8-1-2022

Usefulness of Statins as Secondary Prevention Against Recurrent and Terminal Major Adverse Cardiovascular Events

Kristen M. Tecson

Aaron Y. Kluger

Andrea E. Cassidy-Bushrow
Henry Ford Health, acassid1@hfhs.org

Bin Liu
Henry Ford Health, BLiu2@hfhs.org

Chad M. Coleman
Henry Ford Health, ccolem16@hfhs.org

See next page for additional authors

Authors

Kristen M. Tecson, Aaron Y. Kluger, Andrea E. Cassidy-Bushrow, Bin Liu, Chad M. Coleman, Laney K. Jones, Celeena R. Jefferson, Jeffrey J. VanWormer, and Peter A. McCullough

Usefulness of Statins as Secondary Prevention Against Recurrent and Terminal Major Adverse Cardiovascular Events

Kristen M. Tecson, PhD[a,*], Aaron Y. Kluger, MPH[a], Andrea E. Cassidy-Bushrow, PhD[b], Bin Liu, MPH[b], Chad M. Coleman, MPH[b], Laney K. Jones, PharmD, MPH[c], Celeena R. Jefferson, MIT[c], Jeffrey J. VanWormer, PhD[d], and Peter A. McCullough, MD, MPH[e]

Clinical guidelines recommend statins for patients with atherosclerotic cardiovascular disease (ASCVD), but many remain untreated. The goal of this study was to assess the impact of statin use on recurrent major adverse cardiovascular events (MACE). This study used medical records and insurance claims from 4 health care systems in the United States. Eligible adults who survived an ASCVD hospitalization from September 2013 to September 2014 were followed for 1 year. A multivariable extended Cox model examined the outcome of time-to-first MACE, then a multivariable joint marginal model investigated the association between post-index statin use and nonfatal and fatal MACE. There were 8,168 subjects in this study; 3,866 filled a statin prescription ≤90 days before the index ASCVD event (47.33%) and 4,152 filled a statin prescription after the index ASCVD event (50.83%). These post-index statin users were younger, with more co-morbidities. There were 763 events (315/763, 41.3% terminal) experienced by 686 (8.4%) patients. The adjusted overall MACE risk reduction was 18% (HR 0.82, 95% CI 0.70 to 0.95, p = 0.007) and was more substantial in the first 180 days (HR 0.72, 95% CI 0.60 to 0.86, p <0.001). There was a nonsignificant 19% reduction in the number of nonfatal MACE (rate ratio 0.81, 95% CI 0.49 to 1.32, p = 0.394) and a 65% reduction in the risk of all-cause death (HR 0.35, 95% CI 0.22 to 0.56, p <0.001). In conclusion, we found a modest increase in statin use after an ASCVD event, with nearly half of the patients untreated. The primary benefit of statin use was protection against early death. Statin use had the greatest impact in the first 6 months after an ASCVD event; therefore, it is crucial for patients to quickly adhere to this therapy. **(Am J Cardiol 2022;176:37−42)**

Introduction

Millions of adults in the United States (US) are affected by cardiovascular events each year, reducing their quality of life and increasing their risk for death.[1] Hyperlipidemia is a significant risk factor for the development of atherosclerotic cardiovascular disease (ASCVD), which is present in 47% of young adults with ASCVD.[2,3] Lipid-lowering therapy is a cornerstone of secondary ASCVD prevention, but many patients remain untreated. The near-term consequences of medication underutilization after an acute event are not well understood. Although there is a panoply of lipid-lowering therapies, we chose to limit this analysis to the American Heart Association guideline-recommended first-line medication of statins.[4] Hence, the purpose of this report is to study the association between statin use/nonuse and recurrent major adverse cardiovascular events (MACE) in a cohort of patients across the US who had a recent acute ASCVD event.

