Patterns of Statin Use in a Real-World Population of Patients at High Cardiovascular Risk

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ABSTRACT

BACKGROUND: Widespread use of statins has improved hypercholesterolemia management, yet a significant proportion of patients remain at risk for cardiovascular (CV) events. Analyses of treatment patterns reveal inadequate intensity and duration of statin therapy among patients with hypercholesterolemia, and little is known about real-world statin use, specifically in subgroups of patients at high risk for CV events.

OBJECTIVE: To examine patterns of statin use and outcomes among patients with high-risk features who newly initiated statin monotherapy.

METHODS: Adult patients (aged ≥18 years) at high CV risk who received ≥1 prescription for statin monotherapy and who had not received lipid-modifying therapy during the previous 12 months were identified from the Truven MarketScan Commercial and Medicare Supplemental databases (from January 2007 to June 2013). Patients with atherosclerotic cardiovascular disease (ASCVD) or diabetes were hierarchically classified into 5 mutually exclusive CV risk categories (listed here in order from highest to lowest risk): (1) recent CV event (subcategorized by hospitalization for acute coronary syndrome [ACS] or other non-ACS CV event within 90 days of index); (2) coronary heart disease (CHD); (3) history of ischemic stroke; (4) peripheral artery disease (PAD); and (5) diabetes. Outcomes of interest included changes in therapy, proportion of days covered (PDC), time to discontinuation, and proportion of patients with ASCVD-related inpatient visit during the follow-up period. Statin therapy was subdivided into high-intensity treatment (atorvastatin 40 mg or 80 mg, rosuvastatin 20 mg or 40 mg, or simvastatin 80 mg) or moderate- to low-intensity treatment (all other statins and statin dosing regimens). Follow-up data were obtained from the index date (statin initiation) until the end of continuous enrollment.

RESULTS: A total of 541,221 patients were included in the analysis. The majority of patients were stratified in the diabetes cohort (61.1%), followed in frequency by recent ACS event (15.8%), recent non-ACS CV event (9.9%), PAD (4.7%), CHD (4.4%), and history of ischemic stroke (4.1%). Only 15.0% of the population initiated therapy with a high-intensity statin, and 22.5% of these high-intensity statin initiators switched to a moderate- to low-intensity regimen during the follow-up period. Median time to statin discontinuation was approximately 15 months. Duration of treatment was longer among those who were treated with a high-intensity versus a moderate- to low-intensity statin regimen (21 and 15 months, respectively). The PDC was highest in the recent ACS hospitalization cohort (66.4%) and lowest in the diabetes cohort (55.5%). The PDC was significantly greater among patients who initiated treatment with a high-intensity statin regimen than with a moderate- to low-intensity statin regimen (62.1% vs. 57.5%, respectively; $P<0.001$). At 1 year, Kaplan-Meier estimates of the cumulative rates for ASCVD-related hospitalizations ranged from 3.5% (diabetes) to 21.8% (recent ACS hospitalization).

CONCLUSIONS: Patients at high risk for CV events are suboptimally dosed with statins, have high rates of discontinuation, and have low rates of adherence. Despite the use of statin therapy, ASCVD-related inpatient visit rates were high, particularly among those patients at highest risk because of a recent ACS hospitalization. Future interventions are required to ensure that high-risk patients are effectively managed to reduce subsequent morbidity and mortality.

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What is already known about this subject

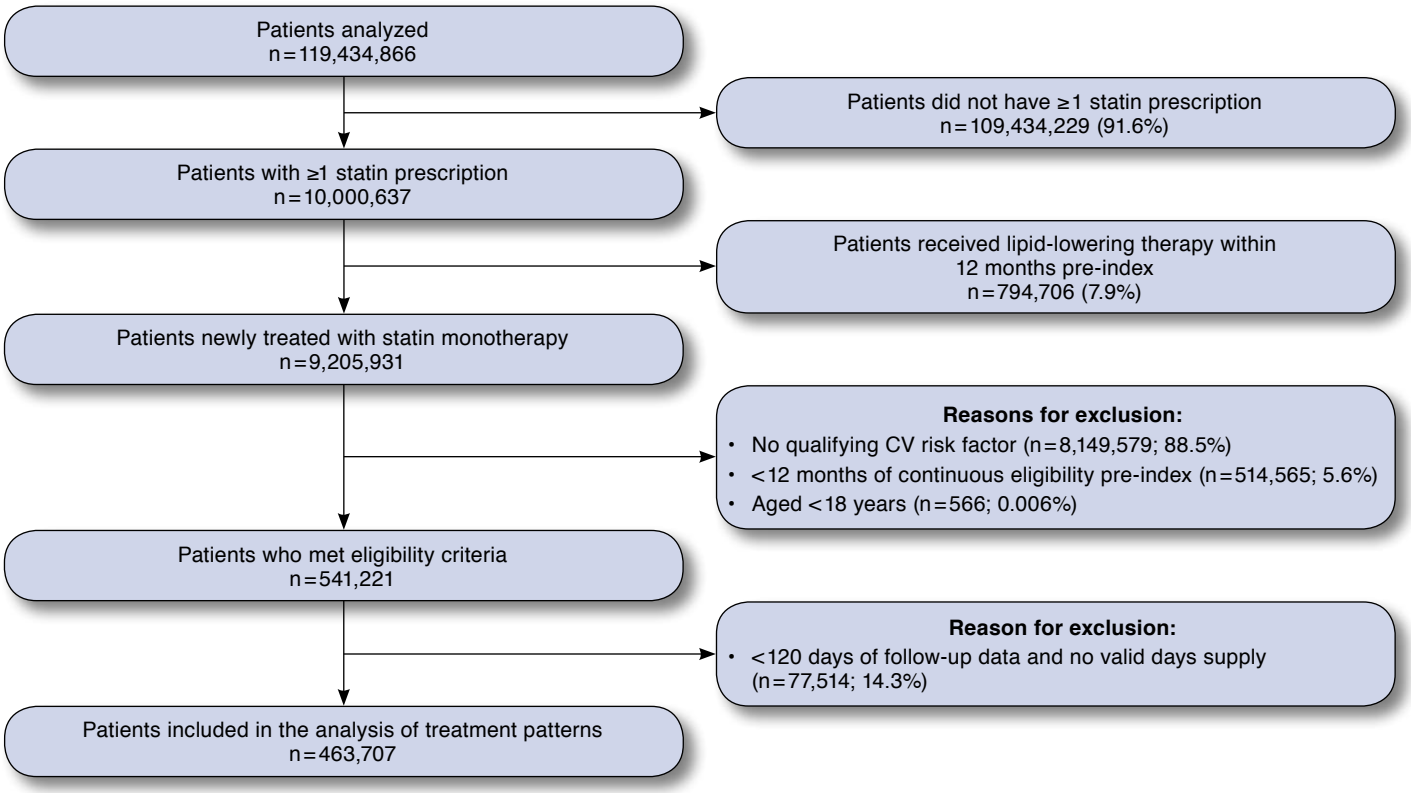
- Patients with established cardiovascular (CV) disease or CV risk factors are at high risk for CV events. For these patients, optimal secondary preventive care, including lipid-modifying therapy, can improve outcomes.
- Available evidence suggests that patients at high CV risk because of the presence of atherosclerotic cardiovascular disease (ASCVD) are not receiving sufficient lipid-modifying therapy to mitigate disease-associated risk.
- The shift toward high-intensity statin therapy recommended in the 2013 American College of Cardiology/American Heart Association guidelines may be challenging, given the large proportion of moderate- to low-intensity statin use.

What this study adds

- High-intensity statin therapy is infrequently prescribed to patients at high risk for CV events, regardless of the underlying risk factor(s) (e.g., recent acute coronary syndrome [ACS] hospitalization, diagnosed coronary heart disease, and diabetes).
- Adherence to statin therapy is suboptimal, with high discontinuation rates among all high CV-risk patient subgroups.
- Despite the use of statin therapy, patients with recent ACS have a high 1-year risk of ASCVD-related rehospitalization.

