

Treatment Gap in Primary Prevention Patients Presenting With Acute Coronary Syndrome



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Previous studies assessing healthcare provider compliance to the 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines indicate a significant underuse of statin therapy at appropriate intensity. However, data are limited in primary prevention patients. Our study aimed to evaluate the impact of the 2013 ACC/AHA guidelines through a retrospective analysis of primary prevention patients presenting with first time acute coronary syndrome (ACS). We retrospectively calculated the 10-year predicted Atherosclerotic Cardiovascular Disease (10yASCVD) risk in 1,265 patients ages 40 to 75 who presented with ACS and no previous ASCVD. In patients without known ambulatory systolic blood pressure, a multivariable linear regression model was used to predict outpatient systolic blood pressure. Outcomes analyzed in each 10yASCVD category included statin status and statin intensity (high/medium/low) with further categorization by type of ACS event and date of left heart catheterization. In both primary analysis and sensitivity analysis (patients with predicted systolic blood pressure), statistical significance was shown with respect to overall statin status, ST Elevation Myocardial Infarction, and date of left heart catheterization. In summary, retrospective calculation of 10yASCVD in patients with a first ACS event showed a significant number of ACS patients would have qualified for statin therapy per 2013 ACC/AHA guidelines before their event but had not been initiated on one. © 2018 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;123:368–374)

Since the release of the 2013 American College of Cardiology/American Heart Association (ACC/AHA) blood cholesterol guidelines, there has been a shift away from treating to a fixed low-density lipoprotein cholesterol target and instead to selecting appropriate intensity statin therapy based on individual Atherosclerotic Cardiovascular Disease (ASCVD) risk and the potential for benefit with evidence-based low-density lipoprotein cholesterol lowering therapy.¹ The studies assessing healthcare provider compliance and impact of these guidelines on statin treatment patterns indicate a significant underuse of appropriate implementation of statin therapy at appropriate intensity.^{2,3} However, the aforementioned studies were predominantly in those with existing clinical ASCVD with limited data on those without previous ASCVD. Our study aimed to evaluate the potential impact of greater compliance with the 2013 ACC/AHA guidelines in primary prevention patients through a retrospective analysis of patients presenting with first time acute coronary syndrome (ACS).

Methods

The Northwestern Electronic Data Warehouse (EDW) was queried to identify patients ages 40 to 75 years who had their first left heart catheterization (LHC) at Northwestern Memorial Hospital with associated diagnosis of unstable angina (UA), Non-ST Elevation Myocardial Infarction (NSTEMI), or ST Elevation Myocardial Infarction (STEMI) between November 2009 and November 2017 (IRB STU00205871). Variables extracted from the EDW included patient demographics, co-morbidities, medical history, systolic blood pressure, and lipid panel within 1 year. Chart review through electronic medical record (EMR) was performed on these patients to verify accuracy of queried data and exclude patients who had evidence of clinical ASCVD or were missing key variables such as lipid panel or medication history.

Using Appendix 7 of the 2013 ACC/AHA Guidelines, a 10-year ASCVD (10yASCVD) risk score was calculated for subjects who met the inclusion criteria. The 10yASCVD calculation includes an ambulatory systolic blood pressure (SBP). If ambulatory SBP were available, then a mean outpatient SBP was used.

Two hundred and forty-four patients had 1 or 2 SBP within 1 year of presentation, which were averaged and used for 10yASCVD calculation. For the remaining patients, we predicted outpatient systolic blood pressure using a multivariable linear regression model. Using model selection strategies, predictors included: diabetes diagnosis, race, smoking status, inpatient systolic blood pressure, and status of whether on HTN medication before LHC. Within

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the subset of patients who had true values of outpatient systolic blood pressure, the difference between those values and the values predicted by the aforementioned linear regression model was tested through Wilcoxon signed rank test and the difference was found to be insignificant (p value = 0.306). Then, within this subset, 10yASCVD values were calculated using both the measured outpatient SBP and the predicted outpatient SBP. The difference in the two values of 10yASCVD was tested also through Wilcoxon-signed rank test and found to be insignificant (p value = 0.218).

