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Emerging Cardiovascular Disease Biomarkers and Incident Diabetes Mellitus Risk in Statin-Treated Patients With Coronary Artery Disease (from the Treating to New Targets [TNT] Study)

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Whether biomarkers associated with cardiovascular disease risk also predict incident diabetes mellitus (DM) is unknown. Our objective was to determine if a panel of 18 biomarkers previously associated with risk of cardiovascular disease also predicts incident DM in statin-treated patients with coronary artery disease (CAD). The Treating to New Targets (TNT) study is a randomized trial that compared the efficacy of high (80 mg) versus low (10 mg) dose atorvastatin for the secondary prevention of coronary heart disease events. Fasting plasma levels of standard lipids and of 18 emerging CAD risk biomarkers were obtained after an 8-week run-in period on atorvastatin 10 mg in a random sample of 1,424 TNT patients. After exclusion of patients with DM at baseline (n = 253), 101 patients developed DM during the median follow-up of 4.9 years. Patients with incident DM had lower levels of total and high-molecular weight adiponectin, lipoprotein-associated phospholipase A2 (Lp-PLA2), soluble receptor of advanced glycation end products, and vitamin D compared with patients without incident DM. In contrast, insulin, soluble CD40 ligand, and soluble intercellular adhesion molecule-1 levels were higher in patients with incident DM compared with those without. Plasma levels of C-reactive protein, cystatin C, lipoprotein(a), monocyte chemotactic protein-1, matrix metalloproteinase-9, myeloperoxidase, neopterin, N-terminal fragment of pro−B-type natriuretic peptide, osteopontin, and soluble vascular cell adhesion molecule-1 were comparable in patients with and without incident DM. After multivariate adjustment, total and high-molecular weight adiponectin as well as Lp-PLA2 were negatively associated with incident DM. Results of this study suggest that plasma lipids and some emerging CAD risk biomarkers, such as adiponectin and Lp-PLA2, may be useful for predicting incident DM in statin-treated patients with stable CAD. **(Am J Cardiol 2016;118:494−498)**

The prevalence of type 2 diabetes mellitus (DM) is increasing in the vast majority of countries around the world.[1] Patients who already cope with chronic diseases such as cardiovascular disease (CVD) are at increased risk of developing type 2 DM.[2] We and others have previously documented that traditional risk factors such as hypertension and obesity, as well as triglyceride and high-density lipoprotein (HDL) cholesterol levels are associated with DM risk in patients with coronary artery disease (CAD).[3] We have also recently shown that plasma levels of some emerging biomarkers of lipoprotein−lipid metabolism, inflammation, and glucose−insulin homeostasis may predict CVD risk in statin-treated patients with CAD.[4] Whether these emerging CVD risk biomarkers are also associated with incident DM and whether they have any clinical value in such patients are unknown. The objective of the present study was to determine whether a panel of 18 biomarkers associated with the risk of CVD also predicted incident DM in statin-treated patients with CAD.

Methods

The study protocol and outcome measures for the Treating to New Targets (TNT) study have been published previously.[5] In brief, patients with clinically manifest CAD commenced 8 weeks of open-label treatment with atorvastatin 10 mg/day. After this run-in period, 10,001 patients with low-density lipoprotein cholesterol levels <130 mg/dl (<3.4 mmol/L) were randomized in a double-blind design to therapy with either 10 mg or 80 mg of atorvastatin per day and followed for a median of 4.9 years. Incident DM was defined prospectively as at least 2 postbaseline fasting blood

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See page 497 for disclosure information.

