lipids. These results strengthen the rationale for studying dyslipidemia treatment to prevent diabetic microvascular disease.

Key words: diabetes (kidney), lipids, renal function, epidemiology, risk prediction, retinopathy
Diabetes is a major cause of microvascular disease that includes kidney disease and retinopathy, and their ultimate consequences, end-stage renal disease and blindness.\textsuperscript{1-4} Hyperglycemia and hypertension are major risk factors for the development of microvascular disease.\textsuperscript{2, 4} Intensive control of blood glucose and blood pressure to, or even beyond, currently recommended targets may provide some additional benefits in the prevention of diabetic microvascular disease, but are often impossible to achieve because of the associated risks of hypoglycemia or hypotension.\textsuperscript{5, 6} Therefore, identifying other targets and treatments is needed to make progress in slowing the development of diabetic kidney disease and retinopathy.

Most epidemiological studies found an association between serum triglycerides and diabetic kidney disease although less consistently for serum HDL-cholesterol.\textsuperscript{7-21} Results diverged among studies on diabetic retinopathy especially in multivariable analysis.\textsuperscript{4, 22-33} In randomized controlled trials, treatment of type 2 diabetic patients with fenofibrate, a PPAR alpha agonist, reduced the rate of decline in renal function\textsuperscript{25, 34}, reduced albuminuria, and reduced the requirement for laser treatment of retinopathy.\textsuperscript{5, 25, 34, 35} However, it is not clear whether these beneficial effects were caused by improvements in triglycerides or HDL-cholesterol, or by other biological effects of PPAR-alpha activation.

The objective of this international study was to determine, in type 2 diabetic patients with LDL-C $\leq$3.4mmol/L (130mg/dL), whether low HDL-cholesterol or elevated triglycerides levels are associated with diabetic kidney disease and retinopathy independent of established determinants of microvascular disease.

**Methods**

The study utilized a case-control design in 24 sites in 13 countries. Sites were either hospitals or
diabetes clinics. The study was approved by the IRB of the coordinating center and each clinical site.

**Population**

Cases and controls were individuals with type 2 diabetes documented in the medical record, at least 40 years old, and with LDL-C ≤ 3.4 mmol/L.

Data were compiled from clinical charts. All consecutive charts of patients with type 2 diabetes meeting selection criteria were processed and required parameters were recorded. The methodology was piloted for feasibility assessment at the site in Brussels, Belgium, and included cases ascertained from 1990 to 2009 (median visit date May 2006). The chart review period was in 2008 to 2010 for all other sites.

**Cases:** Cases were patients with visits for at least one recorded ocular or renal microvascular complication (kidney disease, retinopathy, the latter also including diabetic macular edema). Patients with non-diabetic kidney disease were excluded except if they presented with a known diabetic microvascular complication. Non-diabetic kidney disease was determined by the site PI from the medical records. The index visit for a case was a complication-related visit to which a lipid panel measured within six months could be associated.

**Controls:** Controls were patients with type 2 diabetes mellitus with documented evidence of not having microvascular complications of the kidney and eye as defined below.

**Case definitions**

**Kidney disease:** Kidney disease was defined as either proteinuria >300 mg/L, albuminuria, or estimated glomerular filtration rate <60 ml/min/1.73m². Albuminuria was defined as either albumin/creatinine ratio ≥ 30 μg/mg measured in a single morning urine sample; or >20 μg/min in timed overnight urine collections; or >30 mg/24h in a 24-hour urine. Glomerular filtration rate
was estimated by the Modification of Diet in Renal Disease (MDRD) formula.

Retinopathy: Retinopathy was defined as laser treatment for diabetic retinopathy; or Early Treatment Diabetic Retinopathy (EDTRS) staging ≥ 20 shown by fundus photography; or Diabetic Retinopathy Disease Severity Scale 3, 4 or 5 shown by dilated ophthalmoscopy\textsuperscript{36}; or maculopathy defined as moderate or severe using the Diabetic Macular Edema Disease Severity Scale\textsuperscript{36}, determined by dilated ophthalmoscopy with slit-lamp or by biomicroscopy.

**Measurements**

All data were obtained from reviews of medical records. Fasting samples were obtained from 73% of cases and 76% controls. Non-fasting were obtained in 10% cases and 8% controls. The remainder, 17% of cases and 16% of controls, lacked the information. Total cholesterol, HDL-cholesterol, LDL-cholesterol (measured directly or calculated) and triglycerides were assayed within the 6 months prior to the date of the index visit. Data obtained included age, sex, duration of diabetes, body weight, height, ethnicity, history of hypertension, blood pressure, current medical treatment, medications, smoking, cardiovascular diseases, fasting blood glucose, and hemoglobin A1C.

**Quality control**

Quality control visits by the Data Coordinating Center team were conducted in 17 of the 24 sites. CMIC, a CRO in Japan, monitored the 3 Japanese sites. On-site single entry of data (with programmatic constraints to prevent out-of-range values and to minimize missing data) was performed using data management software developed for this project.

