CHAPTER 7

Editorial: Statins work around the world

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Curr Med Res Opin 2013; 29(7):747-749

Cardiovascular disease (CVD) is the leading cause of death worldwide. CVD accounts for 17.3 million deaths per year, a number that is expected to grow to over 23.6 million by the year 2030 [1;2]. During the last decades the CVD death rates have declined in several developed countries, however in low- and middle-income countries the rates of CVD have risen [2;3]. Eighty percent of the CVD deaths worldwide occur nowadays in the low- and middle-income countries, usually at younger age and involve women more frequently [4]. An important risk factor for CVD is hypercholesterolemia. Many studies have proven the effectiveness of lipid-lowering therapy, predominantly statins, in reducing the incidence of CVD [5]. The successfulness of statin therapy is dependent on the decrease in low-density lipoprotein cholesterol (LDLc) [5], therefore achieving the recommended lipid levels is essential in the treatment of CVD.

In this issue of *Current Medical Research and Opinion*, Lee *et al.* investigated the achievement of the recommended LDLc goals and factors associated with this achievement of 1851 Korean patients with hypercholesterolemia treated with rosuvastatin [6]. The LDLc target was defined according to National Cholesterol Education Program – Adult Treatment Panel III guidelines [7], patients were divided into four groups based on their coronary heart disease risk: low, moderate, high, and very high. The LDLc target was dependent on the risk category, < 130 mg/dL for low or moderate risk subjects, < 100 mg/dL for high-risk subjects, and < 70 mg/dL. The attainment rates were relatively high; overall, 88% of the patients reached their LDLc goal. Next, the authors investigated which factors influenced the achieved targets. It was shown that good adherence with medication was a strong predictor of target achievement.

Lee *et al.* have investigated the target achievement in a Korean population, but are there indications that this would be different in other regions of the world? The INTERHEART study was an international case-control study to assess the importance of risk factors for coronary heart disease worldwide [3]. Although the relative importance of every risk factor varied and was dependent on its prevalence, the effect of the risk factors was consistent across different geographic regions and by ethnic background. Since risk factors are comparable around the world, it would seem logical that treatment strategies for the prevention of CVD are also similar in every country. Statins are used worldwide to lower LDLc levels and thereby decreasing CVD risk. But is the success rate comparable in different geographical regions? The Lipid Treatment Assessment Project 2 (L-TAP 2) was a survey performed in nine countries worldwide, and evaluated the proportion of patients achieving the LDLc treatment goals with statins [8]. The proportion of patients attaining the

treatment goal ranged from 47 to 84% across the different countries, with the highest success rate in Korea en the lowest in Spain. The success rate was dependent on the CVD risk, the higher the risk, the lower the achievement of the LDLc goal, being 86% in low-risk patients, 74% in moderate-risk patients, 67% in high-risk patients, and only 30% in the very-high-risk patients, indicating that it is especially difficult to reach the stringent goals in very-high-risk patients.

The slightly observed differences in success rates between countries are likely due to differences in guidelines, patient characteristics, and healthcare systems among the countries. But pharmacokinetic factors may also influence the rate of goal achievement. A study performed in four different ethnic groups living in Singapore investigated the pharmacokinetics of rosuvastatin [9]. Plasma exposure of rosuvastatin and its metabolites was significantly higher in the Asian groups compared with the white subjects. This higher plasma exposure in Asian subjects might be associated with the higher LDLc goal achievement in Korean subjects as observed in the study of Lee *et al.* and L-TAP 2 [6;8]. Differences in genetic background may also be associated with differences in statin response. For example, the occurrence of genetic risk variants or the allele frequencies can be different across populations [10]. An example of racial differences in statin pharmacogenetics was shown in the Cholesterol and Pharmacogenetics (CAP) study. In the CAP study the association between haplotypes in the Low-density lipoprotein receptor (LDLR) gene and lipid-lowering response to simvastatin was assessed in blacks and whites [11]. The *LDLR* haplotype 5 was associated with smaller LDLc reduction in black but not in the white participants. Recent genome-wide association studies (GWAS) have investigated genetic variants associated with the lipid lowering effects of statins, in which the Lipoprotein(a) and apolipoprotein E genes revealed to be associated with statin response [12]. Another study has investigated genetic variants associated with differential coronary heart disease event reduction after statin therapy [13]. However, until now, the majority of the GWAS studies were performed in Caucasian participants [14]. Since there are differences in genetic background, findings from the current GWA studies may not be generalizable to non-Caucasian patients.

Although there seem to be slight differences in goal achievement rates between ethnicities, overall the achievement rates are reasonable, especially in low-risk patients. The overall success rate in the L-TAP 2 survey was 73%, and even 88% in the study by Lee *et al.* [6;8]. The JUPITER (Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial assessed if there were ethnical differences in the effectiveness of rosuvastatin in reducing first-ever cardiovascular

events [15]. In this trial rosuvastatin was similarly effective in reducing events among whites and nonwhites, including blacks, Hispanics and Asians.

To summarize, statins are used worldwide as lipid-lowering therapy in the prevention of CVD. Despite the many different ethnicities worldwide, the most important risk factors for CVD are for all populations the same. Furthermore, statins seem on average to be effective in all studied populations and thus seem to work all around the world.

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