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Utilization and adherence to guideline-recommended lipid-lowering therapy at an academic medical center

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BACKGROUND: Clinical guidelines for managing blood cholesterol were updated in November 2013.

OBJECTIVE: To evaluate the adherence to the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline recommendations for statin therapy in the treatment of elevated blood cholesterol in high-risk patients.

DESIGN: A single-center, retrospective, observational study.

SETTING: A tertiary care academic medical center in Riyadh, Saudi Arabia.

PATIENTS: Consecutive adult patients discharged with a prescription for any of the statin medications group between 1 June 2015 and 31 December 2015.

MAIN OUTCOME MEASURE(S): Adherence to the 2013 ACC/AHA guidelines for management of cholesterol by statin therapy in high-risk patients.

RESULTS: Of 1094 patients, 753 (68.8%) met the inclusion criteria of the study. Of these 753 patients, 53.5% had atherosclerotic cardiovascular diseases; 29.2% had diabetes; 0.9% had an LDL-C level >190 mg/dL; 10.8% had an estimated 10-year risk >7.5%; and 4.9% had no risk. Two hundred and eight (27.6%) patients received statin therapy at an inappropriate intensity according to their risk group based on the guideline; 126 (16.7%) received less than the ideal intensity.

CONCLUSION: Approximately one-third of patients received statin therapy at an inappropriate intensity according to the guideline recommendation. Wide application of the 2013 ACC/AHA cholesterol guidelines in our practice would optimize the utilization of statin therapy at the ideal intensity in high-risk patients.

LIMITATION: Drug-drug interactions and intolerance to statin therapy were not considered when we evaluated adherence among high-risk patients.

Atherosclerotic cardiovascular diseases (ASCVDs) result from plaques formed in the arterial walls. ASCVDs include coronary artery disease (CAD), peripheral artery disease (PAD), cerebrovascular disease, and aortic atherosclerotic disease.[1,2] The risk factors associated with ASCVD can be divided into: modifiable (cigarette smoking, hypertension, diabetes, and hyperlipidemia) and non-modifiable (male sex and advanced age).[1,2]

ASCVDs are the major cause of mortality worldwide. In Saudi Arabia, the prevalence of CAD and PAD for individuals aged >45 years is 5.5% and 11.7%, respectively.[3-12] To decrease the risk of ASCVD, the American Heart Association (AHA) and the American College of Cardiology (ACC) in collaboration with the National Heart, Lung, and Blood Institute (NHLBI) released a new guideline in November 2013. The aim of the treatment recommended in these guidelines focuses on the intensity of statins instead of the target low-density lipoprotein cholesterol (LDL-C).[3] The guideline identified four primary patient groups labelled as "high-risk patients" for ASCVD, and for whom statin therapy is indicated.[3] The four patient groups that would benefit from statin therapy include

the following: 1) patients with clinical ASCVD, 2) patients with LDL-C >190 mg/dL, 3) patients aged 40-75 years with diabetes and LDL-C from 70-189 mg/dL but without clinical ASCVD, and 4) patients aged 40-75 years with a 10-year ASCVD risk of >7.5% but without clinical ASCVD or diabetes.[3]

High-intensity statin therapy was defined in accordance with the 2013 ACC/AHA guidelines as atorvastatin 40-80 mg and rosuvastatin 20-40 mg. Foody and colleagues studied the cardiovascular outcomes in patients without cardiovascular diseases in which simvastatin or atorvastatin was used initially for primary prevention. In their study, 168 973 patients received atorvastatin (10 or 20 mg) and 50 658 patients received simvastatin (20 or 40 mg); both patient groups were followed up for 1.5 years. They found that atorvastatin significantly reduced the risk of cardiovascular disease compared with simvastatin among patients without cardiovascular diseases.[4] Data have shown that statin monotherapy is better in terms of reducing the risk of fatal and non-fatal cardiovascular diseases in patients with type 2 diabetes at high risk for cardiovascular diseases than a combination therapy (statin plus fibrate).[5] Another RCT has shown that a high-intensity statin therapy reduces the all-cause mortality after acute coronary syndrome (ACS) compared with low-dose statin therapy.[6] All of these findings indicate a beneficial effect of statin therapy for primary or secondary prevention.

