

Physicians Voluntarily Using an EHR-Based CDS Tool Improved Patients' Guideline-Related Statin Prescription Rates: A Retrospective Cohort Study

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Abstract

Background In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) released a revised guideline on statin therapy initiation. The guideline included a 10-year risk calculation based on regression modeling, which made hand calculation infeasible. Compliance to the guideline has been suboptimal, as many patients were recommended but not prescribed statin therapy. Clinical decision support (CDS) tools may improve statin guideline compliance. Few statin guideline CDS tools evaluated clinical outcome.

Objectives We determined if use of a CDS tool, the statin macro, was associated with increased 2013 ACC/AHA statin guideline compliance at the level of statin prescription versus no statin prescription. We did not determine if each patient's statin prescription met ACC/AHA 2013 therapy intensity recommendations (high vs. moderate vs. low).

Methods The authors developed a clinician-initiated, EHR-embedded statin macro command ("statin macro") that displayed the 2013 ACC/AHA statin guideline recommendation in the electronic health record documentation. We included patients who had a primary care visit during the study period (January 1–June 30, 2016), were eligible for statin therapy based on the ACC/AHA guideline prior to the study period, and were not prescribed statin therapy prior to the study period. We tested the association of macro usage and statin therapy prescription during the study period using relative risk and mixed effect logistic regression.

Results Subjects included 11,877 patients seen in primary care, who were retrospectively recommended statin therapy at study initiation based on the ACC/AHA guideline, but who had not received statin therapy. During the study period, 125

Keywords

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- ▶ decision support techniques
- ▶ anticholesteremic agents
- ▶ atherosclerosis

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clinicians used the statin macro command for 389 of the 11,877 patients (3.2%). Of the 389 patients for whom that statin macro was used, 108 patients (28%) had a statin prescribed during the study period. Of the 11,488 for whom the statin macro was not used, 1,360 (13%) patients received a clinician-prescribed statin (relative risk 2.3, $p < 0.001$). Controlling for patient covariates and clinicians, statin macro usage was significantly associated with statin therapy prescription (odds ratio 2.86, $p < 0.001$). **Conclusion** Although the statin macro had low uptake, its use was associated with a greater rate of statin prescriptions (dosage not determined) for patients whom 2013 ACC/AHA guidelines required statin therapy.

Background and Significance

Although many best practice guidelines exist for initiating medication in select patient groups, clinicians prescribe the targeted medications at suboptimal rates.¹ In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) released a revised guideline regarding statin therapy initiation² (see **Fig. 1** and **Supplementary Material** (available in the online version) for a brief overview of the 2013 ACC/AHA statin guideline). Both the 2013 ACC/AHA statin guideline compliance, and the percentage of patients prescribed statin therapy per the guideline, varied by patient population. In 2015, cardiologists prescribed 2013 guideline-compliant, secondary prevention statin therapy to 91% of their patients with atherosclerotic cardiovascular disease (ASCVD).³ However, prevention guideline compliance was suboptimal in primary care patients. In the 4 years following 2013 ACC/AHA statin guideline release, 42% of patients with no history of ASCVD and a 10-year ASCVD risk score $> 7.5\%$ received statin prescription in accordance with the ACC/AHA statin guideline.⁴

A postulated reason for suboptimal 2013 ACC/AHA statin guideline compliance was its complexity.^{5,6} While previous statin guidelines utilized integer-based risk scores that could be determined by hand,⁷ the 2013 ACC/AHA statin guideline utilized four regression-based risk scoring equations that required use of a calculator. Which 2013 ACC/AHA regression equation to use depended on a patient's gender and race. Each regression equation incorporated age, high-density lipoprotein (HDL), total cholesterol, diabetes mellitus (DM) history, systolic blood pressure, antihypertensive medication, and smoking status. The 10-year ASCVD risk calculation determined if statin therapy should be initiated in patients without DM and with low-density lipoprotein (LDL) values between 70 and 189 mg/dL. Although other existing 10-year risk calculators such as Framingham⁸ and QRISK⁹ were available, the ACC/AHA developed their 2013 new 10-year risk calculator based on regression equations. Concurrent with the 2013 ACC/AHA statin guideline publication, the ACC/AHA released mobile and online ASCVD Risk Estimator calculators.^{10,11} However, clinicians had to manually enter information, which was time consuming.¹² These calculators were available prior to the studies showing suboptimal 2013 ACC/AHA statin guideline compliance.⁴ The current study

authors hypothesized that a clinical decision support (CDS) tool that automatically retrieved patient data and performed regression calculation could improve 2013 ACC/AHA statin guideline compliance.

Previous CDS tools improved guideline compliance with modest benefit¹³ for DM,¹⁴ heart failure,¹⁵ and pneumonia.¹⁶ Childhood vaccination rates improved when implemented within electronic health record (EHR) templates, with pre-loaded immunization records, and alerts.¹⁷ In randomized control trials, CDS tools with features such as automation, on-screen display, system initiation, and advice to patients as well as clinicians were more effective. Features such as advise within charting or order entry were less effective.^{18,19}

A systematic review identified 34 previous health care intervention tools tested in randomized control trials for lipid management.²⁰ Five CDS tools were integrated into an EHR. For example, the MayoExpertAdvisor study, based on a Web service with prefilled patient data from the EHR, provided 2013 ACC/AHA ASCVD risk calculation. That study showed decreased time for clinicians to determine a statin therapy recommendation, but did not report whether guideline compliance improved.²¹ In a systematic review, a low percentage of CDS tools evaluated clinical benefit.²²

Within the authors' EHR system, Epic,²³ clinicians can initiate CDS tools during note documentation. Such tools can automatically retrieve patient data and perform calculations. Therefore, study clinicians did not need to exit the EHR to perform calculations on an external platform. Previous macro commands were developed at other institutions for obesity counseling²⁴ and H1N1 swine flu recommendations.²⁵ However, those macros did not retrieve patient data or perform calculations.

We implemented the study's statin macro in July 2014, shortly after the November 2013 ACC/AHA guideline and online calculator publications. Unlike earlier statin CDS tools elsewhere that were not integrated into the EHR,²¹ the current study's statin macro was accessible during EHR note generation. The previous tools had been printed on paper forms,^{26,27} shown on a separate screen,^{14,28} or emailed to clinicians.²⁹

Objectives

We determined if the statin macro was associated with statin prescription, regardless of dose, per the 2013 ACC/AHA statin

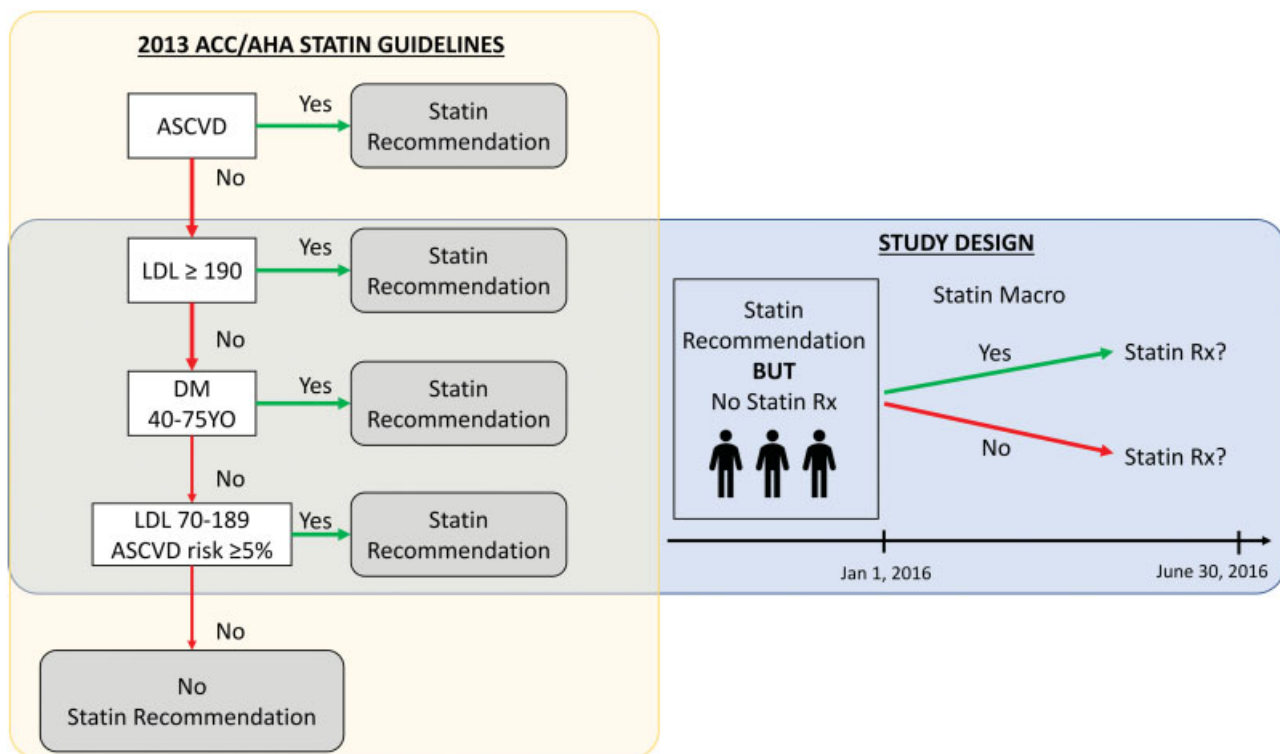


Fig. 1 Central schematic including simplified version of the 2013 American College of Cardiology/American Heart Association (ACC/AHA) statin guideline and study design. For the statin guidelines, patients with a history of ASCVD, LDL ≥ 190 mg/dL, or DM aged 40 to 75 years old were recommended statin therapy. Patients without DM aged 40 to 75 years old and an LDL of 70 to 189 mg/dL necessitated 10-year ASCVD risk calculation. Patients with a 10-year ASCVD risk calculation $\geq 5\%$ were recommended statin therapy while those with a 10-year ASCVD risk calculation $< 5\%$ were not recommended statin therapy. For the study design, patients recommended statin therapy for primary prevention (LDL ≥ 190 mg/dL; DM and 40–75 years old; no DM, LDL 70–189 mg/dL and 10-year ASCVD risk $\geq 5\%$) but not prescribed statin therapy as of December 31, 2015, were included in this study. We tested the association of macro usage and statin therapy prescription during the study period (January 1, 2016–June 30, 2016). Abbreviations: ASCVD, atherosclerotic cardiovascular disease; ASCVD risk, 10-year ASCVD risk calculation; DM, diabetes mellitus; LDL, low-density lipoprotein; Rx, prescription; YO, years old.

guidelines. Specifically, for patients retrospectively recommended (at the time of study initiation) but not prescribed statin therapy, we investigated whether subsequent statin macro usage was associated with statin prescription. We did not determine if each patient's statin prescription met the ACC/AHA 2013 therapy intensity recommendations (high vs. moderate vs. low). **Fig. 1** shows a central schematic of the study design.

