Implications of the New US Cholesterol Guidelines in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

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ABSTRACT

Background: The new US guidelines for the primary prevention of cardiovascular disease have substantially changed the approach to hyperlipidemia treatment. However, the impact of those recommendations in other populations is limited. In the present study, we evaluated the potential implications of those recommendations in the Brazilian population.

Hypothesis: The new U.S. recommendations may increase the proportion of individuals who are candidates for statin therapy.

Methods: We included all participants of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) without known cardiovascular disease. We calculated the indication for statin therapy according to the current Brazilian recommendations and the new US guidelines, using both the 5.0% and the 7.5% risk cutoffs to recommend treatment, and compared their impact in the Brazilian population stratified by age, sex, and race.

Results: Although the current guidelines would recommend treatment for 5499 (39.1%) individuals, the number of individuals eligible for statin therapy increased to 6014 (42.7%) and to 7130 (50.7%) using the 7.5% and 5% cutoffs, respectively ($P < 0.001$). This difference is more pronounced for older individuals, and virtually all individuals age >70 years would be eligible for statins, whereas the new guidelines would reduce the number of candidates for statin therapy in individuals age <45 years.

Conclusions: The application of the new US guidelines for the use of lipid-lowering medications in a large middle-aged Brazilian cohort would result in a significant increase in the population eligible for statins. This is largely driven by males and older individuals. Additional cost-effectiveness analyses are needed to define the appropriateness of this strategy in the Brazilian population.

Introduction

The Brazilian guidelines for treating hyperlipidemia define target low-density lipoprotein cholesterol (LDL-C) according to the individual risk of future cardiovascular disease (CVD) using the 10-year risk estimated by the Framingham risk score (FRS)[1] and use those targets to select candidates for statin therapy. This strategy closely resembles the one proposed by the National Cholesterol Education Program's Third Adult Treatment Panel (ATP III), used in the United States until 2013.[2] In 2013, the American College of Cardiology/American Heart Association (ACC/AHA) released new, substantially different guidelines for managing lipid-lowering therapy in both the primary- and secondary-prevention settings.[3,4]

This study was funded by the Brazilian Ministry of Health (Science and Technology Department), Brasilia, Brazil (grant number FINEP: 06 0115.00 SP).
The authors have no other funding, financial relationships, or conflicts of interest to disclose.
Additional Supporting Information may be found in the online version of this article.

Received: September 30, 2015
Accepted with revision: November 30, 2015

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22511

Among those changes, some aspects are particularly important. First, the 10-year and lifetime risk assessment have been updated using a larger sample size and more complex risk equations. Those recommendations also apply different equations according to race and sex. Unlike the FRS, they also include a broader definition of CVD events, including cerebrovascular events. Additionally, risk-stratified LDL-C targets and thresholds to select candidates for statin therapy were abandoned. Instead of a combination of risk and LDL-C levels, treatment recommendations are dictated solely based on the estimated risk, unless the baseline LDL-C is too low (<70 mg/dL), which would not require treatment, or too high (≥190 mg/dL), when treatment is recommended regardless of the baseline risk. Third, a new risk cutoff was proposed, and lipid-lowering therapy should be considered for individuals with a 10-year atherosclerotic CVD (ASCVD) risk >7.5%, whereas a secondary threshold of 5.0% has also been suggested. Many have criticized these new recommendations, particularly because the new pooled cohort risk equation may have poor calibration, leading to overestimation of risk.[5–9] This potential overestimation, combined with the lower threshold for treatment, may lead to a significant increase in the population of individuals to whom statins would be recommended for primary prevention.[10] A recent study by Pencina et al using National Health and Nutrition Examination Survey (NHANES) data suggested that the population of candidates for statins in the United States would increase by approximately 12 million individuals with the new ASCVD recommendations.[10] This increase is particularly important for older individuals, as the candidate population for treatment almost doubles in size for those age >60 years.

Brazilian guidelines tend to incorporate many of the US recommendations, and those changes may have a significant impact if applied to the Brazilian population. In particular, the Brazilian racial distribution has peculiarities, including a high rate of racial blending, which are not incorporated in the development of those race-specific equations. This may have considerable impact on the risk estimation, and consequently in the recommendation for or against the use of statins. To date, no estimations of the potential impact of those changes have been performed using Brazilian data. In the current study, we have sought to evaluate the potential impact of the new ASCVD recommendations in a large ethnically diverse adult Brazilian cohort.

