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## The Potential Effects of Implementing the 2013 ACC/AHA Cholesterol Guidelines on the Use of Statins in a Large Health Maintenance Organization in Israel

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### ABSTRACT

**Background:** The 2013 American College of Cardiology and American Heart Association (ACC/AHA) guidelines for the management of blood cholesterol identify candidates for statin therapy to prevent atherosclerotic cardiovascular disease (ASCVD). **Objective:** The objective was to estimate the effect of adopting the ACC/AHA guidelines in Maccabi Healthcare Services (MHS), a large health maintenance organization in Israel. **Methods:** This population-based study, conducted in June 2014, included all MHS members 40 years or older. We searched the computerized database of MHS to determine the number of members currently on statins, calculated the number of additional members newly eligible for statin treatment according to the new guidelines, and estimated the cost of implementing the guidelines in MHS. **Results:** In June 2014, there were 798,076 MHS members 40 years or older. Of the 725,784 members included, 30% were receiving statin treatment at baseline. Adopting the new guidelines would increase the

proportion of statin-treated members to 48% (58% and 39% among men and women, respectively). Newly eligible members were more likely to be 55 to 69 years old, men, and have a predicted 10-year ASCVD risk of 7.5% or more. The calculated incremental annual cost for medications is 54 million new Israeli shekels (US \$13.5 million). The cost per cardiovascular event prevented is estimated at 82,000 new Israeli shekels (US \$20,500). **Conclusions:** Adopting the ACC/AHA 2013 cholesterol guidelines would increase the number of MHS members 40 years or older eligible for statin therapy by 60%, with the increase mainly in primary prevention due to the predicted 10-year ASCVD risk. **Keywords:** cholesterol guidelines, application, cost, eligibility, statin therapy, population-based.

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### Introduction

Cardiovascular disease is the second leading cause of death in Israel [1]. Lifestyle and risk factor modification and pharmacological interventions are essential in reducing cardiovascular events. Statins play a key role in both primary and secondary prevention [2,3]. The American College of Cardiology and the American Heart Association (ACC/AHA) published new guidelines for the management of blood cholesterol in November 2013 [4] replacing the National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines published over a decade ago [5].

The ACC/AHA 2013 guidelines abandon the previous paradigm of treating according to specific low-density lipoprotein cholesterol (LDL-C) targets. Instead, the new guidelines recommend statin therapy for patient groups for whom statins reduced the risk of atherosclerotic cardiovascular disease (ASCVD), including coronary heart disease and stroke, in randomized controlled trials. The ACC/AHA 2013 guidelines identify four patient groups

who are candidates for statin therapy: 1) patients with clinical ASCVD (acute coronary syndrome, myocardial infarction, stable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, and peripheral arterial disease of atherosclerotic origin); 2) patients with LDL-C levels of 190 mg/dl or more; 3) 40- to 75-year-old patients with diabetes and LDL-C levels of 70 to 189 mg/dl; and 4) 40- to 75-year-old patients without diabetes, with LDL-C levels of 70 to 189 mg/dl and a predicted 10-year ASCVD risk of 7.5% or more, as calculated by the new pooled cohort equations published along with the guidelines [6].

Following the publication of the new guidelines, concern arose that they would substantially expand the population eligible for statin treatment [7–10]. Pencina et al. [11] estimated that the number of US adults receiving or eligible for statin therapy would increase from 43 million (37.5% of US adults) to 56 million (48.6%). Among 60- to 75-year-old adults not receiving statin therapy, 87.4% of men and 53.6% of women would be eligible for treatment [11].

Conflict of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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The present study was conducted in Maccabi Healthcare Services (MHS), the second largest national health maintenance organization in Israel, in the context of updating statin treatment policy; MHS is considering adopting the ACC/AHA 2013 guidelines. Our aims were to determine the number of members 40 years or older currently on statins, to estimate the number who would be eligible for statins under the new guidelines, and to estimate the cost of treating these additional patients.