Methods

Statin Macro Development

After the November 2013 ACC/AHA statin guideline was published, and prior to the statin macro implementation, we received multiple requests from clinicians to provide a CDS tool for the ACC/AHA statin guideline. We did not assess clinician knowledge of or compliance with the 2013 ACC/AHA statin guideline in our health system. We hypothesized a statin macro could improve knowledge about the 2013 ACC/AHA statin guideline and also guideline compliance.

A multidisciplinary expert panel including cardiologists, internists, neurologists, clinical informaticians, and quality officers developed the statin macro, which was based on the published ACC/AHA statin guideline. Developers tested hundreds of patients for accuracy of the macro's statin guideline

recommendations. During statin macro development, expert panel members revised it several times prior to the study. Revisions led to statin therapy recommendations based on 17 scenarios of a patient's ASCVD history, DM history, LDL level, 10-year ASCVD risk, and medication list (**Supplementary Table S1**, available in the online version). For example, the macro suppressed a statin recommendation if the patient had a statin allergy. Multiple governance committees, including the institutions' primary care leadership, approved use of the macro. The study institution's Institutional Review Board (IRB) approved a waiver of authorization for this study (IRB#: 16-001676).

The clinician-initiated CDS tool was relevant and manageable. The statin macro made a clear recommendation of statin therapy or no statin therapy. The statin macro contained a hyperlink to the 2013 ACC/AHA statin guideline and the ACC/AHA ASCVD Risk Estimator online calculator.¹⁰ The ASCVD Risk Estimator hyperlink allowed clinicians to manually confirm macro recommendations. Errors found in the statin macro could be logged as a ticket to the EHR help desk.

In the study site's Epic EHR terminology, the CDS tool we developed is known as a Smart Phrase. Authors refer to the Smart Phrase herein by its generic name, "macro command," to avoid vendor-specific terminology. While documenting a note, clinicians could type an abbreviated phrase such as "CVRISK"

to invoke the statin macro directly and incorporate its output into the note. Macros of this sort are clinician-initiated CDS tools that are “pulled” by clinicians. Clinician-initiated CDS tools contrast with system-initiated CDS tools that are automatically “pushed” to clinicians as alerts. **Fig. 2** shows a screenshot of the statin macro within a note. Development of the statin macro was consistent with the GUIDES checklist.³⁰ The statin macro automatically retrieved patient data from the EHR. Developers tested hundreds of patients for accuracy of patient data retrieval. In addition to activating the statin macro directly while documenting a clinical note, clinicians could alternatively add the macro to a note template, allowing the macro to upload with every use of the encompassing template.

While EHRs have high consistency, they do not have 100% completeness or correctness.^{31,32} The physician-targeted statin macro delivered consistent, on demand, and fast recommendations within the clinicians’ note documentation workflow. Statin macro versions included those that showed a summary and those that showed all variable values (**Table 1**). Variables were highlighted in blue. Clinicians could customize CDS delivery with these variations.

Statin Macro Implementation

The study institution installed an enterprise-wide version of the EHR from Epic²³ in over 170 urban clinics and 3 hospitals at a large, urban academic medical center from March 2013 to July 2014. Epic was installed in all primary care clinics by July 11, 2013. The statin macro was first accessible to clinicians on July 21, 2014. January 1, 2016 to June 30, 2016 defined the study period.

One of the study sites’ biweekly ambulatory EHR email updates described the statin macro and encouraged usage. Clinician awareness of the statin macro also spread through word of mouth. As a clinician-initiated CDS tool, clinicians

using the macro were likely motivated and believed its usage would improve patient care. The study did not measure the study clinicians’ assessment of their premacro-usage likelihood of prescribing a statin for the patient at hand.

The email advertising the statin macro included instructions. Prior to statin macro implementation, we did not assess factors that would influence guideline compliance. Because the statin macro was a clinician-initiated CDS tool, clinicians were not forced to follow recommendations or explain why they did not follow recommendations. The institution’s clinical leadership supported the statin macro but did not provide incentives for statin guideline compliance.

Study Criteria

January 1, 2016 to June 30, 2016 defined the study period. We chose this 6-month period based on prestudy estimates for the number of times clinicians used the statin macro. As a retrospective cohort study, clinicians did not know during the study period they would be included in this study. Inclusion criteria were patients:

- Who had a primary care visit during the study period. Any outpatient visit with a patient’s primary care clinician defined a primary care visit.
- Who were 40 to 75 years old as of January 1, 2016. The 10-year ASCVD risk calculator was developed for this age range.
- Who did not have a statin prescription before the study period as of December 31, 2015.
- Who were retrospectively identified as candidates for statin therapy based on the 2013 ACC/AHA statin guideline before the study period as of December 31, 2015.



Fig. 2 Screenshot of the statin macro within a note. Blue highlighted text was variable and specific to each patient. The blue “2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline” text included a hyperlink to the 2013 ACC/AHA statin guideline. The blue “here” text included a hyperlink to the online ASCVD Risk Estimator calculator (Screenshot used with permission from © 2019 Epic Systems Corporation).

Table 1 Statin macro examples

Version 1: Recommendation Hyperlinked 2013 ACC/AHA guideline followed by recommendation and statin status	2013 ACC/AHA guideline recommends moderate or high-intensity statin because 10-year ASCVD risk \geq 7.5%. Patient is not taking a statin ^a
Version 2: Brief Hyperlinked 2013 ACC/AHA guideline followed by recommendation and statin status The second line shows the risk calculator results if it should be calculated	2013 ACC/AHA guideline recommends moderate or high-intensity statin because 10-year ASCVD risk \geq 7.5%. Patient is not taking a statin. Ten-year ASCVD risk is 9.0% as of 1:15 PM on January 1, 2016
Version 3: Full Hyperlinked 2013 ACC/AHA guideline followed by recommendation and statin status The second line shows the risk calculator results if it should be calculated The third line shows the optimal risk score The following lines show the values used to calculate ASCVD score	2013 ACC/AHA guideline recommends moderate or high-intensity statin because 10-year ASCVD risk \geq 7.5%. Patient is not taking a statin Ten-year ASCVD risk is 9.0% as of 1:15 PM on January 1, 2016 Ten-year ASCVD risk with optimal risk factors is 3.6% Values used to calculate ASCVD score: Age: 55 years old Gender: Male Race: not African American HDL cholesterol: 30 mg/dL. HDL cholesterol measured 60 days ago Total cholesterol: 200 mg/dL. Total cholesterol measured 60 days ago Systolic BP: 130 mm Hg. BP was measured 2 days ago The patient is not being treated with medication that influences SBP The patient is currently not a smoker The patient does not have a diagnosis of diabetes Click here for the 2013 ACC/AHA Cardiovascular Risk Estimator tool (online calculator)

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.

^aBlue highlighted text was variable and specific to each patient.

Exclusion criteria were patients:

- Who had a statin allergy.
- Who had a history of ASCVD. Patients with a history of ASCVD were recommended statin therapy based on the 2013 ACC/AHA statin guideline for secondary prevention.
- Who did have a statin prescription before the study period as of December 31, 2015.
- Who did not have sufficient data to determine the 2013 ACC/AHA statin guideline recommendation. For example, some patients did not have a LDL measurement or were missing data necessary to calculate the 10-year ASCVD risk (e.g., blood pressure measurement).
- Who were not recommended statin therapy based on the 2013 ACC/AHA statin guideline before the study period as of December 31, 2015.

We extracted EHR data as of December 31, 2015, necessary to determine the ACC/AHA statin guideline recommendation. Data included the patients' age, gender, smoking status, visit diagnoses, and problem list. We extracted the most recent data prior to December 31, 2015, for blood pressure (looking back to January 1, 2014) and cholesterol (total, low-density, and high-density: looking back to January 1, 2011). We extracted statin and antihypertensive medication (December 31, 2015–June 30, 2016, including start and end date of medications), allergies (as of June 30, 2016), and statin macro usage (January 1, 2016–June 30, 2016). Searching note text for “2013 ACC/AHA guideline*10-year ASCVD risk,” where * indicated additional text that may be between these phrases, identified statin macro usage. All statin macro versions had these phrases.

Exposure and Outcome

Any version of statin macro usage during the study period defined the exposure. Statin therapy prescription of any dosage during the study period defined the outcome. A statin prescription with a start date from January 1, 2016, to June 30, 2016, or an end date after June 30, 2016, defined statin prescription during the study period. Prescriptions that were hand written or called into a pharmacy, and not entered in the EHR, were not accounted for.