Methods

Study Population

In this study, we have used the baseline data from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) cohort. The ELSA-Brasil includes 15 105 civil servants age 35 to 75 years, active or retired, from 6 Brazilian urban centers. All baseline evaluations occurred between 2008 and 2010, at 6 academic institutions. The details of the ELSA-Brasil cohort have been published elsewhere.[11,12] The local institutional review board approved the study in all centers, and all participants signed an informed consent.

All medications reported by participants were reviewed, and the data on medication was categorized following the World Health Organization guidelines for Anatomical Therapeutic Chemical (ATC) Classification System. Then, we classified individuals according to the use of antihypertensive (codes C02, C03, C07, C08, and C09), hypoglycemic (code A10), and lipid-lowering (code C10) medications.

We excluded all participants with prior CVD, defined as stroke, myocardial infarction, angina, heart failure, or prior coronary revascularization procedures. For the included individuals, race was self-reported as Black, Brown (mixed), White, Asian, and Native (Indigenous). The definition of hypertension was the report of use of antihypertensive medication or a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg at ELSA-Brasil baseline assessment. We defined diabetes mellitus (DM) as a medical history of DM, the reported use of hypoglycemic agents or insulin use, a fasting serum glucose ≥126 mg/dL, glycated hemoglobin (HbA_{1c}) level ≥6.5%, or a 2-hour oral glucose tolerance test ≥200 mg/dL. Total cholesterol, high-density lipoprotein cholesterol, and triglycerides were determined by the enzymatic colorimetric method. Low-density lipoprotein cholesterol was calculated by the Friedewald equation or directly with triglyceride >400 mg/dL. The definition of hypercholesterolemia was the reported of use of lipid-lowering treatment or an LDL-C cholesterol level ≥130 mg/dL.

We calculated the FRS according to previously published equations, modified as recommended by the ATP III.[13] For the new ASCVD risk score, we calculated the overall risk of events for each race and sex separately according to published equations. Following the recommendations of the new guidelines, all non-Black individuals had their risk calculated according to the equation for Whites.[3] We then calculated the indications for statins according to the recommendations from the IV Brazilian guidelines for atherosclerosis prevention without the use of the aggravating factors,[1] and compared those with the new recommendations. For the Brazilian guidelines, statin was considered indicated for all individuals already on a statin, those with a LDL-C ≥190 mg/dL, and all DM patients with an LDL-C ≥100 mg/dL. For the other individuals the FRS was calculated. For those with a 10-year risk <10%, statins were indicated if the LDL-C was ≥160 mg/dL; for those with a 10-year risk between 10% and 20%, statins would be indicated if the LDL-C was ≥130 mg/dL; and for those with a 10-year risk ≥20%, statins were indicated if the LDL-C was ≥100 mg/dL. For the new recommendation, statin therapy was considered indicated for all individuals already on a statin, those with an LDL-C ≥190 mg/dL, and all DM patients with an LDL-C ≥70 mg/dL. For the other individuals, the new ASCVD risk equation was calculated, and we modeled 7.5% 10-year risk threshold as indications for treatment. An additional analysis using the 5.0% cutoff was also performed.

Statistical Analysis

All categorical variables are presented in absolute prevalence and percentages and compared using the χ^2 test. Continuous variables are presented as mean ± SD and compared using *t* tests or 1-way ANOVA, as appropriate.

We determined the proportion of participants in whom statins would be appropriate according to each guideline. To

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DOI:10.1002/clc.22511

Table 1. Baseline Characteristics According to Statin Indication in the Brazilian Guideline and the 2013 ACC/AHA Guideline

