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Implications of coronary artery calcium testing on risk stratification for lipid-lowering therapy according to the 2016 European Society of Cardiology recommendations: The MESA study

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Abstract

Aims: The European Society of Cardiology (ESC) guideline on cardiovascular risk assessment considers coronary artery calcium a class B indication for risk assessment. We evaluated the degree to which coronary artery calcium can change the recommendation for individuals based on a change in estimated risk.

Methods and results: We stratified 5602 MESA participants according to the ESC recommendation as: no lipid-lowering treatment recommended ($N = 2228$), consider lipid-lowering treatment if uncontrolled ($N = 1686$), or lipid-lowering treatment recommended ($N = 1688$). We evaluated the ability of coronary artery calcium to reclassify cardiovascular risk. Among the selected sample, 54% had coronary artery calcium of zero, 25% had coronary artery calcium of 1–100 and 21% had coronary artery calcium greater than 100. In the lipid-lowering treatment recommended group 31% had coronary artery calcium of zero, while in the lipid-lowering treatment if uncontrolled group about 50% had coronary artery calcium of zero. The cardiovascular mortality rate was 1.7%/10 years in the lipid-lowering treatment if uncontrolled, and 7.0%/10 years in the lipid-lowering treatment recommended group. The absence of coronary artery calcium was associated with 1.4%/10 years in the lipid-lowering treatment if uncontrolled group and 3.0%/10 years in the lipid-lowering treatment recommended group. Compared with coronary artery calcium of zero, any coronary artery calcium was associated with significantly higher cardiovascular mortality in the lipid-lowering treatment recommended group (9.0%/10 years), whereas only coronary artery calcium greater than 100 was significantly associated with a higher cardiovascular mortality in the lipid-lowering treatment if uncontrolled group (3.2%/10 years).

Conclusion: The absence of coronary artery calcium is associated with a low incidence of cardiovascular mortality or coronary heart disease events even in individuals in whom lipid-lowering therapy is recommended. A significant

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proportion of individuals deemed to be candidates for lipid-lowering therapy might be reclassified to a lower risk group with the use of coronary artery calcium.

Keywords
Cardiovascular disease, coronary artery calcium, risk stratification, primary prevention

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Introduction

There is considerable debate regarding the optimal approach to select individuals for primary prevention of cardiovascular disease (CVD) using lipid-lowering therapy. Many guidelines recommend the use of a clinical risk assessment tool to select higher risk individuals in whom the benefit is expected to outweigh costs and adverse side effects.[1] The clinical assessment tools recommended by guidelines are based on age, gender, risk factors and lipid profile to select candidates for therapy, including the most recent European Society of Cardiology (ESC) guidelines on cardiovascular risk assessment and the management of dyslipidemia.[2] Additional tests, such as the coronary artery calcium (CAC) score are not routinely recommended.

Recent studies have suggested that the CAC score, measured by a non-contrast cardiac computed tomography scan, may aid in the additional risk stratification of those individuals, mostly through the detection of lower risk individuals who have no detectable calcified plaque in the coronary arteries (i.e. CAC of zero). The use of such testing allows more accurate risk stratification and, in individuals who are considered candidates for lipid-lowering therapy as per the current American College of Cardiology/American Heart Association (ACC/AHA) guidelines, could reduce the population of candidates for therapy by half without affecting the events averted.[3]

The ESC guidelines have a more selective approach for the identification of candidates for lipid-lowering therapies than the current US recommendations,[4] and those guidelines have given CAC a IIB recommendation, indicating that more evidence of the benefit of this reclassification is needed, and that it should be used only in selected circumstances.[1,2] Accordingly, we aimed to determine the implications of CAC testing on the ESC lipid-lowering therapy recommendations. We sought to evaluate the effect of CAC testing on the guideline recommendation for lipid-lowering therapy. We also sought to estimate the number needed to treat to reduce one cardiovascular death or coronary heart disease (CHD) based on the expected benefit from statins according to the presence and extent of CAC.