## Methods

### Study Population

The study population included all MHS members 40 years and older on June 2014. Members were stratified into the primary prevention group (i.e., no history of ASCVD events) or the secondary prevention group (i.e., history of ASCVD events). Members whose blood cholesterol levels were never tested were excluded from the study. In the primary prevention group, members with LDL-C levels of less than 190 mg/dl, with no indication of diabetes, who never purchased statins were excluded if data were not available on blood pressure measurement and smoking history because these variables are required for ASCVD risk calculation.

### Study Variables and Definitions

Data for this study were obtained from MHS's computerized databases. For each member, data collected included age; sex; smoking status; last systolic blood pressure measurement; history of clinical ASCVD (i.e., ischemic heart disease, stroke, transient ischemic attack, or peripheral artery disease) as documented in the MHS cardiovascular registry [12]; history of diabetes as documented in the MHS diabetes registry [13]; history of hypertension as documented in the MHS hypertension registry [14]; and results of the most recent blood tests for total cholesterol, LDL-C, and high-density lipoprotein cholesterol, HDL-C. We also collected data from the pharmacy database on antihypertensive medications and statin medications that had been dispensed during the previous 6 months. The most recently dispensed statin was characterized by drug (simvastatin, atorvastatin, rosuvastatin, pravastatin, or fluvastatin) and dose. Intensity of statin therapy was graded according to the ACC/AHA 2013 guidelines [4]. Members for whom no statins had been dispensed during the previous 6 months were defined as not receiving statin treatment.

Members receiving statins were categorized as being treated for primary or secondary prevention. Among members not currently receiving statins, those who would become eligible for statins under the new guidelines were identified according to the ACC/AHA 2013 criteria: 1) clinical ASCVD; 2) LDL-C levels of 190 mg/dl or more; 3) LDL-C levels of 70 to 189 mg/dl in persons aged 40 to 75 years with diabetes; and 4) LDL-C levels of 70 to 189 mg/dl and a 10-year ASCVD risk of 7.5% or more, as calculated by the pooled cohort equations [6], in persons aged 40 to 75 years without diabetes. The variables used to calculate the 10-year ASCVD risk were age, sex, race, systolic blood pressure, total cholesterol, HDL-C, smoking status, use of antihypertensive medications, and history of diabetes [6].

To assess the cost of statin therapy for members eligible for treatment under the new guidelines, we consulted the Israeli Ministry of Health's price list for prescription medications [15]. For moderate-intensity treatment, we used the retail price of generic simvastatin 20 mg, 20.4 new Israeli shekels (NIS) per month per patient (US \$5.1); for high-intensity treatment, we

used the retail price of generic atorvastatin 40 mg, 62.1 NIS per month per patient (US \$15.5).

### Statistical Analysis

Data were summarized descriptively. Continuous variables were reported as mean  $\pm$  SD, or as median with interquartile range if not normally distributed, and discrete values were reported as proportions. Demographic and medical characteristics were compared between members currently on statins and those newly eligible for statins. Statistical analysis was performed using IBM SPSS Statistics, version 21 (IBM Corporation, Armonk, NY).

The study was approved by the institutional review board of Assuta Medical Center, Tel Aviv, which oversees research conducted at MHS.

## Results

In June 2014, there were 798,076 registered MHS members 40 years or older. The data required for inclusion in our analysis were available for 725,784 members (91%). Of these, 72,266 members had a history of ASCVD events (mean age  $69 \pm 12$  years, 70% men) and 653,518 members had no previous ASCVD events (mean age  $56 \pm 12$  years, 44% men). Seventy-nine percent of the members with a history of ASCVD events and 25% of the members with no previous ASCVD events were currently on statins (Table 1). The most frequently dispensed regimen (for either primary or secondary prevention) was simvastatin 10 mg for low-intensity treatment, simvastatin 20 mg for moderate-intensity treatment, and atorvastatin 40 mg for high-intensity treatment.

