Incidence of Hospitalized Rhabdomyolysis in Patients Treated With Lipid-Lowering Drugs

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Context Lipid-lowering agents are widely prescribed in the United States. Reliable estimates of rhabdomyolysis risk with various lipid-lowering agents are not available.

Objective To estimate the incidence of rhabdomyolysis in patients treated with different statins and fibrates, alone and in combination, in the ambulatory setting.

Design, Setting, and Patients Drug-specific inception cohorts of statin and fibrate users were established using claims data from 11 managed care health plans across the United States. Patients with at least 180 days of prior health plan enrollment were entered into the cohorts between January 1, 1998, and June 30, 2001. Person-time was classified as monotherapy or combined statin-fibrate therapy.

Main Outcome Measure Incidence rates of rhabdomyolysis per 10000 person-years of treatment, number needed to treat, and relative risk of rhabdomyolysis.

Results In 252460 patients treated with lipid-lowering agents, 24 cases of hospitalized rhabdomyolysis occurred during treatment. Average incidence per 10000 person-years for monotherapy with atorvastatin, pravastatin, or simvastatin was 0.44 (95% confidence interval [CI], 0.20-0.84); for cerivastatin, 5.34 (95% CI, 1.46-13.68); and for fibrate, 2.82 (95% CI, 0.58-8.24). By comparison, the incidence during unexposed person-time was 0 (95% CI, 0-0.48; $P=.056$). The incidence increased to 5.98 (95% CI, 0.72-216.0) for combined therapy of atorvastatin, pravastatin, or simvastatin with a fibrate, and to 1035 (95% CI, 389-2117) for combined cerivastatin-fibrate use. Per year of therapy, the number needed to treat to observe 1 case of rhabdomyolysis was 22727 for statin monotherapy, 484 for older patients with diabetes mellitus who were treated with both a statin and fibrate, and ranged from 9.7 to 12.7 for patients who were treated with cerivastatin plus fibrate.

Conclusions Rhabdomyolysis risk was similar and low for monotherapy with atorvastatin, pravastatin, and simvastatin; combined statin-fibrate use increased risk, especially in older patients with diabetes mellitus. Cerivastatin combined with fibrate conferred a risk of approximately 1 in 10 treated patients per year.

JAMA. 2004;292:2585-2590 www.jama.com

DISORDERS OF MUSCLE, RANGing in severity from asymptomatic creatine kinase elevation to rhabdomyolysis, are among the most discussed adverse effects associated with use of lipid-lowering agents, especially 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins).[1-5] Fibric acid derivatives (fibrates) have also been associated with primary muscle injury, especially when used in combination with a statin.[6-11]

The epidemiology of statin-associated and fibrate-associated myopathy is poorly described, with most attention focused on rhabdomyolysis. Based on review of case reports, older age, female sex, low body mass index, hypothyroidism, diabetes mellitus, and impaired renal or hepatic function have been cited as potential risk factors for rhabdomyolysis,[10,11] but these have not been confirmed by clinical trials or observational studies. Myopathy, defined as a serum creatine kinase level of more than 10 times the upper limit of normal, has been estimated to occur in 0.1% to 0.5% of patients treated with statins during randomized controlled trials.[10] However, the incidence of rhabdomyolysis has not been reliably estimated. The product labeling for some statins presents incidence estimates for myopathy and rhabdomyolysis combined, although in labeling for other statins the occurrence of rhabdomyolysis is described as rare.[12,13] One epidemiologic study estimated the incidence of myopathy associated with lipid-lowering

See also pp 2622, 2643, 2647, 2655, and 2658.

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Financial Disclosure: Dr Andrade has performed consulting services and received grant support in the past from Merck, Pfizer, and Bristol-Myers Squibb, manufacturers of lipid-lowering drugs.
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drugs at 2.3 per 10 000 person-years of treatment and suggested that fibrate use as monotherapy conferred a 5.5-fold increased risk compared with statin use.[14] Another study reported 1 case of rhabdomyolysis among 2935 patients treated concurrently with a statin and fibrate.[15] Two separate analyses, based on case reports submitted to the US Food and Drug Administration, found that reporting of rhabdomyolysis was greater for simvastatin and cerivastatin than for other statins,[16] and that reporting of fatal rhabdomyolysis was 17- to 79-fold greater for cerivastatin than for other statins.[17]

Following the withdrawal of cerivastatin from the US market in August 2001 because of high reporting of rhabdomyolysis in association with its use,[18] we conducted this study to estimate the incidence of rhabdomyolysis in patients treated with statins and fibrates, alone and in combination, in the ambulatory setting.