Analyses

For patients meeting the inclusion/exclusion criteria, we compared variables between patients for whom the statin macro was and was not used. The Student's *t*-test was used for continuous variables (age, systolic blood pressure, total cholesterol, LDL, HDL) and the binomial test was used for binary variables (gender, race, smoking, DM, antihypertensive medication). For clinicians who did and did not use the statin macro, we compared clinician type, gender, and specialty using the binomial test.

We calculated the relative risk of statin therapy prescription for macro usage compared with no macro usage. To control for patient covariates and clinicians, we used a mixed effect logistic regression model. The response variable was statin therapy prescription. The dependent variables included macro usage and variables used for the ACC/AHA statin guideline recommendation. As multiple patients may have been seen by the same primary care clinician, we included patients' clinician as a random effect, where each clinician had a specific random intercept. We used the likelihood ratio test to determine the significance of variables in

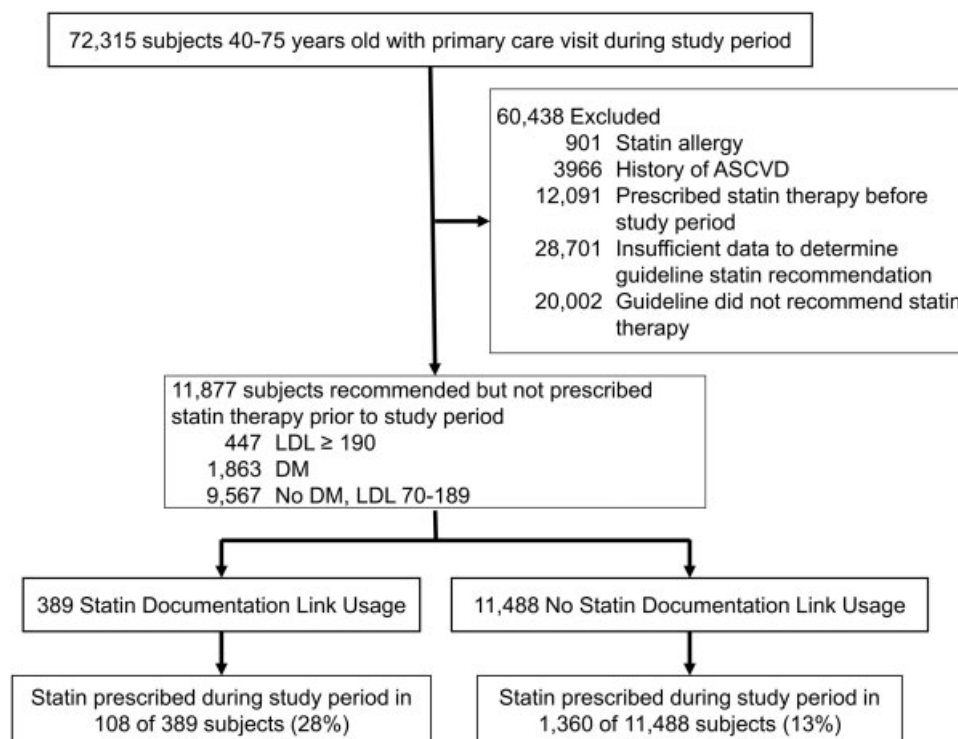


Fig. 3 Flow diagram showing study exclusion criteria, inclusion criteria, and results. 72,315 patients aged 40 to 75 years had a primary care visit during the study period. A total of 60,438 patients were excluded. Counts for categories of excluded patients are shown. 11,877 patients were recommended statin therapy based on the 2013 American College of Cardiology/American Heart Association (ACC/AHA) statin guideline but not prescribed statin therapy prior to the study period. Counts for categories of included patients are shown. Statin therapy was prescribed during the study period in 28% (108 of 389) of patients for whom the statin macro was used compared with 13% (1,360 of 11,488) of patients for whom the statin macro was not used. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; DM, diabetes mellitus; LDL, low-density lipoprotein.

the model. Wald confidence intervals were calculated for odds ratios of fixed effect variables in the model.³³

In this primary analysis, patients without complete data were removed. Because missing data precluded statin recommendation for some patients, we repeated analysis on the final imputed data set of a multiple imputation procedure with predictive mean matching^{34–36} using the Hmisc package.³⁷ See [Supplementary Material](#) (available in the online version) for further details on missing data analysis. All analyses were performed in R (version 3.5.2).³⁸

Results

From January 1, 2016, to June 30, 2016, 72,315 patients aged 40 to 75 years had a primary care visit. Of those, 60,438 patients were dropped based on the study exclusion criteria ([Fig. 3](#)). Thus, 11,877 study eligible patients met the inclusion/exclusion criteria. [Table 2](#) shows baseline characteristics of patients included in the study. DM was significantly less common in the statin macro usage group (11% vs. 16%, $p < 0.05$). In contrast, LDL levels were higher in the macro usage group (127 vs. 123 mg/dL, $p < 0.05$).

A total of 443 primary care clinicians cared for study eligible patients. Of those, 440 clinicians did not use the statin macro on at least one patient while 125 clinicians used the statin macro on at least one patient. Because they used the statin macro for some patients and did not use the statin

macro for other patients, 122 clinicians were in both groups. [Table 3](#) compares type, gender, and specialty of clinicians who did and did not use the statin macro. Most clinicians were internal medicine and family medicine physicians. There were significantly more residents who did not use the statin macro (5%) compared with those who used the statin macro (1%).

For each clinician who used the statin macro at least once in study eligible or ineligible patients, [Table 4](#) shows the total number of patients seen, statin macro usage, and statin prescription stratified by patient study eligibility. The number of study eligible patients seen per clinician who used the statin macro at least once ranged from 1 to 284. For study eligible patients, the top 33 clinician statin macro users (of 125 physicians) contributed 62% of all macro usages. For each clinician who never used the statin macro and prescribed statin therapy at least once, [Table 5](#) shows the number of patients seen and statin prescription in study eligible and ineligible patients. The number of study eligible patients seen per clinician who never used the statin macro and prescribed statin therapy at least once ranged from 1 to 197.

For study eligible patients, the statin macro was used in 3.2% (389 of 11,877) of patients and not used in 11,488 patients. Clinicians prescribed statin therapy during the study period in 28% (108 of 389) of patients for whom the statin macro was used compared with 13% (1,360 of 11,488) of patients for whom the statin macro was not used ([Fig. 3](#)).

Table 2 Baseline characteristics of patients meeting the inclusion/exclusion criteria stratified by statin macro usage ($N = 11,877$)

	Statin macro usage ($N = 389$)	No statin macro usage ($N = 11,488$)	p -Value
Male	55% (213)	55% (6,322)	0.96
Age (y)	62.8 (8.1)	63.3 (7.7)	0.23
Black	11% (44)	8.9% (1,019)	0.12
Smoke	8.2% (32)	7.1% (810)	0.43
DM	11% (42)	16% (1,863)	0.005
Antihypertensive	39% (151)	39% (4,510)	0.9
Systolic BP (mm Hg)	132 (17)	132 (17)	0.84
Total cholesterol (mg/dL)	210 (35)	207 (37)	0.15
LDL (mg/dL)	127 (29)	123 (31)	0.006
HDL (mg/dL)	57 (16)	59 (19)	0.13

Abbreviations: BP, blood pressure; DM, diabetes mellitus; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Note: Numbers in parenthesis correspond to total patients or standard deviation for binary and continuous variables, respectively.

Table 3 Characteristics for clinicians of patients who met the inclusion/exclusion criteria stratified by statin macro usage ($N = 443$)

	Statin macro usage on at least 1 patient ($N = 125$)	No statin macro usage on at least 1 patient ($N = 440$)	p -Value
Type			
Physician	98% (123)	92% (406)	0.023
Resident	1% (1)	5% (24)	0.047
Fellow	1% (1)	2% (7)	0.82
Nurse practitioner	0% (0)	1% (3)	0.82
Sex			
Male	54% (67)	45% (199)	0.12
Female	46% (58)	49% (215)	0.70
Unknown	0% (0)	6% (26)	0.011
Specialty			
Internal medicine	66% (83)	71% (310)	0.45
Family medicine	34% (42)	25% (108)	0.06
Surgery	0% (0)	2% (7)	0.34
Neurology	0% (0)	1% (4)	0.64
Obstetrics and gynecology	0% (0)	1% (3)	0.82
Unknown	0% (0)	2% (8)	0.28

Note: Numbers in parenthesis correspond to total patients.

The relative risk of statin therapy prescription for macro usage compared with no macro usage was 2.3 (95% confidence interval [CI], 1.9–2.8, $p < 0.001$). Statin therapy prescription was significantly more likely in patients for whom the statin macro was used (odds ratio 2.86, 95% CI, 2.24–3.65, $p < 0.001$) while controlling for gender, age, race, smoking status, ASCVD, DM, systolic blood pressure, anti-hypertensive medication, total cholesterol, LDL, HDL, and clinician (→ **Table 6**). Clinician was modeled as a random effect and had a significant variance among clinicians (odds ratio 1.36, $p < 0.001$).

