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Continued Statin Prescriptions After Adverse Reactions and Patient Outcomes

A Cohort Study

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Background: Many patients discontinue statin treatment, often after having a possible adverse reaction. The risks and benefits of continued statin therapy after an adverse reaction are not known.

Objective: To examine the relationship between continuation of statin therapy (any prescription within 12 months after an adverse reaction) and clinical outcomes.

Design: Retrospective cohort study.

Setting: Primary care practices affiliated with 2 academic medical centers.

Participants: Patients with a presumed adverse reaction to a statin between 2000 and 2011.

Measurements: Information on adverse reactions to statins was obtained from structured electronic medical record data or natural-language processing of narrative provider notes. The primary composite outcome was time to a cardiovascular event (myocardial infarction or stroke) or death.

Results: Most (81%) of the adverse reactions to statins were identified from the text of electronic provider notes. Among 28 266 study patients, 19 989 (70.7%) continued receiving statin prescriptions after the adverse reaction. Four years after the presumed adverse event, the cumulative incidence of the composite primary outcome was 12.2% for patients with continued statin prescriptions, compared with 13.9% for those without them (difference, 1.7% [95% CI, 0.8% to 2.7%]; $P < 0.001$). In a secondary analysis of 7604 patients for whom a different statin was prescribed after the adverse reaction, 2014 (26.5%) had a documented adverse reaction to the second statin, but 1696 (84.2%) of those patients continued receiving statin prescriptions.

Limitations: The risk for recurrent adverse reactions to statins could not be established for the entire sample. It was also not possible to determine whether patients actually took the statins.

Conclusion: Continued statin prescriptions after an adverse reaction were associated with a lower incidence of death and cardiovascular events.

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Statins have established beneficial effects on reducing mortality and cardiovascular events in patients at high cardiovascular risk (1–3). Although recent guidelines strongly recommend statin use for secondary prevention and widely advocate it for primary prevention of cardiovascular disease (4), statin therapy is commonly discontinued (5, 6). Studies reveal that 25% to 50% of patients stop taking statins within 6 months to a year after the initial prescription, and after 2 years, the discontinuation rate is as high as 75% (6–10). Discontinuation has been linked to increased risk for cardiovascular events and death (6, 11–13). Adverse reactions, such as myalgia and gastrointestinal or neurologic symptoms, may be important contributors to discontinuation of statin therapy (14–16).

Previous studies suggest that many reported adverse reactions are not actually caused by statins and that most patients rechallenged with statins after an adverse reaction can tolerate these drugs long term (5, 17, 18). However, many patients do not reattempt statin therapy and remain without treatment for prolonged periods, if not indefinitely (5). Furthermore, statin therapy frequently is restarted at a lower dosage after an adverse reaction, and the dosage may not be increased. Patients also may be less adherent to therapy, fearing recurrence of the adverse reaction (17, 19). Consequently, uncertainty exists regarding whether continued statin therapy after an adverse reaction is as beneficial as statin treatment in patients who tolerate these medications well. Improving our understanding of the benefits and risks of continuing statin treatment after an initial adverse reaction is critical to helping patients and their clinicians make informed decisions regarding statin management.

Data are lacking on this topic, likely because adverse reactions frequently are recorded only in narrative documents (20). We used validated natural-language processing software (20) in an electronic medical record (EMR) as a unique tool that allowed us to test the hypothesis that patients who continue statin therapy after a reported adverse reaction can do so safely and with a lower risk for future cardiovascular events and death.

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METHODS

Design

We conducted a retrospective cohort study to investigate the relationship between continued statin prescriptions during a 12-month period after a presumed adverse reaction to a statin and subsequent cardiovascular events (myocardial infarction [MI] and stroke) or death from any cause.

Study Cohort

Study participants included adults (aged 18 years and older) who were receiving statin prescriptions and being seen by primary care providers affiliated with Brigham and Women's Hospital or Massachusetts General Hospital between 2000 and 2011. Participants had to have had an adverse reaction that was presumed to have been caused by a statin and documented by a provider (of any specialty) in the EMR between 1 January 2000 and 31 December 2011 (sample identification period; see **Supplement Figure 1**, available at Annals .org). The index date was defined as the date of the first documented adverse reaction to a statin.