METHODS

Inception cohorts of statin and fibrate users were established retrospectively from patients enrolled in 11 geographically dispersed US health plans, which included independent practice associations, staff, and group-model health maintenance organizations.[19,20] Each of these health plans provides pharmacy benefits to its enrollees and has automated claims files covering prescription drugs, outpatient medical encounters, hospitalizations, and medical procedures. Using prescription claims, a separate inception cohort was created for each statin (atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin) and fibrate (fenofibrate, gemfibrozil) marketed in the United States from January 1, 1998, through June 30, 2001. A patient was entered into an inception cohort if on the date of first prescription with an administered lipid-lowering drug during the study period, there had been no prescription for the same drug in the preceding 180 days. With drug switching, a patient could contribute exposure to more than 1 cohort.

Person-time on drug was estimated for each patient based on the days supply field from his/her prescription claims. To account for imperfect compliance, gaps of less than 30 days between the expected and actual fill-date of successive prescriptions were counted as exposed days as was the 30-day period following the end of a patient's final prescription within a given cohort. Person-time within each drug cohort was classified as either monotherapy or combined statin-fibrate therapy, to permit separate risk estimates to be obtained for each type of exposure.

To identify potential cases of rhabdomyolysis, medical records were sought and abstracted for selected hospitalizations of inception cohort members occurring during the study period. Hospitalization claims were used to flag the following discharge diagnoses possibly indicative of severe muscle injury: a primary or any secondary discharge diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] code) of myoglobinuria (791.3); a primary discharge diagnosis of other disorders of muscle, ligament, and fascia (728.89, includes rhabdomyolysis), myositis (729.1), myopathy (359.4, 359.8, 359.9), polymyositis (710.4), muscle weakness (728.9), musculoskeletal symptoms of the limbs (729.8X), or adverse effect from antihyperlipidemic agents (E942.2); any secondary discharge diagnosis for a muscle-related disorder (any of the previous diagnoses) plus a laboratory claim for serum creatine kinase measurement within 7 days before admission or after discharge; a primary discharge diagnosis of acute renal failure (584 and subcodes) plus any muscle-related secondary diagnosis; or any discharge diagnosis of acute renal failure plus a serum creatine kinase test within 7 days before admission or after discharge.

Information abstracted from each medical record included age, sex, symptom onset, hospital course, outcome, laboratory test results (urine myoglobin, and serum creatine kinase, potassium, alanine aminotransferase, aspartate aminotransferase, creatinine), and drug exposure history (if any). Past history of diabetes mellitus, liver disease, and renal failure was identified from automated claims data.

Medical record abstracts were reviewed by 3 authors (D.J.G., J.A.S., and L.L.G.) who were blinded to statin or fibrate exposure status. A patient was classified as having rhabdomyolysis if medical record review showed that severe muscle injury was present at the time of hospital admission and, in addition, the patient's physician had made a diagnosis of rhabdomyolysis or the patient's creatine kinase level was more than 10 times the upper limit of normal. Severe rhabdomyolysis was defined as the subset of these patients with serum creatine kinase exceeding 10 000 IU/L or with serum creatine kinase of more than 50 times the upper limit of normal.

Relative risk (RR) estimates of rhabdomyolysis adjusted for age, sex, and diabetes mellitus were calculated using Poisson regression. Incidence rates of rhabdomyolysis per 10 000 person-years of treatment with 95% confidence intervals (CIs) and number needed to treat to observe a case of rhabdomyolysis were calculated.[21] All analyses were performed using Stata version 7 (StataCorp, College Station, Tex). This study was approved by institutional review boards for the participating health plans.