Since their introduction in the late 1980s, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) have become the cornerstone of hypercholesterolemia treatment. Although recommendations in guidelines for cholesterol management differ, major guidelines endorse statin therapy to reduce cardiovascular (CV) risk for patients with elevated cholesterol levels for whom lifestyle change alone is insufficient.[1-4] In 2013, the American

FIGURE 1 Patient Selection Flowchart[a]



[a]*Patients with a CV-risk condition who initiated statin therapy and met the eligibility criteria were included in the baseline assessments. Treatment patterns were analyzed for patients who had >120 days of continuous enrollment post-index and who had valid (i.e., no missing values for the given time period) days supply data available.*
CV=cardiovascular.

College of Cardiology and the American Heart Association (ACC/AHA) guideline on cholesterol management shifted away from specific low-density lipoprotein cholesterol (LDL-C) levels to overall atherosclerotic CV disease (ASCVD) risk reduction.[3] This guideline recommends the use of high-intensity statins in patients at highest risk (e.g., ASCVD) for CV events.

Approximately 35.9 million Americans, or 15% of the population aged 18 years and older, have either ASCVD or diabetes mellitus.[5] The downstream consequences of uncontrolled hypercholesterolemia, including ASCVD events such as those related to coronary heart disease (CHD), ischemic stroke, and peripheral artery disease (PAD), are a significant burden for patients and for the health care system. CHD alone accounted for approximately 1 of every 6 deaths in the United States in 2010,[6] and it is projected to result in direct and indirect costs of nearly $220 billion in 2030.[7] Despite these known risks, statin therapy is widely underutilized across patient populations and clinical conditions.

Patients at high risk for CV events, especially those with ASCVD, stand to gain the most from statins.[3] This effect has been demonstrated in several randomized, placebo-controlled clinical studies.[8-10] Furthermore, studies indicate that intensive dosing reduced CV events more than standard doses of statins.[11,12] Nonetheless, research from real-world studies indicates that statin use is suboptimal in populations with high CV risk.[13-17] Available evidence also suggests that clinicians frequently opt for a less aggressive statin regimen, even when treatment goals are not achieved.[18-22] As with the primary prevention population, adherence to therapy is a significant challenge to maintaining adequate risk reduction in patients with established CV disease (CVD).[17,23,24]

To further understand statin use among subgroups of patients with ASCVD, we conducted a large-scale, comprehensive evaluation of statin intensity, modification, adherence, and associated outcomes in a treatment-naive cohort of patients at high risk for CV events.

Methods

Study Population and Data Source

This retrospective study identified patients from the Truven MarketScan Commercial and Medicare Supplemental

TABLE 1 Demographics and Baseline Characteristics of the Study Population (N = 541,221)

Parameter	Recent CV Event (n = 139,222)		CHD (n = 23,621)		Ischemic Stroke (n = 22,431)		PAD (n = 25,357)		Diabetes (n = 330,590)	
	ACS Event[a] (n = 85,272)	Non-ACS Event[b] (n = 53,950)								
Mean age [SD], years	60.5 [13.1]	63.9 [13.7]	60.3 [12.2]		66.0 [12.8]		64.9 [12.8]		54.7 [11.4]	
Age group, years, % (n)										
18-44	8.9 (7,589)	6.6 (3,561)	7.8 (1,842)		4.0 (897)		4.2 (1,065)		17.5 (57,853)	
45-64	61.8 (52,698)	52.2 (28,162)	64.6 (15,259)		48.2 (10,812)		52.2 (13,236)		69.1 (228,438)	
≥ 65	29.3 (24,985)	41.3 (22,281)	27.6 (6,519)		47.7 (10,700)		43.6 (11,056)		13.4 (44,299)	
Female, % (n)	32.8 (27,969)	44.1 (23,792)	42.3 (9,992)		51.7 (11,597)		46.8 (11,867)		49.7 (164,303)	
Region, % (n)										
Northeast	13.7 (11,682)	13.8 (7,445)	12.2 (2,882)		14.3 (3,208)		16.9 (4,285)		10.7 (35,373)	
South	39.0 (33,256)	38.6 (20,825)	48.8 (11,527)		39.0 (8,748)		37.1 (9,407)		46.6 (154,055)	
Midwest	31.8 (27,116)	31.9 (17,210)	27.6 (6,519)		32.2 (7,223)		31.5 (7,987)		28.0 (92,565)	
West	15.5 (13,217)	15.7 (8,470)	11.5 (2,716)		14.5 (3,252)		14.5 (3,677)		14.7 (48,597)	
Hypertension, % (n)	52.2 (44,512)	62.6 (33,773)	62.5 (14,763)		60.6 (13,593)		58.4 (14,808)		45.3 (149,757)	
Cancer, % (n)	6.6 (5,628)	8.1 (4,370)	7.5 (1,772)		9.0 (2,019)		9.1 (2,307)		4.6 (15,207)	
Diabetes, % (n)	21.1 (17,992)	23.0 (12,409)	29.9 (7,063)		28.1 (6,303)		34.1 (8,647)		100.0 (330,590)	
Mean Charlson comorbidity score [SD]	2.0 [1.8]	2.3 [1.8]	1.8 [1.9]		2.6 [1.9]		2.5 [1.9]		1.7 [1.2]	
Mean follow-up duration [SD], months	20.2 [16.3]	19.5 [16.0]	19.9 [15.8]		19.5 [15.7]		19.3 [15.5]		20.8 [16.2]	

[a]*ACS event category includes patients with ≥ 1 inpatient hospital stay for acute myocardial infarction or unstable angina within 90 days pre-index.*
[b]*Non-ACS CV event category includes patients with ≥ 1 inpatient hospital stay for revascularization or ischemic stroke within 90 days pre-index.*
ACS = acute coronary syndrome; CHD = coronary heart disease; CV = cardiovascular; PAD = peripheral artery disease; SD = standard deviation.

databases from January 2007 through June 2013. These databases contain medical, pharmacy, and enrollment data from large self-insured employers representing approximately 30 million lives. Major data contributors include employers and health plans that cover employees and their dependents through a variety of offerings, including fee-for-service, fully capitated, and partially capitated health plans. The Truven MarketScan Medicare Supplemental database encompasses 2.9 million covered lives of individuals aged ≥ 65 years who had Medicare coverage plus employer-paid commercial plans. The datasets fully integrate pharmacy and medical claims and provide longitudinal information on patient treatment history.

Adult patients (≥ 18 years) who newly initiated statin monotherapy (index date) and had ≥ 1 medical claim for 1 of the following ASCVD conditions or diabetes during the pre-index period were included in the analysis: acute coronary syndrome (ACS), history of myocardial infarction (MI), stable or unstable angina, coronary or other arterial revascularization, ischemic stroke, PAD, or diabetes. Patients were required to have continuous enrollment for 12 months pre-index.

