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Review

Gender related differences in treatment and response to statins in primary and secondary cardiovascular prevention: The never-ending debate

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ABSTRACT

Statins are a main curbstone in the prevention of cardiovascular disease (CVD), pandemic in 21st century. CVD displays evident sex and gender differences, not only in clinical manifestation and outcomes but also in pharmacological treatment. Whether statin therapy should be differentially prescribed according to sex is a matter of debate. Aside a different pharmacological action, statins are not proven to be less effective in one gender comparing to the other, nor to be less safe. Nevertheless, up to date evidence shows that statins have not been adequately tested in women, especially in primary prevention trials. Since data-lacking, making a treatment decision on women is potentially harmful, although female individuals represent the majority of the population and they have a greater lifetime CVD risk. Therefore, adequately powered randomized control trials with longer follow-up are warranted to establish if a benefit on CV events and mortality prevention exists in both sexes. The aim of the present review is to summarize the sex and gender differences in statin use: it raises concerns and updates perspectives towards an evidence-based and sex-tailored prevention of CVD management.

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1. Introduction

Cardiovascular disease (CVD) continues to be a prominent cause of mortality and morbidity throughout the world despite improvements in diagnosis and management. In the last decade, the mortality in men due to CVD has decreased substantially. The rate of cardiac deaths, primarily caused by coronary artery disease (CAD), is significantly higher in women compared to men (51 vs. 42%) [1]. Nevertheless, women are at lower risk for CVD than men; therefore, women require less urgent CVD prevention treatments, that include lipid-lowering or antiplatelet drugs [2]. In fact, women experience the first event of coronary heart disease (CHD) usually ten years later compared to men. Conversely, the incidence of CVD in women increases considerably for the lack of cardio-protective effect from ovarian hormones after menopause [3].

The pathogenesis of CVD is always multifactorial and is related to well-known risk factors. Changes in traditional cardiovascular (CV) risk factors, such as smoking, hypertension and dyslipidemia, are responsible for more than a 50% reduction in CV mortality in the general population [4]. Unfortunately, the control of these CV risk factors is still insufficient. Lipid abnormalities are the more prevalent risk factors in women, detectable in around 50% of cases [5]. Notably, premenopausal women are less affected by hypertension and have lower lipid levels than men of the same age, while the sex disparity disappears in the elderly [6]. Therefore, the impact of high cholesterol levels is typically observed after menopause but not in pre-menopause, where cholesterol levels can be acceptably elevated [5,6].

Nowadays, cholesterol lowering agents [7,8] are a cost-effective strategy to prevent CVD in individuals with high CV risk. Because statins provide the most effective pharmacologic approach to CVD risk reduction, a likely difference in sex-dependent response in CVD reduction and in lipid changes deserves to be deeply examined. However, women are underrepresented in statin trials, challenging the assessment of sex-related disparities in lipid response. The rate of female enrollment spreads from 14% to 69% in statin trials [9] and rarely sex-stratified analysis of outcomes are provided.

Available data indicate that statins are effective in women for secondary CVD prevention. Benefits outweigh disadvantages of statin therapy in those with a high CV risk, while several doubts exist for the primary prevention of women at low-intermediate CV risk.

Thus, the present review summarizes the sex and gender differences in statin use. It raises concerns and updates perspectives towards an evidence-based and sex-tailored prevention of CVD management.

2. Sex-dependent differences in pharmacology of statins

Statins are essential for the treatment and prevention of CVD. Their CV benefits are not exclusively linked to the lipid-lowering effect. Despite the reduction of low-density lipoprotein cholesterol (LDL-C) levels through the direct inhibition of the 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, statins exert other advantageous and pleiotropic effects that help explaining their effectiveness in CVD prevention and treatment. These effects occur through the modulation of atherosclerosis progression and the inhibition of inflammation pathways. In particular, they promote a reduction of oxidative stress and an increase in antioxidant defenses [10] and show also effectiveness in reverting endothelial dysfunction, independently from the reduction of cholesterol levels [11], both increasing the expression and activity of endothelial Nitric Oxide (NO) Synthase through post-transcriptional mRNA modulation and restoring NO levels in endothelial cells [12]. This protective effect of statins could be of particular relevance among women. Thus, it has been recently shown that CHD in women seems to be associated with impaired coronary flow reserve [13]. Such a phenomenon may be related to enhanced inflammation and endothelial dysfunction and microvascular ischemia [14]. Moreover, statins showed to directly inhibit platelet activation via downregulation of platelet NADPH oxidase and reactive oxidant species generation, independently of its cholesterol-lowering effect. [15] Statins were also found to be effective in modulating expression and levels of several pro-inflammatory cytokines, including TNF-alpha, IL-6 and also C-Reactive Protein (CRP) [16]. Markedly, women are more responsive to statin effects on the pro-inflammatory state than men [17].

Straightforward gender-related differences in pharmacokinetics and pharmacodynamics of drugs have been constantly reported, including statins [18]. Noteworthy, it is already known that gender differences play an important role in the development of hypercholesterolemia [19,20], and biochemical evidences about the interplay between sexual hormones and CV risk factors are nowadays available: for example, polymorphisms in the CYP19A1 gene, encoding the aromatase enzyme involved in estrogen synthesis, showed a sex-driven association with CV risk factors such as apolipoprotein B levels, hypertension and insulin resistance [21].

Clinical studies [22–25] documented that, dyslipidemic women experience an attenuated cholesterol decrease under HMG-CoA inhibitors and a less frequent achievement of the recommended lipid targets. Thus, large observational studies [23–25] showed a clear treatment gap in LDL-C success rate between genders: high-risk women are less likely to be prescribed adequate doses of statins or combination lipid-lowering therapy. These studies also suggested that a reduced lipid-lowering activity of statins may occur in women. To address this issue, a recent observational study was performed to evaluate gender-related differences in statin responses. After adjusting for dose and statin power, a significantly greater reduction in total cholesterol and LDL-C after 1-year treatment was observed in men in a cohort of 337 (49% women) dyslipidemic patients [22].

All these data suggest a plausible diverse response to statin therapy within the sex.

The hormonal state may partially account for sex-disparity in treatment efficacy. In fertile women, the high estradiol levels are associated with increased LDL receptors and a concomitant decrease in the activity of HMG-CoA reductase. After menopause, the reduction of LDL-C levels within statin treatment is mitigated since low level of estrogens interfere with LDL receptor expression and metabolism [26,27].

In general, the typical female constitution may affect the pharmacokinetic profiles of drugs conditioning their distribution volume. Such occurrence can be a low body mass index, a smaller dimension of organs, a reduced glomerular filtration rate and a more consistent adipose tissue that secretes different plasma adipokines and affect the pharmacokinetic profiles of lipophilic drugs by increasing their volume of distribution. All these conditions may explain why women may have higher plasma concentrations of statins than men [19]. However, statin metabolism seems to be faster in women than in man. Excluding pravastatin, all lipophilic statins are metabolized by the highly polymorphic hepatic cytochrome P-450 3A4 (CYP3A4) [19], that is more active in women compared with men, as confirmed by the twice larger messenger RNA expression in liver biopsies from women [28]. The 2-fold higher activity of CYP3A4 in women leads to a faster and more extensive statin metabolism. This could explain why atorvastatin and simvastatin could be less effective in women as recently reported [22]. However, gender differences in pharmacokinetics and pharmacodynamics are difficult to quantify as genetic background could also play a role. For example, it has been reported that the polymorphism in estrogen receptor α can be associated, in