A 5% random sample of medical charts corresponding to digital study data was requested for review by Data Coordinating Center. 21 of the study sites complied with the request. Values of participant age, gender, race, LDL-C, triglycerides, HDL-C and outcome status were checked
for concordance between the medical records and the study database. The overall discordance rate was 1.2%. Precision and accuracy of laboratories used by participating sites were assessed (see online Supplemental Material).

**Sample Size Determination**

Prevalence and incidence statistics derived from the PROCAM study (G. Assmann, personal communication) were used to obtain a target sample size of 100 cases in each clinical site, matched 1:1 with controls, which would provide 80% power to identify a relative risk of microvascular complications of 2.0 in any site, assuming a 30% prevalence of dyslipidemia among controls. Collection of data on additional controls when available was allowed as a means of increasing power.

**Data analysis**

The primary outcome was a diagnosis of one or both of kidney disease or retinopathy, according to the protocol. Kidney disease and retinopathy were analyzed as individual outcomes in secondary analyses that included sites that reported at least 10 cases of either event for each site. Multivariable data on all \( N_1 \) cases and \( N_2 \) controls was assembled into a distance matrix of dimension \((N_1+N_2) \times (N_1+N_2)\). The optimal partitioning of the full dataset into strata including at least one case and one control per stratum is determined using Hansen and Klopfer's procedure (which in turn employs graph-theoretic optimization procedures due to Bertsekas and Tseng); no control is used in more than one stratum. The partitioning is optimal in the sense that no other partition has a smaller sum of within-stratum distances -- that is, the groupings together of cases and controls maximizes the similarities of cases to controls among all possible groupings. Strata were required to be homogeneous in gender, and were formed to minimize the sum of squared Mahalanobis distances over all possible groupings of cases and controls within...
sites. Mahalanobis distance was computed based on values of LDL-cholesterol, number of years elapsed subsequent to diabetes diagnosis, and age.

Statistical modeling proceeded along three main axes. Case prediction models took several different forms. Most parsimoniously, quintiles of triglycerides and HDL-C were scored 0-4 and a single degree of freedom test for trend was used. Separate quintile effects were also estimated to assess adequacy of the linearity assumption. Third, tests of triglycerides and HDL-C effects were conducted marginally (unadjusted); adjusted for statin treatment, hypertension status, and quintile scored HbA1c; and with “mutual” adjustment, in which triglycerides and HDL-C effects are assessed simultaneously. For one site (Toronto (2)), the hypertension covariate was unavailable and models for that site excluded this variable.

Statistics were summarized across sites using a random-effects meta-analysis methodology. Finally, several sensitivity analyses were done on subsamples of the cases, and on cases with the 4 specific retinopathy definitions. Results are presented as odds ratio (95% confidence limits). For some subgroups full covariate adjustment was infeasible owing to data sparseness, and adjustments were limited to feasible variables.

Results

Characteristics of cases and controls

A total of 2535 cases were reported and they were matched, within sites and within strata defined by gender, to 3683 controls. A total of 2034 strata were formed by the optimal matching procedure. The most common structure for strata was a 1:1 match (1125 such strata were formed), and 92% of strata consisted of one or two cases matched to a group of at most 6 controls. Within sites, the median within-stratum age range was computed as a measure of
departure from perfect matching on age; its median over all sites was 4.25y. For duration of diabetes, the median within-site departure over all sites was 3y, and for LDL-C level, the median within-site departure over all sites was 0.23 mmol/L. Characteristics of cases and controls are shown in Table 1. The meta-analytic estimates of differences between cases and controls (denoted Δ) in these characteristics in the matched analyses that were used in the meta-analysis to compute odds ratios were very small and not clinically meaningful, e.g. difference in duration of diabetes was 0.9 years. Information was not available on menopausal status of the women. However, the mean age of the cases who were women was 66y; 89% were at least 50y.

Kidney disease was present in 1891 cases and retinopathy in 1218 cases. 574 cases had both kidney and eye disease. For the secondary analysis of kidney disease or retinopathy, separately, sites were included that reported at least 10 cases. The kidney disease analysis included all 24 sites and 1891 cases, whereas the retinopathy analysis included 21 sites and 1202 cases. Characteristics of the cases and controls are shown in Table 1, and in each of the sites in Supplemental Table 1. Characteristics of the cases of diabetic kidney disease and retinopathy were similar.

The primary analysis considered microvascular complication case status consisting of a diagnosis of at least one of diabetic kidney disease, retinopathy, or maculopathy. Using linear scoring of triglyceride quintiles, the odds ratio for a microvascular complication corresponding to a difference of one quintile (approximately 0.5 mmol/L) was 1.16 (95%CI 1.11, 1.22), including the covariates stated in the methods (Figure 1). Using categorical factors for triglyceride quintile membership, the odds ratio comparing fifth to first quintiles was 1.76 (95%CI 1.38, 2.25). For linear scoring of HDL-cholesterol quintiles, the odds ratio for a one-quintile difference (approximately 0.2 mmol/L) was 0.92 (95% CI 0.88, 0.96) (Figure 1). The
odds ratio comparing fifth to first quintiles of HDL-cholesterol was 0.73 (95% CI 0.60, 0.90). When the linear quintile scoring model was fit including triglyceride and HDL-cholesterol simultaneously, the odds ratio for a one-quintile difference of triglyceride was estimated at 1.15 (95% CI 1.09, 1.22) and that for a one-quintile difference in HDL-cholesterol at 0.96 (95% 0.91, 1.01). Site-to-site variability in triglyceride effects was not statistically significant (p = 0.22) with 22 of 24 sites yielding odds ratio estimates greater than one in the marginal, linear scoring model. Site-to-site variability in the HDL-cholesterol effect was also not statistically significant (p = 0.42), and 20 of 24 sites yielded odds ratio estimates less than one for this association. Tests for heterogeneity were generally not significant for any of the analyses (see figure legends).

