RESEARCH

Sex differences in the effectiveness of statins after myocardial infarction

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Abstract

Background: We sought to investigate the sex differences in the effectiveness of statins in patients with acute myocardial infarction (AMI).

Methods: Linking hospital discharge and drug claims databases from Quebec, Canada (1998–2004), we identified statin users (n = 14 710) and non-users (n = 23 833) discharged from hospital after an AMI-related hospital stay and followed up for as long as 7 years.

Results: All-cause death rates were 4.1 and 14.6 per 100 person-years among users and non-users, respectively, whereas cardiac death rates were 2.2 and 7.4 per 100 person-years. For death from any cause, the adjusted hazard ratios associated with statin use in women were 0.61 (95% confidence interval [CI], 0.54–0.69) within 1 year of follow-up, 0.55 (0.48–0.63) at 1–3 years and 0.38 (0.31–0.49) at > 3 years; in men, the corresponding estimates were 0.54 (0.48–0.60), 0.48 (0.42–0.55) and 0.34 (0.30–0.39). For cardiac-related death, the adjusted hazard ratios associated with statin use in women were 0.70 (0.60–0.81) within 1 year, 0.56 (0.46–0.68) at 1–3 years and 0.44 (0.31–0.62) at > 3 years of follow-up, whereas in men, the estimates were 0.59 (0.51–0.69), 0.47 (0.39–0.58) and 0.37 (0.30–0.45), respectively.

Interpretation: Statin therapy after an AMI was associated with reduced rates of all-cause and cardiac mortality. The effect increased with time in both sexes, but the degree of risk reduction was less for women than for men.

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S tatins have been shown to be effective medications for prevention of secondary events in patients with coronary heart disease (CHD).[1–3] However, because women have been underrepresented in clinical trials on statins,[4] potential sex differences in the efficacy of statins have not been well studied. Among the studies that explored this issue, some indicated a possibly greater cardiovascular risk reduction among men,[5,6] whereas others suggested that statins were as effective in women as in men, or even more effective.[7–10] This latter proposition would indeed be consistent with the greater low-density lipoprotein (LDL) cholesterol and total cholesterol reductions in women than in men in response to the use of statins that were reported from some earlier studies.[11–13]

Current knowledge about the magnitude of the statin-induced risk reduction in death rates among women with CHD or cardiovascular disease (CVD) in general is even less definitive. Whereas at least 2 studies have reported a potential benefit of statins in women,[14,15] a recent systematic review[16] concluded that lipid-lowering medications, including statins, did not reduce total mortality rates among women with CVD, just as they did not among women without CVD. However, the review did find statistically significant reductions in CHD-related deaths, nonfatal myocardial infarction, revascularization and total CHD events accompanying lipid-lowering therapy in women with CVD.[16]

Thus, the current evidence on potential quantitative differences in the efficacy of statins for prevention of secondary events in men and women with CHD is still inconclusive. We conducted this study to investigate possible statistical sex–statin interaction in patients after a myocardial infarction (AMI).

Methods

The Quebec hospital discharge summary database, which includes information on all hospital admissions for AMI, was linked to provincial databases of physician and drug claims. In Quebec, people younger than 65 years typically receive drug benefits through employee plans; those without employee benefits or who are aged 65 years and over receive prescription coverage at minimal cost. Thus, our source of drug data included information on patients of all ages. For completeness, vital status information was obtained from the same databases, which are linked to pension, car insurance and death registry services. The patients' unique, encrypted health care insurance number was used to link the data within and between the databases. During the linkage, a total of 53 subjects could not be matched and were therefore excluded from our analyses.

Patients with a first record of an AMI-related hospital admission who were discharged alive between April 1, 1998 and March 31, 2004 were included in the cohort. (The interval was based on the most recently available data from the hospital discharge database.) All patients had AMI (ICD-9-CM code 410)[17] recorded in the hospital discharge database as the most responsible diagnosis — that is, the principal diagnosis contributing to the greatest extent to the patient's hospital stay.