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Table 1
Baseline characteristics of patients with diabetes mellitus at baseline and in patients with and without incident diabetes mellitus during follow-up in the TNT study

Baseline Follow-up	Diabetes Mellitus		
	No		Yes (N=253)
	Without incident DM (N=1070)	With incident DM (N=101)	
Atorvastatin 80 mg	528 (49.4%)	56 (55.5%)	123 (48.6)
Men	872 (81.5%)	80 (79.2%)	186 (73.5%)*
White	1013 (94.7%)	92 (91.1%)	228 (90.1%)*
Age (years)	60.9±9.0	61.1±8.0	64.0±7.8*†
Body mass index (kg/m^2)	27.9±4.0	31.0±4.9*	31.0±5.6*
Systolic blood pressure (mmHg)	129.4±16.1	133.9±15.9*	135.3±18.0*
Diastolic blood pressure (mmHg)	77.6±9.0	78.5±8.0	76.2±10.3*†
Hypertension	566 (52.9%)	53 (52.5%)	193 (76.3%)*†
Smoker			
Current	11 (10.9%)	155 (14.5%)	15 (5.9)*
Past	72 (71.3%)	652 (60.9)*	176 (69.6)*
Never	18 (17.8%)	263 (24.6)	62 (24.5)
Metabolic syndrome	506 (47.3%)	78 (77.2)*	210 (83.0)*
Estimated glomerular filtration rate (mL/min/1.72 m^2)	64.9 ± 10.8	64.7 ± 11.3	63.6 ± 12.9
Angiotensin-converting-enzyme inhibitors	561 (53.8%)	49 (49.5%)	145 (58.7%)
Angiotensin II receptor blockers	170 (16.3%)	16 (16.2%)	35 (14.2%)
Beta blockers	727 (69.8%)	64 (64.6%)	172 (69.6%)
Calcium channel blockers	412 (39.5%)	34 (34.3%)	103 (41.7%)
Antiplatelets	146 (14.0%)	9 (9.1%)	43 (17.4%)
Vitamin K antagonists	162 (15.5%)	20 (20.2%)	39 (15.8%)
Other anticoagulants	6 (0.6%)	0 (0%)	0 (0%)
Aspirin	957 (91.8%)	84 (84.8%)	226 (91.5%)

Data are shown as n (%) for categorical variables and mean ± SD for continuous variables.
* Significantly different than patients without incident diabetes.
† Significantly different than patients with incident diabetes; $p < 0.05$.

glucose measurements >7 mmol/L and at least 1 post-baseline fasting blood glucose measurement >2 mmol/L above baseline. We also included patients for whom incident DM was identified through adverse event reporting. Only patients from whom informed consent was obtained for measuring nonlipid biomarkers (in addition to that originally collected for the primary study) were selected for this substudy. Biomarker concentrations were measured in a random sample of 1,424 patients. Biomarkers concentrations were measured in fasting plasma samples collected at the time of randomization (after the 8-week atorvastatin 10 mg run-in period) and again 1 year after randomization. The biomarkers were selected based on previous studies linking them with cardiovascular risk and were selected in such a way that they represent specific biologic pathways associated with CVD. For instance, systemic inflammation is represented by C-reactive protein (CRP), macrophage recruitment/activity is represented by monocyte chemotactic protein-1, neopterin, soluble intercellular adhesion molecule-1, and soluble vascular cell adhesion molecule-1, oxidative stress is represented by myeloperoxidase and lipoprotein-associated phospholipase A2 (Lp-PLA2), tissue remodeling is represented by matrix metalloproteinase-9, and osteopontin, platelet activation/thrombosis is represented by soluble CD40 ligand and lipoprotein(a), insulin resistance is represented by insulin, adiponectin, high-molecular weight (HMW) adiponectin, HMW/total adiponectin (ratio), receptor for advanced glycation endproducts and vitamin D, congestive heart failure is represented by N-terminal fragment of pro−B-type natriuretic peptide and kidney function by cystatin C. The methods used for the measurements of lipid and nonlipid biomarkers as well as the differences in biomarkers levels between baseline and one year have been published previously.[4] The study was approved by the local research ethics committee or institutional review board at each center.

