

The gender-specific clinical pharmacology of statins: an update

Andrea Cignarella

Department of Medicine, University of Padua, Italy. Received 16 June 2018; accepted 23 July 2018.

Summary. When overlooked, underrepresentation in clinical trials and the difference in cardiovascular disease (CVD) symptoms in women may lead to worse outcomes and the recurrence of CVD. The efficacy of statins in women with CVD has been established in randomised clinical trials. However, the use of statins should be broadened and not be denied to women with high-risk CVD, in whom the benefits may be greater than those observed in men. There is also a major gender difference in the use of lipid-lowering drugs between men and women with CVD. Statin doses should be adjusted in patients with a high probability of potential side effects, especially with polydrug use. Although the association between statin use and incident diabetes is known, this risk appears to be higher amongst elderly women and shows a dose-response effect. Increasing evidence from observational studies indicates that the use of statins may delay the progression of breast cancer and other malignancies affecting women. Furthermore, interventional studies have shown that statin use may have benefits with regard to prevalent female conditions such as preeclampsia and polycystic ovary syndrome, suggesting novel gender-specific treatment options.

Key words: statins, cardiovascular disease, incident type 2 diabetes, gender, cancer, endocrinological disease.

La farmacologia clinica specifica per sesso delle statine: un aggiornamento

Riassunto. La sottorappresentazione negli studi clinici e le manifestazioni diverse delle malattie cardiovascolari (CVD) nelle donne, se trascurate, possono condurre a esiti sfavorevoli e alla ricorrenza di CVD. L'efficacia delle statine nelle donne con CVD è stata stabilita in studi clinici randomizzati. Tuttavia, l'uso delle statine dovrebbe essere allargato e non essere negato alle donne ad alto rischio di CVD le quali, in effetti, potrebbero avere un beneficio superiore rispetto agli uomini. Inoltre, esiste un'importante differenza di genere nell'uso dei farmaci ipolipidemizzanti fra uomini e donne con CVD. Il dosaggio delle statine dovrebbe essere aggiustato nelle pazienti con un'alta probabilità di potenziali effetti avversi particolarmente a causa della politerapia. Anche se la relazione fra uso di statine e diabete incidente è nota, questo rischio sembra aumentato nelle donne anziane e mostra un effetto di dose-risposta. Prove crescenti dagli studi osservazionali indicano che l'uso delle statine può ritardare la progressione del cancro al seno e di altri tumori che

interessano le donne. Ancora, alcuni studi d'intervento mostrano un beneficio potenziale del trattamento con statine in patologie prevalenti nelle donne quali la pre-eclampsia e la sindrome dell'ovaio policistico, suggerendo delle nuove possibili opzioni terapeutiche genere-specifiche.

Parole chiave: statine, malattie cardiovascolari, diabete incidente di tipo 2, genere, cancro, malattie endocrinologiche.

Introduction

When statins first appeared on the market in the late 1980s, the management of vascular risk was a major problem in most patients and the understanding of the benefits of lowering cholesterol was still in its infancy. All of the most commonly-used statins available today seem to achieve a 20-50% reduction in the risk of a cardiovascular event. They decrease the risk of stroke and peripheral vascular disease, are effective in old and young of both sexes^{1,2}, are effective in patients with concomitant diseases such as hypertension and diabetes and there is growing evidence that the lower the cholesterol level, the better the outcome. Whilst the golden age of statin trials that ended about 10 years ago witnessed their effectiveness in preventing atherothrombotic cardiovascular disease, in several studies women were underrepresented and there was a lack of statistical power for gender stratification³. For instance, the landmark WOSCOPS primary prevention trial only enrolled men between 45 and 64 years of age⁴. CVD manifestations and susceptibility to risk factors differ between men and women⁵. The efficacy of statins in women with CVD was well established in recent randomised clinical trials⁶. Yet the use of statins (in particular high intensity statin therapy) should be broadened and not be denied to women with CVD, who, in actual fact, may obtain greater benefits from this kind of therapy than men⁷. The demonstration of a treatment-sex interaction in the SATURN study⁸, along with a greater clinical benefit in terms of LDL-C reduction in TESTS IT-TIMI 22⁹, points to an inherent biological tendency for women to benefit more from statin treatment. In the prolonged high-intensity statin therapy setting, particularly in those achieving very

low LDL-C levels, plaque regression is more evident in women than in men. Although the incidence of major adverse cardiac events tended to be higher in women than in men on statin treatment following percutaneous coronary intervention (PCI), this difference was no longer present after adjustment by age and gender, suggesting that statin treatment may be equally effective in preventing post-PCI cardiovascular events in both men and women¹⁰. However, clinical trials regarding CVD prevention enrolling mainly women suggest that more individualised therapeutic strategies are required in order to halt atherothrombotic disease¹¹.