Information on presumed adverse reactions to statins was obtained from a combination of structured EMR data and computational analysis of narrative electronic provider notes by using natural-language processing software. The software was specifically validated for identification of adverse reactions to statins, achieving a sensitivity of at least 86.5% and a positive predictive value of at least 91.9% in chart reviews (20). Determining whether the statin actually caused the reported adverse reaction was not possible, and the literature suggests that not all symptoms believed to be the result of statins are actually caused by them (5, 17, 18, 21). Thus, we use the term *presumed adverse reactions* to describe the statin-related adverse events documented in the EMR. Presumed adverse reactions were classified according to the Medical Dictionary for Regulatory Activities (MedDRA). Patients were excluded if they had a previous adverse reaction to a statin, had missing demographic information, or were not followed before the first documentation of an adverse reaction (potentially leading to missing baseline data).

Whether statin prescriptions were continued was determined during the 12 months after the adverse reaction (treatment assessment period); patients were excluded if they were not followed in a primary care practice for this entire period. Continuation of statin prescriptions was ascertained before the follow-up period began (for outcome assessment). Patients were followed until the end of a 12-month period beginning after the last primary care note, an outcome event, or the end of the study period (31 December 2013), whichever occurred first. This study was approved by the institutional review board at the Partners HealthCare System with a waiver of written informed consent.

Study Measurements

Demographic, medication, and laboratory data were obtained from the EMR at Partners HealthCare System, an integrated health care delivery network in eastern Massachusetts that includes Brigham and Women's Hospital and Massachusetts General Hospital (for details, see the **Supplement**, available at Annals .org). No changes pertinent to the subject of this study were made to the EMR during the study period. Patients were categorized as continuing to receive statin prescriptions if they received another prescription for any statin during the treatment assessment period. Patients who did not receive statin prescriptions after the adverse reaction served as the comparison group.

Patient age was calculated at the index date. Diagnoses of coronary artery disease (CAD), MI, stroke, or diabetes mellitus (DM); family history of CAD and stroke; and smoking status were obtained from the EMR data before the index date. Highest low-density lipoprotein cholesterol (LDL-C) level was defined as the highest level recorded before the study exit. Estimated glomerular filtration rate (eGFR) was calculated by using the Modification of Diet in Renal Disease formula (22). Baseline body mass index (BMI), blood pressure, and eGFR were calculated as the average value in the 12 months before the index date because of the relatively high volatility of these measures. Charlson comorbidity index (CCI) score was calculated at the index date. Coronary artery disease, stroke, diabetes, and chronic kidney disease were excluded from the CCI calculation because they were already included in the analysis as individual variables. Patients were categorized as having been evaluated by a cardiologist if they had at least 1 note in a cardiology clinic within the Partners HealthCare System during the 12 months after the presumed adverse reaction to a statin.

The composite primary outcome was time to the first of the following events: MI, stroke, or death from any cause. Time to death from any cause and time to the first cardiovascular event (MI or stroke) served as secondary outcomes. Date of death was identified by using the Social Security Administration's Death Master File. Cardiovascular events were ascertained from administrative data by using International Classification of Diseases, Ninth Revision, codes. Time to all outcomes was calculated starting at 12 months after the presumed adverse reaction.

Statistical Analysis

An individual patient served as the unit of analysis. Summary statistics were calculated by using frequencies and proportions for categorical data and means (SDs), medians, and ranges for continuous variables. Baseline characteristics of patients with and without continued statin prescriptions were compared by using *t* and chi-square tests. Cox multivariable proportional hazards models were constructed to estimate the association between continued statin prescriptions and patient outcomes. The models were stratified by age (<50, 50 to 59, 60 to 69, 70 to 79, 80 to 89, and >90 years) and included patient demographics (sex, race, median income by ZIP code, marriage, health insurance, and primary language); smoking status; CCI score; history of CAD, stroke, and DM; family history of CAD and stroke; evaluation by a cardiologist; baseline

systolic and diastolic blood pressure and BMI; maximum LDL-C level; and log(eGFR) as covariates. The proportional hazards assumption was evaluated by using the cumulative martingale residual approach (23). Competing risk analysis also was used to evaluate time to the first cardiovascular event (24). Both comparisons of baseline patient characteristics and Cox multivariable analyses were adjusted for multiple testing by using the Simes–Hochberg method (25, 26).