Patient Subgroups

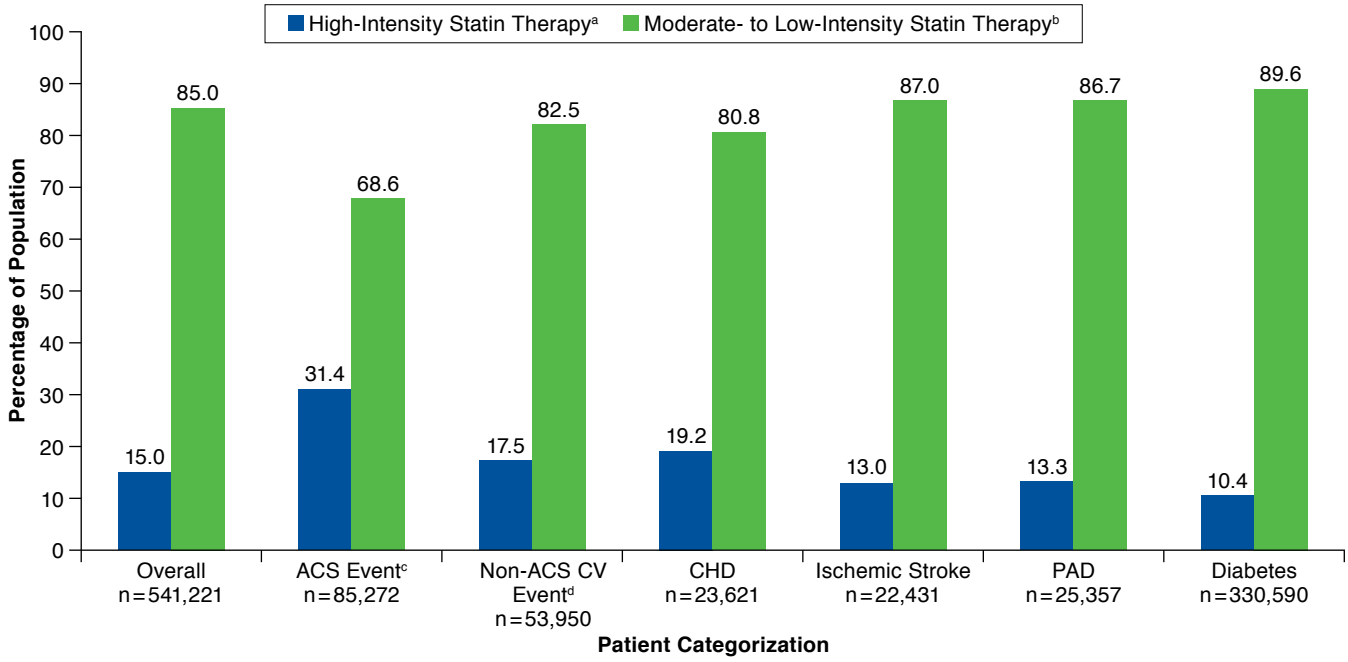
Patients were hierarchically classified into the highest mutually exclusive CV risk category.[25] Stratification was performed such that a patient was assigned a CV risk category based on the presence or absence of the foremost risk factor using the following organizational scheme: (a) recent CV event (subcategorized by hospitalization for ACS or other non-ACS CV event); (b) CHD; (c) history of ischemic stroke; (d) PAD; and (e) diabetes. CVD/CV risk factors were identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnostic codes[26] and procedure codes in the Current Procedural Terminology, 4th edition (CPT-4), Healthcare Common Procedure Coding System Level II (HCPCSII), or revenue code format. A complete list of included ICD-9-CM diagnostic codes and CPT and HCPCSII procedure codes is provided in the Appendix (available in online article).

The following definitions were applied to patient classification:

- Recent CV event
  - Recent ACS hospitalization: ≥ 1 inpatient stay for acute MI or unstable angina within 90 days pre-index
  - Recent non-ACS CV event: ≥ 1 inpatient stay for revascularization or ischemic stroke within 90 days pre-index
- CHD: ≥ 1 inpatient or ≥ 2 outpatient visits for stable angina or a prior MI (≥ 90 days) during the 12 months pre-index
- History of ischemic stroke: ischemic stroke that occurred between 90 days and 12 months pre-index
- PAD: ≥ 1 inpatient or ≥ 2 outpatient visits for PAD or carotid artery disease during the 12 months pre-index
- Diabetes: ≥ 1 inpatient or ≥ 2 outpatient visits for diabetes management during the 12 months pre-index

According to this stratification algorithm, a patient with diabetes and CHD would be classified within the CHD CV

FIGURE 2 Intensity of Statin Therapy at Index



[a]*High-intensity statin treatment was defined as atorvastatin 40 mg or 80 mg, rosuvastatin 20 mg or 40 mg, or simvastatin 80 mg.*
[b]*Moderate- to low-intensity statin treatment included all other statins and statin dosing regimens.*
[c]*Includes acute myocardial infarction and unstable angina.*
[d]*Includes revascularization and ischemic stroke within 90 days pre-index.*
ACS = acute coronary syndrome; CHD = coronary heart disease; CV = cardiovascular; PAD = peripheral artery disease.

risk category. The existence of CV risk factors was determined by their presence in medical claims records within 12 months before statin initiation, with the exception of recent CV events, which were evaluated 90 days pre-index.

Study Definitions and Measures

Statin monotherapy was defined as a prescription for a drug within the HMG-CoA reductase inhibitor drug class (i.e., atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin) without any concomitant lipid-modifying therapies at baseline. Statin therapy was subdivided into high-intensity (atorvastatin 40 mg or 80 mg, rosuvastatin 20 mg or 40 mg, or simvastatin 80 mg) or moderate- to low-intensity (all other statins and statin-dosing regimens) treatment.

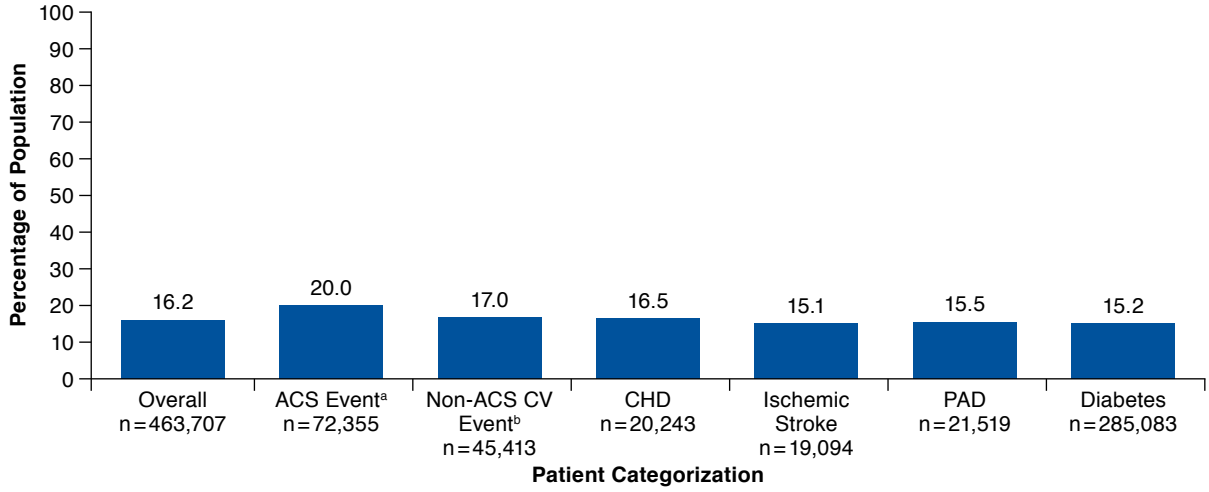
A variable follow-up period was used, with patients tracked from the index date until the end of continuous enrollment. Follow-up measures included statin discontinuation, changes to the statin therapy regimen, proportion of days covered (PDC) by a statin, and the occurrence of ASCVD-related hospitalization. A patient was considered to have discontinued statin therapy if he or she failed to receive any statin treatment for 90 consecutive days. Modifications of the statin monotherapy regimen included switching to another statin class member, adding concomitant lipid-modifying therapy or prescription of a fixed-dose combination (e.g., ezetimibe-simvastatin), and upward or downward adjustments to the intensity of statin therapy. PDC for statin therapy was calculated as the total number of covered days with statin supply divided by the total number of days from index until the end of continuous enrollment. The proportion of patients experiencing an ASCVD-related hospitalization was determined based on the presence of an ICD-9-CM code indicative of ≥1 ASCVD condition of interest (i.e., ASCVD conditions used to identify high CV risk during patient selection, such as MI, unstable angina, and ischemic stroke).