Several analyses were performed using the calculated 10yASCVD score from the subset of patients with measured SBP available. Statin status and intensity of therapy were analyzed in each 10yASCVD category. Further sub-analysis was performed by type of ACS event and date of LHC with November 2013 serving as binary cutoff since it was the online publication date of the 2013 ACC/AHA Cholesterol Guidelines. Agreement between 10yASCVD and statin status was assessed through Cohen's kappa test of agreement for overall sample, by ACS event, and by date. Agreement was defined as 10yASCVD $\geq 7.5\%$ on statin therapy and 10yASCVD $< 5\%$ not on statin therapy – excluding people who had diabetes mellitus. As a sensitivity analysis, all the above analyses were repeated using calculated 10yASVD scores from predicted outpatient SBP.

In the subset of those with ASCVD $\geq 7.5\%$, 2 binary outcomes for proper status and proper intensity were created. Proper status was considered correct if the patient was on a statin. Similarly, proper intensity was considered correct if the patient was on a high or medium intensity statin. Using these two outcomes, assessment of the relation between age, gender, and race and both outcomes were conducted using univariate logistic regression.

Results

Four thousand one hundred and forty-eight patients were identified from our EDW query. Of those, 1,265 patients were included after chart review as defined in methods. Baseline demographic and laboratory data of patients is provided in Table 1.

Tables 2 and 3 summarize overall statin status and intensity on admission for all patients categorized by 10yASCVD risk. Agreement between ASCVD and statin status through Cohen kappa test was statistically significant in both the primary analysis and sensitivity analysis (Table 6).

Further analysis was done on statin status at admission by ACS event type (Figure 1, Table 4). Statin intensity on admission with categorization by ACS event type is shown in Figure 2 and Table 5. Kappa test for agreement were significant for UA and STEMI in both measured and predicted SBP groups whereas NSTEMI was only significant in patients with predicted SBP (Table 6).

Before November 2013, 41% of patients (32 of 78) in the primary analysis group with 10yASCVD $\geq 7.5\%$ were on statin therapy compared with 42.9% (30 of 70) after November 2013 (Figure 3). In the patients with predicted SBP, 33.6% (155 of 461) with 10yASCVD $\geq 7.5\%$ were on

Table 1
Demographics and laboratory data

Variable	N = 1265
Men	805 (63.64%)
Women	460 (36.36%)
White	750 (64.38%)
Black	271 (23.26%)
Asian	36 (3.09%)
Other	108 (9.27%)
Diabetes Mellitus	312 (24.66%)
On hypertension medications prior to left heart catheterization	583 (46.04%)
Current smoker	289 (22.95%)
Statin intolerance at time of left heart catheterization	31 (2.46%)
	Mean (Standard Deviation)
Age (years)	58.29 (8.83)
Weight (lbs)	192.94 (47.20)
Low-density lipoprotein cholesterol (mg/dl)	107.94 (39.13)
High-density lipoprotein cholesterol (mg/dl)	43.89 (15.23)
Total cholesterol (mg/dl)	178.97 (46.67)
Hemoglobin A1C	6.44 (1.81)

Table 2
Statin status on admission

10 year Atherosclerotic Cardiovascular Disease Risk	Primary Analysis (n = 244)	
	Statin Status on Admission	
	+	–
$\geq 7.5\%$	62 (41.9%)	86 (58.1%)
$< 7.5\%$	26 (27.4%)	69 (72.6%)
$\geq 10\%$	56 (45.5%)	67 (54.5%)
$< 10\%$	32 (26.7%)	88 (73.3%)
$< 5\%$	16 (24.2%)	50 (75.8%)
5–7.5%	10 (34.5%)	19 (65.5%)
	Sensitivity Analysis (n = 1178)	
	Statin Status on Admission	
	+	–
$\geq 7.5\%$	254 (34.5%)	483 (65.5%)
$< 7.5\%$	87 (19.8%)	352 (80.2%)
$\geq 10\%$	226 (37.1%)	384 (63.0%)
$< 10\%$	115 (20.3%)	451 (79.7%)
$< 5\%$	47 (16.6%)	237 (83.5%)
5–7.5%	40 (25.8%)	115 (74.2%)