RESULTS

A total of 252 460 patients contributed 225 640 person-years of monotherapy for a statin or fibrate and 7300 person-years of combined therapy (TABLE 1). The proportion of patients with diabetes mellitus was greater among fibrate users, consistent with the use of these agents to treat hypertriglyceridemia.[22] Because usage of fluvastatin and lovastatin was very low, these drugs were excluded from subsequent analyses.

Each of the statins included in this study were in use at the start of the study, with cerivastatin appearing during the first quarter of 1998 (FIGURE). Cerivastatin use increased slowly but did not achieve high-volume use within the health plans studied. Atorvastatin

Table 1. Description of Inception Cohorts for Patients Using Statin and Fibrate Drug Therapy

	Statins						Fibrates	
	Atorvastatin (n = 130 865)	Cerivastatin (n = 12 695)	Fluvastatin (n = 4706)	Lovastatin (n = 1207)	Pravastatin (n = 35 713)	Simvastatin (n = 46 799)	Gemfibrozil (n = 14 677)	Fenofibrate (n = 5808)
Person-years, No.								
Monotherapy	129367	7486	3292	775	33149	40940	8102	2529
Combined therapy	2664	89	25	10	543	552	2512	905
Patients using the agent, %								
Aged ≥65 y	24.7	33.9	49.1	49.5	26.5	30.7	21.3	18.2
Women	43.9	50.1	54.9	52.3	46.5	44.5	37.7	35.1
Diabetes mellitus	14.4	13.3	11.6	11.1	13.1	13.0	20.5	23.7
Liver disease	0.7	0.7	0.5	0.8	0.9	0.5	1.2	1.3
Renal disease	0.5	0.3	0.3	0.8	0.5	0.5	0.6	0.5
Rhabdomyolysis cases, No.								
Monotherapy	7	4	0	0	0	2	3	0
Combined therapy	1*	6†	0	0	0	1‡	4†‡	1*

*One patient was included in both the atorvastatin and fenofibrate combination therapy inception cohorts.
†Three patients were included in both the cerivastatin and gemfibrozil combination therapy inception cohorts.
‡One patient was included in both the simvastatin and gemfibrozil combination therapy inception cohorts.

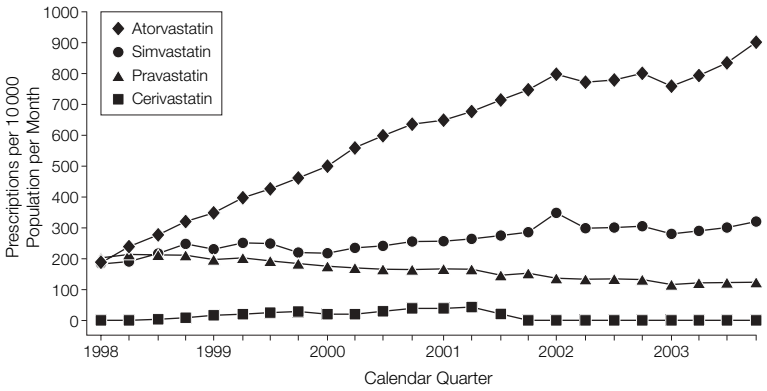
use increased steadily with a corresponding decline in pravastatin use through 2003.

Of 194 potential cases, hospital medical records were obtained for 174 patients (90%). In 139 records, the serum creatine kinase level was less than 10 times the upper limit of normal and there was no diagnosis of rhabdomyolysis in the chart. Acute myocardial infarction was responsible for creatine kinase elevations in 3 patients and 1 patient, admitted for elective surgery, developed rhabdomyolysis postoperatively. The remaining 31 patients met the case definition for incident rhabdomyolysis. Seven of these patients were excluded from analysis because their rhabdomyolysis event occurred during a period when, according to automated claims data, they were not exposed to a lipid-lowering drug and therefore were not contributing exposed time to an inception cohort. In each of these instances, however, the hospital record explicitly noted that the patient had been taking a statin at the time of the event (atorvastatin-1, cerivastatin-1, fluvastatin-1, pravastatin-3, simvastatin-1). Among these patients, 2 died, of whom 1 patient also underwent hemodialysis.