We investigated only the clinicians who had evidence of statin macro usage. From → **Table 4**, clinicians that used the statin macro at least once in study eligible or ineligible patients saw a total of 9,515 study eligible patients. These clinicians prescribed statin therapy during the study period in 28% (108 of 389) of patients for whom the statin macro was used compared with 12% (1,110 of 9,126) of patients for whom the statin macro was not used. The relative risk of statin therapy prescription for macro usage compared with no macro usage was 2.3 (95% CI, 1.9–2.7, $p < 0.001$). Statin therapy prescription was significantly more likely in

Table 4 For clinicians who used the statin macro at least once, clinician statin macro usage and prescription stratified by patient study eligibility

Clinician ID	Study eligible patients				Study ineligible patients			
	Total no. of patients	No. of patients macro used	No. of patients macro used more than once	No. of patients statin prescribed (macro used, macro not used)	Total no. of patients	No. of patients macro used	No. of patients macro used more than once	No. of patients statin prescribed (macro used, macro not used)
16419	284	20	0	19 (5, 14)	657	19	0	290 (11, 279)
18983	222	1	1	4 (1, 3)	942	3	0	139 (1, 138)
15692	212	4	0	18 (3, 15)	614	2	0	269 (1, 268)
15026	189	12	2	23 (7, 16)	1,085	43	0	249 (15, 234)
21490	173	1	0	11 (0, 11)	442	3	0	150 (1, 149)
17711	167	1	1	12 (1, 11)	549	2	0	196 (1, 195)
19343	165	3	0	20 (2, 18)	553	2	0	214 (0, 214)
15688	153	2	0	13 (1, 12)	424	5	0	198 (2, 196)
19301	140	9	2	5 (1, 4)	256	9	2	69 (0, 69)
16389	139	0	0	17 (0, 17)	634	2	0	325 (1, 324)
15007	132	1	0	11 (0, 11)	552	2	0	143 (0, 143)
15684	131	11	2	20 (7, 13)	588	25	3	185 (5, 180)
26752	131	1	0	24 (0, 24)	498	6	0	196 (0, 196)
9121	130	1	0	4 (0, 4)	451	2	0	117 (0, 117)
29618	127	3	0	8 (1, 7)	336	4	0	80 (0, 80)
11186	126	13	1	8 (2, 6)	273	9	0	115 (1, 114)
20857	116	1	0	13 (0, 13)	434	2	0	115 (0, 115)
19609	110	3	0	9 (1, 8)	438	2	1	108 (1, 107)
14796	109	1	0	13 (1, 12)	259	1	0	116 (0, 116)
15368	102	5	0	10 (2, 8)	427	6	0	115 (2, 113)
23513	101	0	0	11 (0, 11)	261	1	0	95 (0, 95)
13589	100	3	0	2 (1, 1)	381	14	0	85 (3, 82)
15267	100	0	0	8 (0, 8)	240	1	0	76 (0, 76)
17479	99	2	0	11 (1, 10)	554	5	0	213 (0, 213)

Table 4 (Continued)

Clinician ID	Study eligible patients				Study ineligible patients			
	Total no. of patients	No. of patients macro used	No. of patients macro used more than once	No. of patients statin prescribed (macro used, macro not used)	Total no. of patients	No. of patients macro used	No. of patients macro used more than once	No. of patients statin prescribed (macro used, macro not used)
5838	96	11	1	8 (1, 7)	439	29	1	147 (2, 145)
14749	91	3	0	15 (1, 14)	336	13	3	117 (2, 115)
15348	91	5	1	18 (1, 17)	358	15	0	126 (2, 124)
9825	89	11	0	24 (3, 21)	373	15	1	163 (1, 162)
7776	88	0	0	4 (0, 4)	222	1	0	58 (1, 57)
25950	86	4	0	7 (1, 6)	371	9	0	95 (4, 91)
30320	86	0	0	10 (0, 10)	540	2	0	106 (0, 106)
31344	85	7	0	15 (1, 14)	324	7	0	87 (0, 87)
18108	84	5	0	23 (3, 20)	562	11	0	204 (1, 203)
26751	84	1	0	14 (0, 14)	400	6	0	153 (2, 151)
14900	83	4	0	14 (1, 13)	423	6	0	132 (3, 129)
31643	83	0	0	19 (0, 19)	284	1	0	103 (0, 103)
30342	82	0	0	7 (0, 7)	560	1	0	97 (0, 97)
30340	80	3	0	23 (3, 20)	831	31	0	207 (10, 197)
28599	79	4	0	18 (2, 16)	307	5	0	103 (3, 100)
17436	78	0	0	10 (0, 10)	420	4	0	153 (0, 153)
17873	76	9	3	9 (3, 6)	517	18	0	119 (2, 117)
19243	76	6	0	11 (1, 10)	275	1	0	101 (1, 100)
30337	76	5	0	15 (1, 14)	563	18	1	107 (2, 105)
31406	75	3	0	11 (1,10)	411	12	0	128 (1, 127)
19090	74	5	0	8 (1, 7)	315	2	0	63 (1, 62)
6162	71	2	0	8 (1, 7)	474	3	0	180 (1, 179)
14821	70	1	0	8 (0, 8)	186	0	0	74 (0, 74)
27277	70	11	3	3 (0, 3)	322	24	2	98 (5, 93)
30329	68	0	0	11 (0, 11)	687	1	0	178 (0, 178)

(Continued)

Table 4 (Continued)

Clinician ID	Study eligible patients				Study ineligible patients			
	Total no. of patients	No. of patients macro used	No. of patients macro used more than once	No. of patients statin prescribed (macro used, macro not used)	Total no. of patients	No. of patients macro used	No. of patients macro used more than once	No. of patients statin prescribed (macro used, macro not used)
27338	67	6	1	5 (0, 5)	333	18	1	81 (5, 76)
25053	66	0	0	7 (0, 7)	344	2	0	108 (1, 107)
26849	66	2	0	3 (0, 3)	185	4	0	51 (0, 51)
27632	63	3	1	10 (0, 10)	283	4	0	53 (1, 52)
15000	62	4	1	5 (2, 3)	144	2	0	70 (0, 70)
28934	62	0	0	14 (0, 14)	305	11	0	110 (6, 104)
29225	62	4	0	7 (1, 6)	367	7	0	118 (6, 112)
22153	61	0	0	3 (0, 3)	237	10	1	70 (4, 66)
14891	59	1	0	6 (0, 6)	221	0	0	64 (0, 64)
15240	59	4	1	12 (1, 11)	259	9	1	115 (4, 111)
28297	59	2	0	15 (1, 14)	286	6	0	81 (1, 80)
18276	58	1	0	9 (0, 9)	82	2	0	54 (2, 52)
19733	58	2	0	6 (1, 5)	366	5	0	124 (3, 121)
30311	56	0	0	4 (0, 4)	520	2	1	63 (0, 63)
30332	56	0	0	9 (0, 9)	526	1	0	77 (0, 77)
28044	54	8	0	13 (1, 12)	388	14	0	139 (5, 134)
30327	54	1	0	6 (0, 6)	512	28	0	87 (2, 85)
30341	53	1	0	5 (0, 5)	659	35	1	100 (6, 94)
12997	52	0	0	0 (0, 0)	154	2	0	60 (0, 60)
27079	52	3	1	6 (2, 4)	132	3	0	59 (2, 57)
30322	52	3	2	9 (0, 9)	532	34	5	112 (9, 103)
15384	51	1	0	2 (0, 2)	252	7	1	88 (1, 87)
18673	51	1	0	0 (0, 0)	527	0	0	35 (0, 35)
19506	51	1	0	9 (0, 9)	245	0	0	61 (0, 61)
26777	51	8	0	9 (1, 8)	294	27	0	77 (11, 66)
31365	50	0	0	5 (0, 5)	204	1	0	55 (1, 54)
5996	50	7	0	7 (2, 5)	427	30	1	148 (2, 146)
8183	50	3	0	6 (0, 6)	239	5	0	71 (0, 71)
20912	49	6	1	8 (0, 8)	145	3	0	74 (0, 74)
25156	48	7	3	15 (3, 12)	224	23	2	96 (6, 90)
25372	48	2	0	7 (1, 6)	170	1	0	55 (0, 55)
25720	48	0	0	4 (0, 4)	316	7	0	61 (2, 59)

Table 4 (Continued)

Clinician ID	Study eligible patients				Study ineligible patients			
	Total no. of patients	No. of patients macro used	No. of patients macro used more than once	No. of patients statin prescribed (macro used, macro not used)	Total no. of patients	No. of patients macro used	No. of patients macro used more than once	No. of patients statin prescribed (macro used, macro not used)
30394	48	3	0	15 (1, 14)	442	9	0	119 (3, 116)
17237	47	8	1	12 (2, 10)	350	8	0	104 (3, 101)
30408	47	8	4	16 (3, 13)	209	12	1	88 (3, 85)
31351	47	1	0	2 (0, 2)	261	0	0	58 (0, 58)
24906	46	2	0	14 (0, 14)	297	4	1	63 (0, 63)
30343	46	0	0	6 (0, 6)	552	10	1	116 (4, 112)
13939	45	1	0	4 (1, 3)	128	0	0	66 (0, 66)
19338	45	0	0	9 (0, 9)	218	3	0	116 (2, 114)
22879	45	0	0	1 (0, 1)	376	3	0	82 (0, 82)
25225	43	2	0	3 (0, 3)	222	5	0	62 (0, 62)
26841	43	0	0	4 (0, 4)	465	1	0	43 (0, 43)
24399	42	0	0	6 (0, 6)	85	2	0	43 (1, 42)
31430	42	2	0	9 (0, 9)	161	0	0	36 (0, 36)
32271	42	0	0	5 (0, 5)	143	3	0	68 (2, 66)
9187	42	1	0	3 (0, 3)	129	2	0	60 (0, 60)
19189	41	1	0	8 (1, 7)	334	7	0	93 (2, 91)
14961	40	1	0	4 (0, 4)	332	4	0	64 (0, 64)
27642	39	0	0	9 (0, 9)	181	1	0	63 (1, 62)
31098	39	0	0	2 (0, 2)	414	2	0	37 (1, 36)
30335	37	0	0	9 (0, 9)	301	1	0	65 (1, 64)
23235	36	1	0	5 (0, 5)	286	1	0	51 (0, 51)
15866	35	3	0	10 (2, 8)	244	19	1	115 (6, 109)
18117	35	2	0	9 (0, 9)	192	11	3	41 (0, 41)
31644	35	2	0	6 (1, 5)	244	17	0	54 (4, 50)
11213	34	1	0	8 (0, 8)	106	1	0	48 (0, 48)
22866	34	2	0	5 (1, 4)	250	3	0	62 (0, 62)
27268	34	1	1	8 (1, 7)	211	7	0	55 (2, 53)
23603	33	1	0	0 (0, 0)	163	0	0	20 (0, 20)
31840	33	2	0	11 (1, 10)	168	11	0	32 (2, 30)
13272	32	0	0	7 (0, 7)	482	2	0	69 (0, 69)
29296	32	2	0	11 (2, 9)	123	4	0	44 (1, 43)
8494	32	1	0	6 (0, 6)	75	1	0	40 (1, 39)
24383	30	2	1	4 (0, 4)	141	5	0	46 (0, 46)
6308	30	4	0	5 (0, 5)	72	4	0	54 (2, 52)