statin before November 2013 compared with 35.9% (99 of 276) after November 2013. A more significant difference was seen in proportion of patients with 10yASCVD $\geq 7.5\%$ on statin therapy being placed on high or medium-intensity statins with 79.3% (25 of 32) before November 2013 compared with 89.6% (26 of 29) after November 2013 in the primary analysis group (Figure 4). The same pattern applied to the sensitivity analysis with 81.7% (117 of 145) of patients with 10yASCVD $\geq 7.5\%$ on statin being initiated on high or medium intensity statin before November 2013 compared with 89.2% (83 of 94) after November 2013 (Figure 4). Kappa test for agreement between ASCVD and

Table 3
Statin Intensity on admission

Primary Analysis (n = 244)			
10 year Atherosclerotic Cardiovascular Disease Risk	Statin Intensity on Admission		
	High	Medium	Low
≥7.5%	9 (14.8%)	42 (68.9%)	10 (16.4%)
<7.5%	6 (25.0%)	17 (70.8%)	1 (4.2%)
≥10%	9 (16.4%)	36 (65.5%)	10 (18.2%)
<10%	6 (20.0%)	23 (76.7%)	1 (3.3%)
<5%	4 (28.6%)	9 (64.3%)	1 (7.1%)
5–7.5%	2 (20.0%)	8 (80.0%)	0 (0.0%)

Sensitivity Analysis (n = 1178)			
10 year Atherosclerotic Cardiovascular Disease Risk	Statin Intensity on Admission		
	High	Medium	Low
≥7.5%	39 (16.3%)	161 (67.4%)	39 (16.3%)
<7.5%	16 (20.8%)	57 (74.0%)	4 (5.2%)
≥10%	36 (16.8%)	145 (67.8%)	33 (15.4%)
<10%	19 (18.6%)	73 (71.6%)	10 (9.8%)
<5%	7 (17.5%)	30 (75.0%)	3 (7.5%)
5–7.5%	9 (24.3%)	27 (73.0%)	1 (2.7%)

statin status was significant pre- and post-November 2013 in primary analysis of measured SBP and sensitivity analysis of predicted SBP (Table 6).

Binary outcomes for proper status and proper intensity were created (Table 7). Age was found to be significant with respect to proper status but not proper intensity in both primary analysis and sensitivity analysis. No other variables with respect to statin status or intensity had statistical significance in both primary and sensitivity analysis.

Discussion

The aim of this study was to evaluate the impact of the evidence based 2013 ACC/AHA cholesterol guidelines on statin therapy in patients who presented with ACS and had no previous clinical ASCVD. This study used a novel method of identifying patients at first ACS event and

retrospectively calculated 10-year ASCVD risk scores to assess if they had been prescribed a statin at an appropriate intensity. Through this method, “high-risk” patients were identified who would have likely benefited from statin therapy that might have delayed or prevented their event.

As shown in our data, there are still a significant number of statin eligible patients for primary prevention that are not on statin therapy when they present with ACS. STEMI has the highest mortality and morbidity along ACS spectrum^{4,5} and it is noteworthy that only 1 in 5 statin eligible patients based on retrospective 10-year ASCVD score were prescribed a statin before this event. NSTEMI and UA have significant short-term and long-term morbidity and mortality and yet a vast majority of statin eligible patients in our data were not on any statin therapy before event. The efficacy of statins in reducing fatal and nonfatal CVD and overall mortality as well as overall tolerance of statin therapy for primary prevention has been well-established.⁶ Given this, our data are indicative of significant missed opportunities for initiating statin therapy per recent guidelines.

