



Comparison of the application of treatment Panel III and American College of Cardiology/American heart Association guidelines for blood cholesterol treatment in Saudi Arabia

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Background: One of the major risk factors for cardiovascular diseases is hyperlipidemia. The primary aim of this study was to estimate the proportion of individuals between 40–75 years old that would be eligible for statin therapy based on ACC/AHA guideline as compared to ATP-III guideline in a population of patients in Saudi Arabia. We also intended to extrapolate the results to the entire Saudi population, and estimate the cost implications of the ACC/AHA treatment guideline.

Methods: This study was a retrospective, observational study involving adult patients aged between 40-75 years old. The study was conducted at the primary health care clinics at King Abdul-Aziz Medical/Riyadh. The eligibility for statins use was assessed and compared for each patient based on both the recent 2013 ACC-AHA guideline and the 2002 ATP-III guideline. The cost implication of applying the ACC/AHA treatment guideline was estimated based on the average cost for 40 mg Atorvastatin in the Saudi Market.

Results: A total of 1005 patients were included in the study. Using the ATP-III guideline, there were 139 male (43.7%) and 279 female (40.6%) eligible to receive statin therapy. Based on the 2013 ACC/AHA guideline, treatment is recommended in 315 males (99.1%) and 564 females (82.1%). On the other hand, high-intensity statin was recommended in 302 male (95%) and 400 female (58.2%). Only 74 (10.5%) patients were prescribed high-intensity statin of the 702 eligible patients. Extrapolating the results to the entire Saudi population, 2.369 million additional patients

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would be eligible for statin therapy when applying the ACC/AHA guideline. Applying the new guideline would result in a cost increase of at least 4.318 billion SR per year.

Conclusions: The eligibility for statin therapy was much higher when applying the ACC/AHA guideline as compared to ATP-III guideline. Applying the recent ACC/AHA dyslipidemia guideline increased the number of patients eligible for statin therapy to approximately two folds. This would be associated with a substantial increase in cost and possibly side effects. The concerns surrounding the ACC/AHA guideline should be addressed at the national level.

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Keywords: Hyperlipidemia, Dyslipidemia, ATP-III guideline, ACC/AHA guideline, Comparison, Cardiovascular risk

1. Introduction

Cardiovascular diseases (CVD) are the most common cause of morbidity and mortality worldwide, including Saudi Arabia [1,2]. Screening, early detection, and treatment to prevent further complications are very important for patients who are at risk for CVD. The common approach for primary prevention of CVD is to identify high-risk patients and individualize their treatment using lifestyle intervention and pharmacological agents.

Until recently, hyperlipidemia was managed according to the Adult Treatment Panel III (ATP III) guideline, which was published in 2002 [3]. According to the ATP III guideline, patients with CVD or CVD risk equivalent and low-density lipoprotein (LDL) level 100 mg/dL or higher are eligible for statins therapy [3]. Moreover, primary prevention is also recommended based on the assessment of both LDL and the 10 years risk of coronary artery disease based on Framingham calculator. The ATP III guideline was widely accepted and implemented in clinical practice.

In 2013, the American College of Cardiology/American Heart Association (ACC/AHA) released a new guideline for managing blood cholesterol

and preventing atherosclerotic cardiovascular events in adults [4]. Although it has been several years since the introduction of the new guideline, many physicians are still reluctant to apply the new recommendations and still relying on the old guideline. In fact, The ACC/AHA guideline has been received with significant controversy [5]. For example, although the ATP III guideline was based on the 10-year risk of coronary heart disease (CHD) only [3], the ACC/AHA guideline extends to include all hard atherosclerotic cardiovascular disease (ASCVD), including CHD and stroke [4], using a new risk assessment calculator [6]. The use of the Pooled Cohort Equations for assessment of the 10-year risk for ASCVD is, perhaps, the most controversial aspect of the new guideline [7]. The equation overestimated risk by 75–150% according to one study [8]. The ACC/AHA guideline has also lowered the risk level for sustain eligibility from 20% CHD risk in the ATP III guideline to 7.5% ASCVD risk. Eliminating fixed LDL-C targets and proposing 50% or 30–50% LDL-C reductions according to ASCVD risk was another substantial change in the new guideline [8]. Many patients who were not eligible for treatment should now receive treatment based on the new recommendations. The potential implications of these changes in largely expanding the number of patients eligible for statin therapy have received much attention [8–11].

