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Hypertriglyceridemia and residual dyslipidemia in statin-treated, patients with diabetes at the highest risk for cardiovascular disease and achieving very-low low-density lipoprotein-cholesterol levels

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BACKGROUND: As the result of the high prevalence of comorbidities and conventional risk factors among patients with type 2 diabetes (T2DM), most patients belong to the highest cardiovascular disease risk category, and have a target low-density lipoprotein cholesterol (LDL-C) of <70 mg/dL. Because substantial residual risk persists at LDL-C <70 mg/dL, a more comprehensive control of non-LDL-C and particles was recommended in the joint 2008 American Diabetes Association/American College of Cardiology Consensus.

OBJECTIVE: To ascertain, in statin-treated T2DM patients belonging to this greatest-risk group, with on-statin LDL-C <70 mg/dL, (1) the proportion of patients meeting all three critical levels (LDL-C <70 mg/dL, non-high-density lipoprotein cholesterol [HDL-C] <100 mg/dL, apoB <80 mg/dL) and (2) the variables associated with target attainment versus nonattainment.

PATIENTS AND METHODS: Among 675 unselected patients with T2DM, 367 were both at very high cardiometabolic risk and taking statins; 118 of these patient had LDL-C levels <70 mg/dL. Patients meeting all three criteria (LDL-C, non-HDL-C, and apoB; $n = 79$; all three at goal group) were compared with those only reaching LDL-C ($n = 49$; only LDL-C at goal group).

RESULTS: LDL-C was 54 (12) for the all three at goal group versus 57 (10) mg/dL for the only LDL-C at goal group (NS). The two groups were similar regarding age, gender, diabetes duration, body mass index, waist circumference, blood pressure, renal function and micro-/macroangiopathy prevalence. A statin plus fibrate was given to 16% of patients in the all three at goal group and 32% in the only LDL-C at goal group. The two groups did not differ in baseline (prestatin) LDL-C, HDL-C, and non-HDL-C, except for pre-/post-lipid-lowering drug(s) triglycerides (TG): 177 (95)/118 (56) for all three at goal versus 279 (134)/ 241 (103) mg/dL for only LDL-C at goal ($P = .0230$ and $P = .0001$). The only LDL-C at goal group had lower HDL-C (vs. all three at goal): 41 (12) vs. 47 (14) mg/dL ($P = .0237$), with atherogenic dyslipidemia [hypo-HDL-C + hyper-TG] prevalence of 35% in the all three at goal versus 56% in the only LDL-C at goal group ($P < .0001$). *log*(TG)/HDL-C was 0.049 (0.021) for all three at goal versus 0.063 (0.021) for only LDL-C at goal ($P < .0001$). The LDL-C/apoB ratio was 0.92 (0.24) for all three at goal vs. 0.67 (0.18) for only LDL-C at goal ($P < .0001$), suggestive of smaller/denser LDL.

CONCLUSION: The presence of atherogenic dyslipidemia was associated with a failure to meet all three critical modifiable targets for hypercholesterolemia, such a nonachievement being found in a large

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proportion (one-third) of very-high risk T2DM patients with very-low on-statin LDL-C. Attainment of all three targets will require (1) titration/permutation of statins, (2) lifestyle (re)inforcement; and/or (3) statin-fibrate bitherapy.

Standards of care in type 2 diabetes mellitus (T2DM) management include optimization of modifiables risk factors (RFs) to prevent new-onset or progression of micro- and macroangiopathies. Reducing macrovascular disease risk requires a multifactorial intervention that targets multiple RFs, such as hypertension, hypercholesterolemia, sedentary lifestyle, obesity, or smoking. In addition to Therapeutic Lifestyle Changes (TLC), standards of care recommend that major critical modifiable RFs (hyperglycemia [HbA_{1c} as surrogate]), systolic blood pressure, and low-density lipoprotein cholesterol [LDL-C]) should be brought to or below consensual thresholds, although for RFs with a continuous distribution, residual vascular risk (RVR) may persist even when RFs are deemed satisfactory.[1–9]