Statistical Analyses

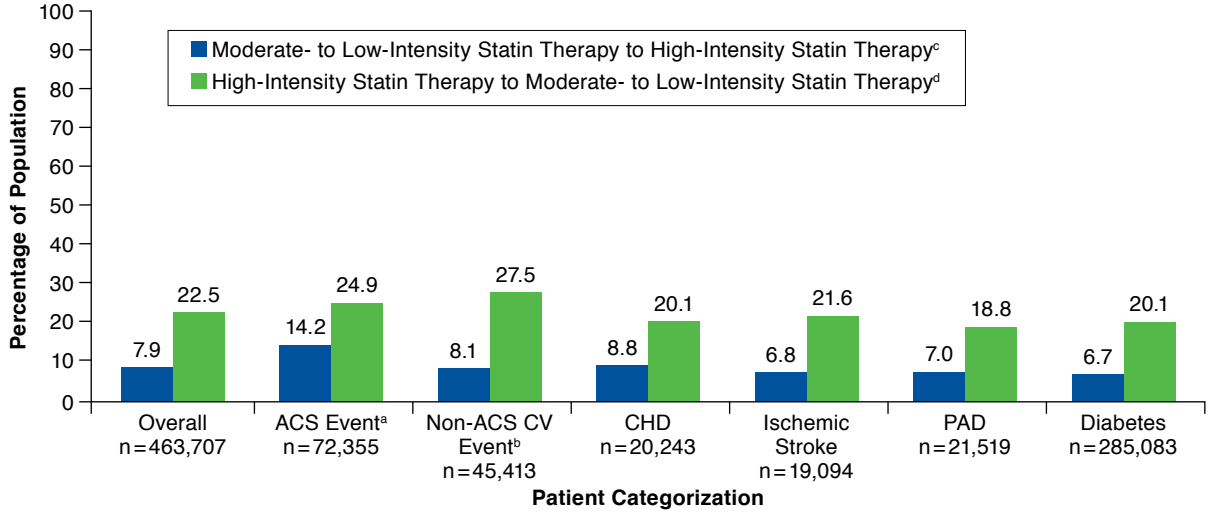
Descriptive statistics were calculated for baseline patient demographic and clinical characteristics and for statin treatment utilization patterns. Analyses of postbaseline treatment patterns (e.g., discontinuation, switching, changes in statin intensity, and PDC) included all patients with >120 days of continuous enrollment post-index. The requirement of >120 days of continuous enrollment was selected to allow patients

FIGURE 3 Changes in Statin Therapy Intensity

A. Stratified by Patient Categorization



B. Stratified by Direction of Therapy Change



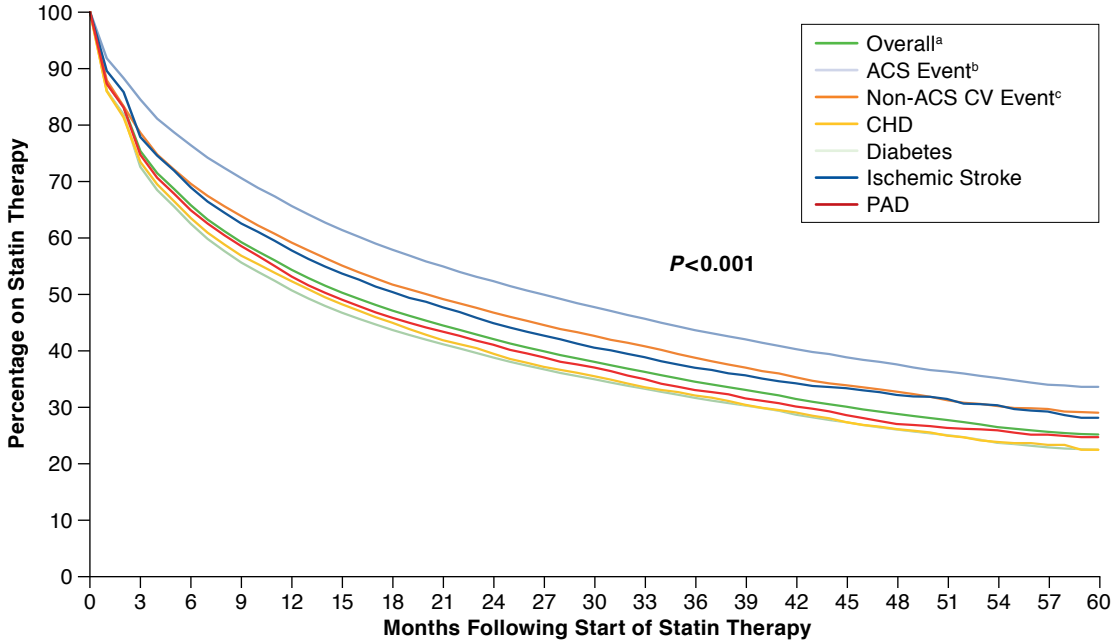
[a]*Includes acute myocardial infarction and unstable angina.*
[b]*Includes revascularization and ischemic stroke within 90 days pre-index.*
[c]*Moderate- to low-intensity statin treatment included all other statins and statin dosing regimens.*
[d]*High-intensity statin treatment was defined as atorvastatin 40 mg or 80 mg, rosuvastatin 20 mg or 40 mg, or simvastatin 80 mg.*
ACS = acute coronary syndrome; CHD = coronary heart disease; CV = cardiovascular; PAD = peripheral artery disease.

sufficient time on the index statin before discontinuing their statin. A minimum of ≥30 days supplied was assumed, and discontinuation was defined as the absence of any statin use for >90 days.

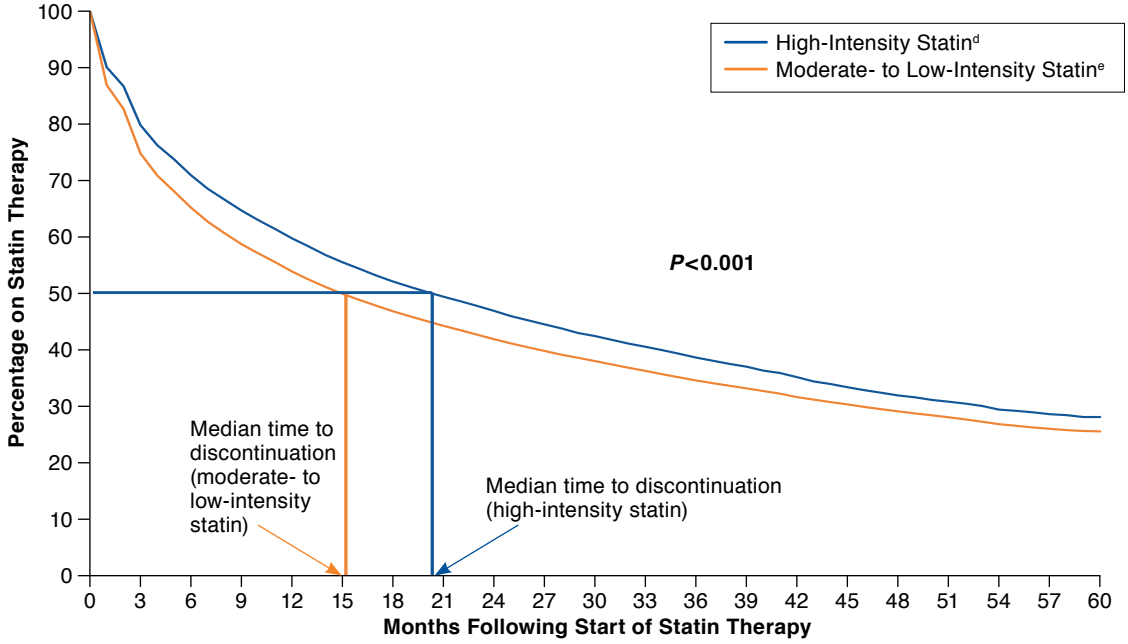
All baseline and outcome measures were stratified by CV risk category (i.e., recent CV event, CHD, history of ischemic stroke, PAD, and diabetes). Kaplan-Meier survival analyses were conducted for time to statin discontinuation and ASCVD-related hospitalizations during the follow-up period, which was defined as index to the end of continuous enrollment. Two-sided log-rank tests comparing across all cohorts were used to determine statistical significance. A Cox proportional hazards regression model was used to estimate the hazard ratio for the relationship between high-risk cohort and discontinuation while adjusting for age, gender, and comorbidity index. The regression analysis on discontinuation was run on

FIGURE 4 Kaplan-Meier Analysis of Time to Statin Discontinuation

A. Stratified by Patient Categorization



B. Stratified by Statin Therapy Intensity at Baseline



Note: Statistical significance was determined using a 2-sided log-rank test comparing across all cohorts.

