Discontinuation of Statins in Routine Care Settings

A Cohort Study

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Background: Systematic data on discontinuation of statins in routine practice of medicine are limited.

Objective: To investigate the reasons for statin discontinuation and the role of statin-related events (clinical events or symptoms believed to have been caused by statins) in routine care settings.

Design: A retrospective cohort study.

Setting: Practices affiliated with Brigham and Women's Hospital and Massachusetts General Hospital in Boston.

Patients: Adults who received a statin prescription between 1 January 2000 and 31 December 2008.

Measurements: Information on reasons for statin discontinuations was obtained from a combination of structured electronic medical record entries and analysis of electronic provider notes by validated software.

Results: Statins were discontinued at least temporarily for 57 292 of 107 835 patients. Statin-related events were documented for 18 778 (17.4%) patients. Of these, 11 124 had statins discontinued at least temporarily; 6579 were rechallenged with a statin over the subsequent 12 months. Most patients who were rechallenged (92.2%) were still taking a statin 12 months after the statin-related event. Among the 2721 patients who were rechallenged with the same statin to which they had a statin-related event, 1295 were receiving the same statin 12 months later, and 996 of them were receiving the same or a higher dose.

Limitations: Statin discontinuations and statin-related events were assessed in practices affiliated with 2 academic medical centers. Utilization of secondary data could have led to missing or misinterpreted data. Natural-language–processing tools used to compensate for the low (30%) proportion of reasons for statin discontinuation documented in structured electronic medical record fields are not perfectly accurate.

Conclusion: Statin-related events are commonly reported and often lead to statin discontinuation. However, most patients who are rechallenged can tolerate statins long-term. This suggests that many of the statin-related events may have other causes, are tolerable, or may be specific to individual statins rather than the entire drug class.

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Hypercholesterolemia is one of the most common chronic conditions and is strongly associated with cardiovascular disease, including cardiovascular death (1–3). 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) decrease mortality rates in patients with hypercholesterolemia (4–10) and are the most commonly used medications for treating hypercholesterolemia in the United States (11).

Despite their well-documented benefits, statins are commonly discontinued (12–15). Statin discontinuation has been linked to increased risk for cardiovascular events and death in patients with coronary artery disease (16–19). Nevertheless, the reasons for discontinuation are only starting to be explored (20–22). Adverse reactions to statins feature prominently in these reports. At the same time, in randomized, placebo-controlled clinical trials, statins are associated with only a slight increase in adverse reactions and no increase in discontinuation of treatment compared with placebo, with a total incidence of adverse reactions of approximately 5% to 10% (9, 23, 24). Whether this difference is real or reflects misattribution of the patients' symptoms is unknown. In particular, whether these symptoms are reproducible when rechallenged with a different or even the same statin is unclear. Hence, it is possible that statins may be discontinued inappropriately or unnecessarily, representing a major barrier to this potentially lifesaving therapy (13).

This lack of information reflects the challenges of studying epidemiology of reported adverse reactions to statins in routine care settings. Prominent among them is the fact that these adverse reactions are frequently documented only in narrative documents (25). To address this gap in knowledge, we used validated natural language–processing software (25) in an electronic medical record (EMR) system to analyze statin discontinuation in a large cohort of patients, with a particular focus on statin-related clinical events that may be interpreted as adverse reactions by patients or their clinicians.

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METHODS

Design

We conducted a retrospective cohort study to evaluate the reasons for statin discontinuation in routine care. We

also analyzed prevalence of statin-related events and long-term (>12 months) statin discontinuation after a statin-related event.

Study Cohort

Adult patients who had at least 1 statin prescription in an EMR at Brigham and Women's Hospital or Massachusetts General Hospital, both in Boston, Massachusetts, between 1 January 2000 and 31 December 2008, were studied. Patients without demographic information or no encounters during the study were excluded. We also excluded patients taking cerivastatin or clofibrate because there were too few to allow meaningful analytic conclusions.

For each patient, we defined study entry as the date of the first note or the date of the first statin prescription during the study. This study was approved by the institutional review board at Partners HealthCare System, an integrated health care delivery network in eastern Massachusetts, and the requirement for written informed consent was waived.