		Statin Indicated			
	All Individuals, N = 14 077	Individuals Already on Statins, n = 1339	Additional Statin Candidates Brazilian Guideline, n = 4160	Additional Statin Candidates ACC/AHA 2013 Guideline (7.5%), n = 4675	Additional Statin Candidates ACC/AHA 2013 Guideline (5.0%), n = 5791
Male sex	6300 (45)	518 (39)	2202 (53)	2978 (64)	3648 (63)
Age, y	52 ± 9	58 ± 8	54 ± 8	57 ± 8	56 ± 8
Lipids, mg/dL					
Total cholesterol	215 ± 42	202 ± 38	250 ± 42	232 ± 48	229 ± 46
HDL-C	57 ± 15	57 ± 13	56 ± 13	54 ± 14	54 ± 14
LDL-C	131 ± 35	117 ± 32	163 ± 33	145 ± 40	143 ± 38
TG	138 ± 104	144 ± 82	163 ± 123	172 ± 140	166 ± 132
Hypertension	4736 (34)	567 (42)	1806 (43)	2441 (52)	2832 (49)
SBP, mm Hg	121 ± 17	123 ± 17	126 ± 19	129 ± 18	128 ± 18
DBP, mm Hg	76 ± 11	76 ± 10	79 ± 11	80 ± 11	80 ± 11
DM	2594 (18)	463 (34)	1750 (42)	2072 (44)	2072 (36)
Smoking					
Former smoker	4113 (29)	491 (37)	1335 (32)	827 (18)	2409 (42)
Current smoker	1841 (13)	126 (9)	703 (17)	1963 (42)	1040 (18)
Race					
White	7271 (52)	795 (59)	1998 (48)	2199 (47)	
Brown	3937 (28)	280 (21)	1228 (29)	1333 (28)	
Black	2222 (16)	178 (13)	732 (18)	921 (20)	
Other	647 (4)	86 (7)	202 (5)	222 (5)	
FRS 10-year risk	6.9 ± 6.2	8.6 ± 6.3	11.5 ± 7.5	11.9 ± 7.0	11.8 ± 6.7
ASCVD 10-year risk	7.6 ± 9.5	11.9 ± 11.3	12.5 ± 11.9	14.8 ± 10.9	13.1 ± 10.4

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; FRS, Framingham Risk Score; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation; TG, triglycerides.
Data are presented as n (%) or mean ± SD.

further explore the main predictors of the discrepancy in the indication for statins, we stratified the population according to age, sex, and race.

All analyses were performed using Stata software, version 13.1 (StataCorp, College Station, TX). A significance level of 0.05 on 2-sided tests was used.

Results

Study Sample

From 15 105 participants, 1001 individuals were excluded due to prior CVD and 27 due to missing information on any of the covariates. Among the other 14 077 individuals, 1339 were already using statins. Among those for whom statins were not prescribed, 250 had LDL-C <70 mg/dL. Finally, from those not on lipid-lowering medication and with LDL-C ≥70 mg/dL, 2074 individuals had DM. The final sample in which risk needed to be calculated was 10 414 non-DM patients, not receiving lipid-lowering medication, with an LDL-C ≥70 mg/dL (see Supporting Information, Figure 1, in the online version of this article). Table 1 presents the baseline characteristics of the included sample.

Although only 1339 individuals were currently on statins, another 4160 (29.6%) would be eligible for statins according to the current Brazilian guidelines. Using the 7.5% 10-year risk cutoff of the ACC/AHA guidelines, this number increases to 4675 (33.2%); and if the optional 5.0% cutoff is used, the additional number of individual eligible for a statin would be 5791 (41.1%). The clinical profile of the additional candidates for statins is presented in Table 1.

The overall population eligible for treatment would increase from 5499 (39.1%) with the current Brazilian