The primary aim of this study was to estimate the proportion of individuals 40–75 years of age who would be eligible for statin therapy based on the 2013 ACC/AHA guideline as compared to the 2002 ATP III guideline in a population of patients attending primary health care clinics in Saudi Arabia. We also intended to extrapolate the results to the entire Saudi population, estimate the cost implication of the ACC/AHA treatment guideline, and to assess physicians' adherence to the new guideline recommendations in Saudi

Abbreviations

ATP III	Adult Treatment Panel III
CVD	Cardiovascular diseases
LDL	Low density lipoprotein
HDL	High density lipoprotein
ESC	The American College of Cardiology/American Heart Association
ACC/AHA	Atherosclerotic cardio vascular disease
CHD	Coronary heart disease
KAMC	King Abdul-Aziz Medical City
DM	Diabetes mellitus
TG	Triglyceride

Arabia. No similar study has previously been conducted in Saudi Arabia.

2. Materials and methods

2.1. Study design and setting

This study was a retrospective, observational study. The study was conducted at the primary health care clinics at King Abdul-Aziz Medical City (KAMC), a 1025-bed tertiary care hospital in Riyadh, Saudi Arabia. The primary health care clinics at KAMC provide comprehensive medical service to a diverse patient population. The clinics operate daily from 7 AM until 9 PM including the weekend. Institutional review board approval was obtained from King Abdullah International Medical Research Center.

2.2. Study participants

Data collection and extraction was conducted in April 2015. Medical files for all patients who attended the clinics from January 1, 2015 until March 31, 2015 were screened for inclusion. All patients aged 40–75 years were eligible for inclusion into the study. We excluded patients who were younger than 40 years or older than 75 years. This age group was chosen to comply with the ACC/AHA guideline for using the pooled cohort equation for estimating ASCVD risk. Patients who had no recent lipid profile (within 3 months) were also excluded. A total of 84,504 patients attended the clinic during the study period, of whom 30,876 were 40–75 years old (mean age = 54.5 ± 9 years). Women accounted for 20,419 (66.1%) of the eligible patients.

2.3. Sample size calculation and data extraction

The minimal required sample size to estimate the proportion of patients who are eligible for statin therapy was 1004. The sample size was estimated using the following parameters: a precision of 4%, confidence level of 99%, population size of 30,876 patients, and assuming that 50% of patients will be eligible for statin therapy (using 50% will provide the highest required sample size). In order to account for missing lipid profile data, we decided to randomly select 1200 patients. The patients' demographic and clinical information (medical history, medication history, lipid profile) was extracted from both chart review and electronic medical records.

2.4. Main outcome measures and data analysis

Data entry and analysis were carried out using SPSS (version 21.0; IBM, Armonk, NY, USA). The main outcome measure was the proportion of patients who were eligible for statin therapy based on the 2013 ACC/AHA guideline as compared with the 2002 ATP III guideline. Adherence of physicians with the 2013 ACC/AHA was also expressed as frequency (%). The difference between the two guidelines with regard to statin eligibility was examined using chi-square test. A p value <0.05 was considered statistically significant.

The ACC/AHA guideline identifies four classes of patients who should receive statins. These classes include patients with established ASCVD, patients with LDL cholesterol levels >190 mg/dL, diabetic patients aged 40–75 years with LDL levels of 70–189 mg/dL, and those aged 40–75 years without diabetes mellitus (DM) or ASCVD but with an estimated 10-year ASCVD of 7.5% or more.

The ATP III guideline recommends statins in patients with CVD or CVD risk equivalent and LDL level of 100 mg/dL or higher. Moreover, the guideline recommended statins for primary prevention for individuals based on both LDL level and 10 years risk of coronary artery disease. Eligibility for statins was then determined based on the most recent lipid profile data and LDL goal for every patient.

2.5. Extrapolation of results to the Saudi population

Extrapolation of the results to the entire Saudi population was based on the population data obtained from the Saudi Arabia General Authority for Statistics for 2015. Extrapolation was based on the assumption that Saudi adults aged 40–75 years have similar demographic characteristics as those in the study sample. The percentage of Saudi citizens aged 40–75 years who would be eligible for statins therapy based on the ATP III guideline and the ACC/AHA guidelines was calculated based on the results obtained from the study sample. In April 2015, there were 5.16 million Saudi adults aged 40–75 years, and the total number of the Saudi population was 20.8 million.