Study Measurements

An individual patient served as the unit of analysis. Information on statin-related events (clinical events or symptoms documented by health care providers as having been caused by a statin) was obtained from a combination of structured EMR data and computational processing of narrative electronic provider notes as previously described. The software uses a sophisticated language model of documentation of clinical events related to medications that includes more than 1200 rules. These rules recognize clinical events that are causally linked in the text to a set of specific medications (for example, atorvastatin) or classes (for example, statins). The software does not identify medication discontinuations or compare results based on text processing with drug-dispensing information within the EMR. Although the software can recognize documentation of clinical events related to any set of medications, it was specifically validated for statins against a set of 242 randomly selected electronic notes that were manually rated by 2 reviewers who were not involved in the design of the software. The reviewers' ratings were subsequently reconciled to create a "gold standard" rating with which the software output was then compared. The software achieved sensitivity of at least 86.5% and specificity of at least 91.9% for identifying documented statin-related events (25).

Only the first statin-related event during the study was considered for each patient to avoid intrapatient correlations. Statin discontinuations were identified by either an explicit discontinuation noted in the EMR or the absence of statin prescriptions for at least 12 months. Electronic medical records used in the study practices require a declaration of the reason for discontinuation when a medication is stopped (for example, "no longer necessary" or "adverse reaction"). Long-term statin discontinuation was defined as having no active statin prescription at 12 months after the statin-related event or absence of any statin prescriptions for at least 12 months after the statin-related event. Statin rechallenge was defined as any documentation of a statin being started after statin discontinuation during the 12 months after the statin-related event. Statin-related events were classified according to the Medical Dictionary for Regulatory Activities, terminology that the U.S. Food and Drug Administration requires pharmaceutical companies to use when reporting adverse events.

Patient age was calculated at study entry. The highest equivalent statin dose was defined as the maximum statin dose during the initial study phase divided by the dose of that particular statin that decreases low-density lipoprotein cholesterol levels by 30% to 40% (for example, 10 mg of atorvastatin, 80 mg of fluvastatin, 40 mg of lovastatin, 40 mg of pravastatin, 5 mg of rosuvastatin, and 20 mg of simvastatin) (4, 26, 27). Diagnoses of coronary artery disease and diabetes mellitus were established on the basis of the administrative data. To ensure specificity of the diagnosis, we defined rhabdomyolysis as a combination of EMR documentation of rhabdomyolysis plus creatine kinase (CK) elevation of at least 10 times the upper limit of normal (ULN). Likely allergic reaction was defined as one of the following statin-related events: angioedema, drug sensitivity, erythema multiforme, eye swelling, face edema, itching, lip swelling, mouth edema, pharyngeal edema, rash, swelling, swelling face, swollen tongue, urticaria, or wheezing.

Demographic information, medication, and laboratory data were obtained from the EMR at Partners HealthCare System, which includes Brigham and Women's Hospital and Massachusetts General Hospital. No changes were made to these systems over the 8 years of this study. The

Context

Statins are discontinued more often in clinical practice than in clinical trials, and the reasons are uncertain.

Contribution

In this large study of patients who took statins over 8 years, more than half of the patients discontinued their statin, at least temporarily. Approximately one fifth of these patients had a statin-related event that may have prompted discontinuation. One half of these patients restarted a statin, and more than 90% of them were taking a statin 1 year later.