If the ACC/AHA 2013 guidelines were fully implemented in MHS members 40 years or older included in our study, 127,010 additional members (17.5%) would be eligible for statin treatment (Table 2). Of these, 15,344 would be eligible for statins for secondary prevention and 111,666 for primary prevention. Comparison of the characteristics of members currently on statins and newly eligible members for secondary prevention is summarized in Table 3, and for primary prevention is summarized in Table 4. Fig. 1 illustrates the distribution of indications for statin treatment eligibility for primary prevention, by sex and age, under the new guidelines. Most of the newly eligible persons

**Table 1 – Demographic and medical characteristics of study sample.**

Characteristic	History of ASCVD* (eligible for statins for secondary prevention) (N = 72,266)	No history of ASCVD (possibly eligible for statins for primary prevention) (N = 653,518)
Age (y), mean $\pm$ SD	69 $\pm$ 11.8	55.8 $\pm$ 11.7
Sex: male, n (%)	50,816 (70.3)	289,832 (44.3)
Diabetes mellitus, n (%)	27,195 (37.6)	79,234 (12.1)
Hypertension, n (%)	49,749 (68.8)	196,589 (30.1)
Smoking current, n/total N (%)	11,888/70,593 (16.8)	103,377/646,359 (16.0)
Currently on statins, n (%)	56,922 (78.8)	163,838 (25.1)

\* Atherosclerotic cardiovascular disease (ASCVD) includes ischemic heart disease, stroke, transient ischemic attack, and peripheral artery disease.

**Table 2 – Comparison of statin treatment and eligibility by sex and age group.**

Sex	Age group (y)	N	Currently on statins, n (%)	Additional members newly eligible for statins, n (%)
Female	40–54	190,518	15,340 (8.1)	7,274 (3.8)
	55–69	130,473	53,836 (41.3)	23,483 (18.0)
	≥70	64,145	37,495 (58.5)	11,621 (18.1)
	All age groups	385,136	106,671 (27.7)	42,378 (11.0)
Male	40–54	172,493	29,029 (16.8)	23,253 (13.5)
	55–69	117,604	54,004 (45.9)	51,333 (43.6)
	≥70	50,551	31,056 (61.4)	10,046 (19.9)
	All age groups	340,648	114,089 (33.5)	84,632 (24.8)
Both	40–54	363,011	44,369 (12.2)	30,527 (8.4)
	55–69	248,077	107,840 (43.5)	74,816 (30.2)
	≥70	114,696	68,551 (59.8)	21,667 (18.9)
	All age groups	725,784	220,760 (30.4)	127,010 (17.5)

are 55 to 69 years old and men, and the main eligibility criterion is a predicted 10-year ASCVD risk of 7.5% or more.

Among MHS members treated with statins, many were not receiving a statin with appropriate intensity as recommended by the ACC/AHA 2013 guidelines [4]. In our sample, only 46% of the members 75 years or younger on statins for secondary prevention were receiving a high-intensity regimen as indicated by the guidelines. Moreover, 8% of the members on statins for secondary prevention and 17% of the members on statins for primary prevention were receiving low-intensity regimens, which are not recommended by the recent guidelines (Table 5). Adopting the new guidelines would therefore necessitate escalating statin treatment for more than 51,000 members. Furthermore, the guidelines recommend a moderate-intensity regimen for secondary prevention in patients older than 75 years. In our sample, 4935 members older than 75 years on statins for secondary prevention were receiving a high-intensity regimen.

**Table 3 – Comparison of members newly eligible for statin treatment for secondary prevention and those currently treated for secondary prevention.**

Characteristic	Newly eligible for statins (N = 15,344)	Currently on statins (N = 56,922)
Age (y), mean ± SD	69.0 ± 14.3	69.0 ± 11.0
Sex: male, n (%)	9,403 (61.3)	41,413 (72.8)
Diabetes mellitus, n (%)	3,850 (25.1)	23,345 (41.0)
Hypertension, n (%)	9,514 (62.0)	40,235 (70.7)
Systolic blood pressure (mm Hg), mean ± SD	130.0 ± 17.6	130.4 ± 16.1
Smoking		
Current, n/total N (%)	2,534/14,805 (17.1)	9,354/55,788 (16.8)
Past, n/total N (%)	708/14,805 (4.8)	3,499/55,788 (6.3)
Cholesterol		
LDL (mg/dl), mean ± SD	115.3 ± 35.3	88.3 ± 30.6
HDL (mg/dl), mean ± SD	48.0 ± 13.0	45.5 ± 11.9
TC (mg/dl), mean ± SD	191.0 ± 43.1	162.0 ± 38.1

HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol.