Although previous randomized control trials have shown the benefit of high-intensity statin therapy, registry data show significant underutilization and non-adherence to these treatment recommendations.[7] In the United States (US), the National Health and Nutrition Examination Survey reported that only 50% of 1 029 633 high-risk patients received statin therapy.[7] Moreover, Hirsh and colleagues found that although 88% of 6748 patients from 31 U.S. hospitals were prescribed a statin at discharge after ACS, only 30% received a high-intensity statin.[8] There are no studies in Saudi Arabia that have examined this issue despite its importance. Thus, we sought to evaluate adherence to the guideline-recommended lipid-lowering strategy and the utilization of statin therapy in high-risk patients in a large academic hospital in Saudi Arabia. Moreover, we explored predictors for the utilization of high-intensity statin therapy in high-risk patients.

PATIENTS AND METHODS

This study was a single-center, retrospective, observational study carried out at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia. KKUH is a 900-bed tertiary teaching hospital at King Saud University. After ethical approval (KSU, NO. E-15-1662), patients were identified using data from electronic medical records. The data were extracted from patient charts from all adult patients who were discharged with a prescription of any statin medication. A standard data collection sheet was created to capture detailed baseline demographics, including age, sex, medical history, cigarette smoking, and 10-year ASCVD risk; clinical data, including medications and dose, duration, and intensity of statin therapy; laboratory data during hospitalization; medications; and procedural data. We matched the clinical data to the guideline-recommended statin therapy to determine adherence to the guidelines. Between 1 June and 31 December 2015, the medical records of consecutive adult patients with a prescription of any statin medications were identified. Trained pharmacists reviewed the medical charts. We excluded patients aged <40 or >75 years, those with abnormal liver function test results (ALT 3 3 times the upper limit of the normal range), and those with insufficient data to determine their risk group. The participants were classified into the following five independent risk groups: 1) patients with clinical ASCVD, 2) patients aged 40-75 years with diabetes and LDL-C from 70-189 mg/dL (without clinical ASCVD), 3) patients with LDL-C >190 mg/dL (without ASCVD or diabetes), 4) patients aged 40-75 years with a 10-year ASCVD risk of >7.5% (without clinical ASCVD or diabetes), or 5 patients with no risk.

We assessed the 10-year ASCVD risk with the 2013 ACC/AHA guidelines using the Assessment of Cardiovascular Risk Calculator (ACC/AHA ASCVD Risk Calculator. http://www.cvriskcalculator.com/. Accessed April 11, 2017). The primary study outcome was adherence to the 2013 ACC/AHA guidelines for the lipid-lowering therapy. We further stratified the five risk groups into three categories to determine their statin therapy adherence pattern. Those receiving statins at the recommended intensity were classified as adherent. We compared the current statin therapy intensity in our practice to the ideal statin therapy intensity according to the guideline recommendations. The secondary study outcome was to determine the predictors for use of high-intensity statin therapy in the four patient groups.

Descriptive statistics were used to identify trends in the data. Summary statistics were used for continuous variables (age, laboratory parameter, 10-year ASCVD risk, and dose of statin therapy), while frequencies and percentages were calculated for categorical variables (sex, type of statin medication, intensity of statin, pa-

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tient risk group, comorbidities, and other concurrent medications). Categorical data were compared using the chi-square test. A multivariable logistic regression analysis was used to determine the factors associated with use of high-intensity statin therapy. A *P* value of <.05 was considered significant for all statistical analyses. Statistical software used for the analysis was Stata, version 14.

Table 1. Characteristics of the study participants (n=753).

Continuous variables	Mean	Standard deviation
Age (years)	58.5	8.9
Systolic blood pressure (mm Hg)	131	21.6
Low-density lipoprotein-cholesterol (mmol/L)	2.2	1.1
10-year estimated ASCVD risk (%)	3.6 (median)	1.5-6.9 (IQR)
Categorial variables	**Number of patients**	**%**
Sex, Male	436	57.9
Patient risk groups		
Atherosclerotic cardiovascular diseases	402	53.5
Diabetes mellitus	225	29.9
LDL-C ≥190 mg/dL	7	0.9
10-y ASCVD risk ≥7.5%	81	10.8
No risk criteria	37	4.9
Type of statin therapy		
Atorvastatin	648	86.1
Rosuvastatin	15	2.0
Simvastatin	90	12.0
Comorbidities		
Hypertension	549	72.0
Coronary artery disease	369	49.0
Dyslipidemia	182	24.2
Peripheral artery disease	11	1.5
CVA/TIA	36	4.8
Diabetes	479	63.6
Heart failure	47	6.2
Chronic kidney disease	123	16.3
GERD	7	0.9
Tobacco history	92	12.2
Concomitant medications		
Angiotensin converting enzyme inhibitor	307	40.8
Angiotensin receptor blocker	135	17.9
Beta blocker	473	62.8
Calcium channel blocker	198	26.3
Thiazide diuretic	26	3.5
P2Y12 inhibitor	265	35.2
Aspirin	439	58.3
Antidiabetic medications	451	59.9

