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Editorial

Reaching low density lipoprotein cholesterol targets

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Abstract

Cardiovascular disease is a major health problem and within the leading causes of death worldwide. Low-density lipoprotein cholesterol (LDL-C) is strongly associated with the development and progression of cardiovascular disease and is among the main targets of lipid lowering therapy. Despite the various lipid lowering agents for the management of hyperlipidemia, a significant number of patients do not reach their LDL-C target goals. Data from studies in various world regions identify an often poor achievement of LDL-C goals, especially in high risk patient groups. The causes of this suboptimal management of hyperlipidemia are multifactorial and measures should be taken in order to identify and address these shortcomings in dyslipidemia therapy.

Cardiovascular disease (CVD) is among the leading causes of morbidity and mortality in adults worldwide[1]. A number of risk factors have been identified as promoting the development and progression of CVD, such as dyslipidemia, hypertension, obesity, smoking and sedentary lifestyle. Among these risk factors, hypercholesterolemia and in particular increased low density lipoprotein cholesterol (LDL-C) levels play a significant role in CVD development. Indeed, a plethora of studies have associated increased LDL-C levels with increased risk of CVD. Furthermore, the reduction of LDL-C levels has also been associated with CVD risk reduction[2]. Statins, together with lifestyle modification, are at the cornerstone of lipid lowering. A number of studies have associated statin treatment with a decrease of CVD risk. The latest European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines have set aggressive goals regarding lowering of LDL-C according to each patient's CVD risk[2]. However, lipid lowering therapies often fall short of achieving their LDL-C targets[3].

In the present issue of *Current Medical Research & Opinion*, Hammoudeh *et al.* present the results of the CEntralized Pan-Levant Survey on tHE Undertreatment of hypercholeSterolemia (CEPHEUS-Levant) study[4]. This multi-center, cross-sectional survey evaluated dyslipidemic patients ($n = 992$) on lipid lowering agents. Among study participants, 64% and 56.8% of patients achieved their LDL-C target according to the National Cholesterol Educational Program Adult Treatment Panel III (NCEP ATP III) and the third Joint European Task Force (TJETF) guidelines, respectively. Moreover, only 24.8% patients in the very high risk group according to the 2004 NCEP ATP III guidelines reached their LDL-C target. This study showed the suboptimal lipid lowering therapy in the Levant region as is the case in many other world regions.

The EUROpean Action on Secondary Prevention by Intervention to Reduce Events (EUROASPIRE I) survey conducted in 1995–1996 showed that only 32.2% of coronary heart disease (CHD) patients eligible for treatment were

treated with lipid lowering medications[3]. In the follow-up surveys (EUROASPIRE II [1999–2000]) and EUROASPIRE III [2006–2007]), these proportions increased to 63% and 89% respectively[3]. There was no significant change regarding the percentage of eligible patients receiving lipid lowering treatment between EUROASPIRE III (89%) and EUROSPIRE IV (2012–2013) (87%). As a result, an increased number of patients with established CHD who achieved total cholesterol levels of less than 190 mg/dl (4.5 mmol/L) according to the 2003 European guidelines was observed from EUROASPIRE I (8.4%), to EUROASPIRE II (28.7%) to EUROASPIRE III (57.3%) and to EUROSPIRE IV (2012–2013) (66%). However, in EUROSPIRE IV only one out of five patients had LDL-C levels <70 mg/dL (1.8 mmol/L)[5] which is the target for very high risk patients according to the ESC/EAS 2011 guidelines.

The results from the Centralized Pan-European survey on the under-treatment of hypercholesterolemia (CEPHEUS) study were similar[6]. Only 55.3% of patients reached the TJETF-recommended LDL-C target level, and 57.4% reached the target recommended by the 2004 NCEP ATP III guidelines[6]. Moreover, data from the Dyslipidaemia International Study (DYSIS) also provide evidence that statin treated dyslipidemic patients often don't achieve their cholesterol target goal[7]. Indeed, almost half of the study's patients did not achieve their LDL-C target[7].

The results regarding cholesterol target achievement in studies conducted in Greek individuals were analogous. About half of the Greek patients participating in the CEPHEUS study did not achieve their respective LDL-C goals according to TJETF targets[8]. Moreover, two-thirds of the Greek participants in the DYSIS study did not reach their LDL-C goal[9]. We have recently published a retrospective study that assessed the achievement of lipid-lowering treatment targets in the setting of our University Hospital Lipid Clinic[10]. LDL-C and non-high density lipoprotein cholesterol (non-HDL-C) goal attainment according to NCEP ATP III and ESC/EAS 2011 guidelines were recorded in 1000 consecutive adult patients followed for ≥3 years (mean 8 years). Ninety-five percent of patients were on active lipid-lowering treatment at the most recent visit: 92% were on statins (67% on statin monotherapy and 33% statin therapy in combination with ezetimibe [25%], omega-3 fatty acids [5%], fibrates [4%] or colesevelam [2%]). A significant percentage of subjects (up to four out of five patients) failed to achieve the current ESC/EAS lipid targets, while this failure was particularly relevant in 'very high' CV risk patients where LDL-C targets are more aggressive. More specifically, LDL-C targets according to NCEP ATP III were attained by 66% and 86% of 'very high' ($n = 477$) and 'high' ($n = 408$) cardiovascular risk patients, respectively. The corresponding rates for non-HDL-C goal achievement were 72% and 87%. Fewer patients were within LDL-C goals according to the ESC/EAS guidelines; among 'very high' CV risk patients only 25% achieved LDL-C levels <70 mg/dL (1.8 mmol/L), while 42% of those at 'high' risk had optimal LDL-C levels (<100 mg/dL [2.6 mmol/L]). The respective rates of non-HDL-C target attainment were 34% and 53%.

Despite widely available treatments for dyslipidemia, patients with hypercholesterolemia remain at suboptimal LDL-C levels. The reasons for this failure in therapeutic management are multifactorial with physicians as well as patients playing a role.

Physicians are sometimes reluctant to up-titrate the statin dosage according to current guidelines or hesitant in selecting either a stronger statin or a combination of lipid lowering therapies. In addition individual risk of each patient may sometimes be underestimated. Moreover, physicians often do not explain enough and in depth to patients the benefits of statin treatment as well as the importance of compliance with therapy. On the other hand, patients often have less than optimal compliance with both lifestyle changes and pharmacological interventions. Moreover, some patients discontinue their lipid lowering therapy once they achieve their LDL-C goal. Furthermore, the patient's economic ability can affect their compliance in statin treatment as well as influence the physician's decision to pursue a more aggressive therapy.

Recently, the American College of Cardiology (ACC) and the American Heart Association (AHA) released new guidelines for the prevention of cardiovascular disease and management of elevated blood cholesterol[11]. These guidelines leave behind the need to define any LDL-C goals. Instead, specific risk groups of patients have been identified that need to be prescribed either moderate or high intensity statin therapy, regardless of their baseline LDL-C levels and without aiming for a particular pre-defined LDL-C target. On the other hand, the management of CVD risk reduction needs to be customized according to each patient's individual cardiovascular profile, and this can often be more specific if targets for LDL-C lowering therapy are defined as is the case with the current ESC/EAS guidelines.

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