Patient characteristics at baseline were compared across 3 patients groups: those without DM at baseline who did not have incident DM, those without DM at baseline who did have incident DM, and those who had DM at baseline. A chi-square test was used for categorical variables, and a Wilcoxon rank-sum test for continuous variables. The association between on-treatment lipids and biomarker levels (at time of randomization), and incident DM was assessed in Cox proportional hazard analyses after adjustment for age, gender, treatment arm, smoking, hypertension, body mass index (BMI), and HDL cholesterol and triglyceride levels, using time to primary end point as the dependent variable.

Results

The clinical characteristics of the 3 study groups are presented in Table 1. Patients with incident DM during

Table 2
Lipid and nonlipid biomarker levels measured at randomization in patients with diabetes at baseline and in patients with and without incident diabetes during follow-up

Baseline Follow-up	Diabetes Mellitus		
	No		Yes (N=253)
	Without incident DM (N=1070)	With incident DM (N=101)	
Total cholesterol	174±24 mg/dL (4.51±0.61 mmol/L)	180±27 mg/dL (4.67±0.70 mmol/L)*	176±25 mg/dL (4.54±0.64 mmol/L)
LDL cholesterol	97±17 mg/dL (2.52±0.45 mmol/L)	99±20 mg/dL (2.56±0.51 mmol/L)	96±18 mg/dL (2.47±0.47 mmol/L)
HDL cholesterol	48±11 mg/dL (1.24±0.29 mmol/L)	46±11 mg/dL* (1.18±0.29 mmol/L)*	44±10 mg/dL* (1.15±0.27 mmol/L)*
Total/HDL cholesterol	3.80 ± 0.85	4.09 ± 0.87*	4.12 ± 0.97*
Triglycerides	133 (101-174) mg/dL (1.50 [1.14−1.96] mmol/L)	154 (120-218) mg/dL* (1.74 [1.35−2.46] mmol/L)*	162 (120-221) mg/dL* (1.83 [1.35−2.50] mmol/L)*
Total adiponectin (μg/mL)	6.75 (4.92−9.54)	5.19 (4.26−7.30)*	6.12 (4.43−9.85)*†
HMW adiponectin (μg/mL)	2.02 (1.21−3.26)	1.45 (1.01−2.01)*	1.80 (1.14−2.87)†
C-reactive protein (mg/L)	1.57 (0.72−3.56)	1.77 (0.76−4.16)	2.10 (0.95−4.58)*
Cystatin C, (μg/mL)	0.77 (0.67−0.90)	0.80 (0.69−0.91)	0.81 (0.67−0.97)*
Insulin (μU/mL)	11 (8−15)	15 (11−20)*	16 (12−27)*†
Lipoprotein(a) (mg/dL)	15 (5−40)	14 (5−34)	13 (4−41)
Lipoprotein-associated phospholipase A2 (ng/mL)	335 (275−395)	310 (237−356)*	305 (241−355)*
Monocyte chemoattractant protein-1 (pg/mL)	98 (74−129)	99 (76−134)	107 (81−147)*
Matrix metalloproteinase-9 (ng/mL)	43.6 (29.8−66.1)	46.0 (30.8−83.4)	43.5 (29.8−68.2)
Myeloperoxidase (ng/mL)	21.3 (10.1−56.3)	19.6 (10.1−50.8)	23.8 (11.0−60.5)
Neopterin (ng/mL)	2.85 (2.30−3.50)	2.80 (2.10−3.62)	3.10 (2.54−3.83)*†
N-terminal pro-B-type natriuretic peptide (fmol/mL)	510.4 (405.0−649.2)	506.7 (392.1−621.8)	512.9 (404.8−668.5)
Osteopontin (ng/mL)	46.2 (32.3−58.8)	45.4 (30.1−59.6)	48.2 (35.1−63.2)
Soluble receptor for advanced glycation end products (ng/mL)	1.34 (1.02−1.80)	1.22 (0.94−1.60)*	1.33 (1.02−1.79)†
soluble CD40 ligand (ng/mL)	3.87 (1.86−9.21)	5.69 (2.51−11.4)*	4.13 (2.16−10.8)
soluble intracellular adhesion molecule-1 (ng/mL)	140 (104−182)	160 (114−202)*	149 (114−195)*
soluble vascular cell adhesion molecule-1 (μg/mL)	1.04 (0.86−1.26)	1.11 (0.92−1.26)	1.09 (0.90−1.32)*
Vitamin D, ng/mL	77.0 (76.0−79.0)	71.5 (67.0−80.0)*	69.0 (65.0−75.0)*