[a]*Overall represents patients in all risk categories (n=463,707).*

[b]*Includes acute myocardial infarction and unstable angina.*

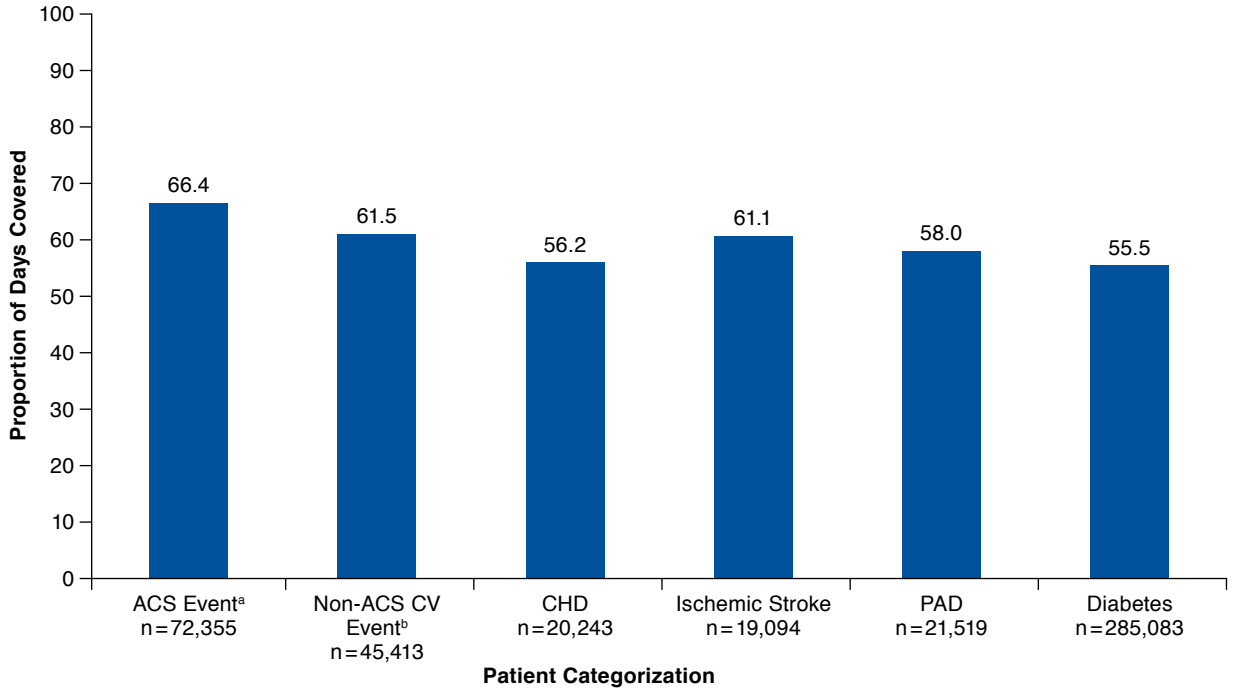
[c]*Includes revascularization and ischemic stroke within 90 days pre-index.*

[d]*High-intensity statin treatment was defined as daily treatment with atorvastatin 40 mg or 80 mg, rosuvastatin 20 mg or 40 mg, or simvastatin 80 mg.*

[e]*Moderate- to low-intensity statin included all other statin dosing regimens.*

ACS=acute coronary syndrome; CHD=coronary heart disease; CV=cardiovascular; PAD=peripheral artery disease.

FIGURE 5 Proportion of Days Covered for Statin Therapy (of Any Intensity)



[a]*Includes acute myocardial infarction and unstable angina.*
[b]*Includes revascularization and ischemic stroke within 90 days pre-index.*
ACS = acute coronary syndrome; CHD = coronary heart disease; CV = cardiovascular; PAD = peripheral artery disease.

a subset of patients with > 120 days of continuous enrollment post-index. Kaplan-Meier survival analysis and Cox regression models were conducted with Statistical Analysis System (SAS) software package, version 9.3 (SAS Institute, Cary, NC). All other analyses of descriptive statistics were conducted using R, version 3.1.2 (The R Foundation, Vienna, Austria).

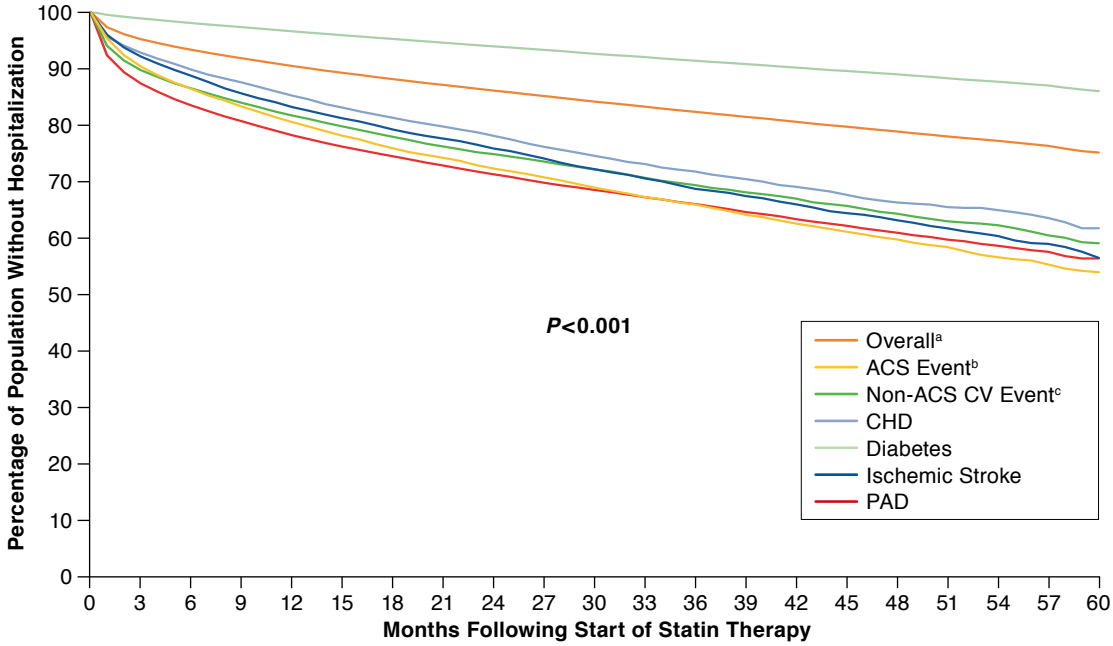
Results

A total of 541,221 patients met the eligibility criteria and were included in the baseline assessments (Figure 1). The proportion of patients per CV risk category were as follows: 15.8% recent ACS event, 9.9% recent non-ACS CV event, 4.4% CHD, 4.1% history of ischemic stroke, 4.7% PAD, and 61.1% diabetes. Age distribution was generally comparable across cohorts, with the exception of the diabetes cohort, which had a younger mean age and more patients in the 18-44 years category (Table 1). The mean Charlson comorbidity score for the overall population was 1.9 and varied by cohort (intercohort range = 1.7 to 2.6). Hypertension and diabetes were prevalent across all CV risk categories. The mean observation period following the index event (i.e., statin initiation) was 20.4 months (median = 16.6 months; range = < 1 to 65.9 months).