Within the inception cohorts, there were 16 cases of rhabdomyolysis with monotherapy (13 with a statin and 3 with gemfibrozil) and 8 cases with combined statin-fibrate therapy. The mean (SD) age of patients with rhabdomyolysis was 64.6 (2.7) years (TABLE 2). Twenty-three patients (94.4%) had symptoms of muscle pain or weakness preceding hospitalization, with a mean symptom duration of 6.9 days (range, 1-30 days) before admission. Eighteen patients (75%) had severe rhabdomyolysis. With monotherapy, cases occurred after a mean length of therapy of 348 days for atorvastatin or simvastatin (range, 21-1050 days), 56 days for cerivastatin (range, 21-106 days), and 77 days for gemfibrozil (range, 21-179 days). The mean time to onset after initiation of combined statin-fibrate therapy was 32 days (range, 18-78 days). Mean hospital length of stay was 5.7 days (range, 1-11 days), during which all patients were treated with hydration and 10 patients (41.6%) with diuretics. Two patients (8.3%) required hemodialysis, 1 of whom died. Five patients were taking thyroid hormone therapy and 1 had concurrent exposure to erythromycin. No patients were taking an azole antifungal agent or cyclosporine.

The incidence rates of rhabdomyolysis with monotherapy of atorvastatin, pravastatin, and simvastatin were statistically indistinguishable, with a summary point estimate of 0.44 per 10000 person-years of use (95% CI, 0.20-0.84) (TABLE 3). A sensitivity analysis including the 7 cases that occurred during time outside the inception cohorts yielded a summary estimate of 0.68 (95%

Figure. Monthly Rate of Prescription Dispensings for Atorvastatin, Cerivastatin, Pravastatin, and Simvastatin per 10000 Population by Calendar Quarter Within 11 Managed Care Health Plans



CI, 0.38-1.15) and the individual incidence rates remained indistinguishable. The incidence rates for cerivastatin and gemfibrozil as monotherapy were similar and both were more than those for the 3 other statins analyzed ($P=.002$ for cerivastatin and $P=.02$ for gemfibrozil). Although there were no cases with fenofibrate monotherapy, the 95% CI for its incidence rate completely bounded that for gemfibrozil monotherapy, which suggested comparability. The summary incidence rate per 10 000 person-years for the 2 fibrates (fenofibrate and gemfibrozil) combined was 2.82 (95% CI, 0.58-8.24). In comparison, there were no unexposed cases during 76 681 person-years of unexposed person-time within the inception cohorts, resulting in an incidence of 0 (95% CI, 0-0.48; $P=.056$). The number needed to treat for 1 year with monotherapy to observe 1 case of hospitalized rhabdomyolysis was 22 727 patients receiving atorvastatin, pravastatin, or simvastatin; 1873 patients receiving cerivastatin; and 3546 patients receiving a fibrate.

The incidence rates for rhabdomyolysis for monotherapy with atorvastatin, pravastatin, or simvastatin remained statistically indistinguishable over time. For therapy intervals of less than 6 months, 6 to 12 months, 13 to 24 months, and more than 24 months, the incidence of rhabdomyolysis per 10 000 person-years was 0.7 (95% CI, 0.3-1.6), 0.2 (95% CI, 0.01-1.2), 0.2 (95% CI, 0.01-1.1), and 0.6 (95% CI, 0.1-2.1), respectively. A similar pattern was observed with cerivastatin and fibrate monotherapy.

Incidence rates of rhabdomyolysis with combined statin-fibrate therapy were higher than those observed with monotherapy (Table 3). Based on the statin-fibrate combinations for which there were cases, the magnitude of the effect appeared to be similar regardless of the statin and fibrate involved, with the exception of cerivastatin. For the other statins, the composite incidence with combined use was 5.98 (95% CI, 0.72-216) per 10 000 patient-years, although inspection of individual cohorts suggested that the point-estimate was probably between 16.9 and 22.5 per 10 000 person-years. For combined cerivastatin-fibrate therapy, 2 separate estimates of the incidence rate of rhabdomyolysis, 1 obtained from the cerivastatin inception cohort and 1 from the gemfibrozil inception cohort, were similar, with point estimates ranging from 789 to 1035 per 10 000 person-years. The number needed to treat for 1 year with combined therapy involving atorvastatin, pravastatin, or simvastatin and fibrate was 1672 patients. With combined cerivastatin and gemfibrozil, the number needed to treat ranged from 9.7 to 12.7 patients.