Inverse probability weighting (27–29) was used to construct adjusted Kaplan–Meier plots that were compared by using weighted log-rank tests. Inverse probability–weighted Kaplan–Meier estimates are presented at 4 years as adjusted cumulative incidence. The inverse probability weighting approach adjusts for imbalance due to measured confounders by weighting patients in each treatment group (continued vs. discontinued statin prescriptions) so that the weighted sample for each group represents the entire patient sample. The probability of treatment group assignment was estimated by using a propensity score approach (for details, see the **Supplement** and **Supplement Table 1**, available at Annals.org) (30). Multiple imputation was used to account for missing data (baseline systolic and diastolic blood pressure, BMI, maximum LDL-C level, and eGFR) in the Cox proportional hazards models and the propensity score estimation (31).

We conducted sensitivity analyses to assess whether patients' cardiovascular risk, intensity of statin therapy, length of treatment assessment period, or change of statin after the adverse reaction affected the relationship between continued statin prescriptions and the primary outcome (for details, see the **Supplement**). We also conducted a sensitivity analysis to quantify the strength of the association of a hypothetical unmeasured binary confounder that would be required to eliminate a statistically significant association (32). All data were analyzed by using SAS, version 9.4 (SAS Institute), and R, version 3.11 (R Foundation for Statistical Computing) (sensitivity analysis for unmeasured confounding).

Role of the Funding Source

The funding sources had no role in the design, data collection, analysis, interpretation, implementation, or conduct of the study; the drafting, revision, or approval of the manuscript; or the decision to submit the manuscript for publication.

Table 1. Characteristics of Study Patients, by Continuation of Statin Prescriptions During the First 12 Months After the Presumed Adverse Reaction

Variable	Patients With Continued Statin Prescriptions		Patients With Missing Information, *n (%)*
	Yes	No	
Study patients, *n (%)*	19 989 (70.7)	8277 (29.3)	–
Mean age (SD), *y**	63.3 (12.2)	62.3 (13.2)	0 (0)
Age category, *n (%)*			
<50 y	2834 (14.2)	1455 (17.6)	0 (0)
50–59 y	5245 (26.2)	2219 (26.8)	0 (0)
60–69 y	6019 (30.1)	2282 (27.6)	0 (0)
70–79 y	3957 (19.8)	1424 (17.2)	0 (0)
80–89 y	1765 (8.8)	796 (9.6)	0 (0)
≥90 y	169 (0.9)	101 (1.2)	0 (0)
Female, *n (%)**	11 611 (58.1)	4702 (56.8)	0 (0)
White race, *n (%)*†	16 173 (80.9)	6716 (81.1)	0 (0)
Mean of median incomes by ZIP code (SD), *$**	73 800 (28 500)	75 100 (28 200)	0 (0)
Married, *n (%)*†	11 022 (55.1)	4536 (54.8)	0 (0)
English as primary language, *n (%)*†	17 889 (89.5)	7477 (90.3)	0 (0)
Government insurance, *n (%)**	10 734 (53.7)	4091 (49.4)	0 (0)
Current smoker, *n (%)*†	4292 (21.5)	1689 (20.4)	0 (0)
Mean CCI score (SD)†‡	2.4 (3.0)	2.5 (3.1)	0 (0)
History of CAD, *n (%)**	3337 (16.7)	1149 (13.9)	0 (0)
History of stroke, *n (%)*†	800 (4.0)	336 (4.1)	0 (0)
Diabetes mellitus, *n (%)**	5069 (25.4)	1610 (19.5)	0 (0)
Family history of CAD, *n (%)**	3384 (16.9)	1244 (15.0)	0 (0)
Family history of stroke, *n (%)*†	1361 (6.8)	506 (6.1)	0 (0)
Cardiologist evaluation, *n (%)**	4752 (23.8)	1549 (18.7)	0 (0)
Mean baseline blood pressure (SD), *mm Hg*			
Systolic†	128.9 (13.2)	128.8 (13.7)	870 (3.1)
Diastolic*	75.7 (8.1)	76.1 (8.4)	870 (3.1)
Mean BMI (SD), *kg/m²**	30.2 (5.9)	29.8 (5.9)	2049 (7.2)
Mean maximum LDL-C level (SD)*			1897 (6.7)
mmol/L	4.1 (1.1)	4.2 (1.0)	–
mg/dL	160 (43)	163 (39)	–
Mean eGFR (SD), *mL/min/1.73 m²*†	76.2 (19.7)	76.1 (19.9)	4746 (16.8)