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DOI:10.1002/clc.22511

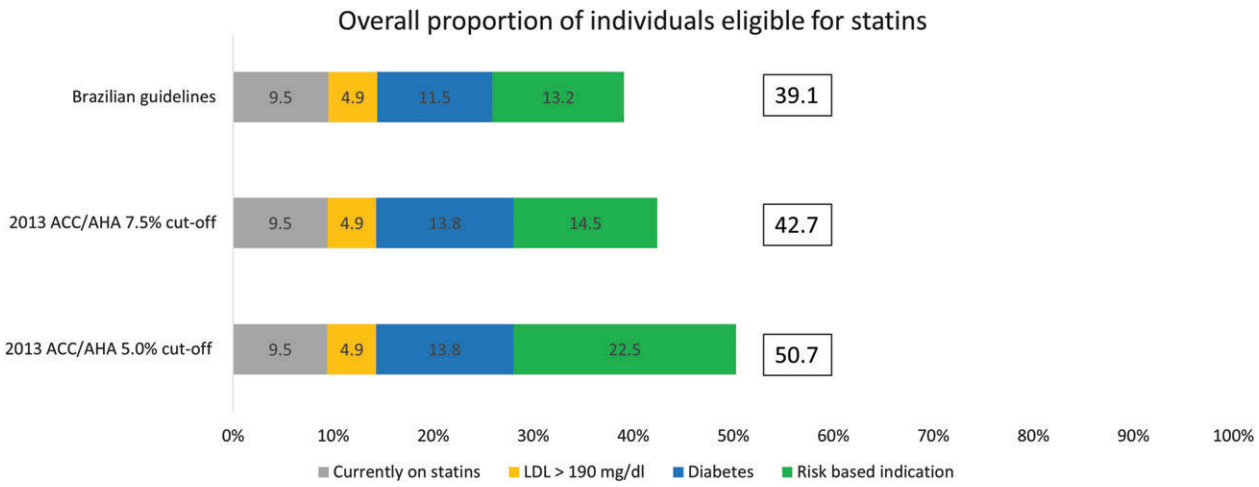

Figure 1. Proportion of individuals eligible for statins according to the Brazilian guideline and the two thresholds for the new 2013 ACC/AHA guideline. The values are in percent of the total population included in the study. Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; LDL, low-density lipoprotein cholesterol.

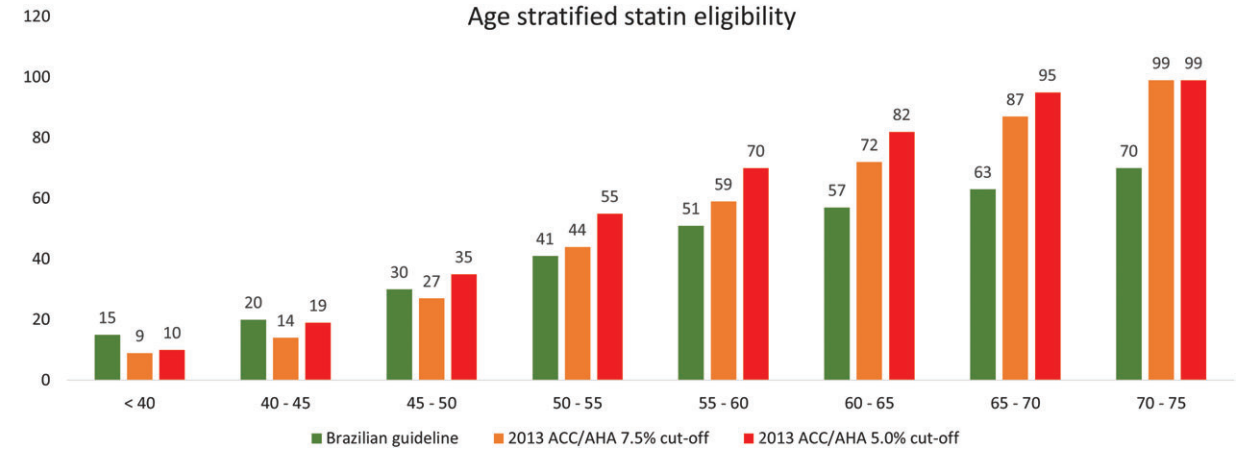

Figure 2. Proportion of individuals eligible for statins according to the Brazilian guideline and the two thresholds for the new 2013 ACC/AHA guideline, stratified by age. Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association.

guidelines to 6014 (42.7%) with the new ACC/AHA guidelines using the 7.5% cutoff for the 10-year risk, and to 7130 (50.7%) if the 5.0% cutoff was used ($P < 0.001$; Figure 1). However, this change in the population eligible for statins is highly dependent on age, sex, and race. Though the use or the recommendations from the new guidelines resulted in fewer individuals eligible for statin therapy until approximately age 50 using the 7.5% cutoff ($P < 0.001$), the difference in the proportion of individuals eligible for statin steadily increased for older individuals, with the large majority of participants qualifying by the age of 60 according to the 2013 ACC/AHA guidelines (Figure 2).

Additionally, the use of the 2013 ACC/AHA guidelines resulted in a large increase in the number of males eligible for statins ($P < 0.001$), whereas the changes for females were largely dependent on the risk cutoff used (Figure 3A). This difference between sexes is driven mainly by a larger discrepancy in the risk estimation between FRS and the ASCVD for women than for men. When stratified by race (Figure 3), the eligibility for statins increased with the new ASCVD recommendations in all races, although the increase was higher in Blacks than in any of the other groups ($P < 0.001$).

