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Research article

Sex differences in statin-associated adverse event reporting: a disproportionality analysis of 348,856 reports to the FDA Adverse Event Reporting System

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Abstract: Statin-associated muscle symptoms are among the most common reasons for statin discontinuation, and women are widely believed to be more susceptible. Whether this belief reflects a genuine excess of muscle injury in women, or an excess of muscle symptoms, has not been established at scale. Case/non-case disproportionality analysis of the FDA Adverse Event Reporting System (FAERS) via the openFDA database. All reports listing an HMG-CoA reductase inhibitor with a recorded patient sex were included. Comparisons were made within the statin cohort, holding drug exposure constant so that only sex varied. Reporting odds ratios (RORs) for women versus men were calculated for pre-specified muscle, renal and cardiovascular outcomes, with Benjamini-Hochberg control of the false discovery rate. 348,856 statin reports were analysed (180,392 from women, 168,464 from men). A severity gradient was evident within a single organ system. Women disproportionately reported subjective muscle complaints: pain in extremity (ROR 1.49, 95% CI 1.43-1.55) and muscle spasms (1.36, 1.30-1.43). Men disproportionately reported objectively verifiable injury: rhabdomyolysis (0.58, 0.55-0.61), death (0.61, 0.58-0.64), myocardial infarction (0.63, 0.60-0.66) and acute kidney injury (0.86, 0.83-0.90). Myalgia (0.99, 0.95-1.03) and muscular weakness (1.02, 0.97-1.08), which lie between these poles, showed no sex difference. Within statin reports, women predominantly report muscle symptoms and men predominantly report muscle destruction. The assumption that women experience more statin muscle toxicity conflates these phenomena. If confirmed in cohort data, a man reporting statin-associated muscle pain may warrant a lower threshold for creatine kinase measurement than a woman with identical symptoms.

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Introduction

Statins are among the most widely prescribed medicines in the world, and their benefit in both primary and secondary prevention of cardiovascular disease is established in men and women alike (Fulcher et al., 2015). Yet discontinuation remains common, and the single most frequently cited reason is muscle symptoms (Stroes et al., 2015). The clinical picture of statin-associated muscle symptoms spans a wide severity range. At one end sit subjective complaints of aching, cramping, and limb pain, which are common, rarely dangerous, and which placebo-controlled n-of-1 trials have shown are frequently not attributable to the drug itself (Herrett et al., 2021). At the other end sits rhabdomyolysis, a rare but life-threatening event defined by

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objective biochemical and clinical criteria, which may progress to acute kidney injury and death (Stroes et al., 2015). These two ends of the spectrum share an organ system, but little else, and conflating them has consequences for how clinicians respond to a patient who reports muscle pain.

It is widely held that women are more susceptible to statin-associated muscle toxicity. The belief has a plausible pharmacological basis: women achieve higher plasma concentrations than men for many drugs at equivalent doses, and sex differences in pharmacokinetics predict higher rates of adverse drug reactions in women across much of the pharmacopeia (Zucker and Prendergast, 2020). However, the evidence specific to statins has not clearly distinguished between an excess of muscle symptoms and an excess of muscle injury. These are different claims with different clinical implications, and the first does not imply the second.

Spontaneous adverse event reporting systems cannot establish incidence, but they are well suited to comparing the relative composition of reported events between groups (von Elm et al., 2007). We therefore asked a deliberately narrow question: among reports that all concern the same drug class, does the profile of reported events differ between women and men? Because exposure to the class is common to both arms, this design removes the prescribing-prevalence confounding that dominates naive comparisons of which drugs generate reports for which sex.

Material & Methods

Data source

The FDA Adverse Event Reporting System (FAERS) is a spontaneous reporting database containing adverse event and medication error reports submitted to the US Food and Drug Administration by manufacturers, health professionals and members of the public. We accessed FAERS through the public openFDA application programming interface. All analyses use the database, comprising 20,692,690 reports. No ethical approval was required. FAERS is a public, de-identified database and the analysis involved no contact with patients and no access to identifiable information.

Cohort definition

Statin reports were identified by the Established Pharmacologic Class term 'HMG-CoA Reductase Inhibitor' applied to any drug listed in the report, irrespective of whether that drug was coded as the primary suspect. Reports were included if a patient sex of male or female was recorded. Reports with missing or unknown sex were excluded from all comparisons.

Adverse events are coded in FAERS using Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms. We pre-specified eight Preferred Terms spanning the severity range of statin-associated muscle injury and its recognised sequelae: rhabdomyolysis, myalgia, muscular weakness, muscle spasms, pain in extremity, acute kidney injury, myocardial infarction and death.

Statistical analysis

The analysis is a case/non-case design conducted entirely within the statin cohort, so that drug exposure is held constant and sex is the exposure of interest. For each Preferred Term, a 2 x 2 table was constructed comparing the number of female reports containing that term against all other female statin reports, and the equivalent quantities for men. The reporting odds ratio (ROR) was calculated as the ratio of these odds, with 95% confidence intervals derived from the standard error of the log odds ratio (Benjamini and Hochberg, 1995; Rothman et al., 2004; van Puijenbroek et al., 2002). An ROR above 1 indicates that the term is reported disproportionately in women relative to men; an ROR below 1 indicates the reverse.