A planned secondary analysis was evaluation of the associations of triglycerides and HDL-cholesterol with each of the two microvascular event types. The odds ratio for a kidney disease complication corresponding to a difference of one quintile in triglycerides (approximately 0.5 mmol/L) was 1.23 (1.16, 1.31) (Figure 2). The odds ratio estimates were greater than 1.0 in 23 of the 24 sites. Using categorical factors, the odds ratio comparing fifth to first quintiles (2.8 vs 0.7 mmol/L) was 2.24 (1.78, 2.83) (Figure 3). The odds ratio for a kidney disease complication corresponding to a one-quintile difference in HDL-cholesterol was 0.86 (0.82, 0.91) (Figure 2). The odds ratio was less than 1.0 in 23 of the 24 sites. Using categorical factors for HDL-cholesterol, the odds ratio comparing fifth to first quintiles was 0.58 (0.47, 0.73) (Figure 3). In models that mutually adjusted for triglycerides and HDL-cholesterol the odds ratio for kidney disease was 1.20 (1.13, 1.28) for a quintile increase in triglycerides and 0.92 (0.87, 0.97) for a quintile increase in HDL-cholesterol (Figure 4). Kidney disease cases could qualify on the basis of albuminuria or low GFR and their characteristics are shown in Supplemental Tables 2 and 3, respectively. The kidney disease odds ratios for triglycerides and HDL-
cholesterol, individually and in mutual adjustment, were significant for low GFR (N=522 cases) and for albuminuria (N=1517 cases) (Figure 5; and Supplemental Figures 1 to 6).

The analysis of retinopathy included 21 sites that submitted at least 10 retinopathy cases, and the total number of cases was 1202. The odds ratio for a retinopathy complication was 1.09 (1.02, 1.16) per quintile of triglycerides, and 0.93 (0.86, 1.0) per quintile of HDL-cholesterol, using models that controlled for the matching factors only. However, additional control for hypertension and hemoglobin A1C weakened these associations and they did not remain significant. For triglycerides the odds ratio was 1.04 (0.98, 1.11), and for HDL-cholesterol it was 0.97 (0.90, 1.05) (Figure 6). The ratio of triglycerides to HDL-cholesterol also did not have a significant association with retinopathy: odds ratio 1.04 (0.98,1.11) per quintile.

The odds ratios for retinopathy per quintile of plasma triglycerides or HDL-C, not mutually adjusted, were determined according to the 4 definitions or conditions: (1) Maculopathy (N=169 cases): triglycerides 1.09 (0.95, 1.26), HDL 0.97 (0.78,1.19); (2) Laser surgery: triglycerides 1.03 (0.93,1.14), HDL 0.93 (0.82,1.06); (3) Fundus photography EDTRS: triglycerides 1.04 (0.92,1.16), HDL 0.98 (0.82,1.17); (4) Dilated ophthalmoscopy DRDS: triglycerides 1.00 (0.92,1.08), HDL 1.01 (0.94,1.10). Therefore, the results were similar and not significant across these retinopathy outcomes.

We evaluated the possible influence of co-existing kidney disease status on odds ratios associated with retinopathy for triglycerides and HDL-cholesterol. There were 630 retinopathy cases that did not have kidney disease comprising 52% of the total retinopathy cases. The odds ratio for retinopathy for triglyceride was 0.97 (0.89, 1.04) for the subset compared with 1.04 (0.98, 1.11) for the total group; and for HDL-cholesterol levels was 1.03 (0.93, 1.14) for the subset compared with 0.97 (0.90, 1.05) for the total group.
Because hemoglobin A1C level was strongly associated with case status, the odds ratios for microvascular disease, kidney or eye, were determined for those with hemoglobin A1C above or below the median, 7.4%. Odds ratios for those with hemoglobin A1C above the median (mean HbA1c 9.0% for 1554 cases, 8.9% for 1659 controls) are triglycerides 1.14 (1.07, 1.22), HDL 0.96 (0.91, 1.03); and for those below the median (mean HbA1c 6.6% for 901 cases and 2007 controls) are triglycerides 1.15 (1.07, 1.24), HDL 0.87 (0.81, 0.93). These models were not adjusted for hemoglobin A1C. Heterogeneity tests for these analyses were not significant.

There were 564 cases who had both kidney disease and retinopathy. The odds ratio for case status of both kidney disease and retinopathy compared to 3318 controls was 1.16 (1.07, 1.25) for a 1 SD increase in triglyceride and 0.88 (0.80, 0.96) for a 1 SD increase in HDL-C, similar to those in the full group.