Despite being more controversial, there is also evidence to support the use of statin therapy for primary prevention in women at higher CVD risk¹². However, in premature myocardial infarction patients (<50 years), risk prediction is insufficiently addressed by the standard CVD risk scoring tools. Retrospective analysis of a cohort from two US academic centres revealed that significantly more women (184; 63%) would not be eligible for statin treatment than men (549; 46%, $p < 0.001$). Thus, current risk assessment tools are inadequate for preventing early manifestations of coronary artery disease (CAD), and improved strategies are urgently needed to identify premature CAD patients in a primary prevention setting¹³.

Gender and age issues in appropriate statin use

There is a major difference in the use of lipid-lowering therapy between men and women with coronary artery disease. Women are at a higher risk of statin noncompliance than men and are more likely to stop or switch their statin therapy because of side effects than men are¹⁴. Although women are less likely to be prescribed a nonstatin lipid-lowering drug than men¹⁵, females were less likely to start an appropriate statin before and after the release of the ACC/AHA cholesterol management guidelines in November 2013¹⁶. The retrospective analyses of electronic outpatient health records showed that women with coronary artery disease are prescribed inadequate doses of statins and combination lipid-lowering therapy and are less likely to achieve their optimal LDL and non-high-density lipoprotein cholesterol goals¹⁷. Amongst individuals with a statin prescription, women are less likely than men to be prescribed a statin, get up-titrated or even initiate a high-intensity statin therapy following hospital discharge for myocardial infarction¹⁸. A retrospective cohort study also showed that use of statins and other pharmacological agents following myocardial infarction was significantly higher amongst male patients than amongst female ones¹⁹. Similarly, the management of the dyslipidaemia that is often found in HIV-seropositive women should be more aggressive²⁰.

The lipid management of elderly patients has been insufficiently addressed in large randomised clinical trials. Data from observational studies may assist clinicians in their quest for reliable evidence on how to manage this growing category of patients. In a retrospective analysis of data collected from 216 elderly patients (>80 years) for 1 year, of which 122 (56.5%) were women, 53% of the women and 47% of the men used statins for ≥ 3 years after hospital admission. Over 3 years, 39% of the women and 51% of the men died. Statins were seen to have a protective effect in the women only. Of the women not using statins, 57.1% died vs. 24.2% of those who used statins ($p < 0.0001$). Clinical benefit was significant in women on statin treatment for both primary and secondary prevention. For elderly men, no benefits were observed, due perhaps to the fact that life expectancy is higher for women than for men²¹.

The gender-specific incremental benefit of add-on therapy: the IMPROVE-IT study

The IMPROVE-IT study included 18,144 post-acute coronary syndrome (ACS) patients, of whom 4416 (24%) were women. Based on a recent sub-analysis of the trial²², the cardiovascular protection action of ezetimibe on top of simvastatin in secondary prevention would appear to be comparable for the two sexes, in line with previous meta-analyses²³. However, despite similar reductions in LDL-C, the absolute reduction of both primary and total events with the addition of ezetimibe was greater in women than men²². Thus, aggressively addressing CVD risk factors may have a significant impact on women's health. In secondary prevention, lowering LDL-C in women provides comparable relative risk reductions, but the impact on absolute risk is more striking. In the IMPROVE-IT trial, women had a relative risk reduction of 12% vs 5% in men. The number of events was reduced by 18% in women vs 6% in men. In high-risk women, efficacy of statin + ezetimibe started early, leading to a 27% relative risk and a 7.4% absolute risk reduction for the primary endpoint²².