2.6. Cost implications of applying the ACC/AHA treatment guideline

The cost implication of applying the ACC/AHA treatment guideline was based on the average cost of 40 mg atorvastatin in the Saudi market. Atorvastatin was selected because it is the most com-

monly prescribed statins. The cost of a 40 mg tablet was selected as most patients would be eligible for high-intensity statin therapy, which is defined as an atorvastatin dose of 40–80 mg/d.

The average cost of 30 tablets of 40 mg atorvastatin in the Saudi market was 151.9 Saudi Riyal (SR) (based on the price of 8 different products). The average cost per patient per year would be 1822.8 SR. One Saudi riyal equals US\$0.27.

3. Results

3.1. Study sample

A total of 1200 patients were randomly selected from the database of 30,876 eligible patients aged 40–75 years. One hundred and ninety-five patients were excluded from the analysis because of missing lipid profile data. Baseline characteristics of the study patients (1005 patients) are presented in [Table 1](#). The mean age of the sample was 55.4 years (standard deviation = 9 years). Females represented 68.4% of the sample. Among the study participants, there were 359 (35.7%) patients who had a history of CVD. The average age for the study population (age 40–75 years) was similar to that of the randomly selected sample (55.9 years vs. 55.4 years). The sex distribution of the study population was also similar to that of

the study sample (females: 67.2% vs. 68.4% of the study sample).

3.2. Comparison of the two guidelines

Comparison of eligibility to statin therapy based on the two guidelines is shown in [Table 2](#). Based on the ATP III guideline, there were 139 male (43.7%) and 279 female patients (40.6%) eligible to receive statin therapy. The total number for whom treatment was recommended is 418 (41.6%).

Based on the ACC/AHA guideline, treatment was recommended in 315 males (99.1%) and 564 females (82.1%). Meanwhile, a high-intensity statin was recommended in 302 male (95%) and 400 female patients (58.2%). Treatment was not recommended in only three male patients (0.9%) and 123 females (17.9%) ([Table 2](#)). The total number of individuals for whom treatment was recommended is 879 (87.5).

Using the ACC/AHA guideline, 461 additional patients (45.9%) would be eligible for statin therapy. The total number of patients eligible for statin therapy is 2.1 times (879/418) that in the old guideline. The difference between the two guidelines was statistically significant ([Table 2](#)). The odds of recommending a statin based on the ACC/AHA is much higher (approximately 10 times) compared to the ATP III guideline ([Table 2](#)).

Table 1. Demographic and clinical characteristics of the study population.

Variable	Females	Males	Total
N (%)	687 (68.4)	318 (31.6)	1005 (100)
Age (y)			
40–49	211 (30.7)	71 (22.32)	282 (28.05)
50–59	282 (41)	108 (33.96)	390 (38.8)
60–69	156 (22.7)	95 (29.87)	251 (25)
70–75	38 (5.5)	44 (13.8)	82 (8.16)
Mean age	57.8 ± 9.5	54.4 ± 8.6	55.5 ± 9
Blood pressure			
Hypertension	399 (58.1)	234 (73.6)	663 (66)
Systolic blood pressure	133.6 ± 13.8	136.4 ± 13.8	134.4
Diastolic blood pressure	72.0 ± 9.7	75.8 ± 9.4	73.2
Body mass index	33.0 ± 7.0	29.9 ± 6.6	32.01
Lipid profile (mg/dL)			
Total cholesterol	180.5 ± 40.0	186.0 ± 35.0	184.2
HDL cholesterol	39.8 ± 8.4	45.7 ± 8.7	43.8
LDL cholesterol	110.5 ± 34.7	113.3 ± 31.4	112.3
TG cholesterol	65.9 ± 31.3	58.7 ± 26.6	61
Current smoking	19 (2.8)	52 (16.4)	71 (7.06)
Diabetes mellitus	355 (65.5)	187 (34.5)	463 (46.1)
Receiving antihypertensive treatment	416 (71.8)	163 (28.2)	579 (57.7)
Receiving statin	459 (67)	209 (65.7)	668 (66.5)
With cardiovascular disease	184 (26.7)	175 (55)	359 (35.7)

Data are presented as n (%) or mean ± SD.