Adjusting for prevalent cardiovascular disease in the matched conditional logistic regression meta-analysis had little impact on key inferences. Odds ratio (95% CI) for increasing adjacent quintiles of TG was 1.23 (1.15, 1.31); and for HDL-C 0.87 (0.82, 0.92).

Additional sensitivity analyses evaluating those whose blood sample was in the fasting state (N=1306 cases for kidney, 803 for eye) showed an odds ratio for a microvascular complication associated with triglycerides of 1.16 (1.09, 1.24) compared to 1.16 (1.11, 1.22) for the total group; and with HDL-cholesterol of 0.91 (0.86, 0.96) compared to 0.92 (0.88, 0.96) for the total group.

Similarly, subgroup analysis of those who were not taking statins or fibrates returned odds ratios that were the same or nearly so as the full sample: For kidney disease in the no lipid-treatment group, the odds ratio for a one SD change in triglycerides was 1.24 (1.14, 1.34) and in HDL-cholesterol was 0.83 (0.77, 0.90) (N=704 cases, 1570 controls). For retinopathy in the no
lipid-treatment group, the odds ratio for triglycerides was 0.99 (0.90,1.10) and for HDL-cholesterol was 0.99 (0.87,1.12) (N=549 cases, 1318 controls).

The associations of triglycerides and HDL-cholesterol with kidney disease or retinopathy were similar among the geographic regions and ethnicities. Eight European sites were preponderantly (74%) white, and nine Asian sites were preponderantly nonwhite (89%). The odds ratios for adjacent quintiles of triglyceride were 1.13 (1.03,1.23) for Europe and 1.21 (1.10,1.34) for Asia; for adjacent quintiles of HDL-cholesterol, 0.89 (0.78,1.01) for Europe and 0.94 (0.86,1.02) for Asia.

Discussion

Diabetes is the major cause of renal failure and vision loss in adults. Current treatments are effective in reducing the risk of development and progression; however, the residual risk for these complications remains high. Since the prevalence of type 2 diabetes continues to increase worldwide, it is expected that its major complications, kidney disease and retinopathy, will increase in parallel. New targets and treatments are urgently needed.

In this study, triglycerides and HDL-cholesterol were significantly and independently associated with diabetic microvascular disease and specifically with kidney disease. The associations with retinopathy were not robust after adjustment for hypertension and hemoglobin A1C. These associations were similar in magnitude among the sites and among geographic regions.

The strengths of the study include its global scope of inclusion of sites, and consistency of findings, demonstrated by lack of heterogeneity in nearly all of the meta-analyses, supporting wide generalizability across regions and ethnicities. The matching procedure that equalizes age,
sex, duration of diabetes, and LDL-cholesterol concentration reduces the probability of confounding and reverse causation. The findings for total microvascular events and for kidney disease were robust after adjustment for hypertension and hemoglobin A1C, two major influences on the occurrence of diabetic microvascular disease. This study has a large number of cases of diabetic microvascular disease. This reduced the chance of a false negative as might have occurred in previous studies on HDL-cholesterol and microvascular disease.

Limitations of this study are its cross-sectional design and the potential for reverse causation. However, a typical example of reverse causation, more aggressive treatment of lipid levels in cases, would bias the results to the null since treatment would decrease triglycerides and raise HDL-cholesterol in the cases, the opposite of the actual results. It seems likely that matching cases and controls on LDL-cholesterol equalized lipid treatment. The finding that lipid treatments were similar in the two groups supports this interpretation. The lipid laboratories at each site were not standardized or calibrated, although the lab survey that we conducted did not find serious differences in accuracy among the sites that participated, and the precision measurements were excellent. In any case, it would be unlikely that measurement error could occur differentially between cases and controls. Although the blood samples were not required to be fasting, most were fasting, the same in cases and controls, and the results for a fasting subgroup were similar to the total group.

Most previous studies reported that high plasma triglycerides were associated with diabetic kidney disease\textsuperscript{8,10,12-14,17,19-21,43} although several did not find an association.\textsuperscript{7,9,16} As regards HDL-cholesterol, the published literature is less consistent with some showing a significant association\textsuperscript{8,16,17,19-21,43}, and others not.\textsuperscript{7,9-12,14,18} Certainly type 2 errors could account for negative studies. We consider the findings in our study that both high triglycerides
and low HDL-cholesterol, considered alone or together in multiple variable models with consistent direction of odds ratios among nearly all the sites and mostly nonsignificant tests of heterogeneity, as compelling evidence, in combination with previous studies, that triglycerides and HDL-cholesterol are indeed strongly associated with diabetic kidney disease.

The associations for retinopathy of triglycerides and HDL-cholesterol were weaker than for kidney disease and less robust after adjustment for known risk factors. The retinopathy literature is mixed as regards triglycerides with some studies showing a significant association and others not or mixed findings. For HDL-cholesterol, all studies did not find a significant association with diabetic retinopathy with one exception. The large number of cases (1202) in our study provided sensitivity to identify even a relatively weak association between retinopathy and triglycerides and HDL-cholesterol if one existed. Measurement error for retinopathy determined by ophthalmoscope or even fundus photography that requires grading has the potential to reduce the strength of associations with triglycerides and HDL-C. However, the results for the association between TG and HDL-C and retinopathy were similar regardless of the specific diagnostic criterion, including laser surgery. The results suggest that associations of triglycerides and HDL-cholesterol with retinopathy may be dependent on confounding by other risk factors for microvascular disease, specifically hypertension and hemoglobin A1C, as we found.