Methods

This study is a collaboration between 4 US health care systems (Baylor Scott & White [BSW], Texas; Henry Ford, Michigan; Geisinger, Pennsylvania; and Marshfield Clinic, Wisconsin) participating in the Health Care Systems Research Network (HCSRN). The HCSRN maintains data standards between health care organizations to create a common data model to assemble pooled data sets to answer multicenter research questions.[5] For this project, BSW developed and distributed code to collaborators to extract the minimum necessary care, administrative, and claims data to yield a deidentified dataset. This study received approval from the Baylor Scott & White Research Institute's institutional review board through expedited review and a waiver of informed consent. Henry Ford and Marshfield ceded to the Baylor Scott & White Research Institute's institutional review board with a reliance agreement, and Geisinger's institutional review board

[a]Baylor Heart and Vascular Institute, Baylor Scott & White Research Institute, Dallas, Texas; [b]Department of Public Health Sciences, Henry Ford Hospital, Detroit, Michigan; [c]Center for Pharmacy Innovation and Outcomes, Geisinger, Danville, Pennsylvania; [d]Center for Clinical Epidemiology & Population Health, Marshfield Clinic Research Institute, Marshfield, Wisconsin; and [e]Cardiorenal Society of America, Phoenix, Arizona. Manuscript received January 24, 2022; revised manuscript received and accepted April 5, 2022.

See page 41 for disclosure information.

*Corresponding author: Tel: 214.820.5451, Fax: 214.820.7393.
E-mail address: Kristen.Tecson@bswhealth.org (K.M. Tecson).

https://doi.org/10.1016/j.amjcard.2022.04.018

determined that the study did not involve human subjects and was not subject to their oversight.

We used a retrospective cohort design to answer our research question. Eligible adults survived an index ASCVD hospitalization from September 30, 2013 to September 30, 2014 and were followed up to 1 year. We extracted demographics (gender, age, race, Hispanic ethnicity, and insurance type), and used *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes and prescription fills during the year prior to the index to identify co-morbidities (type II diabetes mellitus, chronic kidney disease, hyperlipidemia, and hypertension). We recorded statin use 90 days before and after the index. The primary outcome was MACE (acute myocardial infarction, ischemic stroke, revascularization, unstable angina, acute presentation of chronic ASCVD, all-cause death) within 1 year of index.

We created a multivariable extended Cox model with robust sandwich estimates to investigate the association between post-index statin use (assessed through prescription fill) and time-to-first recurrent MACE while accounting for clustering (by healthcare system), demographics (gender, age, race), and co-morbidities (type II diabetes mellitus, chronic kidney disease, hyperlipidemia, hypertension, ASCVD history). After analyzing the time-to-first MACE, we considered an alternate analytic framework using the marginal joint model of Huang and Wang[6] to make inferences using the comprehensive profile of recurrent and terminal events.[7] This model implies that the subject-specific event rate is positively correlated with the risk of terminal event (i.e., subjects who survive longer tend to have lower event rates); although, this model has also been shown to yield unbiased estimates for independent processes.[7] Herein, we distinguished MACE as being nonfatal (recurrent) or fatal (terminal). Because the model could not provide stable estimates for the third or fourth events owing to the small event counts, we included information only through the second MACE. We used the same covariates as the first model but dichotomized age and race to improve computational efficiency. We used a nonparametric bootstrap method for clustered data by repeatedly sampling the subjects with replacement to estimate standard errors and obtain 95% confidence intervals (CIs) and p-values. Analyses were performed in SAS version 9.4 (Cary, North Carolina) and the 'reReg' R package.[8]

Results

There were 8,168 patients in this study, with the 3 leading causes of entry being acute presentation of chronic ASCVD (2,337, 28.6%), acute myocardial infarction (2,156, 25.4%), and ischemic stroke (1,458, 17.9%). There were 3,866 patients (47.33%) who filled a statin prescription in the 90 days before the index event; statin users increased to 4,152 within 90 days after index (50.83%). These post-index statin users were younger with more co-morbidities than nonusers (Table 1). Of the pre-index statin users, 3,274 continued treatment after the index event (84.69%); 878 of pre-index nonusers (20.41%) were initiated on statins after index. There were 763 events experienced by 686 patients (8.4%) within 1 year (Table 2). Of all events, 315 were terminal (41.3%); most deaths (284, 90.2%) occurred as the first MACE in follow-up.