BMI = body mass index; CAD = coronary artery disease; CCI = Charlson comorbidity index; eGFR = estimated glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol.
* $P < 0.001$ (significant after Simes–Hochberg threshold adjustment).
† P value not significant after Simes–Hochberg threshold adjustment.
‡ Excludes CAD, stroke, diabetes, and chronic kidney disease, which are represented by individual variables.

Table 2. Organ System Distribution of the First Documented Adverse Reaction Among Study Patients, by Continuation of Statin Prescriptions During the First 12 Months After the Presumed Adverse Reaction*

Adverse Reaction Category	All Patients (n = 28 266)	Patients With Continued Statin Prescriptions	
		Yes (n = 19 989)	No (n = 8277)
Myalgia or myopathy	6943 (24.6)	4903 (24.5)	2040 (24.7)
Musculoskeletal and connective tissue disorders other than myalgia or myopathy	5044 (17.8)	3594 (18.0)	1450 (17.5)
General disorders and administration site conditions†	3521 (12.5)	2517 (12.6)	1004 (12.1)
Hepatobiliary disorders	2965 (10.5)	2036 (10.2)	929 (11.2)
Drug intolerance‡	2223 (7.9)	1489 (7.5)	734 (8.9)
Gastrointestinal disorders	2517 (8.9)	1809 (9.1)	708 (8.6)
Nervous system disorders	1021 (3.6)	751 (3.8)	270 (3.3)
Other	4032 (14.3)	2890 (14.5)	1142 (13.8)

* Values are numbers (percentages). Adverse reactions were classified according to the Medical Dictionary for Regulatory Activities. A single adverse reaction could be classified only in a single category.
† Includes "generalized weakness," "cold sweats," and "lack of energy."
‡ Includes "intolerance" and "decreased tolerance."

RESULTS

Study Cohort

Of 201 645 adults receiving statin prescriptions between 1 January 2000 and 31 December 2011, 44 940 had at least 1 presumed adverse reaction to a statin documented in the EMR. Of these patients, 28 266 were included in the study (**Supplement Figure 2**, available at Annals.org); after the presumed adverse reaction, 19 989 patients (70.7%) continued to receive statin prescriptions and 8277 did not. Most adverse reactions (80.9%) were identified solely from the text of narrative EMR provider notes, 10.8% were identified solely from the structured EMR data, and 8.3% were found in both data sources. The distribution of the adverse event's source differed between patients who continued to receive statin prescriptions and those who did not (**Supplement Table 2**, available at Annals.org). A plurality of patients (12 385 or 43.8%) continued receiving the same statin, but many (7604 or 26.9%) changed to a different medication (**Supplement Figure 3**, available at Annals.org). The patients who continued to receive statin prescriptions were more likely to be older and have a higher income, government insurance, a history of CAD and DM, a family history of CAD, an evaluation by a cardiologist, lower diastolic blood pressure, a higher BMI, and a lower LDL-C level (**Table 1**). Myalgia or myopathy and hepatobiliary and other gastrointestinal disorders were among the most common categories of adverse reactions (**Table 2**).