HDL = high-density lipoprotein; LDL = low-density lipoprotein; SD = standard deviation; TG = triglyceride.

Table 2. Treatment recommendations based on ACC/AHA guidelines as compared to ATP III guidelines (N = 1005).

Treatment categories	ACC/AHA N (%)	ATP III N (%)	p ^a	Odds ratio for treatment recommended (confidence interval)
Total number for whom treatment is recommended	879 (87.5)	418 (41.6)	<0.0001	9.8 (7.8–12.3)
Females (N = 687)			<0.0001	6.7 (5.2–8.6)
Treatment recommended	564 (82.1)	279 (40.6)		
High intensity	400 (58.2)	NA		
Moderate intensity	164 (23.9)	NA		
Treatment not recommended	123 (17.9)	408 (59.3)		
Males (N = 318)			<0.0001	135.2 (42.5–430.6)
Treatment recommended	315 (99.1)	139 (43.7)		
High intensity	302 (95.0)	NA		
Moderate intensity	13 (4.1)	NA		
Treatment not recommended	3 (0.9)	179 (56.3)		

ACC/AHA = American College of Cardiology/American Heart Association; ATP III = Adult Treatment Panel III; NA = not available.

^a Using chi-square test.

3.3. Adherence of physicians to the recent ACC/AHA treatment guideline

Physician prescribed statins in only 668 (76%) of the 879 eligible patients. Only 74 (10.5%) of the 702 eligible patients were prescribed high-intensity statin.

3.4. Extrapolation of results to the Saudi population

Extrapolating the study results to 5.16 million Saudi adults aged 40–75 years, an estimated 2.146 million adults (41.6% of those aged 40–75 years, and 10.3% of the 20.8 million Saudi population in 2015) would be eligible to receive statin therapy, according to the 2002 ATP III guideline. In contrast, the estimated number of statin users would be expanded to 4.515 million (87.5% of those 40–75 years of age, and 21.7% of the 20.8 million Saudi population in 2015) according to the ACC/AHA guideline. Overall, 2.369 million additional Saudi patients would be eligible for statin therapy when applying the ACC/AHA guideline.

3.5. Cost implications of applying the ACC/AHA treatment guideline

The cost implications of applying the ACC/AHA treatment guideline are illustrated in Table 3. The cost of statins use would be increased by 110% when applying the new guideline. Extrapolating the result to the entire Saudi population, applying the new guideline would result in a cost increase of at least 4.318 billion SR per year.

4. Discussion

There are substantial differences between the recent ACC/AHA guideline on the treatment of blood cholesterol to reduce cardiovascular risk in adults [4] and the previous ATP III guideline on high blood cholesterol management [3]. Although both guidelines target primary and secondary cardiovascular prevention, their approach is fundamentally different. One of the major concerns regarding the new guideline is the potential substantial expansion in the number of individuals

Table 3. Cost implications of applying the ACC/AHA treatment guideline.^a

Statin	Cost based on ATP III guideline per year (n = 418 out of 1005)	Cost based on ACC/ AHA guideline per year (n = 879 out of 1005)	Increase in cost per year when applying ACC/AHA guideline	Cost increase per year when applying ACC/ AHA guideline extrapolated to all Saudi patients aged 40–75 y (for additional 2.369 million patients)
If all eligible patients received Atorvastatin 40 mg	761,930 SR	1,602,241 SR	840,311 SR (110.3%)	4.318 billion SR

ACC/AHA = American College of Cardiology/American Heart Association; ASCVD = atherosclerotic cardiovascular disease; ATP III = Adult Treatment Panel III; CHD = coronary heart disease; CVD = cardiovascular diseases; DM = diabetes mellitus; HDL = high-density lipoprotein; KAMC = King Abdul-Aziz Medical City; LDL = low-density lipoprotein; TG = triglyceride.

^a Cost was calculated based on the average market price for 40 mg atorvastatin per patient per year (1822.8 SR).

who should receive statin treatment [9,11,12]. In this study, we examined the impact of the new guideline recommendations on expanding the number of patients aged 40–75 years eligible for statin therapy in Saudi Arabia.