The integrity of the blood-retinal barrier protects the retina against potentially harmful effects of extravasation of plasma lipoproteins. ApoB lipoproteins may damage retinal capillaries leading to extravasation and they are present in retinas of diabetic people in proportion to the severity of retinopathy. These mechanistic findings and the present results support the concept that mechanisms involved in regulation or dysregulation of intraretinal lipid transport might be
potentially more important than plasma lipid levels in the pathogenesis of diabetic retinopathy.\textsuperscript{46} This may differ from the effects of lipoproteins on kidney disease where extravasation of lipoproteins may more readily occur than in the retina.

Finally, the present study is restricted to information in clinic and hospital records that contain only standard lipid measurements needed for clinical management. It is possible that specific lipoprotein subfractions could be involved in retinopathy, such as apoC-III containing LDL and HDL that are strongly associated with coronary events\textsuperscript{47,48} and adversely affect endothelial cells\textsuperscript{49} or oxidized lipoproteins.\textsuperscript{45}

In conclusion, this global study of lipid risk factors for diabetic microvascular disease provides strong evidence for independent associations for high triglycerides and low HDL-cholesterol. These associations apply to kidney disease. It is possible that retinopathy may also be affected by triglyceride or HDL-cholesterol levels but the association appears weak. Nevertheless, larger populations and meta-analyses could be helpful to further investigate the relationship between retinopathy and dyslipidemia. Current guidelines for lipid treatment give more emphasis than before on using triglycerides and HDL-cholesterol for treatment thresholds and targets for macrovascular disease.\textsuperscript{50} In view of the large and growing health burden of renal failure in diabetes, these findings have considerable importance in support of additional lipid targets other than LDL-cholesterol to benefit the diabetic population at high residual risk for microvascular disease despite current standards of care.

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**Conflict of Interest Disclosures:** Dr. Sacks was a Board Member of the Residual Risk Reduction Institute (R3i), the sponsor of this research, until April 12, 2012. In 2011, he was also paid by R3i for his Research/Product Development services. This interest was reviewed by Brigham and Women’s Hospital and Partners HealthCare in accordance with their institutional policies. He has given expert testimony in patent litigation on the side of Abbott. Dr. Hermans is a Board Member of the Residual Risk Reduction Institute (R3i), the sponsor of this research, and he was also paid by R3i for his Research/Product Development services. Dr. Goldenberg has received speakers fees, consultant fees & research fees from Abbott Laboratories, Merck, AstraZeneca, & Pfizer. Dr. Leiter has received research funding from, have provided CME on behalf of, and/or have acted as a consultant to: Abbott, AstraZeneca, Boerininger, BMS, Eli Lilly, GSK, Merck, Novartis, Novo Nordisk, Roche, Sanofi, and Servier. Dr. Bunnag has received honoraria from Abbott. Dr. Wanner has received honoraria from Merck and Astellas. Dr. Valensi has received honoraria from Abbott. Dr. Simo has participated on advisory panels for Novartis, Novo Nordisk, Lilly and Abbott, and has received travel, honorarium and research support from these companies. Dr. Reiner has received honoraria from Abbott, Sanofi-Aventis, AstraZeneca, & MSD. Dr. Carey provided and was compensated for consulting services to the R3I Foundation.
References:


Table 1. Descriptive statistics of cases and controls

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<td>41%</td>
<td>51%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mean, SD)</td>
<td>65 (11)</td>
<td>65 (11)</td>
<td>64 (10)</td>
<td>62 (11)</td>
<td>0.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes duration, y (mean, SD)</td>
<td>14 (9)</td>
<td>14 (9)</td>
<td>16 (9)</td>
<td>10 (8)</td>
<td>0.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Lipids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tot. CHOL</td>
<td>4.30 (0.92)</td>
<td>4.26 (0.84)</td>
<td>4.36 (1.02)</td>
<td>4.30 (0.83)</td>
<td>0.01*</td>
<td>0.03</td>
</tr>
<tr>
<td>LDL-C</td>
<td>2.31 (0.63)</td>
<td>2.28 (0.64)</td>
<td>2.34 (0.62)</td>
<td>2.35 (0.85)</td>
<td>0.0*</td>
<td>0.34</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.20 (0.44)</td>
<td>1.18 (0.46)</td>
<td>1.23 (0.40)</td>
<td>1.26 (0.45)</td>
<td>-0.04*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.78 (1.14)</td>
<td>1.85 (1.17)</td>
<td>1.72 (1.18)</td>
<td>1.61 (1.20)</td>
<td>0.12*</td>
<td>&lt;0.01</td>
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<tr>
<td><strong>Hemoglobin A1C</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.1% (1.7%)</td>
<td>8.0% (1.7%)</td>
<td>8.3% (1.8%)</td>
<td>7.6% (1.6%)</td>
<td>0.46</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrate use [N, (%)]</td>
<td>195 (7.7%)</td>
<td>163 (8.6%)</td>
<td>81 (6.7%)</td>
<td>291 (7.9%)</td>
<td>0.0**</td>
<td>0.69</td>
</tr>
<tr>
<td>Statin use [N, (%)]</td>
<td>1326 (52%)</td>
<td>1053 (56%)</td>
<td>571 (48%)</td>
<td>1880 (51%)</td>
<td>0.01**</td>
<td>0.23</td>
</tr>
<tr>
<td>antiDM use [N, (%)]</td>
<td>2385 (94%)</td>
<td>1782 (94%)</td>
<td>1146 (95%)</td>
<td>3301 (90%)</td>
<td></td>
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<tr>
<td><strong>Clinical condition</strong></td>
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<td></td>
</tr>
<tr>
<td>Nephropathy [N, (%)]</td>
<td>1891 (75%)</td>
<td>1891 (100%)</td>
<td>566 (47%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinopathy [N, (%)]</td>
<td>1218 (48%)</td>
<td>574 (30%)</td>
<td>1202 (100%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension [N, (%)]</td>
<td>2076 (82%)</td>
<td>1588 (84%)</td>
<td>981 (82%)</td>
<td>2427 (66%)</td>
<td>0.15**</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