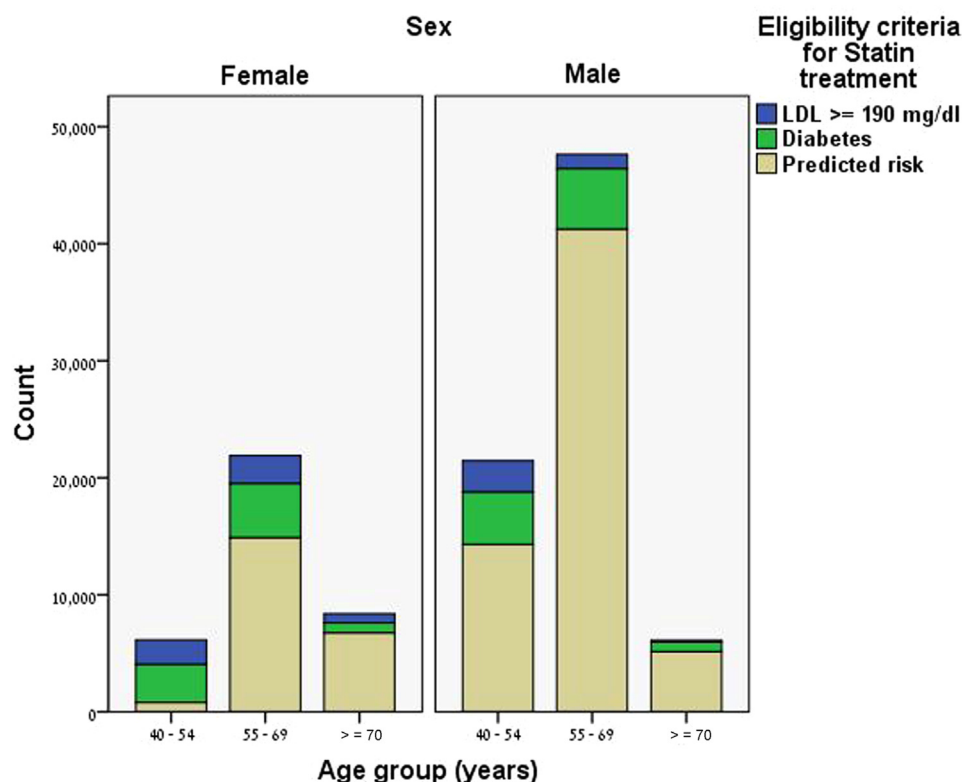
The guidelines do not generally recommend statin treatment for primary prevention in patients older than 75 years unless LDL-C levels are 190 mg/dl or more. In our sample, 26,545 members receiving statins for primary prevention were older than 75 years, potentially needing re-evaluation of treatment indication (Table 5).

We examined results of LDL-C tests in members newly eligible for statins to determine what proportion of them had LDL-C levels below the cutoff at which treatment is recommended in the ATP III guidelines. In members with ASCVD newly eligible for statin treatment for secondary prevention, the mean LDL-C level was 115 ± 35 mg/dl and 35% had an LDL-C level of less than 100 mg/dl, the LDL-C target for secondary prevention recommended by the ATP III guidelines [5]. In members with diabetes newly eligible for statin treatment for primary prevention, the

**Table 4 – Comparison of members newly eligible for statin treatment for primary prevention and those currently treated for primary prevention.**

