Preoperative Triglycerides Predict Post–Coronary Artery Bypass Graft Survival in Diabetic Patients

A sex analysis

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OBJECTIVE — Hypertriglyceridemia is commonly observed in association with diabetes. Despite cross-sectional studies and isolated longitudinal analyses in patients without coronary artery disease, the suggestion that triglyceride levels are relevant to subsequent cardiovascular events in the setting of diabetes remains controversial. This study evaluates the predictive value of serum triglyceride levels on mortality in post–coronary artery bypass graft (CABG) diabetic patients with subsequent analysis by sex.

RESEARCH DESIGN AND METHODS — This longitudinal observational study involving a large metropolitan hospital consists of 1,172 diabetic post-CABG patients (792 men and 380 women) with lipid data collected between the years 1982 and 1992. Cox proportional hazards regression models were used to estimate the risk of mortality and cardiac events associated with triglyceride levels in the highest quartile (>2.90 mmol/l for men and >3.12 mmol/l for women).

RESULTS — Elevated preoperative serum triglyceride values in post-CABG subjects with diabetes were correlated with increased overall mortality (hazard ratio [HR] 1.26, 95% CI 1.00–1.59). The greatest influence of triglyceride levels was observed on overall (1.89, 1.30–2.73) and event-free survival (1.49, 1.06–2.08) in women. High triglyceride values were also modestly related to risk of cardiac events in diabetic men (1.28, 0.99–1.66).

CONCLUSIONS — These data suggest that increased preoperative triglyceride levels predict increased late mortality and cardiac event risk in diabetic post-CABG patients, more strongly in women than in men.

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Elevated triglyceride levels are common in diabetic patients (1), and a physiological interaction exists between the presence of diabetes, its metabolic control, and serum triglyceride concentrations (2,3). Triglyceride and diabetes are separately associated with an increase in cardiovascular disease (CVD) (4). Furthermore, the onset of coronary heart disease (CHD) in type 2 diabetic patients without known baseline coronary artery disease (CAD) has been found to be independently associated with elevation in triglyceride values (5,6). In contrast, little is known about the impact of triglycerides on future cardiac events in diabetic patients with known CAD.

Women are particularly sensitive to the CVD risk associated with elevated triglyceride levels (7). Women experience a more significant increase in triglyceride levels with the onset of diabetes (8) and are thought to be more susceptible to the vascular consequences of diabetes than men (9). There is some evidence that VLDL and intermediate triglyceride-rich particles, unlike LDL and total cholesterol levels, correlate with the severity of CAD in women. LDL and total cholesterol levels correlate better with angiographic disease in men (10). However, sex differences relating to the influence of triglyceride on CVD risk remain unclear (6). We hypothesized that triglyceride values may predict survival in post–coronary artery bypass graft (CABG) diabetic women, perhaps to an extent further than that predicted in diabetic men.

Therefore, for this study, we attempted to characterize the CVD influence of triglyceride values in diabetic patients during 15 years of postsurgical follow-up and to separately define the overall and event-free survival for diabetic men and women.

RESEARCH DESIGN AND METHODS

Background

The Cardiovascular Information Registry (CVIR) was initiated at the Cleveland Clinic in the early 1970s; follow-up of patient survival and events was conducted on an interval basis. Between 1982 and 1992, 2,082 diabetic patients (17.4% of the total population) underwent a primary isolated CABG. Of these patients, 424 did not have triglyceride and/or total cholesterol values collected before surgery. A total of 36 patients were excluded from this study because of operative mortality, and 12 more were excluded because height and weight were not recorded. The first ~1,000 patients who underwent CABG surgery in each calendar year were followed at 5-year intervals after surgery using clinical visits and/or telephone interviews. The actual number has varied from year to year across the study

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Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; CVIR, Cardiovascular Information Registry; HR, hazard ratio; IMA, internal mammary artery; LVF, left ventricular function; MI, myocardial infarction; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Presentation characteristics of diabetic CABG patients at the time of surgery*