Patients were excluded (for the reason in parentheses) if they met any of the following criteria: the AMI was coded as

an in-hospital complication (to minimize the possibility of including iatrogenic AMI cases); the AMI-related hospital admission was a transfer from another hospital (to avoid counting the patients more than once); the total length of hospital stay was less than 2 days (to exclude patients with ruled-out AMI cases and those admitted only for procedures); the patient was discharged to a long-term care institution or rehabilitation centre, or moved out of the province (since data on prescriptions would then be unavailable); or the health care number was invalid. More details of the rationale for these criteria can be found elsewhere.[18]

Statin use was defined as data indicating a prescription filled for any of the 6 statin medications, which are considered to be of similar effectiveness for the prevention of secondary events in patients with CHD: atorvastatin, pravastatin, simvastatin, lovastatin, rosuvastatin and fluvastatin.[19] Available prescription information (type of drug, dosage category, frequency and duration) was used to calculate daily dosages, which were converted into equivalent atorvastin doses and the corresponding number of Defined Daily Doses (DDD), as defined by the World Health Organization.[20] Based on the patient's statin-prescription status at the time of discharge (time zero), 2 study groups were retrospectively defined: patients who were prescribed a statin (statin users) and those not prescribed a statin (statin non-users, the control group). Each patient was followed from time zero until the occurrence of either of the study end-points (all-cause death and cardiac death [ICD-9-CM codes 390–450, 785 or v588]),[17] the end of study follow-up (March 31, 2005), loss to follow-up, or discontinuation of the statin use/non-use regimen initially adopted, whichever came first. In the last case, statin users were considered to have discontinued statin use if at least 30 consecutive days passed during which they did not fill a prescription for a statin. Among statin users, switching the type of statin used (i.e., among the 6 statin medications) would not represent a discontinuation. On the other hand, switching from a statin medication to a nonstatin drug or to a statin other than the 6 types already mentioned would represent a statin discontinuation for the purposes of our study.

Potential confounders were taken into consideration, as follows. Patient demographic characteristics and comorbidities at discharge were determined from the hospital discharge databases at the index admission. Comorbidities included coexisting cardiovascular and lung diseases, chronic kidney or liver conditions, diabetes mellitus, dementia and malignant disease. Use of major cardiac medications at discharge was also recorded: β-blockers, angiotensin-converting-enzyme (ACE) inhibitors, antiplatelet drugs (ASA, clopidogrel), calcium-channel blockers, diuretics, warfarin and digoxin. Information was also obtained on any in-hospital procedure performed (catheterization, percutaneous coronary intervention, coronary artery bypass graft surgery), the year it was performed (according to the hospital's fiscal year), length of the hospital stay, the specialty of the treating physician (cardiologist, internist, other specialist, general practitioner), type of hospital (teaching or rural) and availability of a cardiac catheterization facility in the hospital. Finally, it was documented whether the patient was prescribed a statin within the 12 months before the AMI-related hospital admission.

Descriptive statistics were computed to compare baseline patient characteristics between the 2 study groups according to sex. Next, for both outcome end-points, hazard ratios associated with statin use were estimated in Cox regression models. In investigating the association between statins and the study outcomes, it was important to allow for the possibility of time-dependence (i.e., an accumulation of effect of statins over time), including time-dependent effects that are nonlinear.[21] This was done by adding 3 product terms between the indicator of statin use and 3 follow-up periods after discharge (< 1 yr, 1–3 yr and > 3 yr) to the Cox models. The potential modifying effect of sex on the effectiveness of statin therapy was investigated by the addition of a product term between the indicator of statin use and the male/female indicator. In addition to the unadjusted Cox regression, multivariable Cox models were fitted that also adjusted for age, marital status, presence of comorbidities, use of cardiac medications at baseline (time zero), use of statins during the 12 months before the index hospital admission, the in-hospital procedure performed, the year the procedure took place, length of hospital stay, specialty of the treating physician and type of hospital.

Because information on the cause of death was unavailable for 223 patients, they were excluded from the primary analyses that used this outcome end-point. However, as part of sensitivity analyses in those analyses involving cardiac death as the outcome end-point, we assessed 2 alternative, "extreme" approaches to handling data for these 223 patients. In the first, all patients who died of unknown cause were assumed to have had cardiac causes, and were thus combined with known cardiac deaths for analysis. In the second, we assumed that all such deaths were noncardiac in origin, and combined them with known cases of noncardiac death. The study was approved by the Ethics Review Board of McGill University.

Results

Of 38 543 patients who were discharged from hospital after AMI who were included in the analysis, 23 815 (61.8%) were men and 14 728 (38.2%), women. At the time of hospital discharge, 14 710 patients (38.2%) were prescribed a statin. Both male and female non-users of statins tended to be slightly older than users (Table 1). The 2 groups were comparable in terms of comorbid conditions except for congestive heart failure, which was more common among non-users than users of statins. In both sexes, statin users tended to have been prescribed other cardiac medications and undergone invasive cardiac procedures more frequently, compared with non-users. The median length of stay in the hospital was similar in the 2 groups. Admissions by fiscal year are available in an online Appendix (www.cmaj.ca/cgi/content/full/176/3/333DC1).