A total of 2535 cases were reported and they were matched, within sites and within strata defined by gender, to 3683 controls. 574 cases had both kidney and eye disease. For the secondary analysis of kidney disease or retinopathy, separately, sites were included that reported at least 10 cases. The kidney disease analysis included all 24 sites and 1891 cases, whereas the retinopathy analysis included 21 sites and 1202 cases.

Difference (Δ) denotes the meta-analytic estimate of the mean difference between cases and controls on general parameters of the study, allowing random intercepts for matched strata.

*denotes Δ estimated after log transformation

**denotes Δ is the meta-analytic odds ratio for the dichotomous characteristic
Figure Legends:

**Figure 1.** Odds Ratio for diabetic kidney disease or retinopathy associated with a quintile increase in blood triglycerides (0.5 mmol/L) or HDL-cholesterol (0.2 mmol/L). Controlled by matching for age, sex, duration of diabetes and LDL-cholesterol level; and by including hypertension and hemoglobin A1C in the multiple variable model. Size of symbols proportional to number of cases. Test for heterogeneity among sites: triglyceride P = 0.22, HDL-cholesterol P = 0.42.

**Figure 2.** Odds Ratios for kidney disease for triglycerides (left) and HDL-cholesterol (right), not mutually adjusted. Matching variables, covariates and symbols are described in the legend to Figure 1. The analysis included all 24 sites and 1891 cases. Test for heterogeneity among sites: triglyceride P = 0.14 , HDL-cholesterol P = 0.58.

**Figure 3.** Quintile-specific odds ratios for diabetic kidney disease associated with levels of blood triglycerides or HDL-cholesterol. Matching variables and covariates are described in the legend to Figure 1. Left panel, triglycerides and HDL-cholesterol not mutually adjusted; right panel, mutually adjusted. The medians for the quintiles are on the horizontal axis.

**Figure 4.** Odds ratio for kidney disease for triglycerides and HDL-cholesterol, mutually adjusted. Matching variables, covariates and symbols are described in the legends to Figures 1 and 2. Test for heterogeneity among sites: triglyceride P = 0.19, HDL-cholesterol P = 0.64.
Figure 5. Odds Ratio for Kidney disease defined by either low estimated glomerular filtration rate (eGFR) (N=522 cases) or albuminuria (N=1517 cases) according to triglycerides or HDL-cholesterol, not mutually adjusted. Matching variables, covariates and symbols are described in the legend to Figure 1. Test for heterogeneity among sites (linear trend) for low eGFR: triglyceride P = 0.24, HDL-cholesterol P = 0.03. Test for heterogeneity among sites (linear trend) for albuminuria: triglyceride P = 0.04, HDL-cholesterol P = 0.65.

Figure 6. Odds Ratio for retinopathy associated with a quintile increase in blood triglycerides (left panel) or HDL-cholesterol (right panel). Matching variables, covariates and symbols are described in Figure 1. Triglycerides and HDL-cholesterol not mutually adjusted. Sites were included that reported at least 10 cases. The retinopathy analysis included 21 sites and 1202 cases. Test for heterogeneity among sites: triglyceride P = 0.30, HDL-cholesterol P = 0.08.
Figure 1
Figure 2

Summary OR(CI)
1.23 (1.16, 1.31)

OR for adjacent quintiles in TG

Summary OR(CI)
0.86 (0.62, 0.91)

OR for adjacent quintiles in HDL-C
Figure 3

Summarized odds ratio

Quintile of site-specific marker distributions

TG Q1 0.74 Q2 1.06 Q3 1.36 Q4 1.77 Q5 2.83
HDL Q1 0.82 Q2 1.02 Q3 1.2 Q4 1.38 Q5 1.7
Figure 5
Figure 6
Association Between Plasma Triglycerides and HDL-Cholesterol and Microvascular Kidney Disease and Retinopathy in Type 2 Diabetes: A Global Case-Control Study in 13 Countries


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Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2013/12/18/CIRCULATIONAHA.113.002529.DC1