	Overall	Men	Women
n	1,172	792	380
Age (years)	63 ± 9	64 ± 9	63 ± 9
Total cholesterol (mmol/l)*	5.90 ± 1.37	5.69 ± 1.29	6.28 ± 1.45
HDL cholesterol (mmol/l)	0.91 ± 0.28	0.85 ± 0.25	0.96 ± 0.28
Triglycerides (mmol/l)*	2.43 ± 1.86	2.34 ± 1.87	2.62 ± 1.83
BMI (kg/m^2)*	29.2 ± 6.1	28.7 ± 5.7	30.4 ± 8.0
Risk factors present			
Left ventricular dysfunction			
None	434 (37)	283 (36)	151 (40)
Mild	345 (29)	235 (30)	110 (29)
Moderate	248 (22)	172 (22)	76 (20)
Severe	145 (12)	102 (13)	43 (11)
History of hypertension	780 (67)	504 (64)	276 (73)
Major coronary arteries with stenosis >50% (*n*)			
One	40 (3)	23 (3)	17 (4)
Two	214 (18)	142 (18)	72 (19)
Three	918 (78)	627 (79)	291 (77)
IMA used as a conduit	972 (83)	688 (87)	284 (75)

Data are means ± SD or *n* (%). *Continuous risk factor.

period for administrative reasons. This follow-up mechanism yielded 1,172 diabetic patients (17.8% of 6,602 patients followed; 792 men and 380 women) with follow-up averaging 7 years. We did not follow 438 diabetic patients with adequate baseline parameters for modeling. Mortality was quantified beyond 30 days' postsurgery ("late-mortality") to avoid the influence of immediate postsurgical complications.

In this database, diabetes was defined as patients who were taking insulin or oral agents. Lipid measurements were drawn in the fasting state a median of 5 days before surgery. Lipid measurements were available from a single preoperative blood sample. The Cleveland Clinic Foundation laboratory was standardized by the Centers for Disease Control [Part III] and was accredited through the College of American Pathology during the study period. Remaining risk factors and surgical variables were collected via chart review after discharge. Information regarding glycemic control, plasma lipids, or pharmacological therapy for lipid control were not available postoperatively.

Statistical methods

Time-to-event data were analyzed according to the primary end point of all-cause mortality (overall survival) and the secondary end point of overall survival free from myocardial infarction (MI) or repeat revascularization with either CABG or interventional cardiology procedures (event-free survival). Survival estimates were generated with the Kaplan-Meier method (11). Cox proportional hazards modeling (PROC PHREG; SAS Institute, Cary, NC) was used to assess the relative importance of baseline risk factors to the end points (12). Tied-event data were handled using Efron's method of approximation (13). Overall model significance was assessed with likelihood ratio tests, and the significance of each variable in the model was determined with the Wald test. Hazard ratios (HRs) are presented (with 95% CI) to show the risk of an event when the factor is present.

To minimize the impact of random variation within the normal range and to facilitate relevance as a clinical tool for modeling purposes, total cholesterol, LDL cholesterol, and triglyceride values were categorized as high (highest quartile) or normal (lower three quartiles). Additionally, HDL cholesterol values were categorized as low (lowest quartile) or normal (upper quartiles). The high-triglyceride group cutoff point was 2.90 mmol/l for men and 3.12 mmol/l for women. The significance of triglyceride levels with regard to overall and event-free survival was confirmed with models treating triglyceride as a continuous variable. The high-triglyceride group cutoff point was >6.31 mmol/l for men and >6.96 mmol/l for women. For HDL, the cutoff points were 0.67 mmol/l for men and 0.75 mmol/l for women. LDL estimates were derived from the Friedewald method. Because this method is conventionally viewed as not valid in patients with triglyceride levels >4.25 mmol/l (*n* = 96) and because LDL could only be derived from a truncated cohort because of a lack of HDL in a significant percentage, LDL was not included as a covariate. Overall and event-free survival models were constructed to test the triglyceride effect adjusted for age, sex, left ventricular function (LVF), extent of disease, internal mammary artery (IMA) use, history of hypertension, BMI, and total cholesterol. The main sex effect was examined in this setting. A sex-specific triglyceride interaction term was then entered to test the hypothesis that men and women exhibited differing survival responses to high triglyceride levels; doing so enabled us to conduct sex-specific analyses. When available (1987 and beyond), HDL cholesterol was incorporated into the models to verify the triglyceride effect.