Our data also indicated a clear increase in intensity of statin therapy in patients with 10yASCVD risk score ≥7.5% and 5% to 7.5% following release of 2013 ACC/AHA guidelines. However, the increase in the number of patients with 10yASCVD ≥7.5% or 5% to 7.5% actually on statin therapy postguidelines is marginal. This is similar to previous studies which evaluated the guidelines impact on statin initiation and appropriateness of intensity, although the majority of these studies were in the context of existing clinical ASCVD.^{3,7,8} Olufade demonstrated an increased initiation of moderate to high intensity statin use in nondiabetic primary prevention patients.⁹ Data regarding impact of guidelines in diabetic primary prevention patients were more mixed.^{9,10} There are several factors why patients may have not been placed on appropriate statin therapy. Although not clearly shown in our logistic regression, multiple studies have found gender and race disparity in statin therapy.^{11–14}

There were key strengths of this study. There were a large number of patients (n = 4,138) who were each individually manually chart reviewed to select 1,265 patients

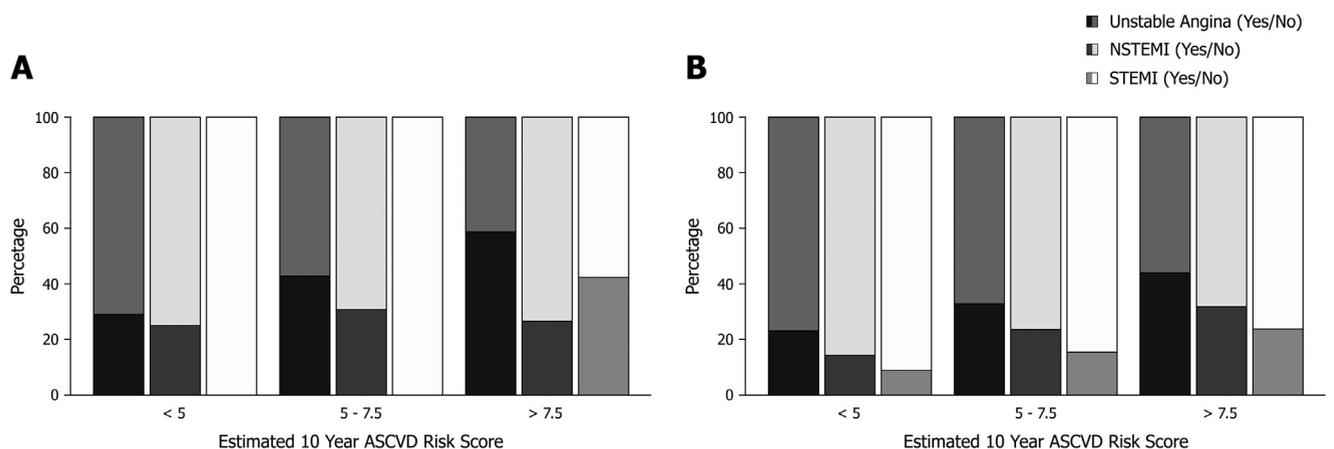


Figure 1. Statin status by calculated 10-year ASCVD risk for all primary prevention patients categorized by ACS event. A – primary analysis; B – sensitivity analysis.