Overall, statin users contributed a total of 28 881 person-years of follow-up to the analysis; statin non-users, 32 792 person-years (Table 2). In the intervention group, 57% of patients in the user group continued to use statins throughout follow-up, whereas 38% of patients in the control group re-

Table 1: Baseline characteristics of patients treated for an acute myocardial infarction, according to statin use and sex.

Characteristic	Women		Men		Total $n = 38\,543$
	Non-users $n = 9\,405$	Users $n = 5\,323$	Non-users $n = 14\,428$	Users $n = 9\,387$	
Age, mean (SD), y	74.6 (11.8)	70.2 (11.2)	68.4 (12.4)	64.6 (12.0)	69.2 (12.5)
Married	3762 (40)	2395 (45)	8801 (61)	5820 (62)	20813 (54)
Comorbidities					
Cardiac dysrhythmia	2069 (22)	958 (18)	3030 (21)	1690 (18)	7709 (20)
Cerebrovascular disease	658 (7)	319 (6)	866 (6)	469 (5)	2313 (6)
Congestive heart failure	2663 (28)	1065 (20)	3030 (21)	1408 (15)	8094 (21)
COPD	1787 (19)	852 (16)	3030 (21)	1408 (15)	6938 (18)
Dementia	282 (3)	53 (1)	144 (1)	94 (1)	771 (2)
Diabetes mellitus	2633 (28)	1384 (26)	3463 (24)	1971 (21)	9636 (25)
Hypertension	4608 (49)	2608 (49)	4473 (31)	3098 (33)	14646 (38)
Liver disease	94 (1)	53 (1)	144 (1)	94 (1)	385 (1)
Malignancy	282 (3)	107 (2)	577 (4)	188 (2)	1156 (3)
Pulmonary edema	188 (2)	53 (1)	144 (1)	94 (1)	385 (1)
Renal failure, acute	470 (5)	213 (4)	721 (5)	282 (3)	1542 (4)
Renal failure, chronic	1129 (12)	426 (8)	1731 (12)	751 (8)	3854 (10)
Shock	94 (1)	53 (1)	144 (1)	94 (1)	385 (1)
Admitting physician					
General practitioner	4420 (47)	2182 (41)	6493 (45)	3943 (42)	16959 (44)
Cardiologist	4044 (43)	2608 (49)	6493 (45)	4506 (48)	17730 (46)
Internist	1034 (11)	532 (10)	1443 (10)	939 (10)	3854 (10)
Medication use					
ASA or clopidogrel	4420 (47)	4418 (83)	6348 (44)	7979 (85)	23126 (60)
Beta-blockers	4044 (43)	4046 (76)	5771 (40)	7416 (79)	21199 (55)
ACE inhibitor	1304 (33)	3087 (58)	4328 (30)	5726 (61)	16188 (42)
Diuretics	2445 (26)	1597 (30)	2453 (17)	1783 (19)	8478 (22)
Ca^{++}-channel blocker	1599 (17)	1118 (21)	1731 (12)	1314 (14)	5781 (15)
Warfarin	940 (10)	692 (13)	1299 (9)	1314 (14)	4240 (11)
Digoxin	564 (6)	266 (5)	721 (5)	375 (4)	1927 (5)
Nitrates, non-sublingual	2445 (26)	1437 (27)	2741 (19)	1784 (19)	1272 (22)
Used statins during 12 mo before index admission	2008 (21)	1811 (34)	3293 (23)	2507 (27)	38543 (25)
Procedure					
Catheterization	3198 (34)	2928 (55)	6204 (43)	5632 (60)	18115 (47)
PCI	1787 (19)	1810 (34)	3607 (25)	3661 (39)	10792 (28)
CABG	376 (4)	373 (7)	1010 (7)	1032 (11)	2698 (7)
Type of hospital					
Urban	8928 (95)	5074 (95)	13702 (95)	8916 (95)	36620 (95)
Rural	476 (5)	249 (5)	726 (5)	471 (5)	1922 (5)
Length of hospital stay, median (IQR), d	9 (6-15)	9 (6-14)	8 (5-13)	8 (5-13)	9 (6-13)

SD = standard deviation, COPD = chronic obstructive pulmonary disease, ACE = angiotensin-converting enzyme, ASA = acetylsalicylic acid, Ca = calcium, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft surgery, IQR = interquartile range.

mained non-users throughout the follow-up period. Similar percentages of male and female patients switched from the initial statin type (19% and 18%, respectively) or stopped statin use during the study follow-up (44% and 41%, respectively). Among statin users, the mean atorvastatin-equivalent dose was similar between patients of either sex: men 19.5 mg, women 19.2 mg.