RESULTS — Table 1 documents the presentation characteristics of this cohort. The adjusted model revealed high triglyceride levels to be significantly related to increased mortality (HR 1.26, 95% CI 1.00–1.59, P = 0.05). Age (1.03, 1.02–1.04), extent of disease (1.28, 1.03–1.60), LVF (1.22, 1.11–1.35), and IMA use (0.70, 0.54–0.90) were also significantly related to increased mortality. Total cholesterol did not provide additional discriminating information for any analysis performed for this study. Adjusted 10-year Kaplan-Meier survival estimates were 56% for patients with normal triglyceride levels compared with 50% for patients with elevated triglyceride levels. Similarly, high triglyceride levels were significantly related to the occurrence of adverse events (i.e., death, repeat revascularization, or MI) in event-free survival analysis (1.32, 1.08–1.61, P = 0.008). History of hypertension (1.26, 1.03–1.53), left ventricular dysfunction (1.14, 1.04–1.24), and IMA use (0.70, 0.56–0.88) were related to the occurrence of adverse events. Adjusted 10-year estimates of event-free survival were 44% for patients with normal triglyceride levels compared with 34% for patients in the highest triglyceride quartile. The main sex effect showed no significant difference between men and women for overall survival (1.09, 0.87–1.35, P = 0.46) or event-free survival (1.11, 0.92–1.35, P =

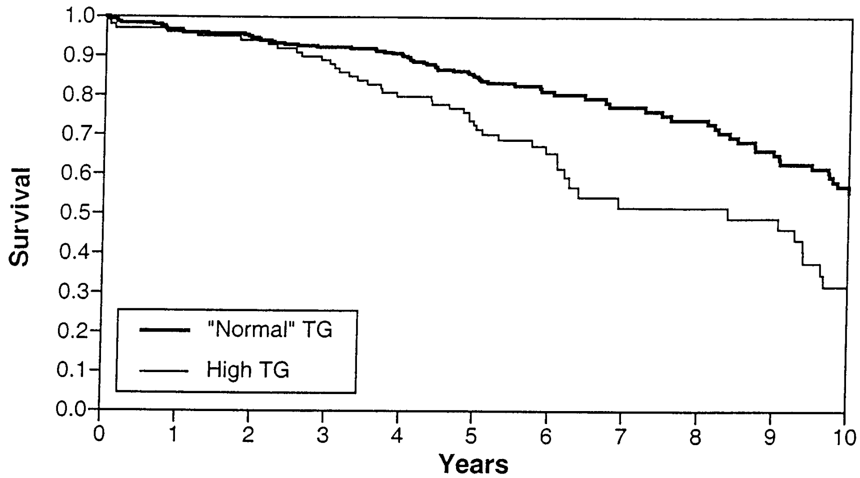

Figure 1—*Adjusted triglyceride (TG) effect on overall survival for diabetic women (normal triglyceride level ≤3.12 mmol/l). Covariates are age at surgery, BMI, history of hypertension, total cholesterol, LVF, number of coronary arteries with >50% stenosis, and use of IMA as a conduit.*

0.27). However, the significant sex-specific triglyceride interaction term (P = 0.009) indicated that the survival response to high triglyceride levels differed between men and women. Therefore, the majority of the current presentation relates to the sex-specific analyses that were subsequently performed.