At the time of index, 15.0% of the overall population was started on high-intensity statin therapy (Figure 2). High-intensity therapy was most frequent among patients with a recent ACS hospitalization (31.4%) and least frequent among patients with diabetes (10.4%). Post-index treatment patterns were analyzed for 463,707 patients who had > 120 days of continuous post-index enrollment and available valid (i.e., no missing values for the given time period) days supply data (Figure 1). During the course of follow-up, 15% to 20% of patients per cohort switched from their index statins to monotherapy with another statin (Figure 3A). Patients who had experienced a recent ACS event changed their statin regimens numerically more frequently than patients in other CV risk categories. Add-on or combination therapy was used by 3% to 4% of patients per cohort. Less than 3% of patients switched from a statin to a nonstatin agent for lipid lowering.

More than 20% of patients initially treated with a high-intensity regimen switched to moderate- to low-intensity therapy (Figure 3B). Reduction in treatment intensity was most frequently observed among patients who had experienced a recent ACS event. Statin intensity was increased (through changing drug or dosage) in 6.7% to 14.2% of patients during follow-up. Overall

FIGURE 6 ASCVD-Related Hospitalizations During Follow-up



Note: Statistical significance was determined using a 2-sided log-rank test comparing across all cohorts.
[a]Overall represents patients in all risk categories (N = 541,221).
[b]Includes acute myocardial infarction and unstable angina.
[c]Includes revascularization and ischemic stroke within 90 days pre-index.
ACS = acute coronary syndrome; CHD = coronary heart disease; CV = cardiovascular; PAD=peripheral artery disease.

and by cohort, patients with high-intensity therapy at index were more likely to switch statin monotherapy than patients who initiated treatment with a moderate- to low-intensity regimen.

During the course of follow-up, 53.0% of patients discontinued statin therapy. Kaplan-Meier curves showed a median time to statin discontinuation of approximately 15 months (Figure 4A). Time to discontinuation was significantly higher in the recent ACS event cohort (median = 27 months) compared with the other CV risk groups (median = 13 to 18 months; log-rank $P < 0.001$ comparing across all cohorts). Patients receiving a high-intensity statin regimen had a significantly longer median time to discontinuation (Figure 4B) and had lower rates of discontinuation (47.9% vs. 53.9%) than patients who started on moderate- to low-intensity treatment (log-rank $P < 0.001$ comparing across all cohorts). Variables significantly associated with statin discontinuation on regression analysis included younger age (18-44 years), female sex, and a Charlson comorbidity score > 2 ($P < 0.001$ for all). Recent ACS event and history of stroke risk categories were associated with lower hazard ratio for discontinuation ($P < 0.001$).

The PDC on statin therapy was 58.2% for all cohorts, ranging from 55.5% (diabetes) to 66.4% (recent ACS hospitalization; Figure 5). Patients who initiated treatment with a high-intensity statin regimen had a significantly greater PDC than patients who initiated treatment with a moderate- to low-intensity regimen (62.1% vs. 57.5%, respectively; $P < 0.001$).

Hospitalizations related to ASCVD occurred in 12.0% of patients during the follow-up period (i.e., index to end of continuous enrollment). These hospitalizations were significantly higher among patients with a recent ACS hospitalization or PAD and lowest for the diabetes cohort (Figure 6; log-rank $P < 0.001$ comparing across all cohorts; comparisons were not made between specific cohorts).

Discussion

This retrospective claims database analysis demonstrated that real-world patients at high risk for CV events are not optimally receiving and maintaining high-intensity statin therapy. Most patients in all CV risk categories initiated treatment with a moderate- to low-intensity statin regimen. Although increases in statin intensity were infrequent, more than one fifth of patients who initiated on a high-intensity statin regimen switched to a moderate- to low-intensity regimen during follow-up. Discontinuation was a common occurrence, regardless of baseline therapy, and the PDC for statin therapy was low.

Widespread use of suboptimal-intensity therapy has been routinely reported in high-risk populations.[18-22] In the current study, 15% of patients initiated treatment with high-intensity statin therapy. These patients were likely to change dosage or switch statin therapy type (possibly to achieve a better response), and approximately half discontinued treatment within 20 months. Previously published data from a large cohort of patients (N = 11,473) with ASCVD or diabetes who had not reached the LDL-C goal of < 70 mg/dL showed that most patients (76%) were initially treated with moderate-intensity statin therapy, and < 2% of patients received a high-intensity statin regimen.[20] After reevaluation of LDL-C levels posttreatment, only 13% of patients were prescribed a higher-intensity regimen either through switching or uptitrating statin therapy or via the addition of another lipid-lowering agent. Notably, 47% of patients not at the LDL-C goal discontinued therapy within 12 months of beginning treatment without first attempting a change in their lipid-lowering regimens. A modestly higher rate of statin intensification (25.3%) was reported in a recent retrospective observational study that evaluated patients with CHD or CHD risk equivalents (N = 656,807), yet the majority of patients (70.2%) continued with their initial regimen or downtitrated statin therapy during the follow-up period.[18] Interestingly, as we had observed in our high-risk patient cohort, add-on therapy was infrequently used as an adjunct to lipid-lowering with a statin.

Analysis of data from the Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) and Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients' Health status (TRIUMPH) registries reinforces the suboptimal utilization of target statin intensity in high-risk patients, specifically those who had experienced an acute MI (n = 6,748).[21] At hospital discharge, one third of patients were prescribed statin therapy at the goal level. Intensification of treatment after hospital discharge was rare, with fewer patients (26%) receiving their target statin doses at the 12-month follow-up time point than at the time of hospital discharge.

The generally low rate of adherence observed in our high-risk cohort is compatible with previous observations for statins.[17,24] Nonadherence to therapy is an ongoing issue in the management of hypercholesterolemia.[27,28] The underlying reasons for statin nonadherence range from concerns about adverse effects to perceived lack of therapeutic benefit.[29,30] Several treatment-related factors that decrease the likelihood of statin adherence, including higher copays and higher drug doses, have also been identified.[31-34] Higher rates of statin discontinuation have also been reported among younger patients and women—findings that are consistent with our observations.[35] Routine monitoring is suggested as a means to promote adherence. Although treating to goal is no longer the emphasis in U.S. lipid management guidelines, it is recommended that practitioners monitor lipid levels within 4 to 12 weeks of initiating treatment to evaluate therapeutic response and patient adherence.[3] It is also advised that adherence to therapy be reinforced at routine follow-up visits every 3 to 12 months.

Statin treatment patterns and adherence to therapy in our study differed among cohorts. Patients with diabetes and no other ASCVD diagnosis were among the least aggressively managed groups in terms of intensity of statin therapy and PDC. Less intensive therapy for this patient subgroup is consistent with the ACC/AHA guideline, which gives a Level I recommendation for moderate-intensity statin therapy in adults aged 40-75 years who have diabetes.[3] High-intensity therapy would be appropriate for those patients who also have a 7.5% or greater estimated risk for ASCVD. Whether more patients in the diabetes CV risk category should have received high-intensity therapy is not possible to ascertain from our analysis because of the lack of CV risk scoring. The observed differences in adherence based on cohort designation align with previous data demonstrating that patients at very high CV risk (i.e., those with ACS or established CVD plus either diabetes or metabolic syndrome) are more likely to be adherent to statin therapy.[17] In our assessment, patients with a recent hospitalization for ACS had the greatest statin therapy PDC (66.4%) and the longest duration of statin treatment (median = 27 months).