Characteristic	Newly eligible for statins (N = 111,666)	Currently on statins (N = 163,838)
Age (y), mean ± SD	60.7 ± 8.4	63.4 ± 10.9
Sex: males, n (%)	75,229 (67.4)	72,676 (44.4)
Diabetes mellitus, n (%)	19,771 (17.7)	53,953 (32.9)
Hypertension, n (%)	45,769 (41.0)	94,732 (57.8)
Systolic blood pressure (mm Hg), mean ± SD	131.4 ± 15.7	129.1 ± 15.2
Smoking		
Current, n/ total N (%)	33,380 (30.2)	24,381 (15.3)
Past, n/total N (%)	3,273 (3.0)	5,326 (3.3)
Cholesterol		
LDL (mg/dl), mean ± SD	134.2 ± 34.0	110.2 ± 36.3
HDL (mg/dl), mean ± SD	48.5 ± 12.7	51.3 ± 13.0
TC (mg/dl), mean ± SD	211.9 ± 40.1	190.5 ± 42.7
10-y risk score (p), median (IQR)	0.12 (0.09– 0.17)	NA

HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; NA, not applicable; TC, total cholesterol.



**Fig. 1 – Newly eligible members for statin treatment by sex, age group, and ACC/AHA 2013 criteria for primary prevention. ACC, American College of Cardiology; AHA, American Heart Association.**

mean LDL-C level was  $118 \pm 31$  mg/dl and 32% had an LDL-C level of less than 100 mg/dl, the LDL-C target for primary prevention in persons with diabetes recommended by the ATP III guidelines [5]. In nondiabetic members newly eligible for statin treatment for primary prevention, the mean LDL-C level was  $138 \pm 34$  mg/dl and 46% had an LDL-C level of less than 130 mg/dl, the LDL-C target for primary prevention recommended by the ATP III guidelines for patients in the intermediate-risk category (multiple risk factors and 10-year risk  $\leq 20\%$ ) [5].

The annual incremental cost of fully implementing the ACC/AHA 2013 guidelines in MHS members was estimated at 11.4 million NIS (US \$2.8 million) for untreated persons eligible for statin therapy for secondary prevention and 32 million NIS (US \$8 million) for untreated persons eligible for statin therapy for primary prevention (7 million NIS [US \$1.7 million] for untreated persons with an LDL level of  $\geq 190$  mg/dl, 4.7 million NIS [US \$1.2 million] for untreated persons with diabetes mellitus, and 20.3 million NIS [US \$5 million] for untreated persons with a predicted risk score of  $\geq 7.5\%$ ). The additional cost of escalating current users' statin therapy to the appropriate intensity as recommended by the new guidelines was estimated at 10.5 million NIS (US \$2.6 million) per year. Thus, the expected total

annual incremental cost of medications for fully implementing the ACC/AHA 2013 guidelines in MHS members was estimated at 54 million NIS (US \$13.5 million).

Assuming the validity of the 10-year risk score in the Israeli population, there would be an estimated 15,600 new cases of ASCVD events over the next 10 years among the 111,666 MHS members eligible for primary prevention who are not currently receiving statin therapy (mean ASCVD risk score of 0.14). The likely effect of fully implementing the guidelines on future ASCVD events in this group, assuming that statin therapy reduces the relative cardiovascular risk by 25% in primary prevention [3], would be approximately 3900 future events prevented. The cost per event prevented is estimated at 82,000 NIS (US \$20,500).

## Discussion

Over the past decade, statin use has steadily increased in Israel and there has been a shift toward statin initiation in lower risk populations, specifically, younger patients with lower LDL-C levels and without a history of ASCVD [16]. The introduction of the ACC/AHA 2013 guidelines on cardiovascular risk assessment