In diabetic women, high triglyceride levels (1.89, 1.30–2.73, P = 0.0008) and left ventricular dysfunction (1.26, 1.07–1.48, P = 0.006) were predictors of time to death. Examination of the Kaplan-Meier survival curves for diabetic women showed that the adjusted triglyceride survival lines comparing the highest quartile patients with the lower three quartiles were similar until approximately year 3 (Fig. 1). Because this observation is contrary to the assumption of proportional hazards (parallel hazard functions), HRs are conservative and should be interpreted as the average effect across the study period. In addition, piecewise exponential models (dividing the study period into the first 3 years and the subsequent years) incorporating the non-proportional hazard functions across time corroborated the Cox model results, showing a significant triglyceride effect after only the first 3 years. There was no evidence of a significant triglyceride effect with regard to overall survival in diabetic men (1.02, 0.78–1.39, P = 0.90) (Fig. 2). Age (P = 0.0001), LVF (P = 0.006), and IMA use (P = 0.001) were statistically significant covariates.

In diabetic women, the triglyceride effect on adverse events (i.e., MI, revascularization, or death) was clear (1.49, 1.06–2.08, P = 0.02) (Fig. 3), though not quite as strong as in the setting of overall survival. Hypertension (P = 0.03) and LVF (P = 0.03) were also related significantly to event-free survival. In diabetic men, the triglyceride effect did not reach statistical significance (1.28, 0.99–1.66, P = 0.06) (Fig. 4), but the marginal significance suggests perhaps a tendency. Age (P = 0.03), LVF (P = 0.05), and IMA use (P = 0.003) were statistically significant covariates.

Using the natural logarithm transformation in overall survival models, the HR for ln[triglyceride value] in men was 1.00 (0.80–1.25), and in women the HR was 1.50 (1.09–2.06). Although the tendency toward a triglyceride main effect for men was seen in event-free survival (1.21, 0.99–1.47), an effect of similar magnitude did not reach statistical significance in women (1.20, 0.91–1.59), in part because of the smaller number of women. There was no evidence (through the addition of a ln[triglyceride value]^2 term) that the triglyceride effect was curvilinear in any of the aforementioned models (P = 0.36, 0.71, 0.13, and 0.68, respectively). Examination of survival curves with four distinct triglyceride quartiles revealed that, although there was some evidence suggesting improved survival for the lowest quartile, the majority of the triglyceride effect can be attributed to patients in the upper quartile.

HDL cholesterol

Information regarding HDL cholesterol was not collected for most patients entered into the CVIR until 1987. HDL cholesterol was included in Cox models for patients with available information (n = 826 [543 men and 283 women]). In diabetic women, high triglyceride levels continued to show added risk of overall mortality (2.15, 1.23–3.78, P = 0.007), but low HDL cholesterol levels did not show a significant risk (0.84, 0.47–1.48, P = 0.54). Neither triglyceride (1.29, 0.82–2.02, P = 0.26) nor low HDL cholesterol (1.04, 0.69–1.58, P = 0.85) showed strong relationships to overall mortality in diabetic men.

Results for event-free survival were less clear. The triglyceride effect was borderline (HR = 1.51, 95% CI 0.92–2.50, P = 0.11) for diabetic women; there was still no evi-