(Continued)

Table 4 (Continued)

Clinician ID	Study eligible patients				Study ineligible patients			
	Total no. of patients	No. of patients macro used	No. of patients macro used more than once	No. of patients statin prescribed (macro used, macro not used)	Total no. of patients	No. of patients macro used	No. of patients macro used more than once	No. of patients statin prescribed (macro used, macro not used)
Missing	29	1	0	3 (0, 3)	160	4	0	46 (0, 46)
12428	29	2	0	5 (1, 4)	282	24	3	68 (7, 61)
19384	29	4	0	6 (0, 6)	96	3	0	57 (0, 57)
10399	28	0	0	5 (0, 5)	243	1	0	42 (0, 42)
13600	27	1	0	1 (0, 1)	79	1	0	39 (1, 38)
15251	27	2	1	7 (1, 6)	161	1	0	55 (0, 55)
19691	27	0	0	3 (0, 3)	69	1	0	25 (1, 24)
30324	27	0	0	2 (0, 2)	443	4	0	75 (0, 75)
17448	25	0	0	2 (0, 2)	176	5	0	39 (0, 39)
30336	25	0	0	4 (0, 4)	419	20	1	35 (3, 32)
27839	24	3	0	3 (0, 3)	64	0	0	25 (0, 25)
25241	23	0	0	6 (0, 6)	132	5	1	63 (1, 62)
28109	22	1	0	9 (0, 9)	182	15	1	55 (4, 51)
31420	22	1	0	2 (1, 1)	331	10	1	35 (0, 35)
9849	22	1	0	2 (0, 2)	45	3	0	15 (1, 14)
26833	21	0	0	2 (0, 2)	147	2	0	38 (0, 38)
32040	21	0	0	3 (0, 3)	361	1	0	29 (0, 29)
15286	20	1	0	2 (0, 2)	110	4	1	24 (1, 23)
19168	20	0	0	1 (0, 1)	66	1	0	24 (0, 24)
21774	20	1	1	3 (0, 3)	128	2	0	27 (0, 27)
27355	20	0	0	2 (0, 2)	367	1	0	50 (0, 50)
28133	19	3	2	7 (1, 6)	90	7	0	35 (1, 34)
28428	17	0	0	0 (0, 0)	66	1	0	6 (0, 6)
26839	16	0	0	1 (0, 1)	119	2	0	25 (1, 24)
26042	15	2	0	2 (1, 1)	65	1	0	1 (0, 1)
6806	15	1	0	1 (0, 1)	24	0	0	16 (0, 16)
26041	14	1	0	6 (1, 5)	79	4	0	23 (1, 22)
9719	14	1	0	4 (1, 3)	33	3	0	11 (1, 10)
22922	13	0	0	2 (0, 2)	69	1	0	21 (1, 20)
25948	13	0	0	1 (0, 1)	56	5	0	25 (1, 24)
28117	13	0	0	1 (0, 1)	41	4	0	6 (2, 4)
90000005	13	0	0	1 (0, 1)	109	1	0	26 (0, 26)
16367	12	4	1	4 (0, 4)	32	4	0	9 (0, 9)
28040	12	1	0	1 (0, 1)	75	6	0	20 (2, 18)
31014	12	1	0	2 (0, 2)	104	5	0	16 (1, 15)
28039	11	0	0	1 (0, 1)	89	5	0	18 (0, 18)
21032	10	1	0	4 (0, 4)	47	0	0	18 (0, 18)
22142	10	2	1	1 (0, 1)	22	0	0	12 (0, 12)

Table 4 (Continued)

Clinician ID	Study eligible patients				Study ineligible patients			
	Total no. of patients	No. of patients macro used	No. of patients macro used more than once	No. of patients statin prescribed (macro used, macro not used)	Total no. of patients	No. of patients macro used	No. of patients macro used more than once	No. of patients statin prescribed (macro used, macro not used)
26838	10	3	0	1 (1, 0)	49	3	0	19 (1, 18)
12413	9	2	0	0 (0, 0)	32	1	0	16 (1, 15)
16570	9	0	0	0 (0, 0)	41	1	0	8 (0, 8)
27912	9	2	0	1 (1, 0)	26	3	1	9 (0, 9)
28857	9	0	0	1 (0, 1)	33	1	0	5 (1, 4)
29484	9	0	0	3 (0, 3)	64	2	0	17 (1, 16)
18575	8	0	0	1 (0, 1)	26	1	0	9 (0, 9)
18661	8	1	0	1 (0, 1)	27	3	0	14 (1, 13)
31977	8	0	0	3 (0, 3)	19	1	0	10 (1, 9)
5944	8	1	0	0 (0, 0)	9	0	0	6 (0, 6)
13089	7	1	1	1 (0, 1)	35	3	0	11 (1, 10)
21782	7	1	0	0 (0, 0)	10	1	0	5 (1, 4)
32336	7	1	0	2 (0, 2)	12	0	0	3 (0, 3)
31975	6	0	0	0 (0, 0)	202	1	0	11 (0, 11)
32626	6	0	0	3 (0, 3)	34	1	0	9 (1, 8)
27207	5	1	0	2 (0, 2)	28	2	0	2 (0, 2)
28878	5	0	0	0 (0, 0)	119	13	0	32 (3, 29)
31849	5	0	0	3 (0, 3)	93	2	0	23 (1, 22)
28883	4	0	0	1 (0, 1)	21	1	0	6 (0, 6)
30488	4	0	0	0 (0, 0)	50	1	0	10 (0, 10)
27471	3	1	0	0 (0, 0)	9	0	0	1 (0, 1)
10682	2	0	0	1 (0, 1)	2	1	0	2 (1, 1)
13088	2	0	0	0 (0, 0)	19	2	0	6 (0, 6)
16535	2	0	0	1 (0, 1)	9	1	1	5 (1, 4)
19413	2	0	0	1 (0, 1)	47	1	0	8 (0, 8)
29736	2	0	0	1 (0, 1)	7	1	0	6 (0, 6)
30640	2	1	0	0 (0, 0)	9	2	0	6 (2, 4)
30647	2	0	0	1 (0, 1)	10	2	0	1 (0, 1)
30656	2	1	0	1 (1, 0)	5	0	0	3 (0, 3)
31340	2	0	0	0 (0, 0)	54	2	0	9 (1, 8)
31574	2	1	1	2 (1, 1)	6	0	0	1 (0, 1)
31583	2	0	0	0 (0, 0)	6	1	0	4 (1, 3)
31598	2	1	0	0 (0, 0)	8	1	0	5 (1, 4)
32041	2	0	0	0 (0, 0)	28	1	1	0 (0, 0)
32285	2	0	0	1 (0, 1)	33	1	0	10 (0, 10)
32340	2	0	0	0 (0, 0)	49	4	0	9 (0, 9)
32462	2	0	0	0 (0, 0)	5	1	0	3 (0, 3)
3860	2	0	0	0 (0, 0)	185	1	0	0 (0, 0)

(Continued)

Table 4 (Continued)

Clinician ID	Study eligible patients				Study ineligible patients			
	Total no. of patients	No. of patients macro used	No. of patients macro used more than once	No. of patients statin prescribed (macro used, macro not used)	Total no. of patients	No. of patients macro used	No. of patients macro used more than once	No. of patients statin prescribed (macro used, macro not used)
28858	1	0	0	0 (0, 0)	9	1	0	4 (1, 3)
29806	1	0	0	0 (0, 0)	11	2	0	6 (1, 5)
30664	1	0	0	1 (0, 1)	12	1	0	7 (1, 6)
30666	1	0	0	1 (0, 1)	11	2	0	5 (0, 5)
30694	1	1	0	1 (1, 0)	1	1	0	0 (0, 0)
31560	1	1	0	1 (1, 0)	2	0	0	0 (0, 0)
31586	1	0	0	0 (0, 0)	7	1	0	5 (1, 4)
31596	1	0	0	0 (0, 0)	10	1	0	2 (0, 2)
32504	1	0	0	0 (0, 0)	1	1	0	1 (1, 0)
7097	1	1	0	1 (1, 0)	4	0	0	3 (0, 3)
10003848	0	0	0	0 (0, 0)	3	1	0	1 (1, 0)
19799	0	0	0	0 (0, 0)	1	1	0	1 (1, 0)
21750	0	0	0	0 (0, 0)	17	1	0	9 (0, 9)
28938	0	0	0	0 (0, 0)	2	1	0	0 (0, 0)
29800	0	0	0	0 (0, 0)	2	1	0	0 (0, 0)
30326	0	0	0	0 (0, 0)	41	1	0	2 (0, 2)
30584	0	0	0	0 (0, 0)	3	1	0	3 (1, 2)
30652	0	0	0	0 (0, 0)	10	2	0	4 (2, 2)
30662	0	0	0	0 (0, 0)	5	1	0	2 (1, 1)
30672	0	0	0	0 (0, 0)	8	1	0	5 (1, 4)
Totals	9,515	389	43	1 218 (108, 1,110)	47,345	1,112	46	13, 269 (272, 12,997)

Abbreviation: ID, identification.

patients for whom the statin macro was used (odds ratio 2.77, 95% CI, 2.16–3.54, $p < 0.001$) while controlling for covariates and clinician in a mixed effect model. Also from **Table 4**, for the study ineligible patients, those same physicians used the statin macro 1,112 times to generate 272 statin prescriptions (24%).