All patients with rhabdomyolysis were taking statins at daily dosages within the dose-range recommended in product labeling (TABLE 4). For atorvastatin and simvastatin, 3 (27%) of 11 cases occurred at the 40-mg dose, half the recommended maximum dose. The remaining 8 cases (73%) occurred at even lower daily doses. For cerivastatin, 3 (30%) of 10 cases occurred at the maximum recommended dose of 0.8 mg, with the remaining 7 cases (70%) occurring at lower daily doses.

Hospitalized rhabdomyolysis with statin monotherapy was increased for patients aged 65 years or older (RR, 5.4; 95% CI, 1.3-21.6) and the point estimate of the RR was increased for patients with diabetes mellitus (2.9; 95% CI, 0.7-11.8). There was no increase in RR among women (0.9; 95% CI, 0.2-3.2). The RRs of rhabdomyolysis with fibrate or cerivastatin use, as monotherapy or combination therapy, were estimated using statin monotherapy (atorvastatin, pravastatin, and simvastatin) as the reference. With monotherapy, fibrate use was associated with a 5.5-fold increase (95% CI, 1.5-20.4) and cerivastatin with a 10.0-fold increase (95% CI, 3.1-32.7) in risk compared with statin use. Combined statin-fibrate use conferred a 12-fold increase in risk vs statin monotherapy (RR, 12.20; 95% CI, 2.59-57.44). The risk of hospitalized rhabdomyolysis for a patient aged 65 years or older with diabetes mellitus, treated with both a statin and fibrate was increased 48-fold (95% CI, 5.2-446.0), translating to a number needed to treat of 484 patients. The risk from

Table 2. Characteristics of Patients Hospitalized With Rhabdomyolysis While Taking Statins and Fibrates Alone or in Combination

	Patients With Rhabdomyolysis (N=24)
Age, mean (SD) [range], y	64.6 (2.7) [41-84]
Women, No. (%)	13 (54.2)
Duration of therapy, mean (SD) [range], d	160 (286) [18-1050]
Hospital stay, mean (SD) [range], d	5.7 (0.6) [1-11]
Muscle pain or weakness symptoms, No. (%)	23 (94.4)
Symptom duration before admission, mean (SD) [range], d	6.9 (1.9) [1-30]
Creatinine, mean (SD) [range], mg/dL	2.1 (2.1) [0.6-8.3]
Creatine kinase, mean (SD) [range], IU/L	49 721 (15 395) [2382-307 846]
Creatine kinase ratio, mean (SD) [range]*	274 (89) [15-1780]

SI conversion: To convert creatinine to µmol/L, multiply by 88.4.
*Creatine kinase ratio = [(creatine kinase)/(upper limit of normal)].

Table 3. Rhabdomyolysis per 10 000 Person-Years of Therapy With Lipid-Lowering Drugs Used as Monotherapy or as Combination Therapy With Another Drug

		Combination Therapy	
Drug	Monotherapy, Incidence Rates (95% CI)	Combination	Incidence Rates (95% CI)
Atorvastatin	0.54 (0.22-1.12)	Atorvastatin + fenofibrate	22.45 (0.57-125)
Cerivastatin	5.34 (1.46-13.68)	Cerivastatin + gemfibrozil	1035 (389-2117)
Pravastatin	0 (0-1.11)	No cases	0 (0-67.71)
Simvastatin	0.49 (0.06-1.76)	Simvastatin + gemfibrozil	18.73 (0.47-104)
Fenofibrate	0 (0-14.58)	Fenofibrate + atorvastatin	16.86 (0.43-93.60)
Gemfibrozil	3.70 (0.76-10.82)	Gemfibrozil + cerivastatin	789 (166-2138)

Abbreviation: CI, confidence interval.