Patients were followed for a mean of 4.4 years. During that time, 3677 patients (13.0%) reached the composite primary outcome, whereas 1872 patients (6.6%) died and 2332 (8.3%) had a cardiovascular event. Of the patients who reached the composite outcome, 1203 (14.5%) did not receive statin prescriptions after the adverse reaction, whereas 2474 (12.4%) did.

Multivariable Analysis

Four years after the presumed adverse reaction, inverse probability–weighted cumulative incidence of the composite primary outcome was 12.2% for patients with and 13.9% for those without continued statin prescriptions (difference, 1.7% [95% CI, 0.8% to 2.7%]; $P < 0.001$) (**Figure**). Similarly, after 4 years of follow-up, 5.4% of patients with and 6.6% of those without continued statin prescriptions died (difference, 1.2% [CI, 0.6% to 1.9%]; $P < 0.001$), and 7.6% of patients with and 8.5% of those without continued statin prescriptions had a cardiovascular event (difference, 0.9% [CI, 0.1% to 1.7%]; $P = 0.024$).

In Cox multivariable analysis, continued statin prescriptions were associated with a hazard ratio (HR) of 0.87 (CI, 0.81 to 0.93; $P < 0.001$) for the composite primary outcome (**Supplement Table 3A**, available at Annals.org), 0.79 (CI, 0.72 to 0.87; $P < 0.001$) for death (**Supplement Table 3B**, available at Annals.org), and 0.92 (CI, 0.84 to 1.00; $P = 0.054$) for cardiovascular events (**Supplement Table 3C**, available at Annals.org). Sensitivity analysis for time to cardiovascular event adjusted for competing risk for death showed similar results (HR, 0.92 [CI, 0.84 to 1.01]; $P = 0.083$). Female sex and higher eGFR were associated with lower risk for both cardiovascular outcomes and death, whereas current smoking; higher CCI score; and a history of CAD, stroke, or DM were associated with higher risk.

Secondary and Sensitivity Analyses

Recurrent adverse reactions to statins could not be established for the entire study cohort, because the timing of the adverse reaction is not always documented in the EMR clearly enough to distinguish a recurrent adverse reaction from the initial reaction. We therefore assessed recurrent adverse reactions in a secondary analysis limited to patients who received a different statin prescription after the first presumed adverse reaction. In this subgroup of 7604 patients, 2014 (26.5%) subsequently had an adverse reaction documented in the EMR that was attributed to the second statin (that is, recurrent). Most of these patients (1696, or 84.2%) continued to receive statin prescriptions (for the same or a different agent). Of the 7604 patients for whom a different statin was prescribed, 903 (11.9%) reached the composite primary end point, compared with 1203 of 8277 patients (14.5%) who did not con-

tinue receiving statin prescriptions (HR, 0.90 [CI, 0.82 to 0.99]; $P = 0.024$).

A subgroup analysis by cardiovascular risk found an HR for the primary outcome of 0.84 (CI, 0.77 to 0.92; $P < 0.001$) in patients with a baseline history of CAD, stroke, or diabetes and 0.87 (CI, 0.77 to 0.97; $P = 0.012$) in patients without these conditions. In multivariable analysis using an 18-month (rather than a 12-month) treatment assessment period, the HR for the primary outcome was 0.89 (CI, 0.82 to 0.97; $P = 0.005$). When a variable representing the intensity of continuing statin prescriptions (high vs. low dose) was included in our analysis models, it was not associated with a difference in risk for the composite primary outcome.