Methods

Study participants

The MESA study has previously been described in detail.[5] The study is a prospective observational cohort of 6814 men and women aged 45–84 years without known CVD at baseline. All participants were enrolled between July 2000 and September 2002 at six centers in the USA (Baltimore; Chicago; Forsyth County, North Carolina; Los Angeles; New York; and St Paul, Minnesota). In the present analysis, we excluded individuals using lipid-lowering therapies at baseline, as well as individuals with missing data on risk factors. The study was approved by each institution's review board and all participants agreed to participate in the study and gave written informed consent.

Risk factor assessment

During the baseline visit, information about cardiovascular risk factors was collected. Total cholesterol and high-density lipoprotein (HDL) cholesterol, and triglyceride measurements were performed at the Collaborative Studies Clinical Laboratory at Fairview-University Medical Center (Minneapolis, MN, USA) in blood samples obtained after a 12-hour fast. Diabetes was defined as fasting blood glucose of 7.0 mmol/l or greater, self-reported diabetes or the use of hypoglycemic drugs. Hypertension was defined as untreated diastolic blood pressure of 90 mmHg or greater, systolic blood pressure of 140 mmHg or greater, or the use of antihypertensive medication. Smoking was defined as the current use of cigarettes.

For the 10-year risk assessment, we have calculated the SCORE risk for both the 'high risk' and 'low risk' countries according to the 2016 ESC guidelines on CVD prevention in clinical practice.[2] We performed a goodness-of-fit analysis to define the most appropriate SCORE for the present MESA data. Although the fit of neither model was rejected, the 'low risk' countries' SCORE seemed more appropriate on visual inspection (see Supplementary Figure 1). In addition, the 'low risk' SCORE would also be the appropriate SCORE as per the guideline definition for cardiovascular mortality in

the USA as well as for the observed mortality in the MESA study.

Using the SCORE, we have derived the treatment recommendation groups as described in the 2016 ESC guidelines for the management of dyslipidemia.[1] These guidelines also provide versions of the equations with HDL-cholesterol as a parameter and versions that are restricted to total cholesterol. In the present analysis the SCORE was calculated with the equation that included HDL-cholesterol. In short, according to the estimated cardiovascular mortality, individuals with a less than 1% cardiovascular mortality in 10 years were classified as low risk, those between 1% and 5% were considered intermediate risk, those from 5% to 10% were considered high risk and those above 10% were classified as having a very high risk. In addition, as proposed by the guidelines, individuals with diabetes or chronic kidney disease, defined by a creatinine clearance less than 60 ml/min/m^2, were also classified as high risk.

To define lipid-lowering therapy eligibility, we followed the ESC guideline recommendations in which treatment options are classified into three groups: individuals for whom no lipid-lowering therapy is recommended, individuals for whom lipid-lowering therapy should be considered if low-density lipoprotein (LDL) cholesterol remains uncontrolled after lifestyle interventions, and individuals in whom lipid-lowering therapy is recommended upfront. The group allocation is defined by both the baseline LDL-cholesterol levels and risk estimation, as follows:

- No lipid-lowering therapy recommended: LDL-cholesterol < 4.9 mmol/L and risk SCORE $<1\%$ or LDL-cholesterol < 2.6 mmol/L and risk SCORE 1–5% or LDL-cholesterol <1.8 mmol/L and risk SCORE 5–10%.
- Consider lipid-lowering therapy if uncontrolled: LDL-cholesterol ≥ 4.9 mmol/L and risk SCORE $<1\%$ or LDL-cholesterol ≥ 2.6 mmol/L and risk SCORE 1–5% or LDL-cholesterol 1.8–2.6 mmol/L and risk SCORE 5–10% or LDL-cholesterol <1.8 mmol/L and risk SCORE $\geq 10\%$.
- Recommended lipid-lowering therapy upfront: LDL-cholesterol ≥ 2.6 mmol/L and risk SCORE 5–10% or LDL-cholesterol ≥ 1.8 mmol/L and risk SCORE $\geq 10\%$.

CAC score measurements

The acquisition and interpretation of coronary calcium score images in MESA have been published elsewhere.[6] Each individual was scanned twice, and the mean Agatston score was used in the analysis.[7] Estimates of radiation dose determined according to the multi-ethnic study of atherosclerosis protocol for a single scan obtained through the heart with the Imatron C150, Volume Zoom, and LightSpeed Pro 16 scanners were as follows: 0.6 and 0.7, 0.9 and 1.1, and 0.9 and 1.1 mSv for men and women, respectively.[8] Participants were informed that they had no CAC, or that it was less than average, average, or greater than average, and that they should discuss the results with their physicians.