Missing data imputation analysis yielded similar results with our primary analysis. Although more patients met the inclusion/exclusion criteria (11,877 primary analysis vs. 20,240 imputed analysis), the relative risk of statin therapy prescription for macro usage and statin macro odds ratio in the mixed effect logistic regression were similar (see **Supplementary Material**, available in the online version).

Discussion

This study described the implementation of a CDS tool, the statin macro, for the 2013 ACC/AHA statin guideline. For

patients recommended but not prescribed statin therapy before the study period, statin macro usage was significantly associated with increased statin prescription during the study period, although the study did not determine if the statin dosages were guideline compliant. This study is the first to show that a 2013 ACC/AHA statin guideline CDS tool was associated with improved statin guideline-related prescription rates. The study cannot establish a cause and effect relationship, in that clinicians might have used the statin macro more frequently after already having decided to prescribe a statin.

Baseline characteristics including DM and LDL were significantly different in patients for whom the statin macro was and was not used. The large sample size lead to statistical significance, but the clinical significance of a 4 mg/dL difference in LDL levels (123 vs. 127 mg/dL) is somewhat trivial. Clinicians may have used the statin macro less often for DM patients as they knew such patients should receive statin therapy.

Table 5 For clinicians who never used the statin macro and prescribed statin therapy at least once, clinician statin macro usage and prescription stratified by patient study eligibility

Clinician ID	Study eligible patients		Study ineligible	
	Total no. of patients	No. of patients statin prescribed	Total no. of patients	No. of patients statin prescribed
14823	197	14	550	207
19002	152	12	356	136
15255	117	9	382	127
26250	93	5	451	168
9561	91	4	301	101
30321	70	8	543	102
9102	70	9	492	118
31052	69	12	315	86
14892	67	3	207	63
25268	61	7	209	55
19052	59	3	289	53
7389	56	12	575	151
30319	54	13	658	190
3502	50	3	123	32
6020	46	6	144	77
25083	43	4	313	40
31022	38	5	416	40
32078	38	7	116	53
23205	32	1	59	39
13661	30	3	157	42
29620	28	2	47	26
31184	26	4	220	39
24257	25	3	146	79
31148	25	2	98	34
26023	24	2	198	33
28660	24	3	193	49
31011	23	2	341	23
4294	23	3	63	34
28747	22	3	122	28
30291	22	3	122	23
14704	19	2	36	13
26731	17	2	48	31
30318	17	2	146	30
21251	16	1	357	24
24646	16	2	32	16
28050	16	1	104	22
31754	16	5	82	31
30292	14	4	298	41
32385	14	5	58	19
28048	13	2	135	32
13583	12	1	61	32

(Continued)

Table 5 (Continued)

Clinician ID	Study eligible patients		Study ineligible	
	Total no. of patients	No. of patients statin prescribed	Total no. of patients	No. of patients statin prescribed
18591	12	0	27	12
27779	11	1	47	14
25376	10	4	82	8
26830	10	1	12	7
30382	10	1	37	15
32005	10	0	125	7
14767	9	2	31	18
17325	9	1	53	32
29279	9	0	19	12
30288	9	2	229	14
6494	9	0	29	14
27456	8	0	13	12
8251	8	0	10	5
10381	7	0	28	13
16407	7	2	19	11
21366	7	1	17	8
24204	7	1	23	13
30379	7	0	39	23
31794	7	0	41	4
32278	7	0	25	9
16391	6	0	5	4
17319	6	2	95	30
17792	6	1	24	7
18273	6	0	14	9
2619	5	0	15	3
28089	5	2	30	10
28611	5	1	4	3
30317	5	0	32	11
30677	5	2	5	1
32357	5	0	13	6
32961	5	0	11	6
14275	4	0	26	3
16953	4	1	2	0
24969	4	0	5	2
26389	4	0	37	16
29741	4	0	20	5
29816	4	1	25	14
30651	4	1	10	4
31591	4	0	10	2
13656	3	2	40	24
14756	3	1	4	3
18769	3	0	19	14

Table 5 (Continued)

Clinician ID	Study eligible patients		Study ineligible	
	Total no. of patients	No. of patients statin prescribed	Total no. of patients	No. of patients statin prescribed
27330	3	0	6	3
27820	3	0	37	3
29649	3	0	8	4
29809	3	0	5	2
30210	3	1	49	1
30644	3	0	10	3
30650	3	1	5	1
31398	3	1	8	2
31566	3	0	4	3
31577	3	0	6	6
10887	2	1	7	5
13093	2	1	4	2
14765	2	0	1	1
15448	2	1	8	4
17383	2	0	7	1
17651	2	0	5	1
20928	2	1	9	5
21472	2	0	4	1
21971	2	0	16	1
26465	2	1	4	0
28148	2	0	8	5
28617	2	0	7	2
29794	2	1	13	5
29818	2	0	8	4
30626	2	0	7	3
30636	2	0	7	1
30641	2	0	9	3
30665	2	0	5	1
31573	2	0	6	2
32474	2	1	4	3
32966	2	0	29	6
33145	2	0	16	7
7020	2	0	61	10
7773	2	0	4	2
9183	2	0	15	1
10001334	1	1	0	0
10115	1	1	0	0
11416	1	0	16	1
15404	1	0	3	1
18103	1	0	7	4
20170	1	0	1	1
20373	1	0	3	1

(Continued)

Table 5 (Continued)

Clinician ID	Study eligible patients		Study ineligible	
	Total no. of patients	No. of patients statin prescribed	Total no. of patients	No. of patients statin prescribed
21033	1	0	3	3
21134	1	0	8	1
21746	1	0	10	1
22769	1	0	10	4
22802	1	0	2	1
23153	1	0	6	3
23424	1	1	2	1
23436	1	0	16	2
25144	1	0	3	2
25963	1	0	10	2
28045	1	0	3	1
28677	1	0	11	5
28914	1	0	4	3
29738	1	0	2	1
29742	1	0	2	2
29743	1	0	2	2
29786	1	0	7	1
29788	1	0	2	2
29795	1	0	1	1
29829	1	0	3	3
30333	1	1	119	11
30581	1	0	2	1
30587	1	0	2	1
30646	1	0	10	3
30653	1	1	9	3
30659	1	0	6	6
30660	1	0	6	3
30661	1	0	13	3
30674	1	0	14	8
30678	1	0	10	7
30679	1	0	8	4
31173	1	0	2	1
31556	1	0	3	2
31559	1	1	6	3
31568	1	1	3	1
31570	1	1	4	3
31571	1	0	6	2
31578	1	0	4	1
32004	1	0	24	5
32290	1	0	10	2
32467	1	0	2	1
32472	1	0	4	2

Table 5 (Continued)

Clinician ID	Study eligible patients		Study ineligible	
	Total no. of patients	No. of patients statin prescribed	Total no. of patients	No. of patients statin prescribed
32482	1	1	2	2
32487	1	0	8	4
32497	1	0	2	2
32674	1	0	10	3
33009	1	0	3	1
4392	1	0	3	3
5606	1	0	2	1
8995	1	0	122	7
90000014	1	0	5	3
10000141	0	0	1	1
10000390	0	0	1	1
10000739	0	0	1	1
10001141	0	0	1	1
10004278	0	0	1	1
10004338	0	0	1	1
10004367	0	0	2	1
10004906	0	0	1	1
10007567	0	0	1	1
10009733	0	0	1	1
10011977	0	0	1	1
10022155	0	0	1	1
10022969	0	0	1	1
10030040	0	0	2	1
10033676	0	0	1	1
10034012	0	0	1	1
10041394	0	0	1	1
10044676	0	0	1	1
10047841	0	0	1	1
11000316	0	0	1	1
11000496	0	0	1	1
11000872	0	0	1	1
11001242	0	0	1	1
11006889	0	0	3	1
11011013	0	0	1	1
11012330	0	0	1	1
11013507	0	0	1	1
11016417	0	0	1	1
11017524	0	0	1	1
11029330	0	0	1	1
11035221	0	0	2	1
11044881	0	0	2	1
11045323	0	0	2	2

(Continued)

Table 5 (Continued)

Clinician ID	Study eligible patients		Study ineligible	
	Total no. of patients	No. of patients statin prescribed	Total no. of patients	No. of patients statin prescribed
11046508	0	0	1	1
11050138	0	0	1	1
11051979	0	0	1	1
12070	0	0	1	1
12446	0	0	4	1
12547	0	0	1	1
12908	0	0	3	1
14744	0	0	1	1
14797	0	0	3	2
17838	0	0	1	1
17850	0	0	3	2
18107	0	0	1	1
18109	0	0	5	2
18125	0	0	6	3
18771	0	0	1	1
18772	0	0	1	1
19131	0	0	1	1
20094	0	0	3	1
20279	0	0	5	1
20402	0	0	3	1
20445	0	0	1	1
20550	0	0	5	3
20637	0	0	2	1
21429	0	0	1	1
21731	0	0	3	3
21735	0	0	1	1
22913	0	0	1	1
22947	0	0	2	2
23497	0	0	2	1
23586	0	0	1	1
23600	0	0	3	2
23719	0	0	5	1
23800	0	0	13	2
23888	0	0	7	3
24287	0	0	1	1
24405	0	0	2	2
24735	0	0	2	2
24765	0	0	3	2
24947	0	0	1	1
25157	0	0	1	1
25748	0	0	2	1
25882	0	0	2	1