The unadjusted effect of post-index statin use was associated with a 20% reduction in the risk of 1-year MACE (HR: 0.80, 95% CI: 0.69 to 0.93, p = 0.0043) and was similar after adjusting for demographics and co-morbidities (adjusted HR: 0.82, 95% CI: 0.70 to 0.95, p = 0.0074). We observed a time-dependent effect of statin use (interaction term between time and statin use: p <0.0001) and achieved the proportional hazards assumption by dichotomizing the follow-up time as ≤180 and >180 days. This unadjusted model showed a 29% risk reduction (HR: 0.71, 95% CI: 0.59 to 0.85, p = 0.0003) in the initial 180 days after the index for those who used a statin versus those who did not. However, it was not associated with the MACE outcome after 180 days (HR: 1.04, 95% CI: 0.80 to 1.35, p = 0.7663). Similarly, the adjusted model showed a 28% risk reduction (HR: 0.72, 95% CI: 0.60 to 0.86, p = 0.0004) in the initial 180 days after the index event for those who used a statin compared with those who did not (Figure 1). All-cause death was a substantial driver of the MACE risk difference, with 93 post-index statin users (2.24%) dying versus 191 nonusers (4.76%).

In the alternate analytic framework, which distinguished MACE as nonfatal (recurrent) and terminal, we found that taking a statin after index was associated with a (nonsignificant) 20% reduction in the number of nonfatal MACE recurrences (rate ratio = 0.80, 95% CI 0.46 to 1.39, p = 0.429) and a 67% reduction in the risk of all-cause death (HR 0.33, 95% CI 0.23 to 0.49, p <0.001). The effect of taking a statin was similar after adjusting for demographics and co-morbidities (Table 3). From this multivariable joint model, we found that taking a statin was associated with a (nonsignificant) 19% reduction in the number of nonfatal MACE recurrences (rate ratio = 0.81, 95% CI 0.49 to 1.32, p = 0.394) as well as a 65% reduction in the risk of all-cause death (HR 0.35, 95% CI 0.22 to 0.56, p <0.001). Being older than the median age of this cohort (i.e., >73.79 years) more than doubled the risk of all-cause death and being White was associated with more than a 2-fold increase in risk of recurrent (nonfatal) MACE. Figure 2 depicts the patients under observation and their MACE according to statin use.

Discussion

In this multicenter study of 8,168 patients, we found that approximately half of the cohort did not fill a statin prescription within 90 days after an ASCVD event. About 8% had ≥1 MACE within 1 year after their index ASCVD event, but post-index statin users had approximately 19% less risk of 1-year MACE. Statin protection was highest (28% risk reduction) in the first 180 days of hospitalization. Considering recurrent and terminal event processes jointly, the primary benefit of statin use was protection against early death.

Overall, statin use in this cohort was low, although the results were similar to those from a large database representative of patients with ASCVD in the US.[9] That study found an increasing trend of statin use from approximately 50% to 60% between 2007 and 2016.[9] Another study had similar

Table 1
Patient characteristics of statin users and non-users

Characteristic	Statin use after index event		P-value
	Yes (n = 4,152)	No (n = 4,016)	
Male	2,346 (56.5%)	2,176 (54.18%)	0.0350
Age (years)	72.3 [62.2, 81.0]	75.2 [65.9, 83.5]	<0.0001
Age category (years)			<0.0001
18−34	8 (0.19%)	62 (1.54%)	
35−44	85 (2.05%)	72 (1.79%)	
45−54	334 (8.04%)	250 (6.23%)	
55−64	835 (20.11%)	555 (13.82%)	
65−74	1,115 (26.85%)	1,015 (25.27%)	
75+	1,775 (42.75%)	2,062 (51.34%)	
Race			0.0032
Black	378 (9.1%)	406 (10.11%)	
White	3,287 (79.17%)	3,056 (76.1%)	
Other/unknown	487 (11.73%)	554 (13.79%)	
Hispanic			0.0003
Yes	80 (1.93%)	52 (1.29%)	
No	3,619 (87.16%)	3,425 (85.28%)	
Unknown	453 (10.91%)	539 (13.42%)	
Insurance			<0.0001
Commercial	1,644 (39.60%)	1,295 (32.25%)	
Medicaid	213 (5.13%)	181 (4.51%)	
Medicare	2,241 (53.97%)	2,383 (59.34%)	
Other payors[†]	54 (1.30%)	157 (3.91%)	
Current smoker	645 (15.53%)	604 (15.04%)	0.5345
Type I diabetes mellitus	424 (10.21%)	336 (8.37%)	0.0041
Type II diabetes mellitus	1,902 (45.81%)	1,615 (40.21%)	<0.0001
Chronic kidney disease	1,108 (26.69%)	1,142 (28.44%)	0.0767
Hyperlipidemia	3,496 (84.2%)	3,020 (75.2%)	<0.0001
Hypertension	3,624 (87.28%)	3,402 (84.71%)	0.0008
Index event			<0.0001
Acute myocardial infarction	1,143 (27.53%)	1,013 (25.22%)	
Angina pectoris	60 (1.45%)	93 (2.32%)	
Ischemic stroke or transient ischemic attack	736 (17.73%)	859 (21.39%)	
Peripheral arterial disease	445 (10.72%)	592 (14.74%)	
Revascularization	547 (13.17%)	343 (8.54%)	
Other	1,221 (29.41%)	1,116 (27.79%)	
History of ASCVD (in year prior to index)	602 (14.5%)	563 (14.02%)	0.5350