Table 4
Statin status by acute coronary syndrome event

Primary Analysis (n = 244)						
10 year Atherosclerotic Cardiovascular Disease Risk	Unstable Angina Pectoris		Non-ST Elevation Myocardial Infarction		ST Elevation Myocardial Infarction	
	+	-	+	-	+	-
≥7.5%	34 (58.6%)	24 (41.4%)	17 (26.6%)	47 (73.4%)	11 (42.3%)	15 (57.7%)
<7.5%	15 (33.3%)	30 (66.7%)	11 (26.8%)	30 (73.2%)	0 (0.0%)	9 (100%)
≥10%	30 (63.8%)	17 (36.2%)	15 (27.3%)	40 (72.7%)	11 (52.4%)	10 (47.6%)
<10%	19 (33.9%)	37 (66.1%)	13 (26.0%)	37 (74.0%)	0 (0.0%)	14 (100%)
<5%	9 (29.0%)	22 (71.0%)	7 (25.0%)	21 (75.0%)	0 (0.0%)	7 (100%)
5-7.5%	6 (42.9%)	8 (57.1%)	4 (30.8%)	9 (69.2%)	0 (0.0%)	2 (100%)

Sensitivity Analysis (n = 1178)						
10 year Atherosclerotic Cardiovascular Disease Risk	Unstable Angina Pectoris		Non-ST Elevation Myocardial Infarction		ST Elevation Myocardial Infarction	
	+	-	+	-	+	-
≥7.5%	113 (43.9%)	144 (56.0%)	101 (31.8%)	217 (68.2%)	38 (23.8%)	122 (76.3%)
<7.5%	44 (26.7%)	121 (73.3%)	35 (17.3%)	167 (82.7%)	8 (11.3%)	63 (88.7%)
≥10%	105 (50.0%)	105 (50.0%)	86 (32.0%)	183 (68.0%)	33 (25.6%)	96 (74.4%)
<10%	52 (24.5%)	160 (75.5%)	50 (19.9%)	201 (80.1%)	13 (12.8%)	89 (87.3%)
<5%	24 (23.1%)	80 (76.9%)	19 (14.2%)	115 (85.8%)	4 (8.9%)	41 (91.1%)
5-7.5%	20 (32.8%)	41 (67.2%)	16 (23.5%)	52 (76.5%)	4 (15.4%)	22 (84.6%)

without clinical ASCVD. The study included a novel approach to identifying “high-risk” patients who may have benefitted from statin therapy. In comparison to most studies which only looked at patients 1 to 2 year after the publication of 2013 ACC/AHA guidelines, our study extended to 4 years post guidelines.^{2,9,15}

There were several limitations of this study. This was a retrospective study with its inherent limitations and potential for bias. It is possible that patients were not put on a statin because they had not seen a clinician the year before their LHC. The retrospective calculation of 10-year ASCVD also came with limitations as described in methods. We acknowledge the limitations of kappa test used for agreement and other statistical analysis done in this paper. Additionally, limitations apply to the use of 10yASCVD

scores calculated from predicted outpatient SBP. Thus, the analysis based on predicted outpatient SBP should only be considered as a sensitivity analysis and interpreted with caution. Furthermore, the 2013 ACC/AHA guidelines allow for flexibility in determining who received statin therapy. The guidelines indicated that although there was evidence for benefit from statin therapy in patients with 10yASCVD risk score ≥7.5% in those ages 40 to 75, attaining this threshold did not indicate automatic statin assignment. A clinician-patient risk discussion was recommended before a decision to initiate statin therapy.

Finally, if every clinician-patient risk discussion resulted in statin assignment per the guidelines, all ACS or even STEMI events would not be captured. About 30% of patients with STEMI had 10yASCVD <7.5% and 20% had