Because eight comparisons were made, the false discovery rate was controlled using the Benjamini-Hochberg procedure, and adjusted q values are reported alongside each estimate. Significance was assessed at $q < 0.05$. Comparisons of proportions between sexes used the chi-squared test with continuity correction, and binomial proportions are reported with Wilson score intervals.

To assess whether differences in who submitted reports could account for the findings, the distribution of reporter qualification and the proportion of reports flagged serious were compared between sexes within the statin cohort. Analyses were performed in Python 3 using SciPy.

Reporting

The study is reported in accordance with the STROBE statement for observational research (von Elm et al., 2007).

Results

Cohort

Of 20,692,690 reports in FAERS, 373,640 listed an HMG-CoA reductase inhibitor. Of these, 348,856 recorded a patient sex and formed the analysis cohort: 180,392 reports concerning women (51.7%) and 168,464 concerning men (48.3%). Reports concerning women were more often submitted by consumers (44.2% versus 37.6%) and less often by health professionals (53.9%, 95% CI 53.7-54.2, versus 60.9%; difference -7.0 percentage points, $p < 0.001$). Reports concerning men were more often flagged serious (75.6%, 95% CI 75.4-75.8) than those concerning women (68.7%, 68.5-68.9; $p < 0.001$). Cohort characteristics are given in **Table 1**.

Table 1. Characteristics of statin adverse event reports by patient sex.

Characteristic	Women (n = 180,392)	Men (n = 168,464)	p
Reports, n (% of cohort)	180,392 (51.7)	168,464 (48.3)	—
Reporter: consumer	74,332 (44.2)	59,061 (37.6)	< 0.001
Reporter: physician	41,644 (24.8)	43,170 (27.5)	
Reporter: other health professional	34,688 (20.6)	34,849 (22.2)	
Reporter: pharmacist	14,451 (8.6)	17,718 (11.3)	
Reporter: lawyer	3,170 (1.9)	2,317 (1.5)	
Any health professional	90,783 (53.9)	95,737 (60.9)	< 0.001
Report flagged serious	123,866 (68.7)	127,370 (75.6)	< 0.001

Percentages for reporter qualification are of reports with qualification recorded (168,285 women; 157,115 men). Comparisons by chi-squared test with continuity correction.

Sex differences in reported events

Reporting odds ratios for the eight pre-specified Preferred Terms are given in **Table 2**. Six of the eight comparisons were significant after control of the false discovery rate, and the pattern of those differences was ordered by severity rather than scattered across the outcome set. Two terms were reported disproportionately in women. Pain in extremity was reported in 6,202 female and 3,928 male reports (ROR 1.49, 95% CI 1.43-1.55; $q = 9.9 \times 10^{-84}$) and muscle spasms in 3,817 and 2,628 reports respectively (ROR 1.36, 1.30-1.43; $q = 6.9 \times 10^{-34}$). Both are subjective, patient-perceived complaints requiring no investigation to report.

Table 2. Reporting odds ratios for women versus men within statin reports.

MedDRA Preferred Term	Women, n	Men, n	ROR (95% CI)	q
Pain in extremity	6,202	3,928	1.49 (1.43–1.55)	9.9×10^{-84}
Muscle spasms	3,817	2,628	1.36 (1.30–1.43)	6.9×10^{-34}
Muscular weakness	2,936	2,686	1.02 (0.97–1.08)	0.51
Myalgia	5,846	5,508	0.99 (0.95–1.03)	0.64
Acute kidney injury	4,481	4,834	0.86 (0.83–0.90)	2.5×10^{-12}
Myocardial infarction	2,779	4,103	0.63 (0.60–0.66)	4.7×10^{-80}
Death	3,602	5,454	0.61 (0.58–0.64)	2.4×10^{-116}
Rhabdomyolysis	2,847	4,526	0.58 (0.55–0.61)	8.5×10^{-114}

ROR, reporting odds ratio. Values above 1 indicate disproportionate reporting in women; below 1, in men. Denominators are 180,392 female and 168,464 male statin reports. q values are Benjamini-Hochberg adjusted across the eight comparisons; significance at $q < 0.05$. Terms are ordered by ROR to show the severity gradient.

Four terms were reported disproportionately in men, and all four are objectively verifiable. Rhabdomyolysis appeared in 2,847 female and 4,526 male reports (ROR 0.58, 0.55-0.61; $q = 8.5 \times 10^{-114}$), corresponding to a 1.7-fold excess in men. Death was reported in 3,602 and 5,454 reports (ROR 0.61, 0.58-0.64), myocardial infarction in 2,779 and 4,103 (ROR 0.63, 0.60-0.66), and acute kidney injury in 4,481 and

4,834 (ROR 0.86, 0.83-0.90). Elevated blood creatine phosphokinase appeared in 1,932 male reports but did not reach the 100 most frequent terms among women, placing the female count below 1,534 and implying a male excess of at least 1.5-fold.