[†] Includes health maintenance organizations, indemnity plans, patient-funded, and unknown/missing insurance data.
ASCVD = atherosclerotic cardiovascular disease.

conclusions about the ASCVD population in the US in 2013, in which they estimated 45% were not taking any kind of lipid-lowering therapy.[10] Conversely, a study of more than 1 million records in the Veterans Affairs (VA) database revealed that 80.1% of patients with ASCVD were taking statins and 23.8% were on high-intensity statins.[11] This exceeds the percent of statin users in our study, although it is likely a function of different underlying sociodemographic characteristics in VA samples, which tend to include fewer women and minorities (who are less likely to receive statin therapy).[12,13] More recently, Heitmann and coworkers[14] estimated an approximate 39% statin adherence rate for patients in the 2 years after coronary artery bypass graft surgery. Similarly, Elkomos et al[15] found a 43% adherence rate for patients 2 years after admission for coronary heart disease.

Table 2
Description of all major adverse cardiac events

Event Type	Major Adverse Cardiac Event Within 1 y of Index				
	First	Second	Third	Fourth	Total
Acute myocardial infarction	141 (20.6%)	12 (16.7%)	1 (25.0%)	0	154 (20.2%)
Angina pectoris	63 (9.2%)	9 (12.5%)	1 (25.0%)	0	73 (9.6%)
Ischemic stroke	66 (9.6%)	7 (9.7%)	0	0	73 (9.6%)
Revascularization	132 (19.2%)	15 (20.8%)	0	1 (100%)	148 (19.4%)
Death	284 (41.4%)	29 (40.3%)	2 (50.0%)	0	315 (41.3%)
Total Events	686	72	4	1	763