The population for whom both guidelines were concordant on the eligibility for statin therapy was older, with more risk factors and higher risk on both the FRS and the ASCVD risk scores, than those for whom guidelines were concordant that statins should not be used (Table 2). When comparing the discordant sample, the current Brazilian guidelines are more likely to recommend treatment for younger individuals, females, individuals with a higher total cholesterol and LDL-C, higher high-density lipoprotein cholesterol, lower triglycerides, less likely to be hypertensive or a former smoker, and of lower FRS and ASCVD score ($P < 0.0001$ for all comparisons; Table 2).

Discussion

In the present analysis, we have shown that the 2013 ACC/AHA guidelines significantly change the number of

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DOI:10.1002/clc.22511

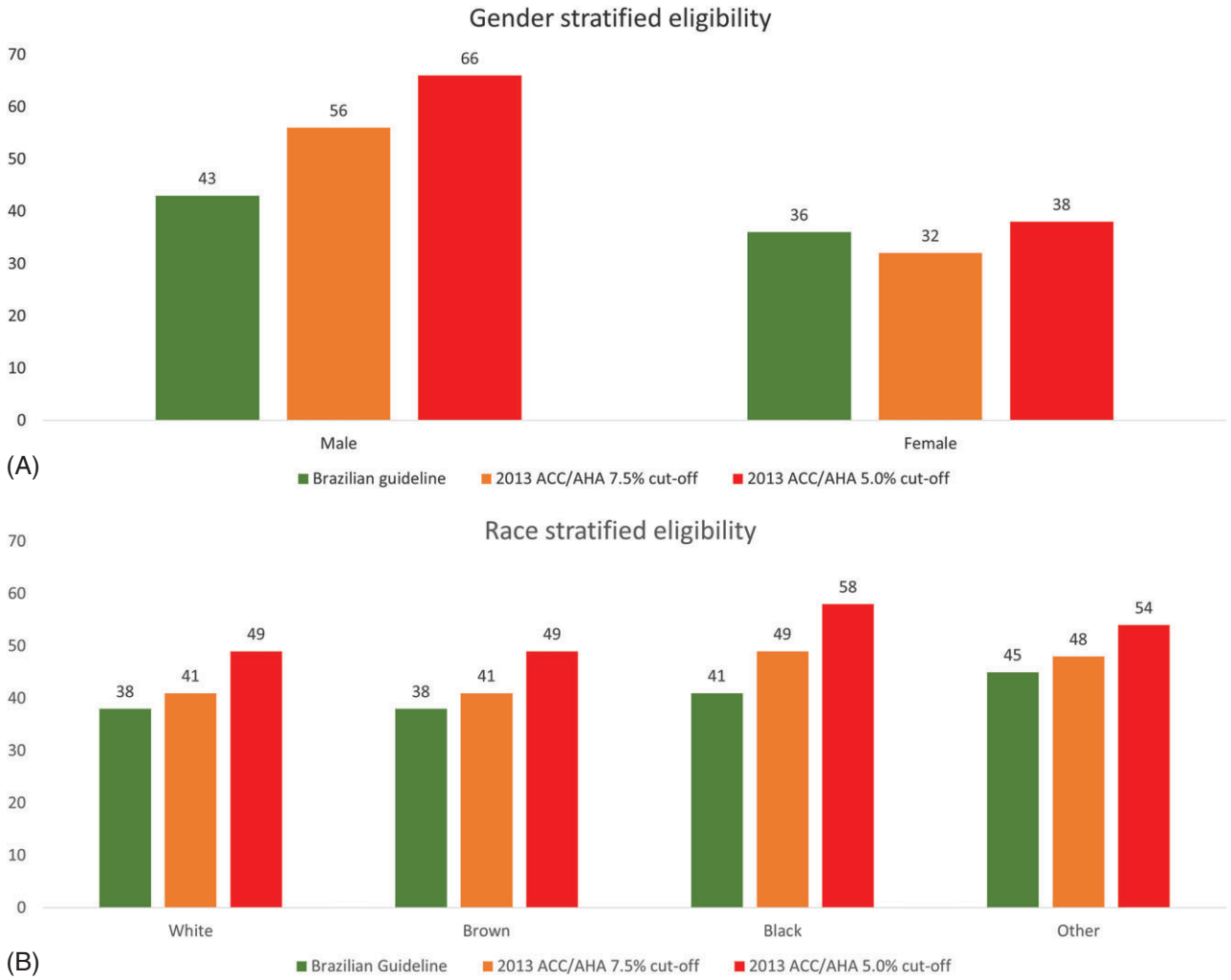

Figure 3. Proportion of individuals eligible for statins according to the Brazilian guideline and the 2 thresholds for the new 2013 ACC/AHA guideline, stratified by (A) sex and (B) race. Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association.