Caution

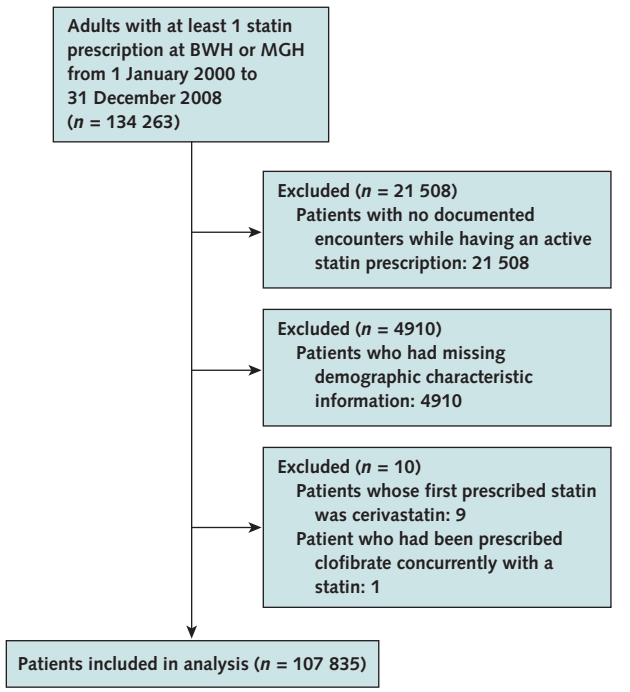
This study was limited to patients at 2 academic medical centers.

Implication

Many statin-related events are tolerable, are specific to individual statins, or have other causes.

—The Editors

Figure 1. **Study flow diagram.**



BWH = Brigham and Women's Hospital; MGH = Massachusetts General Hospital.

Partners HealthCare EMR contains all prescription and laboratory records starting in 2000 (and earlier for many patients).

Statistical Analysis

Summary statistics were calculated by using frequencies and proportions for categorical data and means (SDs), medians, and ranges for continuous variables.

All data were analyzed using SAS, version 9.2 (SAS Institute, Cary, North Carolina).

Role of the Funding Source

This study was funded by the National Library of Medicine, the Diabetes Action Research and Education Foundation, and the Chinese National Key Program of Clinical Science. The funding source had no role in the study design, conduct, or implementation; collection, analysis, or interpretation of data; drafting, revision, or approval of the manuscript; or decision to submit the manuscript for publication.

RESULTS

We identified 134 263 adults with at least 1 statin prescription at Brigham and Women's Hospital or Massachusetts General Hospital from 1 January 2000 to 31 December 2008. Of these, 107 835 were included in the study (**Figure 1**). Atorvastatin was the most common statin taken by the study patients, followed by simvastatin; 5% of patients were taking fibrates at the same time (**Table 1**); and 38.7% of patients had a history of coronary artery disease or diabetes.

Documented Reasons for Statin Discontinuation

More than one half of study patients (57 292 patients [53.1%]) had their statin discontinued at least once; 39 568 (69.1%) of them had a reason for discontinuation recorded in structured EMR data (**Table 2**). The default reason for discontinuation in our EMR ("no longer necessary") was the most common reason for patients with a statin-related event and second most common for patients without one. Adverse reaction was selected as the reason for discontinuation for 2233 patients. Other common reasons included decision-support prompts about duplicate medications in the same class (these commonly trigger when 1 statin is being switched to another) and insurance or financial reasons.

Statin-Related Events

Of all study patients, 18 778 (17.4%) had a statin-related event documented during the study. Of these, fewer than one third (30.0%) had documentation of a statin-related event in structured EMR data. Myalgia or myopathy was the most common category of statin-related events, affecting 27.0% of patients who had any statin-related event documented and 4.71% of all patients in the study. Other common statin-related events included other musculoskeletal and connective tissue disorders, general disorders, administration-site conditions, hepatobiliary disorders, unspecified drug intolerance, gastrointestinal disorders, and nervous system disorders (**Table 3**). Only 0.006% of patients had rhabdomyolysis. Memory problems were reported for 0.06% of study patients.

Statin Discontinuation After a Statin-Related Event

Among study patients who ever had a statin-related event documented, 11 124 (59.2%) had the statin discontinued at least temporarily (**Figure 2**). More than one half (6579 out of 11 124) of the patients who had the statin discontinued were rechallenged with a statin over the subsequent 12 months. More than 90% (6064 out of 6579) of the patients who were rechallenged were taking a statin 12 months after the original statin-related event. On average, patients were rechallenged with 1.2 unique statins over 12 months after the statin-related event. More than 40% (2721 out of 6579) were rechallenged with the same statin to which the statin-related event was documented. Nearly one half (1295 out of 2721) of these patients were taking the same statin 12 months after the statin-related event and more than one third (996 out of 2721) were taking the original statin at the same or a higher dose.