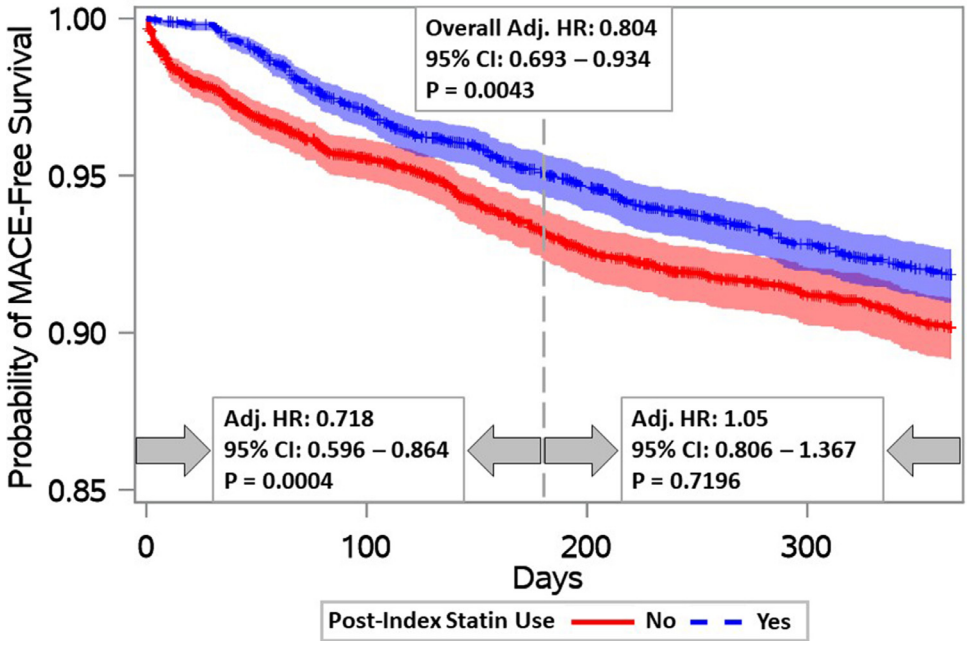

Figure 1. Kaplan-Meier curve stratified by post-index statin use with overall and 180-d stratified adjusted model results.CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular event.

Because the effect of post-index statin use decreased over time, we hypothesize that some patients who filled their initial prescription did not adhere to it long-term. A prior study showed that patients with ASCVD who were 50% adherent to statins had a 30% higher mortality risk than similar patients with a 90% adherence.[16] Patients often discontinue statins without discussing it with their physician once they experience side effects.[17] Statins are generally well-tolerated; however, a small subset of patients may develop myalgias, myopathies, and/or rhabdomyolysis.[18] Some patients are truly statin-intolerant, but approximately 90% of individuals with perceived statin-intolerance who undergo a challenge are able to remain on statin therapy long-term.[19] Such patients typically require more physician contact to find the best type and dose of statin. Patients in a VA study with more than the median number of annual primary care visits (i.e., >3) were more likely to adhere to a statin regimen.[11]

Because nonadherence to statins is a widespread problem, many have researched interventions to improve it. Elkomos and coworkers[15] found that several types of pharmacist-led interventions improved statin adherence, with the most successful type of intervention being between pharmacists and providers. In one such intervention, pharmacists contacted physicians of patients recently admitted for coronary heart disease, and the rates of statin use were 72% for patients in the intervention group versus 43% for patients in the control group at 2 years. Similarly, George and coworkers[20] found that adherence to guideline-directed medical therapy improved when clinical pharmacists performed periodic clinical audits and sent reports to cardiologists. Rana and coworkers[21] found that patients who had been hospitalized for ASCVD were more likely to adhere to statins if they had LDL-C testing after discharge. Lansberg et al[22] suggest that collaboration between physicians and pharmacists is needed to produce patient-directed interventions including counseling, education, removing barriers to care, and medication reminders. Yao et al[23] even detected a better statin adherence rate for patients who were the same gender as their prescribing physician. Taken together, it is clear that combating the problem of nonadherence requires an investment of time, trust, and education from several parties.

Table 3
Results from the joint marginal model for recurrent and terminal major adverse cardiovascular events

	Recurrent Event Process			Terminal Event Process		
Variable	Rate Ratio	95% CI	P-value	Hazard Ratio	95% CI	P-value
Statin use post-index (yes vs. no)	0.81	0.49−1.32	0.394	0.35	0.22−0.56	<0.001
Gender (female vs. male)	1.00	0.59−1.68	0.994	0.94	0.58−1.52	0.794
Caucasian (yes vs. no)	2.45	1.50−4.01	<0.001	1.09	0.54−2.22	0.811
Type II Diabetes Mellitus (yes vs. no)	1.40	0.88−2.21	0.150	0.96	0.58−1.61	0.889
Chronic Kidney Disease (yes vs. no)	1.06	0.67−1.69	0.797	0.94	0.57−1.56	0.816
Hyperlipidemia (yes vs. no)	0.92	0.52−1.63	0.768	0.65	0.32−1.34	0.245
Hypertension (yes vs. no)	0.71	0.26−1.91	0.498	1.12	0.34−3.73	0.852
Age (above vs. below median)	1.52	0.87−2.66	0.145	2.56	1.52−4.29	<0.001
History of ASCVD (yes vs. no)	1.16	0.84−1.60	0.365	1.01	0.55−1.85	0.980