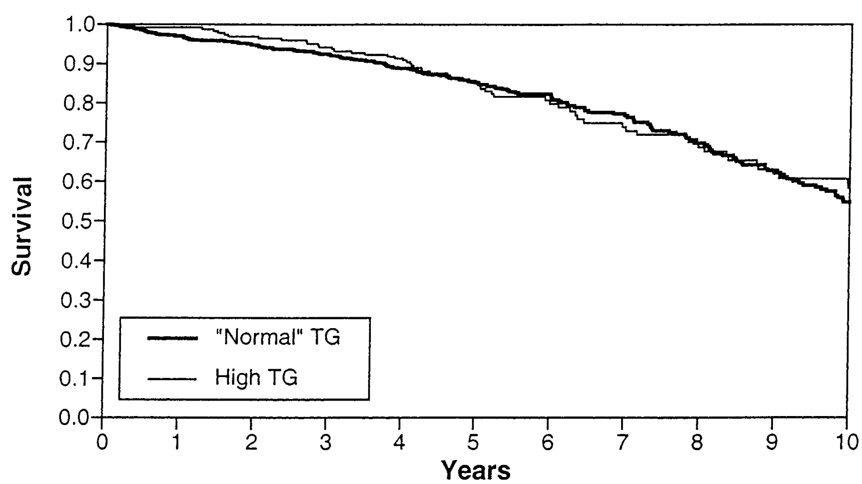

Figure 2—*Adjusted triglyceride (TG) effect on overall survival for diabetic men (normal triglyceride level ≤2.90 mmol/l). Covariates are age at surgery, BMI, history of hypertension, total cholesterol, LVF, number of coronary arteries with >50% stenosis, and use of IMA as a conduit.*

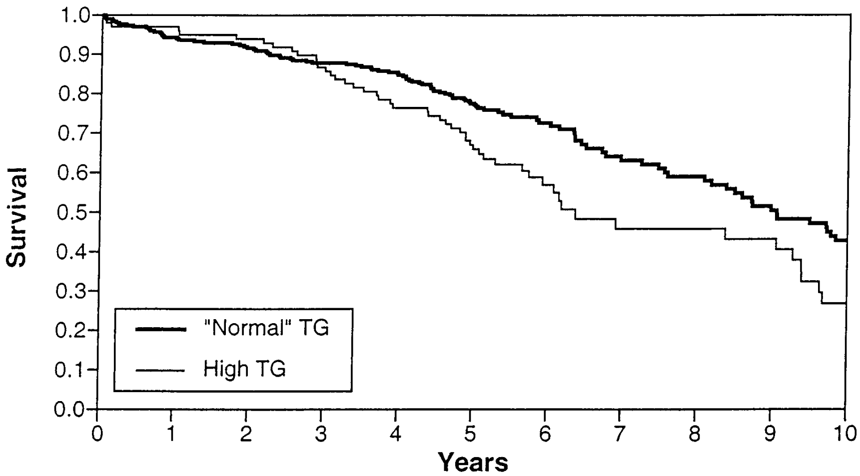

Figure 3—*Adjusted triglyceride (TG) effect on event-free survival (survival free from repeat revascularization or MI) for diabetic women (normal triglyceride level ≤3.12 mmol/l). Covariates are age at surgery, BMI, history of hypertension, total cholesterol, LVF, number of coronary arteries with >50% stenosis, and use of IMA as a conduit.*

dence of an adverse impact of low HDL cholesterol (0.93, 0.57–1.53, P = 0.78). Neither triglyceride nor HDL cholesterol had a significant impact on event-free survival for diabetic men (P = 0.16 and 0.24, respectively). Models including HDL but not triglyceride again showed no evidence that HDL was an independent predictor of survival or event-free survival.

To assess the likelihood of bias as a result of missing triglycerides, we compared survival for diabetic patients with and without available triglyceride values. For men with available triglyceride values, the 10-year survival estimate was 59 vs. 56% for those without available triglyceride values (P = 0.35). Women with triglycerides had a 48% 10-year survival estimate, whereas women without triglycerides had a 50% 10-year survival estimate (P = 0.87). Moreover, presentation characteristics did not differ significantly between those with and without lipid measurements, with the exception of greater IMA use in those without triglyceride measurements (83 vs. 76%, P = 0.02).