Data are number of patients (percent) or mean (standard deviation). The patient risk groups are mutually exclusive so numbers of patients may differ from the numbers by comorbidities.

CVA/TIA: cerebrovascular accident/transient ischemic attack, GERD: gastroesophageal reflux disease, PPI: proton pump inhibitor

RESULTS

Between 1 June and 31 December 2015, 1094 consecutive adult patients with a prescription for any statin medications were identified. Of these 1094 patients, 753 (68.8%) patients met the inclusion. The mean age (standard deviation) of the patients was 58.5 (8.9) years, and 436 (57.9%) were men (**Table 1**). About half had ASCVD (n=402, 53.5%) and almost one-third had diabetes (n=225, 29.9%). Seven (0.9%) had an LDL-C level of >190 mg/dL, 81 (10.8%) had a 10-year risk of >7.5%, and 37 (4.9%) had no risks. The mean estimated 10-year ASCVD risk rate was 4.9 (4.4 %, and the mean (SD) LDL-C level was 83.6 (44.2) mg/dL or 2.2 (1.1) mmol/L. Most had received atorvastatin (n=648, 86.1%). The majority were hypertensive (n=549, 72%) with a mean (SD) systolic blood pressure (SBP) of 131.1 (21.6) mm Hg. Many were taking beta-blocker treatment (473 patients; 62.8%), followed by antidiabetic medication (451 patients; 59.9%) and aspirin (439 patients; 58.3%). Most patients had received high-intensity statin therapy (n=422) (**Figure 1**), which included most patients with ASCVD (n=335, 83.3%) while 26.2% (n=59) of patients with diabetes received high-intensity statin therapy. Most patients with an LDL-C level >190 mg/dL (n=6, 85.7%) and with an estimated 10-year ASCVD risk of >7.5% (n=73, 90.1%) received moderate-intensity statin therapy.

Most patients who should have received high-intensity therapy under the guidelines were treated appropriately (n=544, 72.2%). Of patients who received high-intensity statin therapy, 4.3% should have received no statin therapy and 10.2% should have received intermediate-intensity statin therapy (**Table 2**). Forty-one percent of patients who received intermediate-intensity statin therapy received either high-intensity or no statin therapy. Of patients who received low-intensity statin therapy, 20% should ideally have received no statin therapy, 60% should have received intermediate-intensity statin therapy, and 20% should have received high-intensity, low-intensity, statin therapy. Adherence to the guideline recommendations among patients who received statin therapy was estimated as 72%, while 28% (n=208) were nonadherent (**Figure 2**). Of the nonadherent, 126 (16.7%) received less than the ideal therapy.

In the multiple logistic regression, factors significantly associated with use of high-intensity statin therapy included male sex, CAD, PAD, cerebrovascular accident or transient ischemic attack (CVA/TIA), hypothyroidism, and concomitant use of beta-blockers, P2Y12 inhibitors, and aspirin (**Table 3**). Chronic kidney disease, gastroesophageal reflux disease, tobacco

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Table 2. Actual statin therapy intensity by ideal statin therapy intensity based on the 2013 ACC/AHA guidelines.

Actual statin therapy intensity	Ideal stain therapy intensity			Totals
	No statin therapy	**Intermediate intensity**	**High intensity**	
Low intensity	4 (20.0)	12 (60.0)	4 (20.0)	20 (2.7)
Intermediate intensity	13 (4.2)	183 (59.8)	110 (35.9)	306 (40.9)
High intensity	18 (4.3)	43 (10.2)	361 (85.5)	422 (56.4)
Totals	**35**	**238**	**475**	**748**

Values are percentage of actual therapy total. Not shown is one patient taking no statin therapy who should have received high-intensity therapy and 4 patients taking intermediate-intensity therapy who ideally should have been taking low-intensity therapy.

use history, and proton pump inhibitor use were not significantly associated with the use of high-intensity statin therapy.