Two terms showed no sex difference. Myalgia was reported in 5,846 female and 5,508 male reports (ROR 0.99, 0.95-1.03; q = 0.64) and muscular weakness in 2,936 and 2,686 (ROR 1.02, 0.97-1.08; q = 0.51). These two terms occupy the middle of the severity range, between subjective limb discomfort and objectively documented muscle destruction.

Assessment of reporter channel as an explanation

Because reports concerning women were more often consumer-submitted, differential reporting channel is a candidate explanation for the observed gradient and was examined directly. The data do not support it. If consumer reporting were generating a female excess of subjective complaints, myalgia should be the most female-skewed term in the set: it is the archetypal patient-recognised statin complaint, requires no investigation, and is the symptom patients are explicitly warned about. Myalgia showed no sex difference whatever (ROR 0.99, 95% CI 0.95-1.03). Muscular weakness, equally subjective and equally accessible to a lay reporter, was likewise null. The female excess was confined to two specific somatic terms while two other subjective terms showed no difference at all, which is not the pattern a general reporting-channel artefact would produce.

The magnitude of the channel difference is also modest relative to the effects observed. A 7.0 percentage point difference in the proportion of health-professional reports is unlikely to generate 1.5- to 1.7-fold differences in opposite directions across the severity range.

Discussion

In 348,856 statin adverse event reports, the distribution of reported muscle events differed between women and men along a clear severity gradient. Women disproportionately reported limb pain and cramp; men disproportionately reported rhabdomyolysis, elevated creatine kinase, acute kidney injury, myocardial infarction and death. Between these poles, myalgia and muscular weakness were reported equally. This pattern reframes a common clinical belief (Olfson et al., 2015; Sakaeda et al., 2013). The proposition that women are more susceptible to statin muscle toxicity is not so much wrong as imprecise, because it collapses two distinct phenomena. On these data, women report more muscle symptoms and men report more muscle destruction. Those are different events with different prognoses and different management, and the distinction matters at the bedside.

The clinical implication follows directly. A clinician seeing a patient on a statin who reports muscle pain is performing a triage decision: is this a benign and probably non-attributable symptom, or the beginning of something dangerous? Our findings suggest that the prior probability of the latter differs by sex, and in the opposite direction to the conventional assumption. If these associations reflect real differences in underlying event rates, a lower threshold for measuring creatine kinase in men would be justified. We emphasise that this is a hypothesis generated by reporting data, not a validated decision rule.

Several mechanisms could contribute. Greater skeletal muscle mass in men yields higher baseline and peak creatine kinase, making biochemical thresholds easier to cross and rhabdomyolysis easier to document. Men are more often treated for secondary prevention and therefore receive higher-intensity regimens. Differences in renal function, concomitant medication and alcohol use may also contribute. Conversely, higher plasma statin concentrations in women at equivalent doses[4] would predict the opposite gradient to the one observed, which makes the finding harder to attribute to pharmacokinetics alone and more interesting as a result.

The symptom side of the gradient should be read alongside the n-of-1 trial evidence showing that most statin-attributed muscle symptoms are not caused by the statin (Herrett et al., 2021). A female excess of reported limb pain and cramp is therefore not, by itself, evidence of greater drug toxicity in women. It may instead reflect differences in symptom perception, attribution, or in the likelihood of a symptom being reported to a pharmacovigilance system at all.

Study limitations: The limitations of spontaneous reporting apply in full. FAERS has no denominator of exposed patients, so no incidence, risk or rate can be calculated, and a reporting odds ratio is a measure of

disproportionate reporting rather than of risk.[5,6] Reporting is voluntary, incomplete and subject to stimulation by publicity and litigation. Causality is not established for any individual report, and a drug listed in a report is not necessarily the cause of the event. Specific limitations apply here. We could not adjust for age, renal function, statin intensity, indication, or concomitant medication, any of which may differ by sex and confound the comparison; in particular, the higher prevalence of secondary prevention in men is a plausible partial explanation that these data cannot exclude. Reports were attributed to the class if any listed drug was a statin, irrespective of suspect status, which is conservative with respect to specificity. A formal sensitivity analysis restricted to clinician-submitted reports would have addressed reporter channel directly, and we were unable to perform it: the public openFDA interface rejects queries combining three simultaneous field restrictions, so sex, drug class, reporter qualification and reaction term cannot be cross-tabulated in a single query. The argument against reporter channel as an explanation given above is therefore inferential rather than empirical, and a replication using the downloadable quarterly FAERS files, which permit arbitrary stratification, would strengthen or refute it. Finally, the count of elevated creatine phosphokinase in women is bounded rather than exact, because the term fell outside the retrievable frequency range for that stratum.

Conclusions

Within a cohort of 348,856 statin adverse event reports, reported events were distributed along a severity gradient that differed by sex: women predominantly reported muscle symptoms and men predominantly reported muscle injury, with no sex difference at the midpoint of that range. The widely held view that women experience more statin muscle toxicity conflates symptom reporting with tissue damage. These findings are hypothesis-generating and require confirmation in cohort data with a defined denominator, but they suggest that a patient's sex presenting with statin-associated muscle pain should inform, rather than be absent from, the decision to investigate.

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