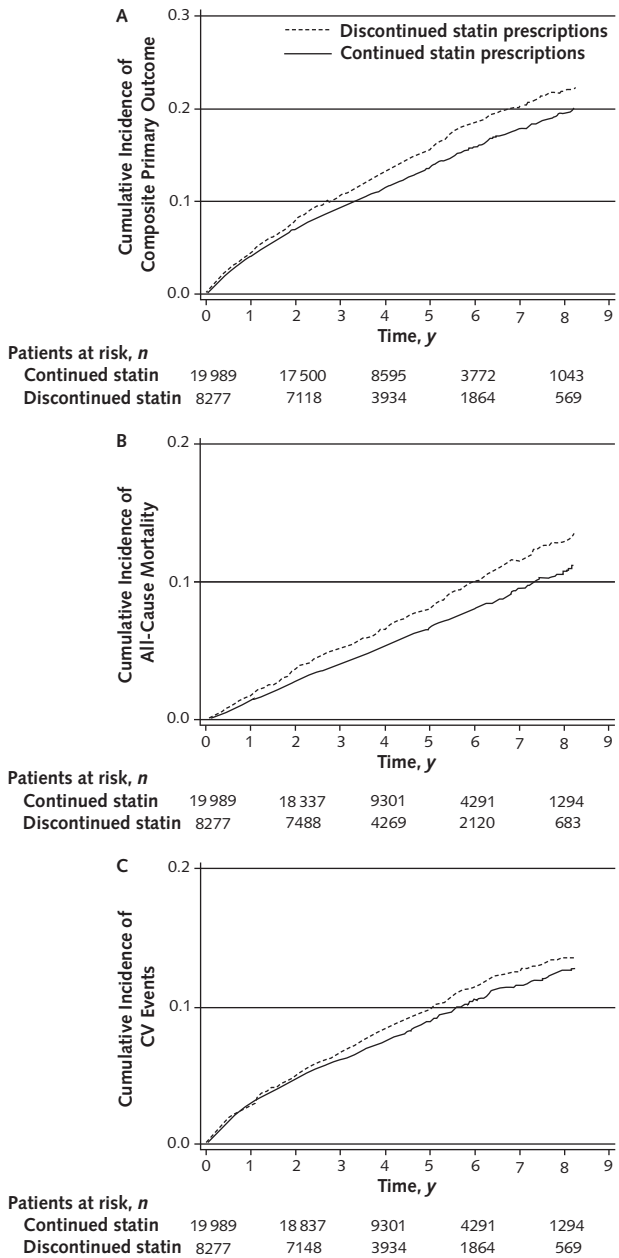
Our finding of decreased hazard for the composite outcome among patients who continued receiving statin prescriptions may have resulted from an unmeasured confounder that decreased the hazard for this outcome and had greater prevalence among patients who continued statin therapy than those who did not. Assuming a degree of association similar to that observed among measured covariates (HR, 0.75), we calculated that an unmeasured binary confounder would need to be at least 22.6% more prevalent among patients who continued statin therapy to explain our main findings (**Supplement Table 4B**, available at Annals.org). A stronger confounder with an HR of 0.50 (**Supplement Table 4A**, available at Annals.org) would need to be at least 7.5% more prevalent in patients continuing statin therapy. For a normally distributed confounder with unit standard deviation in each comparison group and an HR of 0.60, the difference of confounder means would have to be at least 0.144 to explain our main result.

DISCUSSION

Although randomized controlled trials suggest that statins are associated with only a slight increase in adverse reactions and no increase in discontinuation of treatment compared with placebo (33, 34), observational studies performed in routine clinical practice paint a different picture, reporting adverse reaction rates as high as 20% (5, 15, 35). These reactions are considered an important contributor to discontinuation of statin therapy (14–16), and optimal clinical management of discontinuation after an adverse reaction remains uncertain. Options include a rechallenge (possibly with a different statin or the same statin at a lower dosage) and prescription of a lipid-lowering medication from a different class (such as a PCSK9 or cholesterol absorption inhibitor). Despite the potential effect of these different choices, data are lacking regarding outcomes related to either option.

Our findings indicate that 30% of patients did not receive statin prescriptions after a presumed adverse event. We also found that patients who continued to receive statin prescriptions had a 10% to 20% lower incidence of both cardiovascular events and death from any cause. This finding is consistent with results of clinical trials showing that statin treatment reduces all-cause mortality and major vascular events by about 10% to 20% per millimole-per-liter reduction in LDL-C (1, 3). Although a previous investigation comparing continuation with discontinuation of statin therapy after

Figure. Inverse probability–weighted cumulative incidence curves: continued versus discontinued statin prescriptions during the first 12 months after the presumed adverse reaction.