candidates for statin therapy in a large sample of admixed race Brazilian adults when compared with the Brazilian guidelines we used in the present analysis. Among those changes, the new guidelines have expanded the proportion of individuals eligible for statins from 39.2% to 42.1% of the current cohort. Importantly, this change was highly variable according to age and sex. Although the new guidelines reduced the proportion of individuals eligible for treatment at younger ages, the proportion significantly increased with age, including virtually every study participant age >70 years. Similarly, the impact of the new guidelines was more pronounced in men, where the proportion of individuals eligible for statins increased from 43% to 55%, whereas the proportion of women eligible for treatment actually decreased from 36% to 32%.

This pronounced increase in the population eligible for statin therapy has previously been demonstrated both in a US study as well as in a European study.[10,14] The main reason for the difference between those studies and our current sample is the mean age of the cohort. The US study used the NHANES data, which has a median age of 56 years, but the European study had a mean age of 65. Our cohort on the present study was significantly younger, with a mean age of 51 years. In our analyses stratified by age, the results for the age range between 60 and 70 years in the present study closely resemble the results of the European study. Interestingly, the proportion of individuals eligible for treatment in the Brazilian guidelines are comparable with the European guidelines reported in the same study, which are slightly higher than the ATP III recommendations.

One novel finding on the association of the 2013 ACC/AHA recommendations with age in the present study is that in the lower age range (<45 years) there actually was a reduction in the population eligible for statins. This fact may be associated with the different definition of candidates for treatment on the 2 guidelines. Though the old guidelines may recommend treatment to lower-risk individuals if their LDL-C is too high, the new recommendations rely solely on the estimated risk to define the recommendations. Thus, younger individuals, who are more likely to have a lower predicted risk, may have indication for treatment based on higher LDL-C, but not solely on the estimated

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DOI:10.1002/clc.22511

Table 2. Agreement in Statin Indication Between the Brazilian Guideline and the New 2013 ACC/AHA Guideline

	Concordant Recommendations		Discordant Recommendations		
	Both Do Not Recommend Considering Treatment, n = 6994	Both Recommend Considering Treatment, n = 4430	Brazilian Guideline Recommends Considering Treatment, New ACC/AHA Does Not, n = 1069	New ACC/AHA Recommends Considering Treatment, Brazilian Guideline Does Not, n = 1584	*P* Value
Male sex	2452 (35)	2368 (53)	352 (33)	1128 (71)	<0.001
Age, y	47 ± 7	57 ± 8	49 ± 7	58 ± 8	<0.001
Lipids, mg/dL					
Total cholesterol	200 ± 31	234 ± 49	257 ± 19	202 ± 34	<0.001
HDL-C	59 ± 15	55 ± 13	59 ± 13	53 ± 15	<0.001
LDL-C	119 ± 25	147 ± 41	171 ± 9	117 ± 25	<0.001
TG	114 ± 74	164 ± 123	134 ± 65	168 ± 146	<0.001
Hypertension	1279 (18)	2334 (53)	244 (23)	704 (44)	<0.001
SBP, mm Hg	115 ± 14	127 ± 19	118 ± 14	130 ± 17	<0.001
DBP, mm Hg	74 ± 10	79 ± 11	76 ± 10	80 ± 11	<0.001
DM	59 (0.8)	2213 (50)	0 (0)	322 (20)	<0.001
Smoking					<0.001
Former smoker	1466 (21)	1633 (37)	193 (18)	821 (52)	
Current smoker	766 (11)	707 (16)	122 (11)	246 (16)	
Race					<0.001
White	3710 (53)	2226 (50)	567 (53)	768 (48)	
Brown	2009 (29)	1193 (27)	315 (30)	420 (27)	
Black	982 (14)	769 (17)	141 (13)	330 (21)	
Other	293 (4)	242 (6)	46 (4)	66 (4)	
FRS 10-year risk	3.5 ± 2.4	12.0 ± 7.6	5.7 ± 2.8	8.7 ± 3.8	<0.001
ASCVD 10-year risk	2.5 ± 2.7	14.6 ± 12.1	3.3 ± 2.0	13.1 ± 7.4	<0.001

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; FRS, Framingham Risk Score; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation; TG, triglycerides.
Data are presented as n (%) or mean ± SD.
P values are for the comparison between the 2 samples in which guidelines are discordant.

risk. However, additional studies are needed to evaluate whether any subgroup of younger individuals would benefit from more aggressive treatment as defined in the current Brazilian guidelines.