Patients with a recent hospitalization for ACS were also more likely than patients in other CV risk categories to initiate treatment with a high-intensity statin regimen. We observed a significant difference in PDC between statin intensity groups, with a greater PDC (62.1%) for high-intensity treatment compared with patients who received a moderate- to low-intensity regimen (57.5%; $P < 0.001$). Data from previous evaluations of prescription/administrative data have reported that higher statin dose/intensity was associated with lower adherence rates.[31,32] However, previous studies have not specifically assessed patients who were newly initiating statin therapy and who had high CV risk conditions. In the recent study by Virani et al. (2014),[32] the difference in PDC between high-intensity and moderate- to low-intensity statin regimens in patients with established CVD (i.e., CHD, PAD, or ischemic stroke) who were receiving ongoing statin therapy was statistically significant (86% and 87%, respectively; $P < 0.0001$) but not considered to be clinically relevant. Importantly, patients with diabetes and no other ASCVD diagnosis—a group that made up a substantial proportion of our study population and had both the lowest PDC rates and the lowest high-intensity therapy rates—were not included in the analysis.

The rate of ASCVD-related hospitalizations in the current analysis underscores the high-risk status of these patients and the lack of adequate risk mitigation with current management strategies. Twelve percent of patients experienced an

ASCVD-related hospitalization during a median follow-up duration of 20.4 months. These values varied substantially by CV risk cohort, ranging from 5% among patients in the diabetes CV risk category to 23% for patients who had experienced a recent CV event. Some possible factors affecting the hospitalization rate were the prevalence of statin nonadherence and the high rate of statin discontinuation. Both of these factors have been shown to adversely affect CV outcomes.[23,24,36,37] Accumulating evidence suggests that patients with established CV or cerebrovascular disease who discontinue chronic statin therapy are at increased mortality risk compared with those who maintain therapy and, in some cases, patients who had never been treated with a statin.[24,36,37]

Limitations

Several limitations inherent to the nature of the data source affect the conclusions that can be drawn from this assessment. The claims databases did not capture information on the reasons for initial therapy choice or for modifying or discontinuing therapy. Clinical considerations such as contraindications or conditions that increase the risk for treatment-related adverse effects may have led to the selection of less intensive therapy. For patients on statin treatment, discontinuation or switching to a nonstatin lipid-modifying therapy, the latter of which occurred in 2%-3% of patients per cohort in our study, could have been the result of apparent statin intolerance. Clinicians may have chosen not to intensify statin therapy during the follow-up period for patients who were tolerating and adhering to therapy because of the minimal additional reduction in LDL-C that is observed with statin dose escalation and/or the increased likelihood for side effects and intolerance at higher doses.[38,39] Experiencing a treatment-emergent side effect increases the probability that a patient will discontinue therapy altogether. In the Understanding Statin Use in America and Gaps in Education (USAGE) survey, side effects, particularly muscle-related side effects, were the predominant reason cited by former statin users for discontinuing therapy.[40,41] Emerging concerns regarding an increased risk for new-onset diabetes[42-44] or acute kidney injury[45,46] with high-intensity statin therapy may also have factored into the decision to limit treatment to a moderate- to low-intensity regimen.

An additional consideration regarding study interpretation is the method by which statin discontinuation was detected. Discontinuation was identified based on a 90-day gap in statin treatment; use of any other statins was not assessed after this 90-day gap. Therefore, we were unable to distinguish between "temporary" and "permanent" treatment discontinuation, potentially overestimating our discontinuation rates. The metric used to gauge adherence is also subject to limitations that may underestimate (e.g., missing prescriptions filled outside the insured setting) or overestimate (e.g., assuming a prescription filled is a prescription consumed) adherence, and it does not distinguish physician-mandated changes from patient choice.

Finally, a number of factors could influence the decision to switch between statins, including the availability of generics, regulatory approval of new agents, or changes in recommended use for a particular agent. For example, in June 2011 (during the data collection window), the U.S. Food and Drug Administration advised physicians to limit the use of simvastatin 80 mg (a high-intensity regimen) because of the risk of muscle injury.[47] The proportion of patients switching from high-intensity therapy was potentially affected by this guidance.

Conclusions

These data indicate a lack of intensive statin-based therapy among patients at high risk for CV events. The continued use of moderate- to low-intensity therapy, failure to intensify treatment, poor adherence, and high rates of discontinuation result in a large number of patients who are inadequately protected from recurrent CV events. The current ACC/AHA lipid management guidelines recommend high-intensity statin treatment for men and women who are aged 75 years or younger and who have clinical ASCVD (e.g., CHD, stroke, or PAD).[3] Similarly, the National Lipid Association advocates the use of moderate- to high-intensity statins for the first-line treatment of hyperlipidemia and consideration of moderate- to high-intensity statin therapy for patients with ASCVD or type 2 diabetes, regardless of baseline atherogenic cholesterol levels.[48] Given the results of this study, health care system-based interventions and new therapeutic paradigms are necessary to optimize patient care, manage risk, and enhance outcomes.

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DISCLOSURES

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All authors contributed to the study design, protocol development, and results interpretation. Lin and Menzin were responsible for conducting the study analyses. All authors were involved in manuscript development and approved the submitted version.

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APPENDIX Diagnostic and Procedure Codes