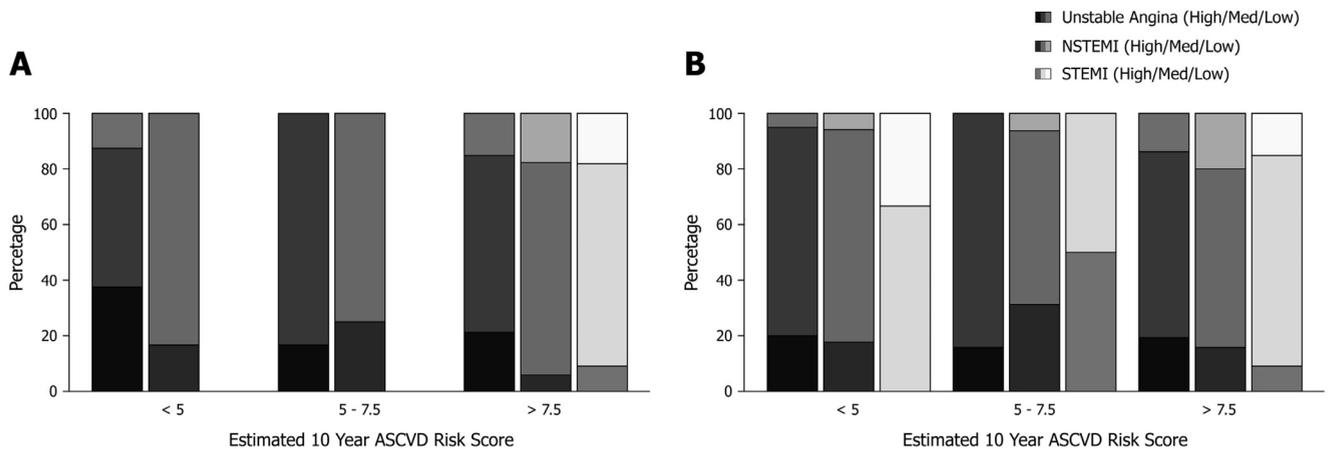


Figure 2. Statin intensity (high/medium/low) by calculated 10-year ASCVD risk categorized by ACS event. A – primary analysis; B – sensitivity analysis.

Table 5
Statin intensity by acute coronary syndrome event

Primary Analysis (n = 244)									
10 year Atherosclerotic Cardiovascular Disease Risk	Unstable Angina Pectoris			Non -ST Elevation Myocardial Infarction			ST Elevation Myocardial Infarction		
	High	Med	Low	High	Med	Low	High	Med	Low
≥7.5%	7 (21.2%)	21 (63.6%)	5 (15.2%)	1 (5.8%)	13 (76.5%)	3 (17.7%)	1 (9.1%)	8 (72.7%)	2 (18.2%)
<7.5%	4 (28.6%)	9 (64.3%)	1 (7.1%)	2 (20.0%)	8 (80.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
≥10%	7 (24.1%)	17 (58.6%)	5 (17.2%)	1 (6.7%)	11 (73.3%)	3 (20.0%)	1 (9.1%)	8 (72.7%)	2 (18.2%)
<10%	4 (22.2%)	13 (72.2%)	1 (5.6%)	2 (16.7%)	10 (83.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<5%	3 (37.5%)	4 (50.0%)	1 (12.5%)	1 (16.7%)	5 (83.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5–7.5%	1 (16.7%)	5 (83.3%)	0 (0.0%)	1 (25.0%)	3 (75.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Sensitivity Analysis (n = 1178)									
10 year Atherosclerotic Cardiovascular Disease Risk	Unstable Angina Pectoris			Non -ST Elevation Myocardial Infarction			ST Elevation Myocardial Infarction		
	High	Med	Low	High	Med	Low	High	Med	Low
≥7.5%	21 (19.3%)	73 (67.0%)	15 (13.8%)	15 (15.8%)	61 (64.2%)	19 (20.0%)	3 (9.1%)	25 (75.8%)	5 (15.2%)
<7.5%	7 (18.0%)	31 (79.5%)	1 (2.6%)	8 (24.2%)	23 (69.7%)	2 (6.06%)	1 (20.0%)	3 (60.0%)	1 (20.0%)
≥10%	21 (20.6%)	67 (65.7%)	14 (13.7%)	12 (15.0%)	53 (66.3%)	15 (18.8%)	3 (10.0%)	23 (76.7%)	4 (13.3%)
<10%	7 (15.2%)	37 (80.4%)	2 (4.4%)	11 (22.9%)	31 (64.6%)	6 (12.5%)	1 (12.5%)	5 (62.5%)	2 (25.0%)
<5	4 (20.0%)	15 (75.0%)	1 (5.0%)	3 (17.7%)	13 (76.5%)	1 (5.9%)	0 (0.0%)	2 (66.7%)	1 (33.3%)
5–7.5	3 (15.8%)	16 (84.2%)	0 (0.0%)	5 (31.3%)	10 (62.5%)	1 (6.3%)	1 (50.0%)	1 (50.0%)	0 (0.0%)