A second important finding of the current study is that the increase in the population eligible for treatment is largely driven by the expansion of statin indications in males. At least for a middle-aged population, such as the ELSA-Brasil cohort, the new guidelines resulted in a reduction in females eligible for treatment. Those results contradict the results of prior studies,[10,14] though this is probably related to the younger age of the present cohort.

A third novel finding of the present study is the differential effect of the new ASCVD score on different races. Due to the socioeconomic, genetic, and cultural differences between individuals from different races, the new guidelines have proposed a separate equation for African Americans. But because data on other racial minorities is scarce, no equations for other races or ethnicities have been developed, and the guidelines suggest that all other non–African American individuals would be more appropriately evaluated by the equation for Whites. In our study, all races had increased proportion of patients eligible for treatment according to the new

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DOI:10.1002/clc.22511

guidelines, although the effect was more pronounced in Black individuals.

Due to historical backgrounds of Brazilian society, Brown individuals have a variable White and Black ancestry. Characteristics of Brown individuals are usually similar either to those of Whites or Blacks, or they may lie between those found in these 2 groups. In our study, frequencies of statin indication in Browns were closer to those found in Whites than in Blacks. This is consistent with previous ancestry analyses in the Brazilian population that found higher White than Black ancestry in the Brown population.[14] In addition, this is aligned to the findings of carotid intima-media thickness distributions in the ELSA-Brasil sample,[15] with values in Brown individuals closer to those described in Whites than in Blacks. However, due to the cross-sectional design of this study, we are not able to define whether these findings are accurate or if this is an effect of inadequate fit of the model for this population.

In fact, the actual performance of this new model has been questioned by recent studies. Both a large European cohort study and a large multiethnic American study have reported that the new risk-stratification strategy overestimates the true event rate, though the overestimation may be more substantial in European populations.[7,14,15] Because the true benefit of statins is closely associated with the absolute risk of events, the overestimation may lead to treating some individuals who may not derive net benefit from treatment, though they might be exposed to significant side effects and costs. It is important to note, however, that overestimation is not exclusive to the new guidelines, and similar findings were recently demonstrated for virtually all currently recommended risk scores.[7]

Finally, our study has demonstrated that even according to the current Brazilian guidelines, only a small fraction of the individuals eligible for statins are actually taking them. Although a small proportion might have been intolerant to statin therapy, the majority was probably not taking statins for other reasons, including the fact that Sistema Único de Saúde (SUS), the Brazilian national health system, has never developed clear guidelines for the use of statins in primary prevention. Thus, a larger impact would be expected from better access to primary preventive care and development of strategies to increase adherence than any change in the population eligible for statins.

The present analysis, however, should be read in the context of its current design. First, although the ELSA study is a population-based cohort, it was not designed to be representative of the entire Brazilian population, although the overall risk-factor distribution, race, sex, and age resemble the majority of the adult Brazilian population.[11] Second, because ELSA has yet to evaluate CVD outcomes, we were not able to evaluate if changes in the current guidelines recommendations would direct treatment toward individuals at higher risk of events, nor is it possible to assess the calibration of each score. Third, we assumed all individuals currently on statins meet eligibility criteria, though this may not be correct. However, it would not be possible to provide accurate estimates of risk for those individuals. Fourth, we may have underestimated the true population of individuals eligible for treatment based on the current Brazilian guidelines, as we have not modeled the aggravating factors.[1] On the other hand, the new ACC/AHA guidelines also suggest a risk-based discussion should guide treatment, which would likely result in a lower proportion of individuals actually receiving treatment.[16] Nonetheless, we believe this probably matches real-life practice, as only a minority of individuals are tested for any of those aggravating factors. Finally, it is important to note that the current analysis has not evaluated the appropriateness nor the cost-effectiveness of those strategies. We have only provided an estimate of the magnitude of the potential impact.

Conclusion

The use of the new 2013 ACC/AHA guidelines for lipid-lowering medications in a large middle-aged Brazilian cohort would result in a significant increase in the population eligible for statins. This increase, however, is largely driven by males and older individuals (age >45 years). Additional survival and cost-effectiveness analyses are needed to define the appropriateness of this increase in the population in whom treatment would eventually be recommended.

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DOI:10.1002/clc.22511