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Evaluation of precision and accuracy of measurements of serum lipids

A set of serum standards with blood lipids values that were calibrated to the Centers for Disease Control Lipid Standardization Program, Atlanta, USA, were sent to each laboratory of the participating sites and the blood lipids measured. The standards were taken from four large-volume plasma pools created from plasma collected from 23 healthy volunteers in the laboratory of Dr. Sacks at Harvard School of Public Health. The laboratory study included 11 of the 24 sites. Reasons for not participating were unavailability of import permits for blood plasma (5 sites), lack of a centralized local laboratory (4 sites), and declined (2 sites). In addition, delivery to two sites was delayed for 1 to 2 months, and these sites were excluded. The sites that were included were in Croatia (1), Japan (3), Italy (2), USA (1), Thailand (2), Taiwan (2).

The sites analyzed the standards for triglycerides, total cholesterol, and HDL-cholesterol. The 4 pools, each including a single replicate, were run each day for 3 nonconsecutive days. Linear mixed effects models were used with random effects for site and replicate nested within site. For triglycerides and HDL-C, respectively, the intraclass correlation for replicates was estimated at 0.956 and 0.945; and median correlation with reference values measured at Harvard School of Public Health was 0.998 and 0.991.
Supplemental Table 1. Characteristics of cases and controls in each center

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>N</th>
<th>Cases</th>
<th>Controls</th>
<th>#Male (%)</th>
<th>yrs. w/DM</th>
<th>Stg1 +HTN</th>
<th>Cases</th>
<th>Controls</th>
<th>Statin use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia Bangkok</td>
<td>200</td>
<td>100</td>
<td>96 (32)</td>
<td>13.5 (6.6)</td>
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<tr>
<td></td>
<td>170</td>
<td>70</td>
<td>94 (50)</td>
<td>31.8 (15.2)</td>
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<tr>
<td>Asia Beijing</td>
<td>254</td>
<td>124</td>
<td>81 (35)</td>
<td>15.7 (7.2)</td>
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<td></td>
<td></td>
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<tr>
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<td>300</td>
<td>100</td>
<td>87 (35)</td>
<td>12.6 (6.3)</td>
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<td></td>
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</tr>
<tr>
<td>Asia Tokyo</td>
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<td>100</td>
<td>90 (35)</td>
<td>11.5 (5.2)</td>
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<tr>
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<td>55</td>
<td>79 (35)</td>
<td>14.7 (8.3)</td>
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<td>11.4 (5.3)</td>
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<tr>
<td>Europe</td>
<td>250</td>
<td>100</td>
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<td>Europe Bondy</td>
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<td>196</td>
<td>80 (33)</td>
<td>10.5 (5.6)</td>
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<tr>
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<tr>
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<tr>
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<tr>
<td>Midwest Riyadh</td>
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</tr>
<tr>
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<td>156</td>
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<td>North America</td>
<td>305</td>
<td>102</td>
<td>82 (33)</td>
<td>8.7 (7.6)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>North America</td>
<td>124</td>
<td>63</td>
<td>73 (28)</td>
<td>14.5 (8.5)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>North America</td>
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<td>100</td>
<td>80 (32)</td>
<td>9.5 (8.2)</td>
<td></td>
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</tr>
<tr>
<td>North America</td>
<td>304</td>
<td>104</td>
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<td>10.7 (8.4)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Legend:
- **LDL-C**: Low-density lipoprotein cholesterol
- **HDL-C**: High-density lipoprotein cholesterol
- **TG**: Triglycerides
- **Statin use**: Yes (Y)/No (N)
- **% Male (%)**: Percentage of males
- **N**: Total number of participants
- **Cases**: Number of cases
- **Controls**: Number of controls

Note: All values are expressed as mean (SD) unless otherwise specified.
SUPPLEMENTAL TABLE 2