Safety issues and pharmacokinetics: back to basics

Plasma statin concentrations are pivotal in many of the adverse effects observed. Statin doses should be adjusted in patients with a high probability of potential side effects due to e.g. age, co-morbidities, genetic disposition and, last but not least, co-medications. Knowledge regarding the enzymes that are responsible for statin elimination and are targeted by other pharmacological interventions is also important. All statins except pravastatin

tatin are metabolised by hepatic cytochrome P450 (CYP). Simvastatin, lovastatin and atorvastatin are predominantly metabolised by CYP 3A4. Because in women the expression of CYP 3A4 is twice than seen in men, faster and more extensive statin metabolism may result in lower activity than in men²⁴. By contrast, fluvastatin, pitavastatin, rosuvastatin and pravastatin pose a lower risk for interaction with drugs inhibiting or increasing CYP 3A4 activity. CYP 2E9 is targeted by different concomitant drugs and in this case fluvastatin, pitavastatin and rosuvastatin are more likely to lead to interactions. Alternatively, statin transporters such as OATP1B1, OATP1B3 and P-glycoprotein can also impact plasma concentrations²⁵. In general, women have (a) a lower body mass index and thereby increased risk of myopathy; (b) more adipose tissue and, therefore, a greater volume of distribution for lipophilic statins (e.g. simvastatin) and increased half-life; and (c) a lower glomerular filtration rate than men. Overall, although there are metabolic differences and the % LDL-C change may not be the same as in men, a high-risk woman will still benefit from statin therapy²⁴.

Increased risk of statin-related incident diabetes

The pro-diabetogenic effects of statins were recently brought to light²⁶. The increased cholesterol uptake in the pancreatic islet Beta-cells via the LDL-receptor may have a damaging effect on insulin secretion and even Beta-cell apoptosis²⁷. Older women taking statins face a significantly higher risk of developing diabetes. More specifically, Australian women over 75 faced a 33% higher chance of developing diabetes if they were taking statins, and the risk increased with the dose of statins²⁸. Indeed, of almost 8400 women aged between 76 and 82 years, the risk of new-onset diabetes ranged from 17% with the lowest statin doses to 51% with the highest doses. The impact of statins on incident diabetes in the context of hypertension and gender was recently evaluated in a relatively healthy Korean population²⁹. Over a period of 7-8 years about 40,000 participants from the National Health Insurance System with elevated LDL-C were evaluated. Of over 22,000 statin users, 7.63% developed new-onset diabetes vs. 5.68% amongst statin non-users. For unclear reasons, the association between statin use and incident diabetes was found in normotensive patients only. However, women showed a higher risk of diabetes with continuous statin use regardless of hypertension status, whereas increased risk was observed in normotensive males only²⁹. This suggests that the risk of diabetes associated with statin therapy in the management of patients with dyslipidaemia is higher amongst women.

Emerging evidence of statin benefit in cancer

Because breast cancer expression of the statin target (3-hydroxy-3-methylglutaryl coenzyme-A reductase) is associated with lymph-node negative cancer³⁰, pre-diagnostic statin use may be associated with reduced breast cancer-specific mortality. One cohort study showed that pre-diagnostic statin use in women with breast cancer is associated with a significant reduction in both breast cancer-specific and all-cause mortality, particularly in those with oestrogen receptor-positive breast cancer³¹. In a population of women with newly diagnosed breast cancer, although black women have a worse prognosis than white women, this racial disparity is not accounted for by differences in pre-diagnosis statin use³². However, no SNPs across the genome were identified for a significant interaction with baseline statin use in breast cancer risk³³.

Statin use may afford protection for other cancer types as well. For instance, use of statins, in particular lipophilic statins, is associated with a borderline lower risk of non-Hodgkin's lymphoma and with a significantly lower risk of diffuse large B-cell lymphoma in the large Women's Health Initiative cohort study³⁴. In one retrospective cohort of women diagnosed with ovarian cancer, statin therapy was found to be associated with better overall survival amongst elderly patients³⁵. Consistently, a systematic review and meta-analysis based on relevant studies that together included nearly 20,000 patients with ovarian cancer provides significant evidence of an overall protective effect of post-diagnostic statin use on all-cause and cancer-specific mortality³⁶.

Finally, on a slightly different note, one retrospective study showed that uninterrupted use of statins in women suffering from breast cancer before and during anthracycline chemotherapy is associated with a lower risk of new-onset incident heart failure³⁷. Of the proposed mechanisms, it is conceivable that statin pre-treatment attenuates anthracycline-induced oxidant stress by inhibiting isoprenoid synthesis or microRNAs in cardiomyocytes³⁸.

