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Editorial
Achieving lipid targets in primary care settings

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Abstract

Achieving low-density lipoprotein cholesterol (LDL-C) goals in clinical practice is still unsatisfactory. Furthermore, a significant residual risk remains, even after reaching LDL-C targets, in terms of both fasting and postprandial triglycerides, high-density lipoprotein cholesterol (quantity and quality) and small dense LDL particles. Statins are the first choice for treating lipid abnormalities. Other lipid-lowering agents can be administered when statins are not tolerated and if LDL-C targets are not reached. Furthermore, multifactorial treatment, including a statin, exerts several beneficial effects on cardiovascular and residual risk reduction. The role of novel developing lipid therapies in clinical practice remains to be established.

In the April issue of *Current Medical Research and Opinion* Jameson *et al.*[1] report the results of a retrospective study including 2999 high-risk UK patients with coronary heart disease (CHD), diabetes mellitus (DM), familial hypercholesterolemia (FH) or atherosclerotic vascular disease (AVD) that were prescribed atorvastatin monotherapy between 30 November 2008 and 30 November 2011. Less than 50% of the population achieved the recommended target levels of total cholesterol (TC) (<4.0 mmol/L) or low-density lipoprotein cholesterol (LDL-C) (<2.0 mmol/L) (45.8 and 46.5% of patients, respectively). The percentage was greater (63.7%) for patients with CHD/AVD and DM[1].

In a primary care study based on a pharmacist pay-for-performance system in the USA[2], 80.6% of 299 patients with hypercholesterolemia, evaluated between 1 January 2009 and 28 February 2010, achieved a target LDL-C <130 mg/dl (3.4 mmol/l). However, in this study hypolipidemic treatment was not mentioned and the LDL-C goal did not take into consideration the Framingham risk score or certain diseases (e.g. DM or CHD)[2]. The Dyslipidemia International Study (DYSIS) showed that a greater percentage of UK patients (80%) achieved LDL-C <100 mg/dl (2.6 mmol/l) with a pay-for-performance system compared with German patients (42%) with a budget-restrictive system[3]. UK patients were more likely to receive atorvastatin than German ones (25 vs 4%). Furthermore, the EUROASPIRE IV survey showed that only 58% of patients with established CHD had LDL-C levels <2.6 mmol/l (100 mg/dl), whereas even fewer (21%) achieved LDL-C <1.8 mmol/l (70 mg/dl)[4]. Such findings document the unmet needs in terms of implementing current lipid guidelines. In this context, enhancement programs (e.g. educational courses, printed guidelines and brochures) may improve adherence and achieving guideline goals[5].

One of the reasons for not using statins (especially higher doses) is abnormal liver tests (LTs). However, a *post-hoc* analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study[6] reported that CHD patients with abnormal baseline LTs (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] <3× upper limit of normal [ULN]) benefited significantly more in terms of cardiovascular (CV) risk reduction following

atorvastatin treatment compared with those with normal LTs (68 vs 39% relative risk reduction, $p<0.0001$). LTs also improved in the statin-treated group, whereas they increased in the non-statin group. In a *post-hoc* analysis of the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study[7], CV risk reduction was significantly greater in CHD patients with elevated baseline ALT activity (≥ULN) receiving atorvastatin (mainly 80 mg/day) than those on simvastatin (mainly 20 mg/day) (hazard ratio, 0.556; 95% confidence interval [CI], 0.367–0.842; $p=0.0056$). This benefit was greater than in patients with normal LTs. These findings highlight the potential role of statins in the treatment of non-alcoholic fatty liver disease (NAFLD).

Statin use is also of importance in cases of other co-morbidities such as metabolic syndrome (MetS), hyperuricemia and chronic kidney disease (CKD). MetS patients were found to benefit more from atorvastatin treatment than individuals without MetS in the GREACE study (risk ratio 0.43, 95% CI 0.20–0.64; $p<0.0001$ vs 0.59, 95% CI 0.41–0.79, $p<0.0001$, respectively)[8]. Similarly, atorvastatin was shown to decrease elevated serum uric acid (SUA) levels in several studies including GREACE[8]. In stage 3 CKD patients, atorvastatin therapy significantly improved renal function (assessed by estimated glomerular filtration rate – eGFR) as well as reducing CV risk in the GREACE study[9], the Treating to New Targets (TNT) study[10] and the Collaborative Atorvastatin Diabetes Study (CARDS)[11]. Furthermore, the observed CV risk benefit was greater in patients with CKD than those with normal kidney function[9,12]. The Study of Heart and Renal Protection (SHARP) showed that the combination of simvastatin plus ezetimibe significantly reduced the incidence of vascular events in pre-dialysis patients[13].