Table 6
Kappa statistical analysis

Primary Analysis (n = 244)			
	Kappa	p Value	95% CI
Overall	0.171	0.001	(0.07, 0.27)
Unstable Angina Pectoris	0.291	0.003	(0.11, 0.48)
Non-ST Elevation Myocardial Infarction	0.069	0.292	(-0.05, 0.19)
ST Elevation Myocardial Infarction	0.237	0.035	(0.05, 0.42)
Before November 2013	0.176	0.016	(0.04, 0.31)
After November 2013	0.166	0.033	(0.02, 0.31)

Sensitivity Analysis (n = 1178)			
	Kappa	p Value	95% CI
Overall	0.131	0.000	(0.09, 0.17)
Unstable Angina Pectoris	0.153	0.000	(0.08, 0.23)
Non-ST Elevation Myocardial Infarction	0.142	0.000	(0.09, 0.20)
ST Elevation Myocardial Infarction	0.083	0.015	(0.03, 0.14)
Before November 2013	0.131	0.000	(0.08, 0.18)
After November 2013	0.130	0.000	(0.07, 0.19)

10yASCVD <5%. A larger proportion of NSTEMI and UA cohort were from patients with 10yASCVD <5%. Using the United States Preventive Service Task Force (USPSTF) guidelines, which recommend initiation of therapy with 10yASCVD risk score ≥10%, even more patients in our data set would have been categorized as potentially not-needing statin therapy.¹⁶ Pagidilpati compared eligibility for primary prevention statin therapy using the 2013 ACC/AHA guidelines and 2016 USPSTF guidelines and found that 8.9% of individuals would be recommended statins by ACC/AHA guidelines but not by USPSTF. Among these, 55% would be individuals ages 40 to 59 years with mean 30 year CV risk greater than 30% and 28% would be individuals with diabetes.¹⁷ HOPE-3 demonstrated the benefit in terms of composite cardiovascular death, myocardial infarction, stroke of even moderate intensity statin in intermediate risk patients.¹⁸ Similarly, the Cochrane meta-analysis showed a significant mortality as

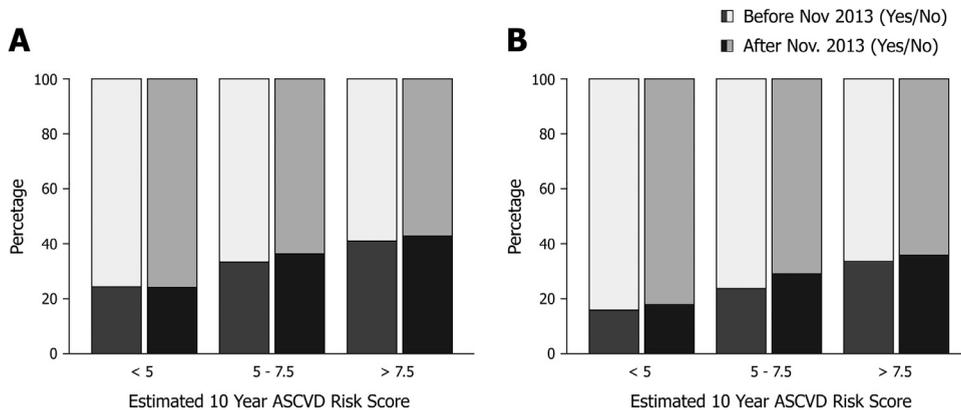


Figure 3. Statin status by calculated 10-year ASCVD risk categorized by date of left heart catheterization. A – primary analysis; B – sensitivity analysis.