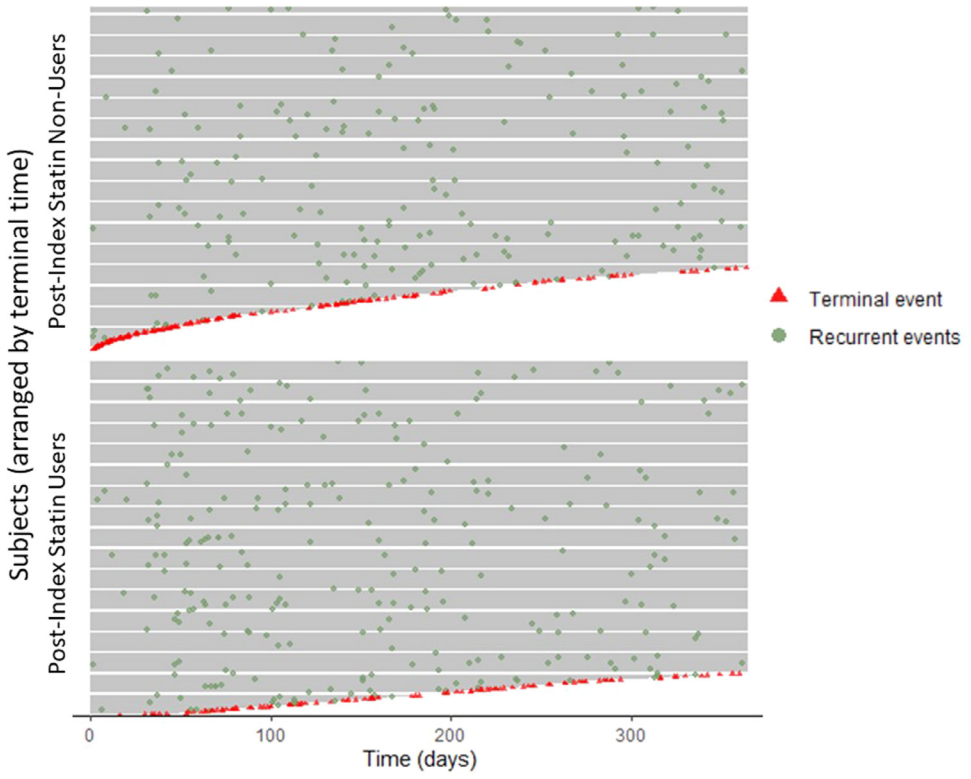

Figure 2. Subjects under observation and the timing of their recurrent (nonfatal) and terminal events according to post-index statin use.

Statins are not only indicated, but also confer the greatest benefit for secondary prevention.[12,24] Long-term statin use may decrease the risk of cardiovascular death by 50% to 55%.[12] A multicenter Spanish study echoed that high-intensity statin therapy, regardless of type, was protective against ASCVD events.[25] Our findings are reflective of those by Lin and coworkers[26] who found low statin adherence, high statin discontinuation, and a high 2-year rate of ASCVD hospitalizations in a cohort of high risk patients. Another study considered primary and secondary prevention, finding that 20.9% and 43.0% of patients had at least 1 cardiovascular event in a 2 years follow-up, respectively. They also found widespread underuse of statins.[27]

Statin-associated protection against fatal events was greater in this study than in clinical trials.[28] Randomized clinical trials (RCTs) identify an isolated treatment effect by eliminating extraneous variability (including behavior/adherence). Results from real-world data analyses, such as ours, are important because they represent a constellation of additional factors that occur in patients' lives (unobserved in RCTs).[29,30] For example, patients who filled scripts may be more likely to engage in healthy lifestyle behaviors.[31] Hence, the results observed in this study may also reflect other health behaviors. Due to the nature of our study, patients could not receive a monetary incentive for adhering to a given study protocol, as occurs in RCTs.[32,33]

The biggest limitation of this study is its retrospective design. Our data were limited to insurance claims; hence, if a patient filled a prescription without insurance, it was not recorded. Further, script fills are indirect measures of adherence. Similarly, we do not know the rate at which providers prescribed drugs or if patients received drug counseling. Due to the definition of the primary variable of interest, immortal time bias may be present.[34] Finally, the study period was chosen to use ICD-9-CM codes; however, newer lipid-lowering therapies are available now.[35] Strengths of this study include the use of previously published ICD and Current Procedural Terminology code sets, its multicenter design, and robust modeling approach.