Among patients with no CK elevation greater than 3 times the ULN, 4854 (26.6%) discontinued all statins for at least 1 year after the statin-related event. In contrast, 150 (40.3%) patients with CK elevation between 3 and 10 times the ULN discontinued all statins for at least 1 year. More than 90% of these 150 patients (140 persons) dis-

continued statins long-term without rechallenge during the study. On the other hand, of the 122 patients who had CK elevation greater than 3 times the ULN and stopped the statin at least temporarily but were subsequently rechallenged, only 10 (8.2%) discontinued statins long-term. More than one fifth of 560 patients (23.4%) who had a possible allergic reaction discontinued the statin without rechallenge.

Among 3858 patients who had a statin-related event, had the original statin discontinued, and were then rechallenged with another statin, a second statin-related event was subsequently documented for 510 (13.2%) persons. Only 381 (9.9%) of these patients had myalgia or myopathy that was severe enough to warrant discontinuation of the rechallenge statin, and none had rhabdomyolysis.

Among 8698 study patients who had documentation of a statin-related event and subsequently had the statin discontinued on a specific date (the other 2426 patients did not have any statin prescriptions for more than 12 months, implying a discontinuation), 5572 (64.1%) did not have any other medications discontinued on the same date. The mean number of nonstatin medications discontinued on the same date for this patient group was 0.79. This finding is consistent with most statin discontinuations being due to the statin-related events rather than, for example, general illness prompting discontinuation of several medications.

Statin Discontinuation in Patients Without a Statin-Related Event

Of 46 168 patients without a statin-related event who discontinued a statin during the study, nearly two thirds (30 412 patients [65.9%]) had another statin prescription over the subsequent 12 months (**Figure 3**). Most of these (21 671 patients) were for a different statin. Overall, more than 98% of patients without a statin-related event who had a statin discontinued and then restarted were still receiving a statin 12 months later.

DISCUSSION

Consistent with previously published studies, we found that statins are commonly discontinued in routine care settings (nearly 1 in 5 patients in our cohort stopped all statins for at least 12 months). Temporary discontinuations were even more common, although many (particularly those for which "therapeutic duplication warning"

Table 1. **Patient Characteristics***

Variable	All Patients Studied	Patients With No Statin-Related Events	Patients With Statin-Related Event and No Discontinuation	Patients With Statin-Related Event and Discontinuation
Total, *n*	107 835	89 057	7654	11 124
Mean age (SD), *y*	61.1 (13.1)	61.2 (13.3)	61.2 (12.2)	60.8 (12.4)
Female sex, *n (%)*	53 911 (50.0)	43 175 (48.5)	4270 (55.8)	6466 (58.1)
Race or ethnicity, *n (%)*				
White	79 336 (73.6)	65 157 (73.2)	5803 (75.8)	8376 (75.3)
African American	5127 (4.8)	3991 (4.5)	460 (6.0)	676 (6.1)
Hispanic	5718 (5.3)	4783 (5.4)	383 (5.0)	552 (5.0)
Asian	1825 (1.7)	1528 (1.7)	126 (1.7)	171 (1.5)
Other†	15 829 (14.7)	13 598 (15.3)	882 (11.5)	1349 (12.1)
Health insurance, *n (%)*				
Government	54 021 (50.1)	44 358 (49.8)	4005 (52.3)	5658 (50.9)
Nongovernment	53 814 (49.9)	44 699 (50.2)	3649 (47.7)	5466 (49.1)
Median annual income (SD), *$*	55 000 (22 400)	55 000 (22 500)	55 000 (22 700)	55 000 (22 000)
History of CAD, *%*	21 637 (20.1)	18 182 (20.4)	1463 (19.1)	1992 (17.9)
History of DM, *%*	28 445 (26.4)	24 392 (27.4)	1612 (21.1)	2441 (21.9)
Concomitant fibrate use, *n (%)*				
Fenofibrate	2806 (2.6)	2294 (2.6)	209 (2.7)	303 (2.7)
Gemfibrozil	2630 (2.4)	2081 (2.3)	211 (2.8)	338 (3.0)
None	102 399 (95.0)	84 682 (95.1)	7234 (94.5)	10 483 (94.3)
First statin prescribed during study, *n (%)*				
Atorvastatin	55 895 (51.8)	46 464 (52.2)	3860 (50.4)	5571 (50.1)
Fluvastatin	1430 (1.3)	1010 (1.1)	164 (2.1)	256 (2.3)
Lovastatin	3979 (3.7)	3296 (3.7)	285 (3.7)	398 (3.6)
Pravastatin	6813 (6.3)	4842 (5.4)	862 (11.3)	1109 (10.0)
Rosuvastatin	4155 (3.9)	3016 (3.4)	463 (6.0)	676 (6.1)
Simvastatin	35 563 (33.0)	30 429 (34.2)	2020 (26.4)	3114 (28.0)
Mean highest relative equivalent statin dose (SD)‡	2.1 (1.8)	2.1 (1.8)	2.3 (2.0)	2.1 (1.9)
Patients with highest relative equivalent statin dose unavailable, *n (%)*	177 (0.2)	162 (0.2)	10 (0.1)	5 (0.1)