Table 5 (Continued)

Clinician ID	Study eligible patients		Study ineligible	
	Total no. of patients	No. of patients statin prescribed	Total no. of patients	No. of patients statin prescribed
26022	0	0	1	1
26325	0	0	2	2
26973	0	0	1	1
27257	0	0	10	2
27290	0	0	3	1
27937	0	0	4	3
28110	0	0	1	1
28146	0	0	2	1
28600	0	0	2	2
28722	0	0	1	1
28936	0	0	2	1
29251	0	0	2	2
29418	0	0	2	1
29420	0	0	14	4
29494	0	0	2	1
29502	0	0	6	1
29526	0	0	1	1
29733	0	0	1	1
29735	0	0	1	1
29737	0	0	5	2
29739	0	0	2	1
29798	0	0	1	1
29801	0	0	2	1
29802	0	0	3	1
29803	0	0	1	1
29804	0	0	5	3
29817	0	0	3	1
29830	0	0	6	2
29831	0	0	5	1
30586	0	0	2	1
30589	0	0	4	2
30591	0	0	2	2
30592	0	0	2	2
30670	0	0	6	1
30671	0	0	10	3
30673	0	0	6	4
30675	0	0	7	4
30693	0	0	2	1
30696	0	0	2	2
31010	0	0	5	1
31093	0	0	1	1
31275	0	0	1	1

(Continued)

Table 5 (Continued)

Clinician ID	Study eligible patients		Study ineligible	
	Total no. of patients	No. of patients statin prescribed	Total no. of patients	No. of patients statin prescribed
31541	0	0	1	1
31544	0	0	1	1
31557	0	0	8	3
31558	0	0	6	3
31562	0	0	6	2
31567	0	0	6	3
31575	0	0	14	6
31576	0	0	4	1
31587	0	0	3	1
31597	0	0	6	1
31599	0	0	1	1
32450	0	0	1	1
32464	0	0	1	1
32466	0	0	1	1
32470	0	0	1	1
32485	0	0	5	3
32490	0	0	3	2
32491	0	0	5	4
32493	0	0	4	4
32494	0	0	3	2
32498	0	0	1	1
32500	0	0	1	1
33011	0	0	4	2
3722	0	0	1	1
4050	0	0	1	1
505804	0	0	1	1
5279	0	0	1	1
5512	0	0	4	2
5777	0	0	1	1
6319	0	0	5	1
6845	0	0	3	3
7231	0	0	1	1
7421	0	0	1	1
9782	0	0	1	1

Abbreviation: ID, identification.

Most clinicians were internal medicine and family medicine physicians. Other specialties were represented because the primary care clinician listed in the EHR can be from any specialty. As our study was performed at a tertiary referral center, neurologists and surgeons may be the EHR-listed primary care clinician.

The statin macro is a clinician-initiated CDS tool. Our results may be confounded as clinicians who used the statin

macro may be more technologically proficient or more compliant to statin guidelines. However, almost all the 125 clinicians who used the statin macro for patients also did not use the statin macro for other patients. Therefore, our results are not due to a small number of clinicians who were the only users of the statin macro.

The statin macro was used for a low percentage (3.2%) of patients recommended but not prescribed statin therapy.

Table 6 Multivariate adjusted mixed effect logistic regression model for statin therapy prescription during study period

	Odds ratio (95% CI) ^a	p-Value ^b
Statin macro usage	2.86 (2.24–3.65)	< 0.001
Male	1.19 (1.04–1.36)	0.011
Age	1.03 (1.02–1.04)	< 0.001
Black	0.88 (0.70–1.09)	0.22
Smoke	1.25 (1.00–1.55)	0.054
DM	2.61 (2.26–3.02)	< 0.001
Antihypertensive	1.32 (1.17–1.49)	< 0.001
Systolic BP	1.00 (1.00–1.00)	0.62
Total cholesterol	1.01 (1.00–1.01)	< 0.001
LDL	1.00 (1.00–1.00)	0.25
HDL	0.98 (0.98–0.99)	< 0.001

Abbreviations: BP, blood pressure; CI, confidence interval; DM, diabetes mellitus; HDL, high-density lipoprotein; LDL, low-density lipoprotein. Note: Bold indicates variables with significant p-values.

^aOdds ratio of variables from mixed effect logistic regression.

^bp-Value based on likelihood ratio test while controlling for other variables in the model. Clinician was included as a random effect.

Other studies of clinician-initiated CDS tools showed very low uptake, which was 0% during some months or at some clinical sites.^{39,40} Aside from low advertisement, the statin macro may have had low uptake as not all primary care visits were focused on prevention. Some visits may have focused on acute issues. CDS features associated with low uptake included clinician perception of loss of autonomy, lack of EHR integration, poor transparency of CDS developers, lack of clinical leadership endorsement, lack of financial incentive, and changing guidelines.^{41,42} Ongoing systematic reviews will further delineate these features.⁴³ Future strategies to improve statin macro uptake include advertisements describing developers, emphasizing clinical leadership endorsement, and financial incentives.

There are many reasons that clinicians may not prescribe statin therapy according to the 2013 ACC/AHA guideline. In 2015, less than half of surveyed clinicians read the guideline, knew the patient groups recommended statin therapy, or knew the definition of statin intensity.⁴⁴ The 2013 ACC/AHA statin guideline was met with controversy as there were no LDL target goals and the number of patients recommended statin therapy would significantly increase compared with previous guidelines.^{45,46} There was also concern that the risk equation overestimated the 10-year ASCVD risk.⁴⁷ The 2013 ACC/AHA guideline considered only LDL-C rather than other lipoprotein measures such as LDL particle number or lipoprotein (a), which were associated with cardiovascular risk.^{48,49} Of clinicians who were knowledgeable about the 2013 ACC/AHA statin guidelines, many disagreed with statin intensity definitions and the groups' recommended statin therapy.⁵⁰

Given the benefits of the statin macro, one could consider developing a system-initiated statin CDS tool. Previous studies showed system-initiated CDS tools improved clinical

outcomes compared with clinician-initiated CDS tools.¹⁸ However, system-initiated CDS tools, such as best practice alerts, may lead to alert fatigue.^{51,52} A future randomized control trial comparing clinician-initiated versus system-initiated statin CDS tools could compare this CDS feature and provide a greater certainty of the statin CDS tool effect size.

There were limitations to this study. We calculated the 2013 ACC/AHA statin guideline recommendation for all patients before the study period as of December 31, 2015. We could not determine the statin recommendation for each patient at the time of statin macro usage or if the statin macro was used in a template versus on demand due to limitations of EHR data archiving. We did not determine if each patient's statin prescription met the ACC/AHA 2013 therapy intensity recommendations (high vs. moderate vs. low). We did not determine if clinicians using the statin macro tool initiated its use because they already decided to prescribe a statin; if so, interpretation of study results may be affected. We plan to collect time-specific patient data for future studies with macros and could implement CDS monitoring.⁵³ Since initiation of the study, a new 2018 ACC/AHA statin guideline was recently published.⁵⁴ Future versions of the statin macro should include updated 2018 ACC/AHA statin guidelines.

Conclusion

Statin macro usage was associated with improved 2013 ACC/AHA statin guideline compliance at the level of statin prescription versus no statin prescription. We did not determine if each patient's statin prescription met the ACC/AHA 2013 therapy intensity recommendations (high vs. moderate vs. low). Macro CDS tools may improve compliance to other societal guidelines.

Clinical Relevance Statement

Although many best practice guidelines exist for initiating medication in select patient groups, these medications are prescribed at suboptimal rates. Clinical decision support tools may improve guideline compliance. Use of a statin macro was associated with improved statin guideline compliance.

Multiple Choice Questions

- The following baseline characteristics were significantly different in patients for whom the statin macro was and was not used:
 - High-density lipoprotein and race.
 - Systolic blood pressure and total cholesterol.
 - Race and systolic blood pressure.
 - Gender and age.
 - Diabetes mellitus and low-density lipoprotein.

Correct Answer: The correct answer is option e. Baseline characteristics including diabetes mellitus and LDL were

significantly different in patients for whom the statin macro was and was not used. However, the large sample size lead to statistical significance with somewhat trivial clinically significant differences.

2. The following variables were significantly associated with statin prescription in patients who were recommended a statin based on guidelines but not previously prescribed a statin:
 - a. Statin macro usage, diabetes mellitus.
 - b. Race, diabetes mellitus.
 - c. Statin macro usage, race.
 - d. Statin macro usage, systolic blood pressure.

Correct Answer: The correct answer is option a. Statin macro usage and diabetes mellitus were significantly associated with statin prescription while controlling for other covariates.

Protection of Human and Animal Subjects

The University of California, Los Angeles Institutional Review Board approved a waiver of authorization for this study (IRB#: 16-001676).

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Conflict of Interest

None declared.

