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Sex disparity persists in the prevention of cardiovascular disease in women on statin therapy compared to that in men

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Abstract *Background and aims:* The aim of this study was to assess whether women differ from men with regard to lowering lipid levels, achieving target of optimal lipid levels, and analyzing evidence-based dose and intensity of statin prescription in primary care patients.
Methods and results: A multicenter cross-sectional survey was conducted among 1046 patients with dyslipidemia (554 women) who were receiving statin therapy from the Primary Health Care of Andalucía (Spain). A random sample was obtained using data from the electronic health record system. The primary outcomes were the prescription of statin therapy (intensity and dose), lowering lipid levels, and achieving target of optimal lipid levels. Women were less likely to be treated with a more potent statin than men (9.2% vs. 14.4%, $p = 0.009$), and they received lower doses (45 ± 59 mg/day vs. 56 ± 71 mg/day, $p = 0.004$) than men. Total cholesterol and LDL-C levels were higher in women than in men (5.7 ± 1.3 mmol/l vs. 5.2 ± 1.2 mmol/l, $p < 0.0001$ and 3.5 ± 1.2 mmol/l vs. 3.1 ± 1.0 mmol/l, $p < 0.0001$, respectively). Compliance with established goals for total cholesterol (47.7% vs. 31.3%, $p < 0.0001$) and LDL-C (39.7% vs. 25.4%, $p < 0.0001$) was superior in men than in women. In multivariate analysis, adjusted for age, the variables male gender and CVD were associated with a higher compliance with total cholesterol and LDL-C target levels, and the variable diabetes mellitus 2 was associated with a lower compliance with HDL-C and triglycerides target levels.
Conclusions: Women were less likely to be prescribed high-intensity statin to achieve total cholesterol and LDL-C target levels, and mean doses of statin were lower in women than in men. Dyslipidemia is less closely controlled in women than in men.

Introduction

Atherosclerotic cardiovascular disease (CVD) remains the first cause of reported morbidity, disability, and death among women of age 50 years or more in the developed countries [1]. Although the incidence of coronary artery disease in men has decreased in the past years, a similar trend has not occurred in women [2].

Accordingly, statin therapy has shown to decrease CVD morbidity and mortality in both genders [3]. Current guidelines on primary and secondary prevention of CVD recommend that men and women are treated in a similar manner, in accordance with the risk for CVD [4]. In

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patients with CVD, statin therapy has the same benefit in both genders. Moreover, in patients with CVD, intensive statin therapy is more effective than moderate-intensity statin therapy [5]. Additionally, antiplatelet therapy is recommended in patients with CVD or cerebrovascular disease [4].

Nevertheless, results from recent studies suggest that preventive strategies have been less commonly used in women [6]. This is aggravated by the possibility that a reduced lipid-lowering activity of statins may occur in women [7].

Although previously documented studies found gender differences in the care of patients with CVD, most studies have focused on low-density lipoprotein–cholesterol (LDL-C) levels, with few studies assessing the disparities in the receipt of higher doses or more potent statins [6,7].

Given these considerations, evaluating the potential existence of gender-related discrepancy in statin prescription among patients with an elevated level of plasma cholesterol with and without CVD in primary care may be of potential clinical interest. Therefore, the objective of this investigation was to assess whether women differ from men with regard to lowering lipid levels, achieving targets of optimal lipid levels, evidence-based dose and intensity of statin in primary care patients with a diagnosis of dyslipidemia with statin therapy.

Methods

A multicenter cross-sectional survey was conducted among patients with dyslipidemia who were receiving statins using data from the electronic health record system of Primary Health Care of Andalucía (Spain), between September 2014 and August 2015. A random sample, stratified by 10 different towns attended in 15 primary care centers, was obtained. For a population of 55,634 people on treatment with statins, assuming an estimated proportion of dyslipidemia control of 50%, an α error of 0.05, and level of confidence of 95%, the required sample size calculated was 1046 patients. A cluster random sampling was used to categorize depending on population size: large, medium, or small towns.