A total of 6172 patients died during the follow-up, 3053 from a cardiac cause (Table 3), with the overall unadjusted mortality rates being 10.4 all-cause events per 100 person-years and and 5.0 cardiac events per 100 person-years. In both men and women, statin users had lower overall unadjusted rates of both all-cause and cardiac death than did non-users.

The adjusted Cox regression models (Table 4) indicated that the statin-induced risk reduction for both all-cause and cardiac deaths increased with increased duration of treatment ($p < 0.001$ for interaction between statin use and time since discharge, for both end-points). For all durations of follow-up, however, the magnitude of the reduction in risk was greater for men than for women ($p = 0.04$ for interaction between statin use and sex for all-cause death; $p = 0.06$, for cardiac death).

In the sensitivity analysis, when deaths from an unknown cause were assumed to have been of cardiac or noncardiac origin, the point estimates, confidence intervals and conclusions did not differ materially from those derived in the main analyses, which were based on an end-point of cardiac death.

Interpretation

In this study of 38 543 post-AMI patients, we found a gradual accumulation over time of preventive effects from statin therapy that decreased overall and cardiac-related mortality rates in both sexes, with moderate risk reduction in the early follow-up period after discharge from hospital and considerable risk reduction after a longer duration of therapy. However, statin use conferred a lower degree of reduction in the risk of all-cause and cardiac death to women than it did to men.

CVD-related preventive benefits of statins are thought to be mediated largely by LDL-cholesterol reduction,[22–24] with ensuing decreased progression of atherosclerosis, regression of atherosclerotic lesions and slowed development of new lesions. Therefore, the design and analysis of studies attempting to quantify statin-conferred benefits should be lengthy enough to allow for the possibility of a lag between initiation of therapy and achievement of the maximum reduction in the occurrence of clinical events.[21] Nonetheless, statin treatment has been associated with morbidity and mortality benefits early after AMI.[25,26] These early benefits of statins could be mediated via both lipid-lowering and pleiotropic effects.

Several reasons are possible for the survival difference in male versus female patients. Differences in our study cannot be attributed to dose: in our study, men were prescribed virtually the same dose of statins as women (Table 1). Some studies[27,28] have suggested that LDL- and total-cholesterol concentrations in serum may be stronger determinants in men of rates of CVD-related death than in women. A recent meta-analysis[21] of findings from studies of major coronary and major vascular events among patients with and without CHD, however, revealed that men and women exhibited similar reductions in event rates per unit of LDL-cholesterol reduction. In some animal studies, the rate of metabolism of simvastatin was found to be considerably higher in males than in females;[29,30] the statin might therefore be expected to have a

Table 3: Incidence rates per 100 person-years for the study end-points, according to statin use by patients

| End-point: death | Overall n = 38 543 | Women | | Men | |
		Non-users n = 9405	Users n = 5323	Non-users n = 14 428	Users n = 9387
From any cause	10.4	15.8	4.9	13.8	3.6
Cardiac-related	5.0	8.5	2.9	6.7	1.8

Table 2: Number (%)* of patients who were or were not treated with statins, and their pattern of use

| Statin-related characteristic | Statin non-users | | | Statin users | | |
	Women n = 9405	Men n = 14 428	All non-users n = 23 833	Women n = 5323	Men n = 9387	All users n = 14 710
Use of statin within 1 yr before index AMI	2008 (21)	3293 (23)	5301 (22)	1811 (34)	2507 (27)	4318 (29)
Duration of follow-up						
Median (interquartile range), d	215 (27-850)	142 (22-741)	168 (24-791)	577 (274-1057)	577 (279-1053)	577 (277-1055)
Total for entire study population, yr	13 742	19 050	32 792	10 377	18 504	28 881
Change in statin regimen						
Discontinued initial use or non-use	5256 (56)	9523 (66)	14 779 (62)	2194 (41)	4147 (44)	6368 (43)
Switched during follow-up	0	0	0	558 (18)	997 (19)	1555 (19)
Atorvastatin-equivalent dose, mean (SD), mg/d	0	0	0	19.2 (12.0)	19.5 (12.1)	19.4 (12.1)
Dosage, WHO DDD-equivalent, mean (SD)	0	0	0	1.9 (1.2)	1.9 (1.2)	1.9 (1.2)

AMI = acute myocardial infarction, IQR = interquartile range, SD = standard deviation, WHO = World Health Organization, DDD = defined daily dose.
*Unless specified otherwise.

greater clinical effect on males. This hypothesis was nevertheless not corroborated in studies on human volunteers, which, in contrast, showed a lower degree of metabolism of simvastatin and lovastatin in men than in women.[31] Moreover, several epidemiological studies[11–13] have reported greater reductions in both LDL and total cholesterol in response to statins used by women than by men.