The age and sex distributions of the study sample were similar to the patients' population. The main finding of this study is that almost all male patients and the majority of female patients (82.1%) were eligible for statin treatment based on the ACC/AHA guideline [4]. This represents approximately twice the number of individuals eligible for statin treatment based on the ATP III guideline [3]. In addition, almost all male and most female patients (58.1%) were recommended for high-dose statin therapy. The results of this study are very close to the results obtained by Kavousi et al [13] in a European cohort. They found that 96% of male and 66% of female patients would be eligible for statin treatment based on the ACC/AHA guideline compared with 52.0% of male and 35.5% of female patients based on the ATP III guideline. In another similar study, the number of patients eligible for stain therapy increased from 42% using the ATP III guideline to 57% using the ACC/AHA guideline, which represents a 35% increase in eligibility in a study on a sample of US population [14].

The main reason for expanding the eligibility for statins in the new guideline in the study sample was related to the new recommendations related to secondary prophylaxis for patients with CVD and in patients with diabetes. The ACC/AHA guideline recommends drug treatment for all persons with clinical CVD [4]. Based on the ATP III, however, it is possible that individuals with CVD would not be recommended for statins based on their LDL cholesterol levels [3]. In the current study, 35.7% of the sample have CVD and were all eligible for statins based on the ACC/AHA guideline. Additionally, almost all diabetic patients (97%) who did not have CVD were also eligible for statin therapy based on the ACC/AHA recommendations. In comparison, the 2016 updated European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines for the management of dyslipidaemia did not recommend statin use in all patients with CVD or diabetes [15]. However, they retained the SCORE (Systemic Coronary Risk Estimation) system from the 2011 ESC/EAS guidelines to estimate the 10 years risk for CVD rather than adopt a new questionnaire risk calculator that overestimates CVD risk [16].

Supporting the results of the current study, recent review articles have discussed the limita-

tions of the updated ACC/AHA guideline [17,18]. The main limitations included the reduction in the threshold for treatment in primary prevention that will result in a larger number of patients being prescribed statin therapy, and that the pool risk calculator used to assess CVD risk in the guidelines for primary prevention has not been fully evaluated. Given the many concerns raised about the ACC/AHA guideline [9,11,12,19], it was not surprising to find that physician adherence to the new guideline was poor, in which only 10.5% of eligible patients received a high-intensity statin. Clearly, physicians are aware of the controversies surrounding the new guideline.

We have attempted to extrapolate the results to the entire Saudi population based on demographics data for April 2015 obtained from General Authority for Statistics. The results indicate that the majority of people (87.5%) would have to receive statin based on the ACC/AHA guideline. This would also have a substantial additional financial burden of at least 4.138 billion SR per year if all eligible patients received atorvastatin. The cost associated with laboratory monitoring, adverse drug reaction, and drug–drug interactions would also be substantial.

This study has several limitations. The percentage of patients with CVD and diabetes in this study is high and could overrepresent the prevalence in Saudi individuals aged 40–75 years. We could not find published data for this age group to confirm this issue. Still, even if these patients did not have diabetes or CVD, we found that at least 84% of the patients would still be recommended to receive statins based on the ACC/AHA pooled cohort equation (data not shown in the results section) [9]. This indicates the extent to which the new guideline and the pooled cohort equation overestimate the need for a statin. Therefore, the validity of the results may not have been affected much by the possibly higher prevalence of CVD in the study sample. However, current literature indicates a very high prevalence of CVD and CVD risk factors in the Saudi population. A recent review of 295 studies in Saudi Arabia indicated the prevalence of coronary artery disease (18%), stroke (14%), peripheral artery disease (11%), and congenital heart disease (10%) [20]. In another study, ischemic heart disease was present in 32% of the study population [21]. Similar to our study, the Gulf Registry of Acute Coronary Events (RACE) study reported that CVD were more prevalent in male (74%) than in female (24%) patients [22]. Another possible limitation is the inclusion of patients who are already

using a statin. Because the lipid profile may have improved with statin use, the extrapolation may have been underestimated for those patients whose eligibility was based on ASCVD risk estimation. However, the impact is very limited because the results indicate that most patients (87.5% of those aged 40–75 years) were eligible for a statin based on the new guideline.

5. Conclusion

The eligibility of statin therapy is much higher in the ACC/AHA guideline as compared to ATP III. Applying the recent ACC/AHA dyslipidemia guideline will increase the number of patients eligible for statin therapy to approximately two-fold. This will be associated with a substantial increase in cost and, possibly, side effects. The concerns surrounding the ACC/AHA guideline should be addressed at the national level.

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