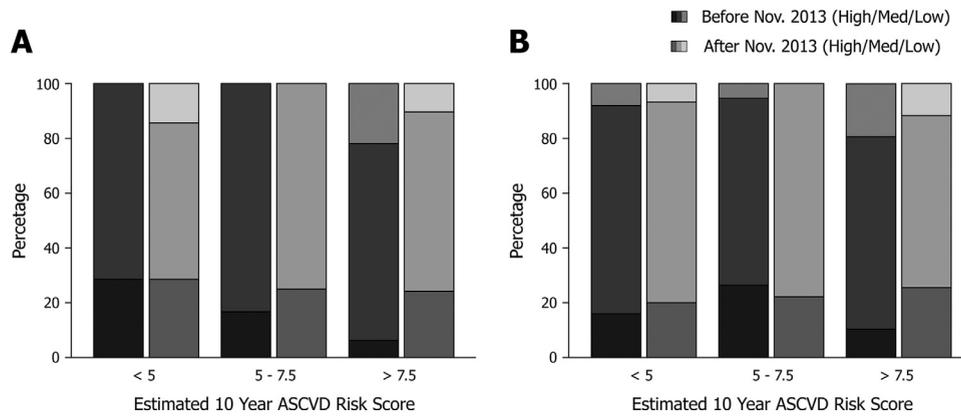


Figure 4. Statin intensity (high/medium/low) by calculated 10 year ASCVD risk categorized by date of left heart catheterization. A – primary analysis B – sensitivity analysis

Table 7

Logistic regression of statin status and intensity

Primary Analysis (n = 244)				
Outcome	Variable	p value	Odds Ratio	95% CI
Proper Status	Age	0.005	1.061	(1.02, 1.11)
Proper Status	Race (Black)	0.537	1.265	(0.60, 2.67)
Proper Status	Sex (Women)	0.043	1.991	(1.02, 3.88)
Proper Status	Ethnicity (Hispanic)	0.563	1.420	(0.43, 4.66)
Proper Intensity	Age	0.825	0.989	(0.90, 1.09)
Proper Intensity	Race (Black)	0.202	0.386	(0.09, 1.67)
Proper Intensity	Sex (Women)	0.528	0.641	(0.16, 2.55)
Proper Intensity	Ethnicity (Hispanic)	0.919	1.125	(0.12, 10.84)
Sensitivity Analysis (n = 1178)				
Outcome	Variable	p value	Odds Ratio	95% CI
Proper Status	Age	0.024	1.022	(1.00, 1.04)
Proper Status	Race (Black)	0.469	1.137	(0.80, 1.61)
Proper Status	Sex (Women)	0.109	1.312	(0.94, 1.83)
Proper Status	Ethnicity (Hispanic)	0.000	2.672	(1.49, 4.78)
Proper Intensity	Age	0.066	1.043	(0.99, 1.09)
Proper Intensity	Race (Black)	0.114	0.547	(0.26, 1.16)
Proper Intensity	Sex (Women)	0.968	0.985	(0.48, 2.04)
Proper Intensity	Ethnicity (Hispanic)	0.766	0.853	(0.30, 2.42)

well as ASCVD benefit for statin therapy in primary prevention.⁶

Conclusions

Calculation of ASCVD in patients with first ACS event showed that a significant amount of primary patients who would potentially qualify for statin therapy per the 2013 ACC/AHA guidelines are not initiated on one. Since the release of the 2013 ACC/AHA guidelines, there has been a clear increase in intensity of statin therapy for primary prevention patients. However, the change in proportion of patients appropriately on statin therapy has been more marginal. Since initiation of statins in primary prevention depends on analyzing both initial ASCVD risk and the potential for overall benefit based on the evidence, our data may help clinicians and their patients understand the potential value of guideline adherence.

Conflict of Interest: None

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