Ascertainment of events

Each participant or family member was contacted by telephone to enquire about interim hospital admissions, outpatient diagnoses of CHD and CVD, and deaths every 9–12 months. To adjudicate those events, copies of all medical records for all hospitalizations and outpatient contacts that resulted in new cardiovascular diagnoses as well as death certificates were obtained. Each event was adjudicated by a MESA study committee of cardiologists, physician epidemiologists and neurologists. In the event of disagreement, the full committee made the final classification. MESA was successful in obtaining medical records for approximately 98% of reported hospitalized CHD and CVD events and information on 95% of reported outpatient cardiovascular diagnostic encounters. Follow-up telephone interviews were completed in 92% of living participants.

In the present analysis, CHD events were classified as myocardial infarction, resuscitated cardiac arrest, CHD death or new episodes of angina. The diagnosis of myocardial infarction was based on a combination of symptoms, electrocardiographic findings, and levels of cardiac biomarkers. Hospital records and family interviews were used to determine whether deaths were related to CHD. A death was considered related to CHD if it occurred within 28 days after a myocardial infarction, if the participant had had chest pain within the 72 hours before death or if the participant had a history of CHD and there was no known non-atherosclerotic, non-cardiac cause of death. Angina was graded using prespecified criteria and defined as definite, probable or absent. Probable angina required clearly documented chest pain or angina equivalent. Definite angina was defined by the same criteria, associated with objective evidence of obstructive coronary artery disease or reversible myocardial ischemia. Cardiovascular mortality was defined as any death due to CHD, stroke, other non-coronary atherosclerotic disease or death due to other CVD. A more detailed description of the MESA follow-up methods is available at http://www.mesa-nhlbi.org.

Statistical analysis

The baseline characteristics of the study participants were analyzed as per the ESC recommendation group. Frequencies and proportions were calculated for categorical variables, and either means with standard deviations or medians with interquartile ranges were calculated for continuous variables. Chi-square tests and one-way analysis of variance were used for comparison of variables between groups. We used Kaplan–Meier estimates of cumulative event-free survival to describe the occurrence of CHD events over time. We also calculated incident rates of events for cardiovascular mortality and for CHD events. To calculate the 10-year risk of events, all events were censored at 10 years to determine if CAC can further stratify risk across lipid-lowering therapy eligibility groups, we have compared cardiovascular mortality and CHD event rates after stratifying by the following CAC score categories: zero, 1–100 and over 100.

A 10-year number needed to treat (NNT_{10}) for statin therapy was estimated for both outcomes, by applying the hazard ratio associated with the expected relative event reduction of 30% with a 1.0 mmol/L reduction in LDL-cholesterol, based on a Cochrane meta-analysis[9] of moderate statin therapy in primary prevention. The NNT_{10} was calculated directly as a reciprocal of absolute risk difference at median follow-up of the cohort, based on Kaplan–Meier estimates, and subsequently adjusted to 10 years according to the Altman–Anderson method.[10] Additional sensitivity analysis was performed using alternative 20% and 40% relative risk reductions with the use of statin therapy. All analysis was performed using Stata 14.0 (StataCorp, College Station, USA)

Results

Study population

Among the 6814 study participants, our study excluded 112 individuals due to missing risk factors, laboratory data or follow-up for any of the main outcomes. In addition, 1100 individuals were excluded due to the use of lipid-lowering medications at baseline. The final study cohort included 5602 individuals.

When applying the 2016 ESC guidelines, 1688 (30.1%) individuals met the criteria for lipid-lowering therapy and 1686 (30.1%) individuals as lipid-lowering therapy should be considered if the LDL-cholesterol levels remained uncontrolled after non-pharmacological lifestyle interventions. Finally, 2228 (39.8%) individuals were categorized as not requiring any lipid-lowering therapy (Figure 1).