In conclusion, this study demonstrated a modest increase in statin treatment after an initial ASCVD event, with nearly half of the patients remaining undertreated. When jointly modeling nonfatal and fatal events, we observed that the primary benefit of statin use was protection against early death. Furthermore, because we observed that statin use may have the greatest impact in the first 6 months after an ASCVD event, it is crucial for patients to quickly adhere to therapy.

Disclosures

The authors have no conflicts of interest to declare.

Funding

This work was funded by a grant from Amgen Inc. to the Baylor Scott & White Research Institute.

1. Pahwa R, Jialal I. Atherosclerosis. *StatPearls* 2021.
2. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Shay CM,

Spartano NL, Stokes A, Tirschwell DL, VanWagner LB, Tsao CW. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2020 update: a report from the. *American Heart Association. Circulation.* 2020;141(9):e139–e596.
3. Vikulova DN, Grubisic M, Zhao Y, Lynch K, Humphries KH, Pimstone SN, Brunham LR. Premature atherosclerotic cardiovascular disease: trends in incidence, risk factors, and sex-related differences, 2000 to 2016. *J Am Heart Assoc* 2019;8(14):e012178.
4. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC, Virani SS, Williams KA, Yeboah J, Ziaeian B. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;140(11):e596–e646.
5. Health Care Systems Research Network. Mission and vision. Available at: http://www.hcsrn.org/en/About/. Accessed June 29, 2021.
6. Huang CY, Wang MC. Joint modeling and estimation for recurrent event processes and failure time data. *J Am Stat Assoc* 2004;99(468):1153–1165.
7. Charles-Nelson A, Katsahian S, Schramm C. How to analyze and interpret recurrent events data in the presence of a terminal event: an application on readmission after colorectal cancer surgery. *Stat Med* 2019;38(18):3476–3502.
8. Chiou SH, Huang CY. Recurrent event regression. CRAN. Available at: https://cran.r-project.org/web/packages/reReg/reReg.pdf. Accessed March 8, 2021.
9. Yao X, Shah ND, Gersh BJ, Lopez-Jimenez F, Noseworthy PA. Assessment of trends in statin therapy for secondary prevention of atherosclerotic cardiovascular disease in US adults from 2007 to 2016. *JAMA Netw Open* 2020;3(11):e2025505.
10. Gorcyca K, Khan I, Wadhera R, Klimchak A, Song X, Sanchez R, Gooch K. Prevalence of atherosclerotic cardiovascular disease (ASCVD) and diabetes populations in the United States. *J Clin Lipidol* 2015;9(3):424.
11. Ahmed ST, Mahtta D, Rehman H, Akeroyd J, Al Rifai M, Rodriguez F, Jneid H, Nasir K, Samad Z, Alam M, Petersen LA, Virani SS. Association between frequency of primary care provider visits and evidence-based statin prescribing and statin adherence: findings from the Veterans Affairs system. *Am Heart J* 2020;221:9–18.
12. Banach M, Penson PE. Statins and LDL-C in secondary prevention-so much progress, so far to go. *JAMA Netw Open* 2020;3(11):e2025675.
13. Salami JA, Warraich H, Valero-Elizondo J, Spatz ES, Desai NR, Rana JS, Virani SS, Blankstein R, Khera A, Blaha MJ, Blumenthal RS, Lloyd-Jones D, Nasir K. National trends in statin use and expenditures in the US adult population from 2002 to 2013: insights from the Medical Expenditure Panel Survey. *JAMA Cardiol* 2017;2(1):56–65.
14. Heitmann LA, Gudmundsdottir IJ, Jonsdottir F, Gudbjartsson T, Sigurdsson MI. A retrospective study on adherence to secondary prevention medications after coronary bypass surgery. *Eur J Cardiothorac Surg* 2022:ezac054.
15. Elkomos M, Jahromi R, Kelly MS. Pharmacist-led programs to increase statin prescribing: a narrative review of the literature. *Pharmacy (Basel)* 2022;10(1):13.
16. Rodriguez F, Maron DJ, Knowles JW, Virani SS, Lin S, Heidenreich PA. Association of statin adherence with mortality in patients with atherosclerotic cardiovascular disease. *JAMA Cardiol* 2019;4(3):206–213.