Statin as a novel therapeutic option for preeclampsia and polycystic ovary syndrome

Preeclampsia (PE) is a serious systemic vascular complication affecting 3-5% of all pregnancies³⁹, and is a risk factor for future CVD⁴⁰. All stages of PE are characterised by vascular changes that, theoretically, could benefit from pharmacological treatments targeting inflammation, cytokines and pro-thrombotic factors. Statin use during the final two trimesters of pregnancy appears to be beneficial in preventing and managing PE patients⁴¹⁻⁴⁴ at least in part via anti-inflammatory effects, in view of the increased levels of inflammatory markers (hs CRP) observed in preeclamptic women. Alternatively, gesta-

Table 1. Emerging gender-specific considerations for statin treatment: the highlights.

Conditions	Comment	HR/OR	Reference
Post-acute coronary syndrome	Add-on therapy with ezetimibe more beneficial in high-risk women than men	Primary composite endpoint in women: HR 0.88; 95% CI 0.79-0.99; in men: HR 0.95; 95% CI 0.90-1.01 Total number of primary events in women: HR 0.81; 95% CI 0.71-0.94; in men: HR 0.94; 95% CI 0.87-1.02	22
New-onset type 2 diabetes	Increased dose-dependent risk due to statin treatment in elderly women	HR 1.33; 95% CI 1.04-1.70	28
Breast cancer	Statin use is associated with improved survival	All-cause mortality: HR 0.78; 95% CI 0.69-0.89 Breast cancer-specific mortality: HR 0.81; 95% CI 0.68-0.96	31
Ovarian cancer	As above	HR 0.66; 95% CI 0.55-0.81 All-cause mortality: HR 0.74; 95% CI 0.63-0.87 Cancer-specific mortality: HR 0.87; 95% CI 0.80-0.95	35, 36
Preeclampsia	Pravastatin appears to be effective and safe for the mother and the newborn	Case reports and small-scale phase I trials	41-44
PCOS	Small intervention studies show endocrinological and metabolic benefit of statin treatment	Improvement in surrogate endpoints and significant reduction in HOMA- β	45, 46

HR: hazard ratio; CI: confidence interval; HOMA: homeostasis model assessment.

tional dyslipidaemia could play an important role in accelerated atherosclerosis in the mother as well as in the newborn. Because of its pharmacokinetic profile, a hydrophilic statin, like pravastatin, is less likely to cross the placental barrier and no serious birth defects effects have been noted thus far. The observed safety of pravastatin, in terms of teratogenicity, should be of interest when managing pregnant high-risk women with (very) high LDL-C plasma levels, due e.g. to familial hypercholesterolemia, plus clinical manifestations of atherosclerotic cardiovascular disease, where interrupting statin treatment could be potentially life-threatening. However, data from ongoing randomised clinical trials are needed to determine efficacy and safety in pregnant women and their offspring.

Finally, two recent randomised, double-blind, placebo-controlled studies highlighted the benefit of statin treatment in women with polycystic ovary syndrome (PCOS). In the first, the experimental group received 20 mg simvastatin for 6 months, resulting in improved metabolic and endocrinological endpoints⁴⁵. In the second, treatment with atorvastatin for 12 weeks significantly reduced HOMA- β and improved insulin resistance without inducing hyperglycaemia or hyperinsulinemia⁴⁶.

Conclusions

Although the benefits of statins outweigh the risks, these medications should be used responsibly, paying greater attention to the hazard posed by e.g. age and polyphar-

macy. Statins should be used carefully in elderly women, who are more susceptible to new-onset type 2 diabetes. On the other hand, high-risk women appear to benefit more than men from statin treatment and should be considered for this kind of treatment. Accumulating evidence also suggests that statins may be beneficial in non-cardiovascular settings such as cancer and endocrinological disease that are prevalent in women (Table 1). Thus, novel opportunities are emerging and further studies are awaited to confirm the clinical effectiveness of statins outside the CVD field.

Key messages

- Statin use should be widened and not be denied to women with cardiovascular disease, who may, in actual fact, achieve greater benefits than men.
- Recommended high-intensity statins are still under-used in women after myocardial infarction.
- Several studies suggest that statin use substantially increases the risk of type 2 diabetes in both men and women. Elderly women should not be exposed to higher doses of statins.
- Statins appear to increase breast- and ovarian cancer-specific as well as overall survival as compared to no statin use.
- Indications such as preeclampsia and polycystic ovary syndrome are emerging for statin use in younger women.

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Correspondence to:

Andrea Cignarella

Department of Medicine

University of Padua

Pharmacology Building

Largo Meneghetti 2

35131 Padova

email andrea.cignarella@unipd.it