CAD = coronary artery disease; DM = diabetes mellitus.
* Percentages may not sum to 100 due to rounding.
† Includes unknown.
‡ Defined as the maximum statin dose during the initial study phase divided by the dose of that particular statin that decreases low-density lipoprotein cholesterol levels by 30% to 40% (e.g., 10 mg of atorvastatin, 80 mg of fluvastatin, 40 mg of lovastatin, 40 mg of pravastatin, 5 mg of rosuvastatin, and 20 mg of simvastatin) (4, 26, 27).

Table 2. **Reasons for Statin Discontinuation**

Reason for Discontinuation	Patients With a Statin-Related Event, *n/N (%)*	Patients Without a Statin-Related Event, *n/N (%)*
Discontinued explicitly*	8698/18 778 (46.3)	30 870/89 057 (34.7)
No longer necessary†	2452/18 778 (13.1)	6942/89 057 (7.8)
Ineffective	208/18 778 (1.1)	878/89 057 (1.0)
Adverse reaction	2233/18 778 (11.9)	0/89 057 (0)
Rejected by patient	627/18 778 (3.3)	1127/89 057 (1.3)
Too expensive	137/18 778 (0.7)	2413/89 057 (2.7)
Change requested by insurance	325/18 778 (1.7)	4863/89 057 (5.5)
Erroneous entry	59/18 778 (0.3)	477/89 057 (5.4)
Inadequately covered by insurance	79/18 778 (0.4)	1333/89 057 (1.5)
Other	2578/18 778 (13.7)	12 837/89 057 (14.4)
Therapeutic duplication warning‡	1407/18 778 (7.5)	9443/89 057 (10.6)
Switch to another drug	74/18 778 (0.4)	1041/89 057 (1.2)
No prescription for 1 y§	2426/18 778 (12.9)	15 298/89 057 (17.2)
Total	11 124/18 778 (59.2)	46 168/89 057 (51.8)

* Patients for whom the reason for discontinuation was explicitly recorded in the electronic medical record.
† Default reason for medication discontinuation in the electronic medical record used at the study sites.
‡ Discontinuation as a result of a decision-support prompt that alerts the user that the patient is already taking a medication in the same class as the one being added to the medication list. The user is then prompted to discontinue either the new or old medication.
§ Patients who did not have a statin prescription for at least 1 y were assumed to have had the statin discontinued.

was given as the reason) represented a change to a different statin rather than complete discontinuation of statin therapy.

Reasons for discontinuations could not always be directly ascertained. Although the EMR used by the study practices prompts providers to declare a specific reason when a medication is discontinued, the default reason of "no longer necessary" is frequently chosen regardless of the actual reason. In addition, for many patients, discontinuations were inferred from the absence of prescriptions for at least 12 months without an explicit declaration of the reason.

Discontinuations, and particularly long-term discontinuations, were more common among patients who had documented statin-related events, corroborating the findings of patient surveys (20–22). Although the causative link between the statin-related event and discontinuation could not always be directly established, many discontinuations that did not have "adverse reaction" declared as the reason could have been due to statin-related events. These include the default reason "no longer necessary," free-text "other" entries, changes to a different statin, and discontinuations without a stated reason. Overall, as many as 87% of statin discontinuations among patients with documented statin-related events could have been due to these events.