17. Rosenson RS. Statin non-adherence: clinical consequences and proposed solutions. *F1000Res* 2016;(5):F1000 Faculty Rev-714.
18. Turner RM, Pirmohamed M. Statin-related myotoxicity: a comprehensive review of pharmacokinetic, pharmacogenomic and muscle components. *J Clin Med* 2019;9(1):22.
19. Robinson JG. New insights into managing symptoms during statin therapy. *Prog Cardiovasc Dis* 2019;62(5):390–394.
20. George NE, Shukkoor AA, Joseph N, Palanimuthu R, Kaliappan T, Gopalan R. Implementation of clinical audit to improve adherence to guideline-recommended therapy in acute coronary syndrome. *Egypt Heart J* 2022;74(1):4.
21. Rana JS, Virani SS, Moffet HH, Liu JY, Coghlan LA, Vasadia J, Ballantyne CM, Karter AJ. Association of low-density lipoprotein testing after an atherosclerotic cardiovascular event with subsequent statin adherence and intensification. *Am J Med* 2021. S0002−9343(21):00794−00794.
22. Lansberg P, Lee A, Lee ZV, Subramaniam K, Setia S. Nonadherence to statins: individualized intervention strategies outside the pill box. *Vasc Health Risk Manag* 2018;14:91–102.
23. Yao S, Lix L, Teare G, Evans C, Blackburn D. The impact of age and sex concordance between patients and physicians on medication adherence: a population-based study. *Patient Prefer Adherence* 2022;16:169–178.
24. Virani SS, Smith SC Jr, Stone NJ, Grundy SM. Secondary prevention for atherosclerotic cardiovascular disease: comparing recent US and European guidelines on dyslipidemia. *Circ* 2020;141:1121–1123.
25. Perez-Calahorra S, Laclaustra M, Marco-Benedi V, Pinto X, Sanchez-Hernandez RM, Plana N, Ortega E, Fuentes F, Civeira F. Comparative efficacy between atorvastatin and rosuvastatin in the prevention of cardiovascular disease recurrence. *Lipids Health Dis* 2019;18(1):216.
26. Lin I, Sung J, Sanchez RJ, Mallya UG, Friedman M, Panaccio M, Koren A, Neumann P, Menzin J. Patterns of statin use in a real-world population of patients at high cardiovascular risk. *J Manag Care Spec Pharm* 2016;22(6):685–698.
27. Punekar RS, Fox KM, Richhariya A, Fisher MD, Cziraky M, Gandra SR, Toth PP. Burden of first and recurrent cardiovascular events among patients with hyperlipidemia. *Clin Cardiol* 2015;38(8):483–491.
28. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996;335(14):1001–1009.
29. Ramagopalan SV, Simpson A, Sammon C. Can real-world data really replace randomized clinical trials? *BMC Med* 2020;18(1):13.
30. Bartlett VL, Dhruva SS, Shah ND, Ryan P, Ross JS. Feasibility of using real-world data to replicate clinical trial evidence. *JAMA Netw Open* 2019;2(10):e1912869.
31. Náfrádi L, Nakamoto K, Schulz PJ. Is patient empowerment the key to promote adherence? A systematic review of the relationship between self-efficacy, health locus of control and medication adherence. *PLoS One* 2017;12(10):e0186458.
32. Parkinson B, Meacock R, Sutton M, Fichera E, Mills N, Shorter GW, Treweek S, Harman NL, Brown RCH, Gillies K, Bower P. Designing and using incentives to support recruitment and retention in clinical trials: a scoping review and a checklist for design. *Trials* 2019;20(1):624.
33. Krutsinger DC, McMahon J, Stephens-Shields AJ, Bayes B, Brooks S, Hitsman BL, Lubitz SF, Reyes C, Schnoll RA, Ryan Greysen S, Mercede A, Patel MS, Reale C, Barg F, Karlawish J, Polsky D, Volpp KG, Halpern SD. Randomized evaluation of trial acceptability by INcentive (RETAIN): study protocol for two embedded randomized controlled trials. *Contemp Clin Trials* 2019;76:1–8.
34. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ* 2010;340:b5087.
35. Feingold KR. Cholesterol lowering drugs. In: Feingold KR, Anawalt B, Boyce A, eds. Endotext. South Dartmouth, MA: MDText.com, Inc.; 2000.