Table 4. Daily Dose of Lipid-Lowering Drugs Taken by 24 Patients Hospitalized With Rhabdomyolysis During Therapy

	Atorvastatin (80 mg)*		Cerivastatin (0.8 mg)*		Simvastatin (80 mg)*		Gemfibrozil (1200 mg)*		Fenofibrate (200 mg)*	
Therapy	Dose, mg	No. of Patients	Dose, mg	No. of Patients	Dose, mg	No. of Patients	Dose, mg	No. of Patients	Dose, mg	No. of Patients
Monotherapy	10	2	0.3	1	20	1	1200	3		
	20	5	0.4	2	40	1				
			0.8	1						
Combined therapy	40	1	0.3	2	40	1	600	2	200	1
			0.4	2			1200	2		
			0.8	2						

*Maximum daily dose as described in product labeling.

combined cerivastatin-fibrate use was increased 1411-fold (95% CI, 496-4013).

COMMENT

Using population-based inception cohorts of patients treated with various statins and fibrates, the incidence rate of rhabdomyolysis was found to be similar for monotherapy with atorvastatin, pravastatin, and simvastatin, currently the 3 most widely prescribed statins in the United States.[17] Compared with statin monotherapy, fibrate use was associated with a 5.5-fold increase in risk and the combined use of a statin and fibrate increased risk by an additional 2-fold vs fibrate alone. The risk of rhabdomyolysis with cerivastatin monotherapy was 10-fold greater than with other statins, and in combination with a fibrate, was increased more than 1400-fold. With an estimated incidence of approximately 1000 per 10 000 person-years of use, rhabdomyolysis might have occurred in approximately 1 of every 10 patients treated with cerivastatin and fibrate for a year. The risk of rhabdomyolysis did not appear to diminish with longer-term use of statins or fibrates as monotherapy. Also, the occurrence of rhabdomyolysis in the absence of statin or fibrate therapy appears to be extremely rare.

In the only published population-based study to our knowledge of myopathy risk with lipid-lowering drugs, monotherapy with fibrates was associated with a 5.5-fold increased risk vs statin monotherapy, and fenofibrate carried the highest individual RR.[14] Our study was considerably larger, involving more than 10 times as many exposed patients, and focused on severe disease requiring hospitalization rather than including nonhospitalized events. In addition, the previous study included patients if their creatine kinase level was even minimally elevated above the upper limit of normal; whereas, in our study, creatine kinase levels for patients ranged from 15 to 1780 times the upper limit of normal.

Statin-associated rhabdomyolysis risk has been described as dose-dependent and concentration-dependent,[4,5] and much work has been performed to identify pharmacokinetic differences between statins in an effort to understand the mechanisms of their myotoxicity. All statins except pravastatin are metabolized within the liver by the cytochrome P450 system, with atorvastatin, cerivastatin, lovastatin, and simvastatin handled by the cytochrome P450 isoenzyme 3A4 (CYP 3A4).[1,23] Competitive inhibition of CYP 3A4 by drugs, such as ketoconazole, erythromycin, or cyclosporine, has been shown to block oxidation of these statins and increase their serum concentration, which in turn has been cited as an explanation for increased rhabdomyolysis risk.[5,23,24] Only 1 case-patient of 24 in our study was concurrently treated with 1 of these potent CYP 3A4 inhibitors. Pharmacokinetic complexity is further increased with the concurrent use of fibrates and statins.[25-30]

The above factors alone may not explain the RRs observed in our study. The magnitude of increase in statin serum concentration observed with combination use of gemfibrozil and a variety of statins only ranged from 2- to 5.5-fold.[25-30] In contrast, we found that the risk of rhabdomyolysis with combined statin-fibrate use was increased 12-fold vs with statin use alone. With cerivastatin, combination use conferred more than a 1400-fold increase in risk. The occurrence of rhabdomyolysis, as a pharmacodynamic response to combined use, appears to be disproportionate to any expected effect on statin serum concentration. This suggests that the mechanism underlying the occurrence of rhabdomyolysis could be nonlinear and possibly independent of pharmacokinetic interactions.