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References

- 1 Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. *Lancet* 2003;362(9391):1225-1230
- 2 Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129(25, Suppl 2):S1-S45
- 3 Housholder-Hughes SD, Martin MM, McFarland MR, Creech CJ, Shea MJ. Healthcare provider compliance with the 2013 ACC/AHA Adult Cholesterol Guideline recommendation for high-intensity dose statins for patients with coronary artery disease. *Heart Lung* 2017;46(04):328-333
- 4 Bavishi A, Howard T, Kim JP, et al. Treatment gap in primary prevention patients presenting with acute coronary syndrome. *Am J Cardiol* 2019;123(03):368-374
- 5 Fischer F, Lange K, Klose K, Greiner W, Kraemer A. Barriers and strategies in guideline implementation-a scoping review. *Healthcare (Basel)* 2016;4(03):36
- 6 Carthey J, Walker S, Deelchand V, Vincent C, Griffiths WH. Breaking the rules: understanding non-compliance with policies and guidelines. *BMJ* 2011;343:d5283
- 7 National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106(25):3143-3421
- 8 D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;117(06):743-753
- 9 Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, May M, Brindle P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. *BMJ* 2007;335(7611):136
- 10 American College of Cardiology. ASCVD Risk Estimator. 2013. Available at: <http://tools.cardiosource.org/ASCVD-Risk-Estimator/>. Accessed December 1, 2013
- 11 American College of Cardiology. ASCVD Risk Calculator. 2013. Available at: https://professional.heart.org/professional/GuidelinesStatements/ASCVDRiskCalculator/UCM_457698_ASCVD-Risk-Calculator.jsp. Accessed December 1, 2013
- 12 North F, Fox S, Chaudhry R. Clinician time used for decision making: a best case workflow study using cardiovascular risk assessments and Ask Mayo Expert algorithmic care process models. *BMC Med Inform Decis Mak* 2016;16:96
- 13 Fretheim A, Flottorp S, Oxman A. Effect of interventions for implementing clinical practice guidelines. Oslo, Norway: The Norwegian Institute of Public Health (NIPH); 2015
- 14 Sequist TD, Gandhi TK, Karson AS, et al. A randomized trial of electronic clinical reminders to improve quality of care for diabetes and coronary artery disease. *J Am Med Assoc* 2005;293(04):431-437
- 15 Smith MW, Brown C, Virani SS, et al. Incorporating guideline adherence and practice implementation issues into the design of decision support for beta-blocker titration for heart failure. *Appl Clin Inform* 2018;9(02):478-489
- 16 Jones BE, Collingridge DS, Vines CG, et al. CDS in a learning health care system: identifying physicians' reasons for rejection of best-practice recommendations in pneumonia through computerized clinical decision support. *Appl Clin Inform* 2019;10(01):1-9
- 17 Au L, Oster A, Yeh GH, Magno J, Paek HM. Utilizing an electronic health record system to improve vaccination coverage in children. *Appl Clin Inform* 2010;1(03):221-231
- 18 Van de Velde S, Heselmans A, Delvaux N, et al. A systematic review of trials evaluating success factors of interventions with computerised clinical decision support. *Implement Sci* 2018;13(01):114
- 19 Roshanov PS, Fernandes N, Wilczynski JM, et al. Features of effective computerised clinical decision support systems: meta-regression of 162 randomised trials. *BMJ* 2013;346:f657
- 20 Aspary KE, Furman R, Karalis DG, et al. Effect of health information technology interventions on lipid management in clinical practice: a systematic review of randomized controlled trials. *J Clin Lipidol* 2013;7(06):546-560
- 21 Scheitel MR, Kessler ME, Shellum JL, et al. Effect of a novel clinical decision support tool on the efficiency and accuracy of treatment recommendations for cholesterol management. *Appl Clin Inform* 2017;8(01):124-136
- 22 Bright TJ, Wong A, Dhurjati R, et al. Effect of clinical decision-support systems: a systematic review. *Ann Intern Med* 2012;157(01):29-43
- 23 Epic Systems. Epic. Verona, WI: Epic Systems; 2016
- 24 Rattay KT, Ramakrishnan M, Atkinson A, Gilson M, Drayton V. Use of an electronic medical record system to support primary care recommendations to prevent, identify, and manage childhood obesity. *Pediatrics* 2009;123(Suppl 2):S100-S107
- 25 Young A. 'SWINEUPDATE': using EMR charting tools as a clinical decision support tool during the H1N1 outbreak. *WJM* 2010;109(04):222-223

- 26 O'Connor PJ, Sperl-Hillen JM, Rush WA, et al. Impact of electronic health record clinical decision support on diabetes care: a randomized trial. *Ann Fam Med* 2011;9(01):12–21
- 27 Tierney WM, Overhage JM, Murray MD, et al. Effects of computerized guidelines for managing heart disease in primary care. *J Gen Intern Med* 2003;18(12):967–976
- 28 van Wyk JT, van Wijk MAM, Sturkenboom MCJM, Mosseveld M, Moorman PW, van der Lei J. Electronic alerts versus on-demand decision support to improve dyslipidemia treatment: a cluster randomized controlled trial. *Circulation* 2008;117(03):371–378
- 29 Lester WT, Grant RW, Barnett GO, Chueh HC. Randomized controlled trial of an informatics-based intervention to increase statin prescription for secondary prevention of coronary disease. *J Gen Intern Med* 2006;21(01):22–29
- 30 Van de Velde S, Kunnamo I, Roshanov P, et al; GUIDES expert panel. The GUIDES checklist: development of a tool to improve the successful use of guideline-based computerised clinical decision support. *Implement Sci* 2018;13(01):86
- 31 Weiskopf NG, Weng C. Methods and dimensions of electronic health record data quality assessment: enabling reuse for clinical research. *J Am Med Inform Assoc* 2013;20(01):144–151
- 32 Johnson SG, Speedie S, Simon G, Kumar V, Westra BL. Application of an ontology for characterizing data quality for a secondary use of EHR data. *Appl Clin Inform* 2016;7(01):69–88
- 33 Bates D, Mächler M, Bolker B, et al. Fitting linear mixed-effects models using lme4. *J Stat Softw* 2015;67:1–48
- 34 Rubin DB. Statistical matching using file concatenation with adjusted weights and multiple imputations. *J Bus Econ Stat* 1986;4:87–94
- 35 Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New York: John Wiley and Sons; 1987
- 36 Van Buuren S. *Flexible Imputation of Missing Data*. Boca Raton, FL: Chapman and Hall/CRC; 2018
- 37 Harrell FE Jr. *Hmisc: Harrell Miscellaneous*. Nashville, TN: Vanderbilt University; 2019
- 38 R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2018
- 39 Eccles M, McColl E, Steen N, et al. Effect of computerised evidence based guidelines on management of asthma and angina in adults in primary care: cluster randomised controlled trial. *BMJ* 2002;325(7370):941
- 40 Hobbs FD, Delaney BC, Carson A, Kenkre JE. A prospective controlled trial of computerized decision support for lipid management in primary care. *Fam Pract* 1996;13(02):133–137
- 41 Liberati EG, Ruggiero F, Galuppo L, et al. What hinders the uptake of computerized decision support systems in hospitals? A qualitative study and framework for implementation. *Implement Sci* 2017;12(01):113
- 42 Moxey A, Robertson J, Newby D, Hains I, Williamson M, Pearson SA. Computerized clinical decision support for prescribing: provision does not guarantee uptake. *J Am Med Inform Assoc* 2010;17(01):25–33
- 43 Kouri A, Yamada J, Gupta S. Identifying factors related to user uptake of computerized clinical decision support systems: a systematic review and meta-regression. PROSPERO 2018: CRD42018092337. Available at: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018092337. Accessed May 17, 2019
- 44 Virani SS, Pokharel Y, Steinberg L, et al. Provider understanding of the 2013 ACC/AHA cholesterol guideline. *J Clin Lipidol* 2016;10(03):497–504.e4
- 45 Ridker PM, Cook NR. Statins: new American guidelines for prevention of cardiovascular disease. *Lancet* 2013;382(9907):1762–1765
- 46 Pencina MJ, Navar-Boggan AM, D'Agostino RB Sr, et al. Application of new cholesterol guidelines to a population-based sample. *N Engl J Med* 2014;370(15):1422–1431
- 47 Amin NP, Martin SS, Blaha MJ, Nasir K, Blumenthal RS, Michos ED. Headed in the right direction but at risk for miscalculation: a critical appraisal of the 2013 ACC/AHA risk assessment guidelines. *J Am Coll Cardiol* 2014;63(25 Pt A):2789–2794
- 48 Otvos JD, Mora S, Shalaurova I, Greenland P, Mackey RH, Goff DC Jr. Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. *J Clin Lipidol* 2011;5(02):105–113
- 49 Erqou S, Kaptoge S, Perry PL, et al; Emerging Risk Factors Collaboration. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA* 2009;302(04):412–423
- 50 Setia S, Fung SS-W, Waters DD. Doctors' knowledge, attitudes, and compliance with 2013 ACC/AHA guidelines for prevention of atherosclerotic cardiovascular disease in Singapore. *Vasc Health Risk Manag* 2015;11:303–310
- 51 Rehr CA, Wong A, Seger DL, Bates DW. Determining inappropriate medication alerts from “inaccurate warning” overrides in the intensive care unit. *Appl Clin Inform* 2018;9(02):268–274
- 52 Ancker JS, Edwards A, Nosal S, Hauser D, Mauer E, Kaushal R; with the HITEC Investigators. Effects of workload, work complexity, and repeated alerts on alert fatigue in a clinical decision support system. *BMC Med Inform Decis Mak* 2017;17(01):36
- 53 Yoshida E, Fei S, Bavuso K, Lagor C, Maviglia S. The value of monitoring clinical decision support interventions. *Appl Clin Inform* 2018;9(01):163–173
- 54 Grundy SM, Stone NJ, Bailey AL, et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;2018:25709