CONCLUSIONS — An upper-quartile triglyceride value was associated with a substantial increase in the risk of late mortality, as demonstrated here for the first time in a group of post-CABG diabetic subjects. Moreover, this risk was particularly marked in women in the highest quartile compared with other women—a finding not observed in men. High triglyceride values only modestly contributed to the prediction of event-free survival in men. Although the influence of triglyceride values on CVD risk could be anticipated on the basis of observations from population-based perspective studies, no data are available on diabetic women, particularly those who already have established CAD. The singular importance of triglyceride values in diabetic women may offer an avenue for the design of treatment strategies to reduce mortality and post-CABG events.

In this cohort of diabetic patients who have undergone surgical revascularization, we evaluated the survival curves related to triglyceride levels, adjusted for other relevant parameters (e.g., extent of baseline cardiac disease and presence of other traditional risk factors). Elevated triglyceride values suggest a 25% greater risk in this setting of diabetes. This is consistent with the findings of Lehto et al. (6), who found that triglyceride levels were relevant to the onset of CAD and were independent of the level of hyperglycemia in type 2 diabetic subjects followed for up to 7 years. This finding supported an earlier study that found triglyceride values to be predictive of CHD death in 943 working men with impaired glucose tolerance or diabetes from the Paris Prospective Study (5). Most recently, Tkac et al. (14) analyzed 174 type 2 diabetic patients, both with and without CAD, and reported that triglyceride-rich lipoproteins best defined the degree of CAD on angiography.

In addition, we found that the impact of triglyceride levels was predominately observed in diabetic women (89% greater risk) in whom, aside from LVF, variations in survival for the presented model were totally attributable to triglyceride values. The more common presence of a metabolic syndrome (including diabetes and increased triglyceride values) in post-MI women versus post-MI men suggests a sex-specific expression and potential vulnerability to triglyceride-related phenotypes (15). Such a metabolic syndrome may more likely be expressed in the presence of type 2 diabetes, thereby defining equivalent phenotypic expression in our cohort for both sexes. However, nonuniform clustering of meta-

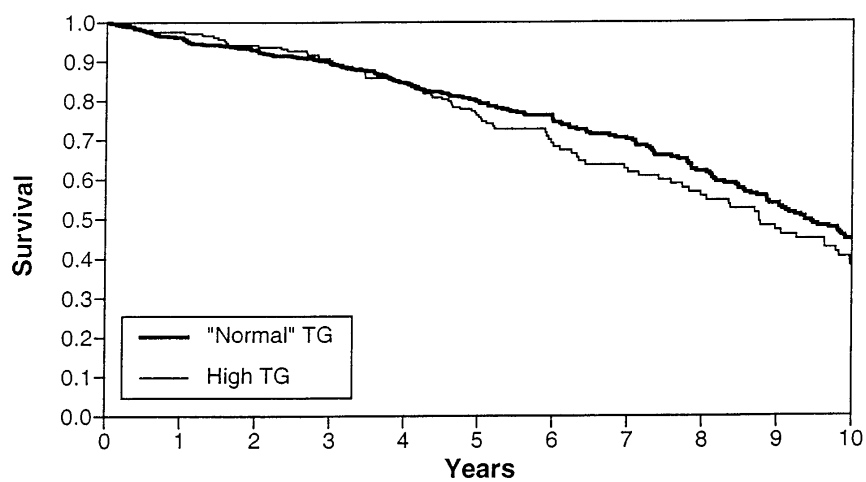

Figure 4—*Adjusted triglyceride (TG) effect on event-free survival (survival free from repeat revascularization or MI) for diabetic men (normal triglyceride level ≤2.90 mmol/l). Covariates are age at surgery, BMI, history of hypertension, total cholesterol, LVF, number of coronary arteries with >50% stenosis, and use of IMA as a conduit.*

bolic variables has been reported in the diabetic patients; this clustering was greater in diabetic women (16). This is supported by the observed higher incidence of hypertension and higher median triglycerides in our female patients than in our male patients. Elevated triglyceride values may be a marker of a high-risk metabolic syndrome in type 2 diabetes, particularly in women (2). Although it has been reported that 1-year post-MI mortality rates of diabetic patients are comparable or perhaps even higher in men than women (17), it has not been clear in previous studies whether a contrast existed for the triglyceride influence on CHD in the setting of diabetes between sexes. Our data on post-CABG subjects would suggest that elevated triglyceride values confer greater risk in diabetic women than diabetic men.