Characteristics of cases of microalbuminuria and controls

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>4985</td>
<td>1517</td>
<td>3468</td>
</tr>
<tr>
<td>Male [N, (%)]</td>
<td>2858 (57.3%)</td>
<td>929 (61.2%)</td>
<td>1929 (55.6%)</td>
</tr>
<tr>
<td>White/European</td>
<td>47.1%</td>
<td>45.7%</td>
<td>47.7%</td>
</tr>
<tr>
<td>Age [mean, SD]</td>
<td>62.65 (10.79)</td>
<td>64.94 (11.04)</td>
<td>61.65 (10.52)</td>
</tr>
<tr>
<td>yrs. w/DM [mean, SD]</td>
<td>11.18 (8.52)</td>
<td>13.86 (9.28)</td>
<td>10.01 (7.89)</td>
</tr>
<tr>
<td>Tot. CHOL</td>
<td>164.78 (31.18)</td>
<td>164.28 (31.71)</td>
<td>165.01 (30.95)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>2.32 (0.62)</td>
<td>2.27 (0.64)</td>
<td>2.34 (0.61)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.24 (0.44)</td>
<td>1.19 (0.41)</td>
<td>1.26 (0.45)</td>
</tr>
<tr>
<td>TG</td>
<td>1.65 (1.16)</td>
<td>1.82 (1.11)</td>
<td>1.58 (1.18)</td>
</tr>
<tr>
<td>Fibrate use (%, N)</td>
<td>7.44 (371)</td>
<td>7.71 (117)</td>
<td>7.32 (254)</td>
</tr>
<tr>
<td>Statin use (%, N)</td>
<td>53.56 (2670)</td>
<td>57.22 (868)</td>
<td>51.96 (1802)</td>
</tr>
<tr>
<td>antiDM use (%, N)</td>
<td>91.9 (4581)</td>
<td>94.53 (1434)</td>
<td>90.74 (3147)</td>
</tr>
<tr>
<td>Nephroropathy (%, N)</td>
<td>30.27 (1509)</td>
<td>99.47 (1509)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Retinopathy (%, N)</td>
<td>9.15 (456)</td>
<td>30.06 (456)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stg1+HTN (%, N)</td>
<td>71.37 (3558)</td>
<td>83.52 (1267)</td>
<td>66.06 (2291)</td>
</tr>
<tr>
<td>HbA1c [mean, SD]</td>
<td>7.74 (1.66)</td>
<td>8.05 (1.72)</td>
<td>7.61 (1.61)</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td>-------------------------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>N</td>
<td>3401</td>
<td>522</td>
<td>2879</td>
</tr>
<tr>
<td>Male [N, (%)]</td>
<td>1914 (56.3%)</td>
<td>325 (62.3%)</td>
<td>1589 (55.2%)</td>
</tr>
<tr>
<td>White/European</td>
<td>54.5%</td>
<td>49.4%</td>
<td>55.5%</td>
</tr>
<tr>
<td>Age [mean, SD]</td>
<td>61.99 (10.64)</td>
<td>68.6 (9.98)</td>
<td>60.79 (10.31)</td>
</tr>
<tr>
<td>yrs. w/DM [mean, SD]</td>
<td>9.99 (8.11)</td>
<td>15.42 (9.82)</td>
<td>9.01 (7.34)</td>
</tr>
<tr>
<td>Tot. CHOL</td>
<td>164.88 (31.97)</td>
<td>160.79 (33.82)</td>
<td>165.62 (31.57)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>2.3 (0.63)</td>
<td>2.16 (0.62)</td>
<td>2.32 (0.63)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.24 (0.48)</td>
<td>1.17 (0.59)</td>
<td>1.25 (0.46)</td>
</tr>
<tr>
<td>TG</td>
<td>1.67 (1.02)</td>
<td>1.9 (1.03)</td>
<td>1.63 (1.02)</td>
</tr>
<tr>
<td>Fibrate use (%, N)</td>
<td>9.29 (316)</td>
<td>13.03 (68)</td>
<td>8.61 (248)</td>
</tr>
<tr>
<td>Statin use (%, N)</td>
<td>54.22 (1844)</td>
<td>63.79 (333)</td>
<td>52.48 (1511)</td>
</tr>
<tr>
<td>antiDM use (%, N)</td>
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<td>93.1 (486)</td>
<td>89.82 (2586)</td>
</tr>
<tr>
<td>Nephropathy (%, N)</td>
<td>15.17 (516)</td>
<td>98.85 (516)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Retinopathy (%, N)</td>
<td>4.65 (158)</td>
<td>30.27 (158)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stg1+HTN (%, N)</td>
<td>68.69 (2336)</td>
<td>89.85 (469)</td>
<td>64.85 (1867)</td>
</tr>
<tr>
<td>HbA1c[mean,SD]</td>
<td>7.6 (1.51)</td>
<td>7.68 (1.42)</td>
<td>7.59 (1.52)</td>
</tr>
</tbody>
</table>
Supplemental Figure 1A: Odds ratio for albuminuria according to triglycerides, not mutually adjusted for HDL-cholesterol. Size of symbols proportional to number of cases.
Supplemental Figure 1B: Odds ratio for albuminuria according to HDL-cholesterol, not mutually adjusted for triglycerides. Size of symbols proportional to number of cases.
Supplemental Figure 2A: Odds ratio for albuminuria according to triglycerides mutually adjusted for HDL-cholesterol. Size of symbols proportional to number of cases.
Supplemental Figure 2B: Odds ratio for albuminuria according to HDL-cholesterol, mutually adjusted for triglycerides. Size of symbols proportional to number of cases.
Supplemental Figure 3. Odds ratio for albuminuria according to quintiles of triglycerides and HDL-cholesterol, not mutually adjusted.
Supplemental Figure 4A: Odds ratio for low GFR and triglycerides, not mutually adjusted. Size of symbols proportional to number of cases.
Supplemental Figure 4B: Odds ratio for low GFR and HDL-cholesterol, not mutually adjusted. Size of symbols proportional to number of cases.
Supplemental Figure 5A. Odds ratio for low GFR and triglycerides, mutually adjusted for HDL-cholesterol. Size of symbols proportional to number of cases.
Supplemental Figure 5B. Odds ratio for low GFR and HDL-cholesterol, mutually adjusted for triglycerides. Size of symbols proportional to number of cases.
Supplemental Figure 6. Odds ratio for low GFR according to quintiles of triglycerides or HDL-cholesterol, not mutually adjusted.