EDITORIAL

The Effects of Anti-Diabetic Drugs on LDL Subclasses: Any Role for Colesevelam?

Editorial to: "Effect of Colesevelam HCl Monotherapy on Lipid Particles in Type 2 Diabetes Mellitus" by R.S. Rosenson et al.

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Introduction: The Clinical Significance of Small Dense LDL

Diabetic dyslipidemia usually includes elevated triglyceride levels, reduced high-density lipoproteins (HDL) cholesterol levels and increased levels of small dense (sd) low-density lipoproteins (LDL) [1]. These alterations can be seen despite normal or near-normal levels of LDL-cholesterol (LDL-C) [2], which means that patients with type-2 diabetes (T2DM) have profound changes in the quality rather than the quantity of LDL [3]. As highlighted by a European Panel of experts who have reviewed the pathophysiology, atherogenicity and clinical significance of LDL Subclasses, LDL are very heterogeneous particles, differing in physico-chemical composition, metabolic behaviour, oxidative susceptibility and atherogenic potential; up to seven distinct LDL subclasses can be distinguished [4].

Smaller, more dense LDL are those more strongly associated with cardiovascular risk, as shown in the last years in more than a hundred studies, including epidemiological and cross-sectional studies, clinical intervention trials as well as angiographic studies [5]. Recently, Hoogeveen et al. [6] have measured sdLDL-cholesterol in 11,419 men and women of the Atherosclerosis Risk in Communities study. These participants were followed up for a period of 11 years during which the incidence of CHD was measured. The authors have confirmed that sdLDL are higher in subjects with T2DM compared with non-diabetics; further, sdLDL-C significantly predicted the risk for CHD, even in individuals considered to be at low cardiovascular risk based on their LDL-C concentrations. This is in line with a number of previous observations, highlighting the role of sdLDL in predicting cardiovascular risk in a better fashion than standard lipids, including plasma LDL-C concentrations [4].

Since a large residual cardiovascular risk is usually seen in large clinical intervention trials, it has been proposed that there is more to predicting vascular disease than just established risk factors [7], highlighting the role of the quality vs. the quantity of atherogenic lipoproteins, including sdLDL. Therefore, in the last two decades a number of clinical studies have assessed the role of cardiovascular medications, particularly lipid-lowering agents, in modulating distinct LDL subclasses. Overall, statins and fibrates have shown strong and significant effects in reducing sdLDL [4], and this is of importance for patients with T2DM, where a predominance of sdLDL is usually present [1].

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The Effects of Anti-Diabetic Therapies on LDL Subclasses

Traditional anti-diabetic therapies, such as insulin and metformin, have no significant impact on sdLDL, but data is very limited. For example, in a study on patients with T2DM who were treated with high doses of sulfonylureas, intensive insulin therapy decreased sdLDL although these changes were associated with those in plasma triglyceride concentrations [8]. In contrast, metformin did not affect LDL size [9].

Regarding thiazolidinediones, pioglitazone overall has more positive effects on plasma lipids and sdLDL compared with rosiglitazone [10]; this differential effect of the two drugs may help to explain the adverse cardiovascular risk profile of rosiglitazone [11]. The most interesting data are available from comparative studies using these two drugs: in a study performed in patients with diabetes and dyslipidemia [12], pioglitazone resulted in a more pronounced increase in LDL size compared with rosiglitazone, whereas LDL particle concentration was reduced with pioglitazone and increased with rosiglitazone. Similarly, in a much smaller study [13], pioglitazone induced significant reductions in sdLDL while rosiglitazone did not.

Interesting data are coming from the novel incretin-based therapies. Under physiological conditions in response to oral food ingestion, humans produce two hormones called "incretins" in the gastro-intestinal tract, in order to help to maintain glucose homeostasis through their coordinated effects on pancreatic islet cells; these two hormones are named the glucagon-like polypeptide (GLP-1) and the glucose-dependent insulinotropic polypeptide (GIP) [14]. Yet, the effect induced by the incretins is diminished or lost in T2DM patients and therefore novel therapies have been developed. Two different class of drugs are present in the market, the incretin glucagon-like polypeptide (GLP-1) receptor agonists, mimicking the action of the endogenous GLP-1, and the dipeptyl peptidase-4 (DPP-4) inhibitors, that inhibit the activity of the enzyme that degrades GLP-1. The Food and Drug Administration (FDA) approved the first GLP-1 receptor analog, exenatide, as adjunctive therapy for T2DM patients in 2005; 1 year later, the FDA approved the first DPP-4-inhibitor, sitagliptin, as monotherapy or in combination with metformin or thiazolidinediones. Since then, a large number of GLP-1 receptor agonists and DPP-4 inhibitors have been developed, some of which have already been introduced in the market.

These new drugs have shown important glycemic and non-glycemic effects, including those on cardiovascular risk factors as well as on clinical and subclinical atherosclerosis [15, 16]. Incretin-based therapies can also favorably manage diabetic dyslipidemia, reducing the plasma concentrations of triglycerides, total cholesterol and LDL-C, with a concomitant increase in plasma HDL-cholesterol levels [14, 17]. Preliminary data also suggest that these novel anti-diabetic drugs may favourably modulate LDL subclasses, since both vildagliptin, a DPP-4 inhibitor, and exenatide, a GLP-1 receptor agonist, seems to be able to reduce sdLDL [18, 19]. Yet, this promising data from these studies need to be confirmed in much larger cohorts, as well as with the use of the other incretin-based agents.

In this context, interesting data are available for colesevelam, a bile acid sequestrant, since this drug has been shown to improve both glycemic and lipid parameters in patients with T2DM when added to metformin, sulfonylureas or insulin [20]. Notably, in T2DM subjects colesevelam can also reduce sdLDL in combination with metformin and/or sulfonylureas [21, 22] as well as in monotherapy, as shown by Rosenson et al. in this issue of Cardiovascular Drugs and Therapy [23]. It therefore seems to be a promising approach to simultaneous glycemic and lipid control.

Conclusions

Clearly, more studies are needed to confirm the efficacy of incretin-based therapies, as well as of colesevelam on lipoprotein subclasses, including sdLDL. Such studies should also investigate whether the reduction of atherogenic lipoproteins by such agents would result in a reduction of cardiovascular outcome in T2DM patients. Clinicians need novel agents able to manage T2DM as well as the associated cardiovascular risk. This is in line with the FDA 2008 guidance that all drugs approved for T2DM should undergo post-approval studies to demonstrate cardiovascular safety [24]. Further, HDL are also heterogeneous particles and it seems that the presence of dysfunctional HDL particles represents a novel important diagnostic and therapeutic target in cardiovascular disease [25]. This may be related to the subclasses of HDL like for sdLDL.

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