To our knowledge, this is the first comprehensive study of rhabdomyolysis incidence associated with statin and fibrate therapy. The use of inception cohorts permitted the identification and classification of incident person-time, both as monotherapy and combination therapy, and accounted for drug switching, which is common among statin users. We used a strict case definition that was validated by medical record review. In addition, the strategy for identifying cases was broad and inclusive, reducing the likelihood that cases were missed. These factors should contribute to reliable estimates of incidence rates and RRs for rhabdomyolysis.

There were also limitations in our study. The primary analysis was based on 24 case-patients, which could be viewed as too small for reliability. Although this may be a relatively low number of case-patients, it represents a large number for rhabdomyolysis. To compensate for the relative rarity of the outcome, we assembled large exposure cohorts and applied a rigorous case-finding strategy. For several drugs, the incidence rate estimates had wide 95%

CIs, reflecting the small number of events. Nonetheless, there was sufficient precision in the estimates to establish the similarity in rhabdomyolysis risk for atorvastatin, pravastatin, and simvastatin. Additionally, there was adequate statistical power to demonstrate the impact of combined statin-fibrate use, especially in higher risk patients such as those aged 65 years or older with diabetes mellitus. Seven cases of rhabdomyolysis were identified during what were thought to be periods of nonexposure to statins. Medical records indicated that all patients were taking a statin at the time of symptom onset, demonstrating that computerized prescription claims did not identify all statin use within the study population. Because of the high expense of prescription statin drugs, a common assumption made by researchers using health claims data has been that patients would not purchase prescription medications out-of-pocket if they could be paid for by insurance.[19,20] Possible explanations for this potential exposure misclassification include use of free product samples, dual–health insurance coverage by case-patients and their spouses, or use of products prescribed for others. A sensitivity analysis showed that inclusion of these cases in the primary analysis did not significantly alter the estimates of rhabdomyolysis risk and would not have altered the qualitative conclusions of our study.

We also encountered one instance in which the exposure status of a case-patient based on prescription claims was classified as fibrate monotherapy, but based on the hospital medical record, may have involved combination therapy with cerivastatin. Per study protocol, this patient was classified as fibrate monotherapy for analysis purposes because exposure classification of all study patients was based on the computerized prescription claims. Also, there was no way to identify similar episodes of unrecognized statin use among the several hundred thousand non–case patients for whom medical records were not reviewed. Additional research is needed to better define the nature and magnitude of rhabdomyolysis risk with fibrate monotherapy and to determine if risks with gemfibrozil and fenofibrate are similar or different.

With the potential for a substantial increase in the number of patients treated with statins over the next several years,[31] our study provides reassurance that the risk of rhabdomyolysis is relatively low with 3 frequently prescribed statins. For patients treated with both statins and fibrates combined, such as persons with diabetes mellitus with elevated cholesterol and triglyceride levels, the higher risk conferred by combination therapy may warrant that physicians instruct their patients to stop therapy and be evaluated if symptoms suggestive of rhabdomyolysis develop.

Author Contributions: Dr Graham had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition of data: Staffa, Shatin, Andrade, Schech, Gurwitz, Chan, Goodman.
Analysis and interpretation of data: Graham, Staffa, Shatin, Andrade, Schech, La Grenade.
Drafting of the manuscript: Graham.
Critical revision of the manuscript for important intellectual content: Graham, Staffa, Shatin, Andrade, Schech, La Grenade, Gurwitz, Chan, Goodman, Platt.
Statistical analysis: Graham, La Grenade, Chan.
Obtained funding: Staffa, Gurwitz.
Administrative, technical, or material support: Graham, Staffa, Shatin, Andrade, Schech, La Grenade, Gurwitz, Chan, Platt.
Study supervision: Staffa, Shatin, Andrade, Gurwitz.
Funding/Support: This study was supported by 2 cooperative agreements, FD-U-002067 (UnitedHealth Group) and FD-U-002068 (HMO consortium of Harvard-Pilgrim Healthplan, Fallon Community Health Plan, and Health Partners), from the US Food and Drug Administration.
Role of the Sponsor: The Food and Drug Administration (FDA) did not participate in the design and conduct of the study, in the collection, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript. Dr Graham and several coauthors are employees of the FDA but functioned as investigators without direction or interference by the FDA.
Acknowledgment: We thank Margaret J. Burgess for her programming assistance and technical support.

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