Cumulative incidence for all 3 outcome categories was estimated during the outcome assessment period, starting 12 mo after the presumed adverse reaction. Analysis was truncated when fewer than 5% of the original study population still had data available. CV = cardiovascular. **A.** The composite primary outcome ($P < 0.0001$, weighted log-rank test). **B.** Death ($P < 0.0001$, weighted log-rank test). **C.** CV events ($P = 0.047$, weighted log-rank test).

an adverse reaction showed a trend toward lower all-cause mortality (cardiovascular events were not examined) (17), it included only 1605 patients and likely was underpowered.

Continued use of statins after an adverse reaction may not be the optimal choice for everyone. Providers should follow a patient-centered approach and engage in a balanced discussion with patients about the risks and benefits of continuing this therapy. Our data indicate that clinicians and patients may be following this paradigm to some extent. Patients at higher cardiovascular risk, as evidenced by personal or family history of CAD, diabetes, or obesity, were more likely to continue receiving statin prescriptions after an adverse reaction. Our main analyses adjusted for cardiovascular risk factors; yet even without this adjustment, continued statin prescriptions were associated with a lower risk for both cardiovascular events and all-cause mortality. Furthermore, provider specialty seemed to play as strong a role as the patient's risk factors: Evaluation by a cardiologist was highly associated with continued statin prescriptions among patients with a presumed statin-related adverse reaction.

One obvious risk of continued statin therapy in patients with a presumed adverse reaction to statins is the possibility of a recurrent adverse reaction. Our analysis estimated the rate of such reactions (to the second statin) at 26.5%, which is high but comparable to the baseline rate of 18.7%. Notably, more than 80% of patients who had a documented recurrent adverse reaction subsequently continued receiving statin prescriptions, suggesting that the symptoms were mild or tolerable. Both the absolute risk and symptom severity must be weighed against the potential benefits of continuing statin therapy after a presumed adverse reaction.

Another important consideration is that in patients with low cardiovascular risk, treatment with statins, especially after a possible adverse reaction, may not be appropriate. The most recent guidelines recommend statins for most patients with a 10-year cardiovascular risk of 7.5% or greater (4). In our analysis, we found a reduction in risk for cardiovascular events and death associated with continued statin prescriptions among high- and lower-risk patients. However, the patients included in our study were a high-risk group on average, with a rate of combined cardiovascular events or death of more than 20% over 10 years. Future studies should be conducted to establish the cardiovascular risk threshold below which a statin rechallenge after an adverse reaction may be more harmful than beneficial for the patient.

The present study has several strengths. Access to EMR data from 2 large hospital systems allowed us to analyze longitudinal data with an average follow-up of more than 4 years from nearly 30 000 patients with diverse backgrounds. Our use of specially designed natural-language processing software gave us the unique ability to identify many reported adverse reactions to statins that were documented only in provider notes (5, 20).

Our study has several limitations, however. The population was drawn from 2 academic medical centers in Massachusetts, limiting generalizability, and it is retrospective and involves data collected in the course of routine care. Thus, we could establish only associations rather than causal relationships. We had information only on statin prescriptions and could not assess whether patients actually took their medications. Most (81%) of the information on statin adverse reactions was obtained from processing narrative EMR notes. We also could not ascertain the timing, severity, or specific causes (for example, drug–drug interaction) of the adverse reactions. A moderate unmeasured confounder might explain the observed association. Finally, we did not have information on patient or provider preferences regarding continuation of statin therapy after an adverse reaction, and cause-of-death information was not available.

Our findings suggest that continued statin prescriptions were associated with a reduced incidence of cardiovascular events and death among patients who had EMR documentation of a presumed adverse reaction. Whether therapy should be continued after an adverse reaction is an important decision that must take into account the balance of potential benefits and risks to the patient. This study's findings may help patients and their clinicians inform their choice of treatment to best fit each patient's circumstances.

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Note: Dr. Turchin had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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