Statin-induced CV risk reduction is lower in smokers than in non-smokers[14], although conflicting results exist[15]. In a *post-hoc* analysis of the GREACE study[16], smokers on a statin had a CV events incidence (19.4%) which was not significantly different ($p=0.27$) from never smokers not on a statin (23.9%). In a *post-hoc* analysis of the TNT and IDEAL studies, all patients were statin treated, but current smokers had a greater risk of CV events[17]. Furthermore, current smoking has been associated with lower adherence to statin therapy[18,19] and not reaching LDL-C target levels[20].

Statin intolerance affects adherence to treatment. Switching to another statin or decreasing statin intake frequency may be an option. Ezetimibe and fibrates are other alternatives[1]. Nicotinic acid was withdrawn from the market based on negative trials[21]. Novel LDL-C reducing drugs are being evaluated. These include cholesterol ester transfer protein (CETP) inhibitors and proprotein convertases ubtilisin/kexin-9 (PCSK9) inhibitors that may be used to treat statin-intolerant patients; microRNA (miR) and gene-based techniques are also being developed[22].

Multifactorial treatment, including a statin, was shown to exert beneficial effects on CV risk. In this context, atorvastatin combined with antihypertensive, hypoglycemic and antiobesity drugs was reported to significantly decrease CV risk in MetS patients in the Assessing The Treatment Effect in Metabolic syndrome without Perceptible diabeTes (ATTEMPT) study[23]; this effect was greater in patients achieving lower LDL-C levels (<100 vs <130 mg/dl; <2.6 vs <3.4 mmol/L). Apart from CV risk reduction, multifactorial intervention significantly improved renal function and SUA levels, especially in patients with stage 3 CKD, as shown in a *post-hoc* analysis of the ATTEMPT study[23]. Similar results with regard to eGFR and SUA were reported in another *post-hoc* analysis of five studies[5], highlighting the importance of a multitargeted approach in high-risk patients, as those with stage 3 CKD. A multifactorial intervention was also recently shown to improve both glycemic control and CV risk in patients with type 2 diabetes mellitus[24].

A substantial 'residual risk' persists, even after achieving LDL-C goals. In this context, elevated fasting or non-fasting triglyceride (TG) levels have been associated with increased CV risk[25]. Apart from high TG levels, atherogenic dyslipidemia also includes low high-density lipoprotein cholesterol (HDL-C) levels and elevated small dense LDL (sdLDL) particles[26,27]. Furthermore, HDL quality seems to play an important role in the atherosclerotic process[26]. Ezetimibe, fibrates and omega-3 fatty acids as well as hypoglycemic and antiobesity drugs can be used to treat these lipid abnormalities[28–30]. Notably, adding ezetimibe in statin treated patients with abnormal LDL-C levels was more effective in achieving lipid targets than doubling the statin dose[31]. The results of the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) comparing the effects of ezetimibe combination with simvastatin versus simvastatin monotherapy on CV events in patients with acute coronary syndromes should elucidate the impact of ezetimibe on clinical outcomes. Colesevelam is another option to reduce LDL-C levels. This drug also has beneficial effects on glycemia[32]. Statin and fibrate combination can be used to further lower LDL-C levels and improve other lipid abnormalities[29]. Novel pipeline therapies influencing lipid metabolism may also prove to be beneficial in terms of residual risk reduction[22].

In conclusion, achieving lipid goals in clinical practice remains unsatisfactory. Apart from LDL-C, other lipid fractions such as TGs (fasting and postprandial), HDL (both quantity and quality) and sdLDL should be considered. Statins are the first-line drugs for treating lipid abnormalities. Other lipid-lowering agents can be used if

statins are not tolerated and LDL-C targets are not reached. Multifactorial treatment, including a statin, seems to exert several beneficial effects on CV and residual risk reduction. Novel lipid therapies may prove to help achieve lipid targets and CV risk reduction.

Transparency

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Declaration of financial/other relationships
V.G.A. has disclosed that he is a member of CMRO s International Advisory Board but has no significant relationships with or financial interests in any commercial companies related to this study or article. N.K. and A.K. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

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