Previous data relating the influence of triglyceride values to post-CABG patients have come from smaller (predominantly male) populations with low diabetic prevalence (18–21). Triglyceride values have been suggested as predictive of occluded grafts (18), the need for near-term repeat CABG (19), and recurrent angina and MI (20,21). All of these data suggest triglyceride levels are relevant to morbidity but not mortality in men. Sergeant et al. (22) conducted the largest study, following 9,600 post-CABG patients for 10 years, in which triglyceride values were a late but modest predictor of mortality. The longer follow-up and/or the higher percentage of women in this latter population (17%) may have positively influenced this result.

The mechanism by which elevated triglyceride levels in the diabetic patient may increase risk for adverse medical outcomes is not entirely clear. Adjustment for available HDL cholesterol values in a large subgroup did not substantially alter the triglyceride impact in women nor distinguish itself as a predictor. Triglyceride-rich lipoproteins in the vessel wall and associated cells (23) lead to fatty streaks, which are noted in saphenous vein grafts within 18 months post-CABG (24). An enhanced blood coagulation–fibrinolytic system may be associated with both serum triglyceride concentrations (25) and the presence of diabetes (5,26). In the postmenopausal period (the typical life-cycle phase for women in this study), hepatic lipase activity rises because of an absence of estrogen, leading to an increase in small dense LDLs (27), particularly observed in the presence of a high concentration of triglyceride particles (28). This VLDL/hepatic-lipase/dense-LDL pathway would be augmented in diabetes because of the increased production of large triglyceride-rich VLDLs, leading to more CAD. Alternatively, triglycerides could be a surrogate marker of diabetic control, in that diabetes can lead to increased synthesis of triglyceride-rich particles (29). In the recent U.K. Prospective Diabetes Study (UKPDS) of predominantly non-CAD patients, improved diabetic control (11% decrease in HbA_{1c}) conveyed a modest advantage of 16% in reducing the combined events of sudden death and fatal or nonfatal MI over the 11-year follow-up ($P = 0.052$) (30). Our population, however, entirely consisted of CAD subjects. The marginal CVD effect observed in the UKPDS could potentially achieve greater distinction in patients with CAD.

There are potential caveats to our analyses and conclusions. Recruitment biases (with and without triglyceride values, followed and not followed) could have resulted in a unique nongeneralizable population. However, baseline characteristics were strikingly similar between subgroups, suggesting the conclusions to be robust. Furthermore, use of β-blockers, whereas generally limited in diabetic patients, may have complicated triglyceride and HDL cholesterol values as survival markers. Yet, such usage would have been expected to moderate any associated deleterious effects. Finally, neither diabetic treatment nor lipid-lowering therapy (if any) on follow-up was characterized. Improved diabetic control and/or infrequently used triglyceride-modifying therapy could have led to lower triglyceride values and improved survival. Moreover, any sex bias in the specific provision of treatments related to triglyceride levels could have influenced our sex-specific results.

In summary, this is the first serial examination of triglyceride predictive potential in post-CABG diabetic women and men and the first such evaluation in diabetic patients with established CAD. In those who have presented for CABG procedures at one hospital in the last 10–15 years, mortality is higher in diabetic patients who present with elevated triglyceride values, a finding that is predominately observed in women. Aggressive preventive strategies in diabetic subjects (31) may be important, particularly in women who present with high triglyceride values at the time of coronary bypass surgery.

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