The rate of reported statin-related events to statins was nearly 18%, substantially higher than the 5% to 10% rate usually described in randomized, placebo-controlled, clinical trials (24). This finding is consistent with previously published observational studies (28–31). Similar to both clinical trials and observational studies (23, 32), musculoskeletal symptoms were predominant, accounting for 40% of statin-related events. Overt rhabdomyolysis was found in only 0.006% of the study patients, also consistent with previous reports that statin-induced myopathy is rare (33). On the other hand, memory loss, highlighted in the recent U.S. Food and Drug Administration changes to the statin labels, was reported by only 0.06% of the study patients.

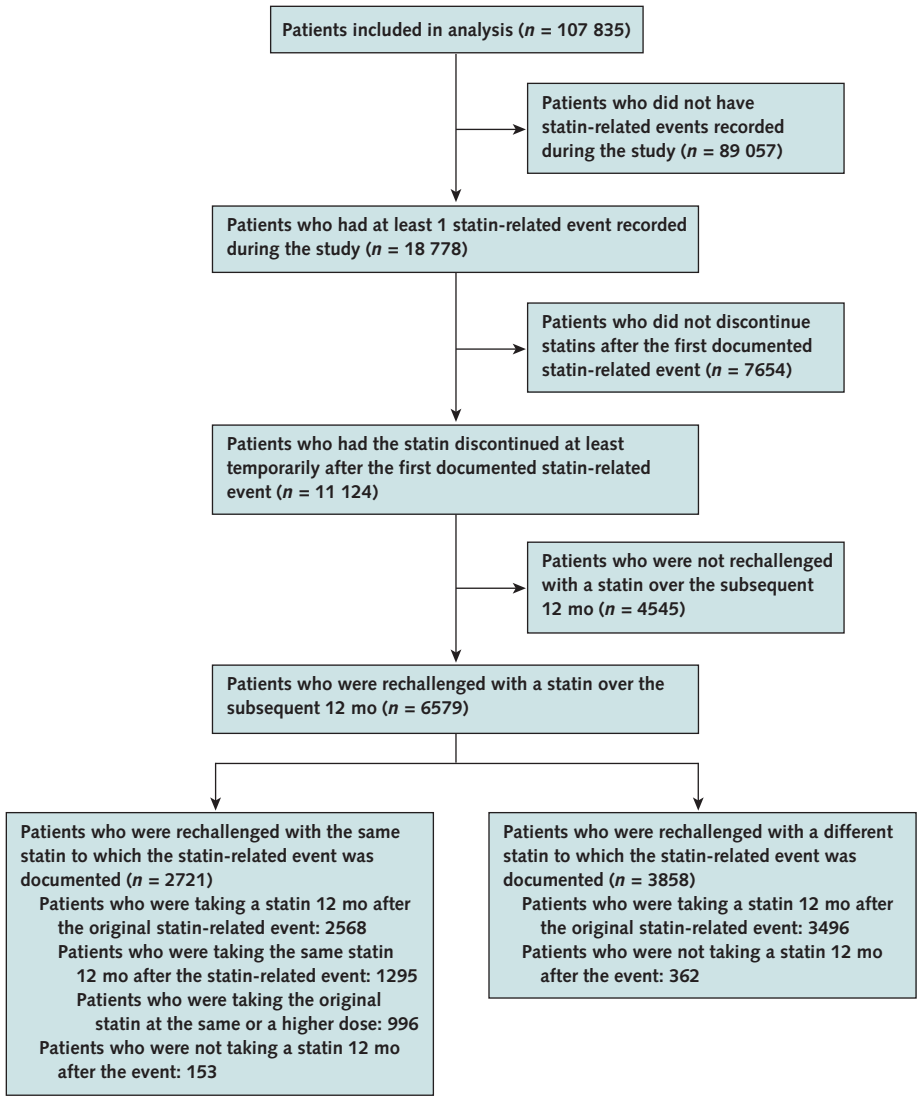
The discrepancy between clinical trials and observations of routine care has been attributed to many factors, including patient selection in randomized trials, which may exclude older participants, enroll insufficient numbers of women, or have a selection bias based on persons willing to participate (31). Patients who have multiple comorbid conditions, take other medications that may affect the metabolism of statins, have adverse effects during the run-in phase, have a history of statin-related adverse events, or are