Another mechanism responsible for a differential effect of statins could be sex-dependent drug clearance, given that the clearance of lipid-soluble statins involves cytochrome P450 system enzymes (CYP)[32–34] and that CYP expression can vary by sex.[35] This could lead to between-sex differences in clearance rates, bioavailability and, consequently, the clinical effects obtained with the same dose of the drug.[36]

Our findings concur with those of earlier studies suggesting that statin therapy leads to a greater reduction in risk of cardiovascular events in men with CVD than in women with CVD.[5,6] However, these previous studies generally included numbers of women that were insufficient to demonstrate the potential sex–treatment interaction or else did not account for the apparent time-dependence of statin-induced risk reductions.

Our study had several advantages. First, we were able to include a large number of patients of both sexes, which provided sufficient power to detect the sex–treatment interaction. Second, the patients included in our study represented a wider clinical and sociodemographic spectrum than those generally enrolled into randomized controlled trials, which should enhance the generalizability of our findings. Third, the patients had sufficiently long follow-up to allow us to demonstrate the added benefits of statin therapy with increased duration.

Some limitations of our study should also be considered. First, we had to rely on data obtained from an administrative database rather than on actual use of statin medications, which could introduce misclassification in statin-use status. However, such misclassification would likely be nondifferential and tend to dilute the associations found. Second, because data on patients' serum lipid profile were unavailable, it was impossible for us to explore whether the apparent effect modification by sex was attributable to the differential effects of statins on LDL-cholesterol concentration or to pleiotropic effects. Third, data on cause of death were not available for all subjects. Still, our sensitivity analyses, where we considered 2 extreme-alternative scenarios with respect to cause of death, showed our findings to be robust. Next, although we adjusted for several codeterminants of all-cause and cardiac deaths, a possibility remains that residual confounding by indication could have introduced bias into our results.[37] Nevertheless, since confounding by indication generally leads to dilution of the effect of the intervention studied,[37] our estimates of the effects of statins are likely to be conservative. Even if the estimates of statins' effects are subject to some degree of residual confounding, it is unlikely that this would explain the differential effects of statins observed between men and women. Finally, because the database did not include such important patient characteristics as tobacco use and obesity status, we were unable to adjust for them; our findings of sex-differential effects of statins could therefore be at least partly attributable to potential differences in the levels of these factors.

Our findings could have potentially important implications for clinical practice. If corroborated by independent studies on the effects of statins on serum cholesterol levels, these results would suggest a possible need for reappraisal of target daily doses for statins: women might require a higher dose to achieve preventive effects similar to those observed in men. Moreover, the differential effect of statins in men and women could translate into differential outputs from cost-effectiveness[38] and risk–benefit analyses of statin therapy.[39]

Future studies should further investigate the apparent interaction between sex and the use of statin. Ultimately, the knowledge would better enable physicians and patients alike to make informed decisions on optimal treatment plans following an AMI.

Table 4: Crude and adjusted* hazard ratios, by sex, for the association between statin use and 2 end-points, for 3 selected durations of follow-up

End-point and years of follow-up	Hazard ratio (95% confidence interval)			
	Women		Men	
	Crude	Adjusted	Crude	Adjusted
Death from any cause				
< 1	0.33 (0.30-0.37)	0.61 (0.54-0.69)	0.28 (0.25-0.30)	0.54 (0.48-0.60)
1-3	0.29 (0.26-0.33)	0.55 (0.48-0.63)	0.24 (0.21-0.28)	0.48 (0.42-0.55)
> 3	0.22 (0.17-0.27)	0.38 (0.31-0.49)	0.18 (0.16-0.20)	0.34 (0.30-0.39)
Cardiac-related death				
< 1	0.37 (0.32-0.43)	0.70 (0.60-0.81)	0.30 (0.26-0.34)	0.59 (0.51-0.69)
1-3	0.29 (0.24-0.35)	0.56 (0.46-0.68)	0.23 (0.19-0.28)	0.47 (0.39-0.58)
> 3	0.24 (0.17-0.34)	0.44 (0.31-0.62)	0.19 (0.16-0.23)	0.37 (0.30-0.45)

*Adjusted for age, marital status, comorbidities, use of cardiac medications at baseline and use of statins in the year preceding the index hospitalization, in-hospital procedure performed, length of hospital stay, fiscal-calendar year, specialty of treating physician and type of hospital (teaching or rural).

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