The inclusion criteria were patients in general practice (>18 years of age) of both genders, with or without CVD, who were prescribed statins at least during the previous 6 months of the study. Pregnant and lactating women, individuals of age below 18 years, terminally ill patients, and psychiatric people were excluded. Patients were regularly followed up by the physicians of the center. Every patient underwent an average of three to four clinical examinations and laboratory analyses per year. Current statin users were defined as individuals receiving a statin at the time of the study, either alone or in combination with another lipid-lowering medication. Equivalent doses of statins were calculated, and high-intensity statins included rosuvastatin 20 mg/day, atorvastatin 40 mg/day, or 80 mg/day [8]. Prescription drug information (statins) was collected and verified on each visit.

We recorded information on demographics (age and sex), treatment time with statin, smoking status, clinical diagnosis of stress, anxiety or depression, regular physical activity (≥30 min/day, 5 days/week), body mass index (BMI; kg/m^2), BMI category (underweight, <18.5 kg/m^2; normal, 18.5–24.9 kg/m^2; overweight, 25–29.9 kg/m^2; and obese, ≥30 kg/m^2), a diagnosis of hypertension, systolic and diastolic blood pressure (SBP, DBP), diabetes mellitus (DM), and previous CVD (all records of atherosclerotic disease were included, as well as stroke and aneurysm of the aorta). Hypertension was defined as SBP > 140 mmHg or DBP > 90 mmHg, and/or use of antihypertensive agents. DM was defined as fasting plasma glucose level ≥ 126 mg/dl (6.99 mmol/l) and/or use of antidiabetic drugs. The CVD risk was estimated using the SCORE model [9].

Data of the most recent levels of fasting plasma lipid profile and metabolic values (glucose, creatinine, and hepatic transaminases) were obtained, which were available from the last contact with the health care system and performed with certified methods using the autoanalyzer Integra 400 (Roche Diagnostics).

The primary outcomes of this study were as follows: (1) prescription of statin therapy (intensity and dose); (2) lowering lipid levels (total cholesterol, LDL-C, and triglycerides) and increasing high density lipoprotein cholesterol (HDL-C); (3) achieving optimal targets of total cholesterol and LDL-C levels of <5 mmol/l (<190 mg/dl) and <3 mmol/l (<115 mg/dl), respectively, in patients at low or moderate CVD risk, as assessed using SCORE; LDL-C levels of <2.5 mmol/l (<100 mg/dl) and 1.8 mmol/l (<70 mg/dl) in subjects at high and very high CVD risk, respectively; recommended levels of HDL-C >1.0 mmol/l (>40 mg/dl) and >1.2 mmol/l (>45 mg/dl) in men and women, respectively; and triglyceride level ≤ 1.7 mmol/l (≤150 mg/dl) [9].

Confidentiality was preserved in accordance with the current Spanish Data Protection Law. Register-based studies in Spain do not require informed consent. The protocol was approved by the Research Ethics Committee of the University Hospital of Puerto Real, Cádiz (Reference Number: HUPR A 06_13).

All analyses were performed using Statistical Package for Social Sciences (SPSS) software, version 23.0. Continuous variables were analyzed for normality; data of continuous variables are expressed as mean, standard deviation, and 95% confidence interval (CI) and those of categorical variables as frequencies. The Student t-test and Mann–Whitney *U* test were used to compare continuous variables across sex groups for normally and non-normally distributed data, respectively. The chi-square and Fisher test was used to compare categorical variables. The percentage of achieving each lipid target level was compared according to sex groups by using the chi-square test. Multivariate logistic regression was performed to assess the association of gender and compliance with therapeutic target levels of total cholesterol, LDL-C, HDL-C, and triglycerides after adjusting for another traditional confounding factor such as age. These results are presented as odds ratio (OR) with 95% CI. A two-sided *p*-value <0.05 was considered statistically significant.