**Table 5 – Distribution of dispensed statins by intensity, indication, and age group.**

Intensity	Currently on statins for secondary prevention (N = 56,922, n (%))		Currently on statins for primary prevention (N = 163,838, n (%))	
	Age $\leq 75$ y (N = 38,593)	Age $> 75$ y (N = 18,329)	Age $\leq 75$ y (N = 137,293)	Age $> 75$ y (N = 26,545)
Low	2,131 (5.5)	2,340 (12.8)	22,362 (16.3)	5,906 (22.2)
Moderate	18,559 (48.1)	11,054 (60.3)	92,147 (67.1)	17,546 (66.1)
High	17,903 (46.4)	4,935 (26.9)	22,784 (16.6)	3,093 (11.7)

further lowers the risk threshold for statin treatment for primary prevention based on a 10-year ASCVD risk of 7.5% or more, thus potentially expanding the population eligible for treatment [6]. We sought to gain insight into the characteristics and number of newly eligible members for statin treatment and estimate the cost of implementing the new guidelines. Our study is unique in including all registered MHS members older than 40 years, and not a selected cohort, for providing a reliable forecast.

The results of this study indicate that adopting the ACC/AHA 2013 guidelines would increase the population eligible for statin therapy by an additional 17.5%, mainly for primary prevention based on a predicted 10-year ASCVD risk of 7.5% or more. Assuming that members currently on statins would remain treated, the proportion of MHS members older than 40 years requiring statin therapy would increase to 47.9% (58.3% of men and 38.7% of women): 73.6% of persons 55 to 69 years old (89.6% of men and 59.3% of women) and 78.7% of persons 70 years or older (81.3% of men and 76.6% of women). Pencina et al. [11] reported similar results in the US population.

The cost of adopting the new guidelines is estimated at 54 million NIS (US \$13.5 million) annually, of which 32 million NIS (US \$8 million) is for primary prevention in newly eligible MHS members. The likely effect of fully implementing the guidelines on future ASCVD events in this group, assuming the validity of the 10-year risk score in the Israeli population, and that statin therapy reduces the relative cardiovascular risk by 25% in primary prevention [3], would be approximately 3900 events prevented in 10 years. The cost per event prevented is estimated at 82,000 NIS (US \$20,500).

Our study has some potential limitations. First, data were obtained from computerized patient records and automated patient registries, thus relying on the accuracy and completeness of these records. We excluded 72,292 members (9% of MHS members 40 years or older): 47,116 members without available blood cholesterol test results and 25,176 members without available smoking history. This group, however, is younger (mean age 51 years) and generally healthy; the prevalence of ASCVD was 0.5%, and the prevalence of diabetes was 0.8%, and only 1364 (1.9%) received statin therapy. Thus, this exclusion did not alter study results significantly. A second limitation is that data on statin treatment were obtained from pharmacy records of dispensed drugs. We did not compare these data with physician orders; some patients eligible for statin therapy may have been prescribed treatment but did not acquire the medication. Third, because this is a cross-sectional survey, we could not evaluate the appropriateness of statin treatment according to the ACC/AHA 2013 guidelines in members already receiving such therapy. A previous study estimated that 0.8% to 1.8% of the patients eligible for statins under the ATP III guidelines would no longer be eligible under the new guidelines [11]. Accurate calculation of 10-year ASCVD risk requires the results of cholesterol tests in the absence of statin treatment, which is not possible in patients currently on statins. Therefore, it is most likely in clinical practice that MHS members who began statins under the old guidelines will continue them under the new guidelines. Fourth, we did not include members younger than 40 years, because the ACC/AHA 2013 guidelines for risk assessment do not have specific guidelines for primary prevention in this group [6]. Fifth, a prospective trial is necessary to validate the pooled cohort equations in the Israeli population [17,18]. Sixth, our cost calculations were based on the current price of statins in Israel. If prices were to decline, the cost-effectiveness of expanding statin therapy would increase. Furthermore, we did not include other direct costs of treatment, such as physician visits and care for adverse effects.

In conclusion, the implementation of the AHA/ACC 2013 cholesterol guidelines in MHS would increase the number of MHS

members 40 years or older eligible for statin therapy by 60%, with the increase indicated mainly for primary prevention based on a predicted 10-year ASCVD risk of 7.5% or more. The cost of adopting the new guidelines is estimated at 54 million NIS (US \$13.5 million) annually. Lowering blood cholesterol in the population at risk, however, would prevent ASCVD events, thus potentially mitigating the potential adverse effects from this therapy and added costs.

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