Brief Code Description	ICD-9-CM, CPT, or HCPCSII Code	Description
Abdominal aortic aneurysm	35081-35103	Open repair of abdominal aortic aneurysm
Abdominal aortic aneurysm	441.3x, 441.3	Abdominal aortic aneurysm
Abdominal aortic aneurysm	441.4x, 441.4	Abdominal aortic aneurysm
Abdominal aortic aneurysm	34800-34805	Endovascular repair of infrarenal abdominal aortic aneurysm
Acute MI	410.xx	Acute myocardial infarction
Carotid artery disease	00.63	Percutaneous insertion of carotid artery stent(s)
Carotid artery disease	38.13, 38.18	Endarterectomy of upper limb vessels/lower limb arteries
Carotid artery disease	433.1x	Occlusion and stenosis of carotid artery without mention of cerebral infarction
Carotid artery disease	35301	Endarterectomy
Carotid artery disease	37215-37216	Stenting of carotid artery
Coronary revascularization procedures	G0290	Transcatheter placement of a drug eluting intracoronary stent(s)
Coronary revascularization procedures	G0291	Transcatheter placement of a drug eluting intracoronary stent(s)
Coronary revascularization procedures	S2205-S2209	Minimally invasive direct coronary artery bypass surgery
Coronary revascularization procedures	00.66	Percutaneous transluminal coronary angioplasty [PTCA] or coronary atherectomy
Coronary revascularization procedures	36.0x	Removal of coronary artery obstruction and insertion of stent(s)
Coronary revascularization procedures	36.1x	Bypass anastomosis for heart revascularization
Coronary revascularization procedures	36.2x	Heart revascularization by arterial implant
Coronary revascularization procedures	36.3x	Other heart revascularization
Coronary revascularization procedures	92980	Transcatheter placement of an intracoronary stent(s)
Coronary revascularization procedures	92981	Transcatheter placement of an intracoronary stent(s)
Coronary revascularization procedures	92982	Percutaneous transluminal coronary balloon angioplasty
Coronary revascularization procedures	92984	Percutaneous transluminal coronary balloon angioplasty
Coronary revascularization procedures	92995	Percutaneous transluminal coronary atherectomy
Coronary revascularization procedures	92996	Percutaneous transluminal coronary atherectomy
Coronary revascularization procedures	33510-33536 (except 33530)	Coronary artery bypass
Diabetes with complication	250.1x	Diabetes with ketoacidosis
Diabetes with complication	250.1	Diabetes with ketoacidosis, type II or unspecified type, not stated as uncontrolled
Diabetes with complication	250.11	Diabetes with ketoacidosis, type I [juvenile type], not stated as uncontrolled
Diabetes with complication	250.12	Diabetes with ketoacidosis, type II or unspecified type, uncontrolled
Diabetes with complication	250.13	Diabetes with ketoacidosis, type I [juvenile type], uncontrolled
Diabetes with complication	250.2x	Diabetes with hyperosmolarity
Diabetes with complication	250.20	Diabetes with hyperosmolarity, type II or unspecified type, not stated as uncontrolled
Diabetes with complication	250.21	Diabetes with hyperosmolarity, type I [juvenile type], not stated as uncontrolled
Diabetes with complication	250.22	Diabetes with hyperosmolarity, type II or unspecified type, uncontrolled
Diabetes with complication	250.23	Diabetes with hyperosmolarity, type I [juvenile type], uncontrolled
Diabetes with complication	250.3x	Diabetes with other coma
Diabetes with complication	250.30	Diabetes with other coma, type II or unspecified type, not stated as uncontrolled
Diabetes with complication	250.31	Diabetes with other coma, type I [juvenile type], not stated as uncontrolled
Diabetes with complication	250.32	Diabetes with other coma, type II or unspecified type, uncontrolled
Diabetes with complication	250.33	Diabetes with other coma, type I [juvenile type], uncontrolled
Diabetes with complication	250.4x	Diabetes with renal manifestations
Diabetes with complication	250.40	Diabetes with renal manifestations, type II or unspecified type, not stated as uncontrolled
Diabetes with complication	250.41	Diabetes with renal manifestations, type I [juvenile type], not stated as uncontrolled
Diabetes with complication	250.42	Diabetes with renal manifestations, type II or unspecified type, uncontrolled
Diabetes with complication	250.43	Diabetes with renal manifestations, type I [juvenile type], uncontrolled
Diabetes with complication	250.5x	Diabetes with ophthalmic manifestations
Diabetes with complication	250.50	Diabetes with ophthalmic manifestations, type II or unspecified type, not stated as uncontrolled
Diabetes with complication	250.51	Diabetes with ophthalmic manifestations, type I [juvenile type], not stated as uncontrolled
Diabetes with complication	250.52	Diabetes with ophthalmic manifestations, type II or unspecified type, uncontrolled
Diabetes with complication	250.53	Diabetes with ophthalmic manifestations, type I [juvenile type], uncontrolled
Diabetes with complication	250.6x	Diabetes with neurological manifestations
Diabetes with complication	250.60	Diabetes with neurological manifestations, type II or unspecified type, not stated as uncontrolled
Diabetes with complication	250.61	Diabetes with neurological manifestations, type I [juvenile type], not stated as uncontrolled
Diabetes with complication	250.62	Diabetes with neurological manifestations, type II or unspecified type, uncontrolled
Diabetes with complication	250.63	Diabetes with neurological manifestations, type I [juvenile type], uncontrolled
Diabetes with complication	250.7x	Diabetes with peripheral circulatory disorders

APPENDIX Diagnostic and Procedure Codes *(continued)*

Brief Code Description	ICD-9-CM, CPT, or HCPCSII Code	Description
Diabetes with complication	250.70	Diabetes with peripheral circulatory disorders, type II or unspecified type, not stated as uncontrolled
Diabetes with complication	250.71	Diabetes with peripheral circulatory disorders, type I [juvenile type], not stated as uncontrolled
Diabetes with complication	250.72	Diabetes with peripheral circulatory disorders, type II or unspecified type, uncontrolled
Diabetes with complication	250.73	Diabetes with peripheral circulatory disorders, type I [juvenile type], uncontrolled
Diabetes with complication	250.8x	Diabetes with other specified manifestations
Diabetes with complication	250.80	Diabetes with other specified manifestations, type II or unspecified type, not stated as uncontrolled
Diabetes with complication	250.81	Diabetes with other specified manifestations, type I [juvenile type], not stated as uncontrolled
Diabetes with complication	250.82	Diabetes with other specified manifestations, type II or unspecified type, uncontrolled
Diabetes with complication	250.83	Diabetes with other specified manifestations, type I [juvenile type], uncontrolled
Diabetes with complication	250.9x	Diabetes with unspecified complication
Diabetes with complication	250.90	Diabetes with unspecified complication, type II or unspecified type, not stated as uncontrolled
Diabetes with complication	250.91	Diabetes with unspecified complication, type I [juvenile type], not stated as uncontrolled
Diabetes with complication	250.92	Diabetes with unspecified complication, type II or unspecified type, uncontrolled
Diabetes with complication	250.93	Diabetes with unspecified complication, type I [juvenile type], uncontrolled
Diabetes without complication	250.0x	Diabetes mellitus without mention of complication
Diabetes without complication	250.00	Diabetes mellitus without mention of complication, type II or unspecified type, not stated as uncontrolled
Diabetes without complication	250.01	Diabetes mellitus without mention of complication, type I [juvenile type], not stated as uncontrolled
Diabetes without complication	250.02	Diabetes mellitus without mention of complication, type II or unspecified type, uncontrolled
Diabetes without complication	250.03	Diabetes mellitus without mention of complication, type I [juvenile type], uncontrolled
Ischemic stroke	433.xx, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91	Occlusion and stenosis of precerebral arteries
Old MI	412.xx, 412	Old myocardial infarction
Other chronic ischemic heart disease	414.xx	Other forms of chronic ischemic heart disease
PAD	37220-37235	Endovascular revascularization, lower extremities
PAD	00.55	Insertion of drug-eluting peripheral vessel stent(s)
PAD	00.61	Percutaneous angioplasty or atherectomy of precerebral (extracranial) vessel(s)
PAD	00.64	Percutaneous insertion of other precerebral (extracranial) artery stent(s)
PAD	39.5x	Angioplasty or atherectomy of other non-coronary vessel(s)
PAD	39.72	Endovascular repair or occlusion of head and neck vessels
PAD	39.74	Endovascular removal of obstruction from head and neck vessel(s)
PAD	39.9x	Insertion of non-drug-eluting peripheral vessel stent(s)
PAD	443.8x	Other specified peripheral vascular diseases
PAD	443.9x	Peripheral vascular disease, unspecified
PAD	444.2x	Embolism and thrombosis of arteries of the extremities
PAD	445.0x	Atheroembolism of extremities
PAD	440.xx, 440.2x, 440.3x, 440.4	Atherosclerosis (Excludes following which are coded separately: basilar, carotid, cerebral, coronary, mesenteric, precerebral, pulmonary, and vertebral)
PAD	35450-35459	Transluminal angioplasty: open (excluding venous)
PAD	35470-35475	Transluminal angioplasty: percutaneous (excluding venous)
PAD	35480-35485	Transluminal atherectomy: cutdown
PAD	35490-35495	Transluminal atherectomy: percutaneous
PAD	35501-35571	Arterial bypass using vein grafts
PAD	35583-35587	Lower extremity revascularization: in-situ vein bypass
PAD	35601-35671	Arterial bypass with synthetic grafts
PAD	37205-37208	Insertion of intravascular stent
PAD	93668	Rehabilitation services: peripheral arterial disease
Stable angina	413.xx, 413.x	Angina pectoris
Transient ischemic attack	v12.54	Transient ischemic attack (TIA), and cerebral infarction without residual deficits
Transient ischemic attack	435.0x	Basilar artery syndrome (Transient cerebral ischemia)
Transient ischemic attack	435.1x	Vertebral artery syndrome (Transient cerebral ischemia)
Transient ischemic attack	435.8x	Other specified transient cerebral ischemias (Transient cerebral ischemia)
Transient ischemic attack	435.9x	Unspecified transient cerebral ischemia (Transient cerebral ischemia)
Unstable angina	411.81	Acute coronary occlusion without myocardial infarction
Unstable angina	411.1x, 411.1	Intermediate coronary syndrome

CPT = Current Procedural Terminology; HCPCSII = Healthcare Common Procedure Coding System Level II; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; MI = myocardial infarction; PAD = peripheral artery disease.