Data are shown as mean ± SD for standard lipids and as median (interquartile range) for triglycerides and biomarkers.
* Significantly different than patients without incident diabetes.
† Significantly different than patients with incident diabetes; $p < 0.05$.

follow-up and those with DM at baseline had a higher mean BMI, mean systolic blood pressure, and higher prevalence of metabolic syndrome than those without DM at baseline and without incident DM during follow-up. These differences in clinical characteristics of study patients who did versus those who did not develop incident DM were comparable to what we have previously reported in the entire TNT study population.[3]

Plasma levels of lipid and nonlipid biomarkers in these patients are presented in Table 2. Patients with incident DM had higher levels of triglycerides and total cholesterol levels and lower levels of HDL cholesterol compared with patients without incident DM. They were also characterized by a higher total cholesterol/HDL cholesterol ratio. With regards to nonlipid biomarkers, patients with incident DM had lower levels of total and HMW adiponectin, Lp-PLA2, soluble receptor of advanced glycation end products, and vitamin D compared with patients without incident DM. However, insulin, soluble CD40 ligand, and soluble intercellular adhesion molecule-1 levels were higher in patients with incident DM compared with patients without incident DM. Plasma levels of low-density lipoprotein cholesterol, high sensitivity CRP, cystatin C, lipoprotein(a), monocyte chemotactic protein-1, matrix metalloproteinase-9, myeloperoxidase, neopterin, N-terminal fragment of pro−B-type natriuretic peptide, osteopontin, and soluble vascular cell adhesion molecule-1 were comparable in patients with versus without incident DM.

We next investigated the relation between nonlipid biomarkers levels and incident DM per 50% decrease in biomarker levels for incident DM. Results presented in Figure 1 show that after adjusting for age, gender, treatment arm, smoking, hypertension, BMI, HDL cholesterol and triglyceride levels, total and HMW adiponectin as well as Lp-PLA2 were negatively associated with risk of incident DM. Further adjustment for angiotensin-converting enzyme inhibitors and beta-blocker use did not change the reported associations.

Discussion

Our results suggest that plasma levels of several emerging biomarkers are either higher or lower in patients

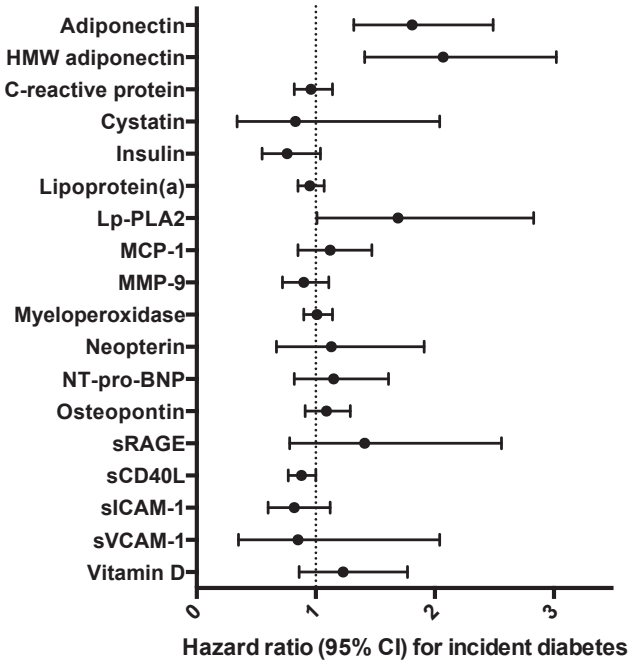

Figure 1. Hazard ratios (95% CIs) per 50% decrease of biomarker for risk of developing incident DM. Hazard ratios are adjusted for age, gender, treatment arm, smoking, hypertension, BMI, and HDL cholesterol and triglyceride levels. MCP-1 = monocyte chemotactic protein-1; MMP-9 = matrix metalloproteinase-9; NT-pro-BNP = N-terminal fragment of pro−B-type natriuretic peptide; sRAGE = soluble receptor of advanced glycation end products; sCD40 L = soluble CD40 ligand; sICAM-1 = soluble Intercellular adhesion molecule-1; and sVCAM-1 = soluble vascular cell adhesion molecule-1.