Table 3. **Frequencies of Statin-Related Events Among Study Patients***

Statin-Related Event Category	Patients, *n (%)*
Myalgia or myopathy	5075 (4.71)
Rhabdomyolysis	7 (0.006)
CK elevation 3–10 times the ULN	992 (0.92)
Musculoskeletal and connective tissue disorders other than myalgia or myopathy	2742 (2.54)
Muscle spasms	882 (0.82)
Pain in extremity	537 (0.50)
Arthralgia	356 (0.33)
Other	967 (0.90)
General disorders and administration site conditions	2493 (2.31)
Pain	1222 (1.11)
Fatigue	313 (0.29)
Asthenia	208 (0.19)
Other	750 (0.70)
Hepatobiliary disorders	2308 (2.1)
Drug intolerant	1827 (1.7)
Gastrointestinal disorders	1681 (1.6)
Nervous system disorders	564 (0.52)
Memory problems	70 (0.06)
Immune system disorders	399 (0.37)
Vascular disorders	399 (0.37)
Psychiatric disorders	333 (0.3)
Unknown	246 (0.23)
Cardiac disorders	133 (0.12)
Injury, poisoning, and procedural complications	112 (0.10)
Skin and subcutaneous tissue disorders	107 (0.10)
Reproductive system and breast disorders	99 (0.09)
Respiratory, thoracic, and mediastinal disorders	82 (0.08)
Drug ineffective	50 (0.05)
Ear and labyrinth disorders	35 (0.03)
Blood and lymphatic system disorders	34 (0.03)
Renal and urinary disorders	23 (0.02)
Eye disorders	20 (0.02)
Metabolism and nutrition disorders	16 (0.01)

CK = creatine kinase; ULN = upper limit of normal.
* Number of patients with statin-related events among 107 835 patients included in the study. Statin-related events were classified according to the Medical Dictionary for Regulatory Activities.

