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EDITORIAL

Is it time to reassess the approach to statin therapy?

Clinical trials over the past decade have clearly established the beneficial effects of statins in the prevention of cardiovascular events, primarily through lowering of serum low-density lipoprotein cholesterol (LDL-C) concentrations. Statins are presently considered as the first line agent for LDL-C lowering both for secondary and primary prevention in European, American and Canadian guidelines. In recent years, studies have shown that the success of achieving LDL-C goals in the community is sub-optimal, especially for high-risk patients. In the Lipid Treatment Assessment Project (L-TAP), a total of 4888 dyslipidemic patients from the US were studied in 1996 [1]. In this cohort, only 38% achieved NCEP-specified LDL-C target levels. The LDL-C goal was achieved in 68% of low-risk patients, 37% of high-risk patients and 18% of patients with coronary heart disease (CHD). The NCEP Evaluation ProjecT Utilizing Novel E-technology (NEPTUNE) II, was a similar national survey conducted in 2003 [2]. In this cohort of 4885 dyslipidemic patients, only 57% of the CHD/CHD equivalent patients achieved their LDL-C target. Of the 1447 patients with cardiovascular disease, 75% could be classified as very high-risk with a LDL-C target of <1.81 mmol/L, and only 17.8% of the patients achieved the target.

Similar findings have also been reported in studies conducted in Europe and in Canada. The Netherlands-based REALITY-PHARMO study reported that only 22.4% of patients achieved the goal of total cholesterol <5 mmol/L, but the success rate rose to 42.3% after the introduction of a more aggressive treatment guideline [3]. In a Norwegian survey of 3935 statin users, with goals of total cholesterol <5 mmol/L and LDL-C <3 mmol/L, only 17% of patients in primary prevention reached the goals and 43.9% in the secondary prevention reached the goals [4]. The Canadian Lipid Study — Observational (CALIPSO) was a cross-sectional study examining lipid levels for 3721 patients taking statins. LDL-C targets were not achieved by 27.2% of all patients and 36.4% of those at high CAD risk [5]. Similar results have also been reported in other regions [6].

In this issue, Rajagopalan et al. conducted a detailed analysis of the pattern of lipid lowering therapy in a secondary prevention cohort of 455 patients treated by both primary care physicians and cardiologists [7]. Overall attainment of the LDL-C goal of <2.59 mmol/L was a disappointing 24.7%, and the success rate was virtually identical between cardiologists and primary care physicians. In this study, the investigators also captured changes in the statin regimen by the treating physicians. The LDL-C achieved did not differ significantly between patients receiving intensification of their therapy and those whose treatment remained unchanged or decreased in intensity. This study adds to a growing body of the literature suggesting a substantial treatment gap in lipid lowering therapy in high-risk patients, and it did not even include patients who were receiving no lipid-lowering medications whatsoever — a substantial proportion, according to other studies [8,9].

Reasons behind the poor attainment of LDL-C targets even in the high-risk population are multifactorial. Poor adherence to statin therapy by patients has been found to be a major factor in a number of studies [5,10,11]. The asymptomatic nature of hyperlipidemia may contribute to the non-adherence [12]. However, physician factors may also play significant roles. In some instances, patients remain on the starting dose of statin which are often insufficient to reach goals, and physicians fail to either increase the statin dose or switch to more potent statins to reach targets [4,13]. In a re-

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cent retrospective, secondary prevention cohort study, statin prescription was found to diminish progressively as baseline cardiovascular risk increased [14]. Misconceptions on the part of the physicians about benefit—harm tradeoffs, especially for the elderly patients, may explain such an apparent paradox.

One area of controversy in statin treatment for high-risk patients is early treatment after acute coronary syndrome: how soon after the event should statins be initiated, and what treatment goals are best? These questions were recently addressed by two large randomized controlled trials, PROVE-IT [15] and A—Z [16], with apparently disparate results. The former demonstrated significant incremental outcome benefit with intense statin therapy whereas the latter did not. A more detailed analysis by Wiviott et al. [17] suggested that the positive results seen in PROVE-IT are virtually entirely attributable to the differences seen during the first 4 months of therapy. Compared to the A—Z study, increased use of coronary interventions at the time of the cardiovascular event and a slightly longer delay in initiating statins both seem to, at least in part, contribute to the better short term outcome seen in the PROVE-IT trial. After 4 months, the outcome benefit relates primarily with the degree of LDL-C lowering in both trials. In this issue, Rajagopalan et al. examined the effect of intensity of LDL-C lowering on the time to recurrence after an index coronary event in the community [18]. Early LDL-C goal attainment within the first six months of an index coronary event impacted positively on recurrence, which is consistent with the analysis by Wiviott et al. However, the use of high potency statins increased the risk of subsequent hospitalization, and by-pass surgery decreased the time to recurrent cardiovascular events, both of which seem counterintuitive. Consideration should be given to the possible inadequacy of the risk adjustment model used in the study. In addition, the analytical methods of the study did not take into account the clustered nature of the data, increasing the likelihood of type 1 error, and further diminishing confidence in these findings. However, if other studies can corroborate that early goal attainment favorably impacts future cardiovascular events, we would need further specific strategies to optimize the management of such high-risk patients.

Increasing evidence suggests that adequate implementation of statin therapy in high-risk patients in the community remains challenging. Physicians must remain vigilant for patients not meeting treatment targets, and should increase doses, increase statin potency or initiate combination therapy. Furthermore, many high-risk patients are not receiving statins at all [8,9], so increasing the number of these patients being treated is also of critical importance. In a hypothetical population where only pravastatin, a modestly efficacious statin is used, the number of lives that would be saved by switching to a higher-potency statin without increasing the proportion of patients being treated is equal to the number of lives that would be saved by increasing utilization of pravastatin by just 8% [19]. Hence, the key factors leading to inadequate treatment of high-risk patients in actual clinical practice (including patient adherence, inadequate follow-up and clinical inertia) need to be addressed. It is very tempting to conclude that the current physician—patient medical model may not be the most suitable for long-term prevention interventions like statin use. Alternate treatment models that include nurse practitioners [20], pharmacists [21] and others deserve careful evaluation. Better understanding of drug adherence from patients' perspectives may yield additional insight for more effective use of statins [22].

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