DISCUSSION

In this observational study, we evaluated adherence to the 2013 ACC/AHA guideline recommendations for statin therapy in the treatment of blood cholesterol in high-risk patients. We found that approximately one-third of patients received statin therapy at an inappropriate intensity according to the guideline recommendations. We also found that most patients who had ASCVD received high-intensity statin therapy. This finding was consistent with those of Zupec and colleagues who reported an increased utilization of high-intensity statins in patients with ASCVD after the release of the 2013 ACC/AHA guidelines.[9] However, our findings on its utilization were higher than the reported high-intensity statin use after ACS in the U.S.[8] The majority of the patients with an LDL-C level of >190 mg/dL received moderate-intensity statin therapy instead of high-intensity statin therapy according to the guideline recommendations. Our findings also indicate that more than half of the patients in the no-risk group received high-intensity statin therapy, which indicates an overutilization of statin therapy in this group.

We also compared the currently used statin therapy intensity for each patient risk group to the ideal statin therapy intensity based on the guidelines. More than half of the patients who should have received high-intensity statin therapy under the guideline recommendations received moderate- and low-intensity statin therapies. Further, 70% of the patients who should have received moderate-intensity statin therapy received either high- or low-intensity statin therapy. Approximately 30% of the patients who should have received no statin therapy received statin therapy. All of these findings show that there was an under-
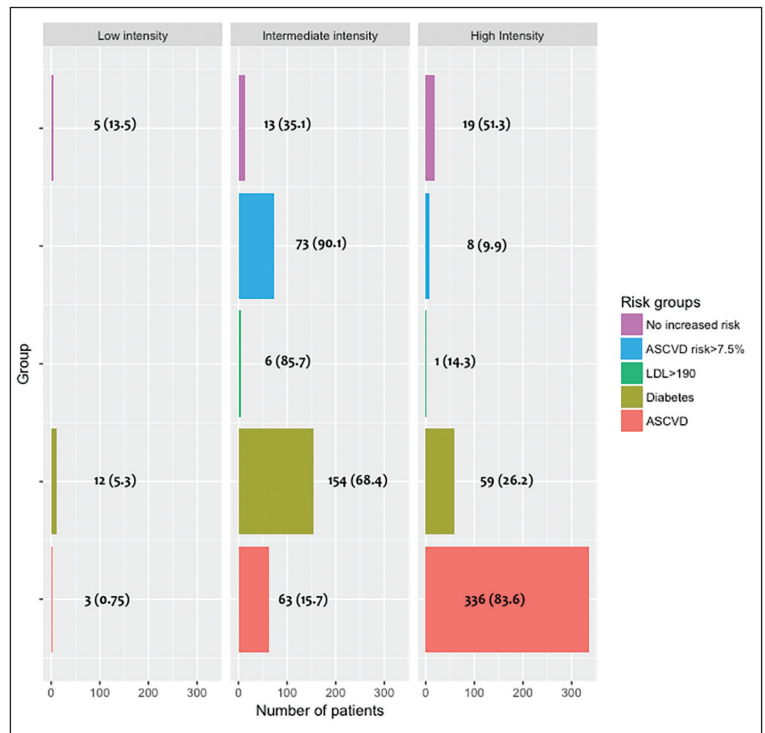

Figure 1. Distribution of statin therapy intensity for each risk group (percentages are within risk-group proportions).

utilization of the guideline recommendations on the appropriate statin therapy intensity in the different risk groups.