Figure 2. **Statin discontinuation by patients with statin-related events.**

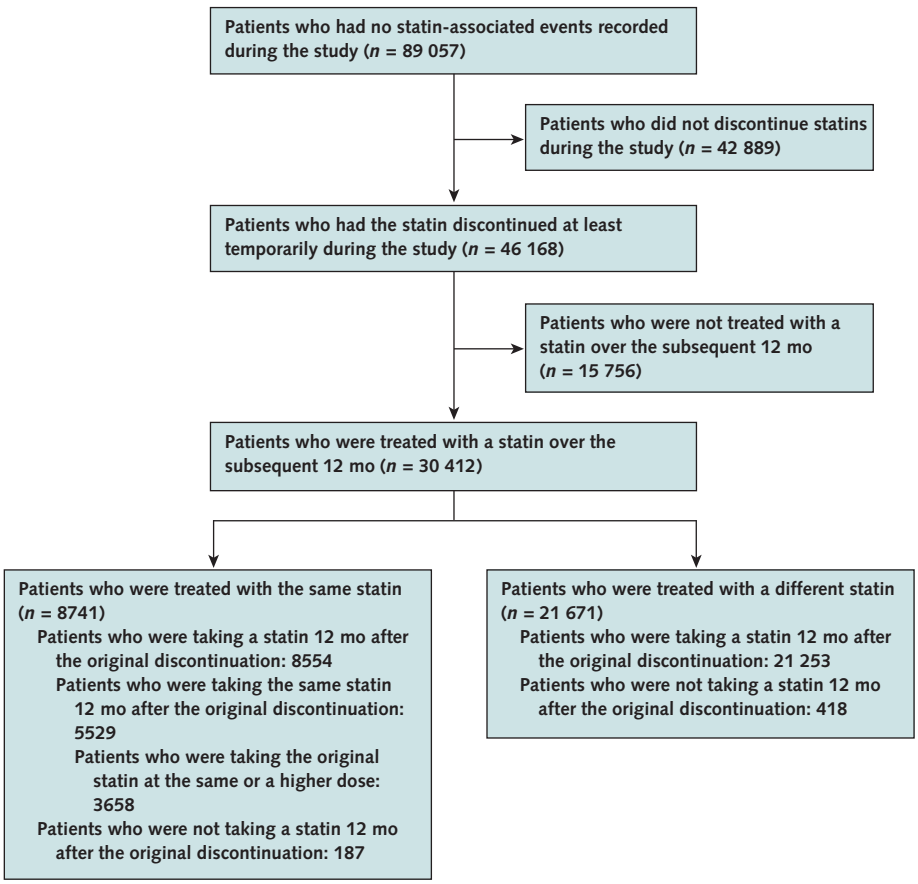


considered to be at high risk for such events are also generally excluded (31). In clinical practice, however, such patients may be prescribed statins. Finally, some of the statin-related events reported by the patients may not be due to statins, as evidenced by the high rates of adverse reactions reported in the placebo group in clinical trials (24).

We found that most patients (more than 90%) who were rechallenged with a statin after a statin-related event could ultimately tolerate one. Few of the rechallenged patients had another statin-related event, and serious reactions, such as rhabdomyolysis, were rare. Patients who were rechallenged were not selected at random and were less likely to have CK elevations. However, among the few patients who had documented CK elevations and were rechallenged with a statin, most could continue statin therapy long-term. Our results, therefore, support the hypothesis that many statin-related events reported in observational studies may not be caused by these medications, whereas other events may either be mild enough to be tolerable or not be reproducible with other statins.

Discontinuation of statins, particularly in high-risk patients, is associated with increased risk for cardiovascular events and may even affect overall mortality (27, 34). Therefore, guidelines generally advocate a conservative approach to stopping statin therapy. Discontinuation due to tolerable myalgia not accompanied by more than 10-fold CK elevations is not recommended, and in the event that the statin is discontinued, most guidelines suggest rechallenging with the same or a different statin (35, 36). Our

Figure 3. **Statin discontinuation by patients with no statin-related events.**



findings support the guidelines. In keeping with previously published studies in much smaller cohorts (37–43), we found that many patients who were rechallenged after a statin-related event could tolerate a statin long-term and that mild CK elevations were not predictive of long-term statin tolerance.

It is unlikely that a randomized clinical trial would or could be designed to include all patients who will be prescribed statins in routine clinical settings. This large study of statin-related events in routine care settings was made possible by a combination of 2 technologies, EMRs (44) and computational analysis of electronic text (natural language processing) (45, 46). We have previously shown that many statin-related events are documented only in narrative provider notes (25). In our study, only 30.0% of patients with a statin-related event had the event recorded in a structured format. To overcome this barrier, we used a specially designed tool capable of processing up to 40 notes per second, enabling analysis of millions of documents. In the future, similar technologies could be used for both retrospective and prospective monitoring for adverse drug reactions.

Our study had several limitations. Our analysis was retrospective in nature and, therefore, could establish only associations rather than causal relationships. Our study population included patients from 2 primarily academic hospitals in eastern Massachusetts, so the results may not be generalizable to patients in other settings. Data used in the study were collected during routine care and are, therefore, not systematic. The exact nature of statin-related events could not always be identified if documentation was incomplete. Many patients did not have laboratory data available, which may have led to underestimation of the frequency of some statin-related events. Accuracy of the natural language processing algorithm, although high, was not perfect; if the errors of the algorithm were distributed unequally with respect to the predictor or outcome variables, it could have biased the results of our analysis. We analyzed only the first reported statin-related event to avoid intrapatient correlations, but this may not represent all of the statin-related events the patients may have had. Further studies are needed to confirm these findings in a prospective manner and extend them to other medication classes.

Our findings indicate that patients who had statin-related clinical events may frequently be able to tolerate statins in the long-term. Permanent cessation of statin therapy under these circumstances could lead to many preventable cardiovascular events and deaths. Providers should consider rechallenging patients who report statin-related events to identify those who can continue taking them.

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