with incident DM compared with those without incident DM. However, after adjusting for DM risk factors, we found that only adiponectin and Lp-PLA2 remained independently associated with incident DM.

Many studies have tested the hypothesis that circulating biomarkers may predict incident DM.[6] However, very few, if any, have tested this hypothesis in statin-treated patients with CAD. A large-scale meta-analysis had previously reported a significant association between low adiponectin levels and incident DM.[7] Our results extend these findings to statin-treated patients with CAD. However, the causality of adiponectin in predicting DM risk has recently been questioned by a large-scale Mendelian randomization study.[8] Although the negative association between Lp-PLA2 and DM incidence is somewhat unexpected, previous cross-sectional studies have documented a negative association between Lp-PLA2 and markers of the glucose−insulin homeostasis in patients with vascular disease.[9] In DM-prone rats, injections of recombinant Lp-PLA2 reduced the incidence of DM.[10] The impact of the Lp-PLA2 inhibitor daraplabib on cardiovascular outcomes was recently tested in 2 large-scale phase 3 trials in patients with acute coronary syndrome[11] and stable vascular disease.[12] In both these studies, darapladib was shown not to reduce the risk of cardiovascular, and there was no apparent effect of darapladib on DM incidence. Therefore, the relation of Lp-PLA2 to DM risk also needs to be further studied. To our knowledge, our study is the first to investigate the relation between CRP and incident DM in patients with established CAD treated with statins. In contrast to primary prevention studies performed in middle-aged men[13] and women,[14] our results suggest that there is no association between CRP and incident DM in this population.

Our study has limitations. For instance, biomarkers were not measured in the entire TNT study population. Therefore, our conclusions are based on relatively few incident DM cases. In this study, levels of lipid and nonlipid biomarkers were measured at randomization, when all subjects had already been on 10 mg atorvastatin treatment for at least 8 weeks. It was therefore not possible to investigate the relation between biomarkers level off-statin therapy with DM incidence. For both of these reasons, it was not possible to identify biomarkers that could potentially explain the possible increased risk of DM associated with statin therapy. It should also be considered that only BMI and not waist circumference was measured in these participants. Waist circumference may have had a bigger influence on the association between biomarkers and incident DM than BMI, especially adiponectin. In addition, most study participants included in TNT were Caucasians. These results may therefore not be applicable to other ethnicities. In conclusion, results of this study suggest that plasma lipids and some emerging CAD risk biomarkers, such as adiponectin and Lp-PLA2, may be useful for predicting incident DM in statin-treated patients with stable CAD. Additional studies validating the clinical usefulness of these biomarkers are warranted.

Disclosures

Dr. Arsenault holds a junior scholar award from the Fonds de recherche du Québec: Santé (FRQS). Dr. Arsenault has received consulting fees/honoraria from Pfizer. Dr. Kohli has received consulting fees/honoraria from Summer Street Research Partners, Consultant Live, Amgen, and Pfizer. Dr. Lambert has received consulting fees/honoraria from Pfizer Inc, Sanofi/Regerenon and Amgen. Dr. Waters has received consulting fees/honoraria from Pfizer Inc, Servier, Roche, Merck/Schering Plough, Biosante, and Cerenis. Dr. Waters is also a member of the data safety monitoring board for Aastrom, Sanofi Aventis, and Shire. Drs. DeMicco, Laskey, and Messig are employees of Pfizer Inc. The other author has no conflicts of interest to disclose.

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