Among lipid-related RFs in T2DM, the reduction of LDL-C, usually via the use of statins as preferred first agent, is highly effective in reducing the risk of cardiovascular disease (CVD), both in primary or secondary prevention, as confirmed from landmark statins trials and meta-analyses of statins trials. Because of the effectiveness of LDL-C lowering with statins, the administration of this class of lipid-lowering drugs (LLDs) is considered beneficial to most patients with T2DM either because (1) baseline LDL-C values are elevated, (2) estimated CVD risk is high, or (3) regardless of baseline lipids, patients with the common form of T2DM are considered secondary prevention-equivalent with a high risk of new-onset CVD in the absence of CVD.[1–4,6–8,10–13] Yet, even with LDL-C at target, a solely LDL-C–based approach will leave a substantial component of lipid-related RVR unaltered, all the more so that poststatin RVR is rarely quantified in routine practice. Achieving low levels of LDL-C (<70 mg/dL), on the other hand, does not imply that all the CVD risk associated with non-LDL dyslipidemia will be under control, as shown by clinical trials in which investigators demonstrated greater CV residual risk when high-density lipoprotein cholesterol (HDL-C) was low (<40 mg/dL).[14–19]

A recent joint consensus statement from the American Diabetes Association and the American College of Cardiology Foundation recommends two sets of targets goals for LDL-C, non-HDL-C, and apoB for patients with cardiometabolic risk, such as those with atherogenic dyslipidemia (AD), the hallmark of which is increased levels of triglycerides (TG) and low HDL-C. Accordingly, LDL-C, non-HDL-C and apolipoprotein B_{100} (apoB) levels <100 mg/dL, <130 mg/dL, and <90 mg/dL, respectively, are recommended for patients without diabetes or known CVD but with ≥2 additional major CVD RFs, or with diabetes and without major CVD RFs. LDL-C, non-HDL-C, and apoB levels <70 mg/dL, <100 mg/dL, and <80 mg/dL, respectively, are recommended for patients at the greatest risk of CVD, ie, known CVD or diabetes plus ≥1 additional major CVD RFs.[2]

Because of the high prevalence of MetS, CV comorbidities, and conventional RFs among T2DM, 80% to 90% of them qualify as being at the greatest risk for CVD.[2,9] The aim of the present study was to ascertain, in statin-treated T2DM patients belonging to this greatest-risk group, and with on-statin LDL-C <70 mg/dL: (1) the proportion of patients meeting all three critical targets, namely non-HDL-C <100 mg/dL and apoB <80 mg/dL in addition to LDL-C <70 mg/dL and (2) the variables associated with attainment versus nonattainment of those three critical modifiable targets.

Patients and methods

The study design was cross-sectional. We evaluated 675 consecutive adult outpatients with T2DM who were followed at the diabetes center of a tertiary academic hospital in Brussels, Belgium, between October 2009 and October 2010. Sixty-percent (n = 407) were treated with statins, among whom 367 (90%) were classified as "very high-cardiometabolic risk" according to the *2008 Joint ADA-ACC Consensus* statement.[2] When we considered achieved poststatin LDL-C values, we found that 249 (68%) patients from this very high-risk group did not reach LDL-C target (≥70 mg/dL) and were excluded from this analysis, whereas the remaining 118 (32%), at LDL-C goal <70 mg/dL, represent the population of interest for this study. These 118 patients were split into two groups, analyzed in parallel, according to whether they also met additional lipid targets as regards non-HDL-C and/or apoB levels. Thus, patients meeting all three criteria (LDL-C, non-HDL-C, and apoB; n = 79; thereafter described as [all three at goal]) were compared with those only reaching LDL-C without meeting non-HDL-C and/or apoB targets (n = 39; [only LDL-C at goal] group).

The following sociodemographic and clinical variables were recorded: age, gender, achieved educational level, age at diabetes diagnosis, diabetes duration, familial history (premature-onset cardiovascular disease, diabetes mellitus), current medications (oral antidiabetic drugs, insulin, blood-pressure [BP]-lowering drugs, aspirin, lipid-lowering drugs