In the multiple logistic regression analysis, the factors associated with use of high-intensity statin therapy were male sex, CAD, PAD, CVA/TIA, hypothyroidism, and use of beta-blockers, P2Y12 inhibitors, and aspirin. The association between ASCVD (CAD, PAD, and CVA/TIA) and use of high-intensity statins may be related to its use for secondary prevention as recommended in the guidelines. Furthermore, antiplatelet and P2Y12 inhibitors were used with high-
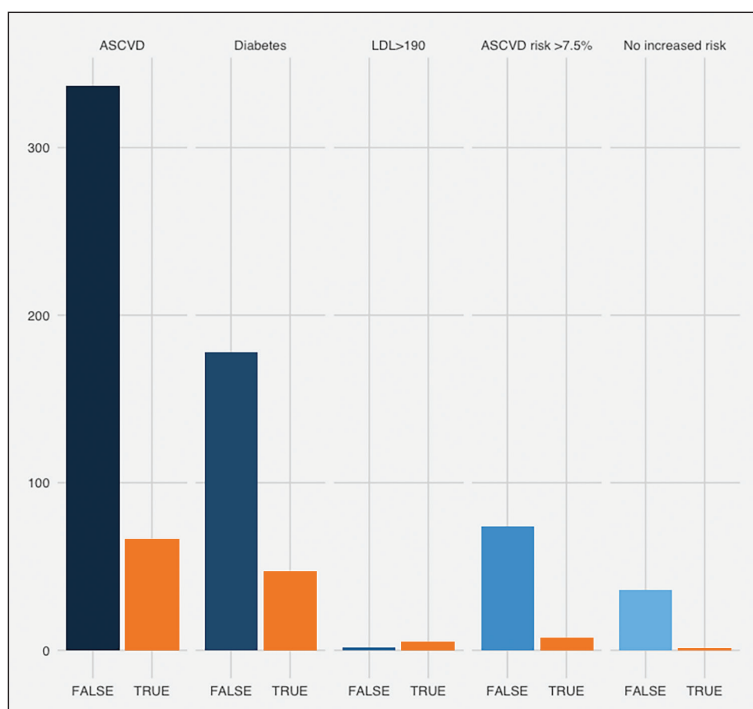
Figure 2. Adherence to the 2013 ACC/AHA guidelines among patients receiving statins by risk group. (TRUE: nonadherent patients receiving less than the ideal statin intensity (n=126, 16.7%).

Table 3. Factors associated with the use of high-intensity statin therapy.

Factor	Odds ratio	95% CI	P value
Male sex	2.056	1.328–3.183	<.01
CAD	4.730	2.940–7.612	<.001
PAD	9.863	1.009–96.45	<.05
CVA/TIA	3.854	1.586–9.366	<.01
Hypothyroidism	2.736	1.280–5.846	<.01
CKD	1.589	0.910–2.774	.104
GERD	5.547	0.890-34.57	.066
Beta-blocker	1.893	1.84–3.027	<.01
P2Y12 inhibitor	3.263	1.969–5.407	<.001
Aspirin	3.067	1.970–4.775	<.001
PPI	0.748	0.494–1.123	.170
Tobacco history	1.794	0.815–3.948	.147

A multivariable logistic regression analysis was used to estimate factors associated with high-intensity statin use. Factors were chosen based on clinical significance. Interaction was not tested. The C statistic was 89.7%. The Hosmer-Lemeshow test with ten groups indicated a good fit for the model.

CAD: coronary artery disease, PAD: peripheral artery disease, CVA/TIA: cerebrovascular accident/transits ischemic attack, CKD: chronic kidney disease, GERD: gastroesophageal reflux disease, PPI: proton pump inhibitor.

intensity statin therapy for the primary and secondary prevention of ASCVD. Beta-blockers were used with statin therapy for secondary prevention post-MI. Hypothyroidism was associated with use of high-intensity statin therapy owing to its association also with atherosclerosis risk.[10]

We observed underuse of appropriate statin therapy intensity based on the guideline recommendations, especially for primary prevention. Multidisciplinary quality improvement initiatives like transition of care and health care bundles may improve utilization. Further research studies are needed to investigate the causes of this underutilization and the impact of certain quality initiatives on the utilization rate. Our study has strengths, including a large sample size of adult patients with different medical conditions; furthermore, it is the first study to investigate this issue in Saudi Arabia, which could promote other research studies in this area. Further future research studies are warranted to measure adherence while considering the drug-drug interactions and intolerance to statin therapies.

Limitations included a lack of complete documentation and missing patient data. With this design, we cannot estimate the cause of the underutilization of the 2013 ACC/AHA guideline recommendations. Furthermore, certain drug-drug interactions and intolerance to statin therapy were not considered when we evaluated adherence among high-risk patients.

In conclusion, approximately one-third of the patients did not receive statin therapy at an ideal intensity in the different patient risk groups according to the guideline recommendations. Wide application of the 2013 ACC/AHA Cholesterol Guidelines in our practice would optimize the utilization of statin therapy at the ideal intensity in high-risk patients.

Conflict of interest
The authors declare no conflict of interest.

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