Baseline characteristics

The baseline characteristics of our study population were associated with the recommended treatment groups (Table 1). A more aggressive pharmacological recommendation was more likely to be associated with older age, male sex, a higher prevalence of cardiovascular risk factors, and higher levels of total cholesterol, LDL-cholesterol and triglycerides, as well as lower levels of HDL-cholesterol.

Among the sample included in the present analysis, 2991 (54%) had CAC of zero, 1428 (25%) individuals

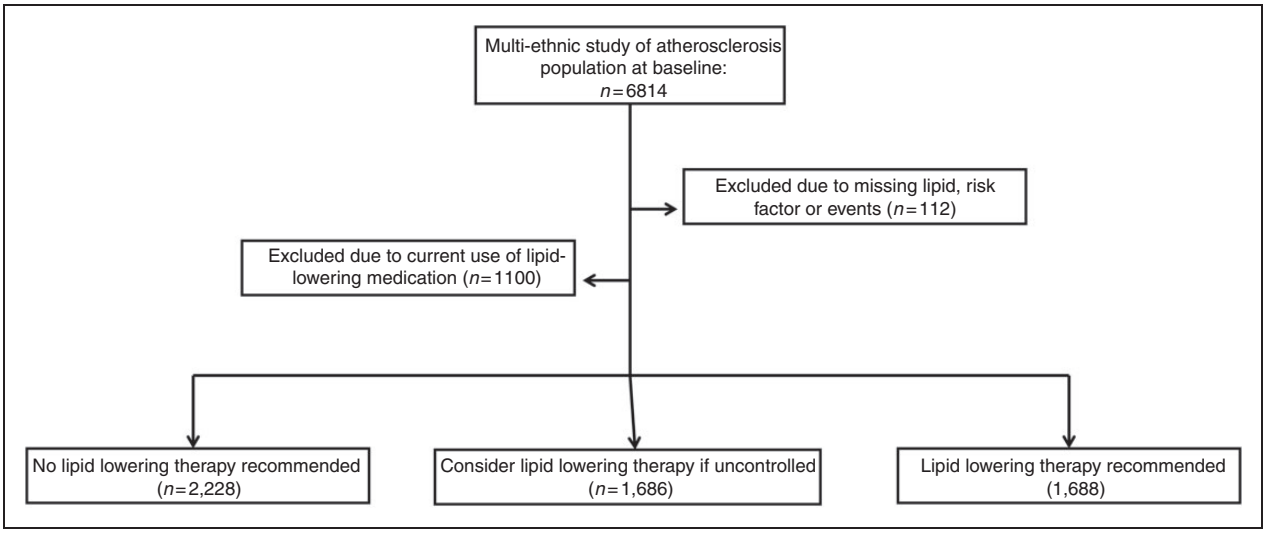

Figure 1. Flowchart of included individuals.

Table 1. Baseline characteristics.

	No lipid-lowering therapy recommended	Consider lipid-lowering therapy if uncontrolled	Lipid-lowering therapy recommended	*p*-value
Number of subjects ($n = 5602$)	2228	1686	1688	
Age (years)	54 ± 7	63 ± 7	70 ± 8	<0.001
Men (%)	807 (36%)	924 (55%)	906 (54%)	<0.001
Race (%)				0.018
White	809 (36%)	649 (38%)	645 (38%)	
Black	598 (27%)	449 (27%)	502 (30%)	
Hispanic	525 (24%)	383 (23%)	366 (22%)	
Asian	296 (13%)	205 (12%)	175 (10%)	
Diabetes (%)	0 (0%)	35 (2.1%)	384 (22.7%)	<0.001
Hypertension (%)	525 (24%)	679 (40%)	1,109 (66%)	<0.001
Smoking (%)				<0.001
Never	1,235 (55%)	790 (47%)	805 (40%)	
Former	709 (32%)	637 (38%)	670 (40%)	
Current	284 (13%)	259 (15%)	213 (13%)	
Family history (%)	797 (37%)	689 (44%)	663 (43%)	<0.001
BMI (kg/m^2)	28.1 ± 5.7	28.1 ± 5.3	28.4 ± 5.3	<0.001
Total cholesterol (mmol/L)	4.82 ± 0.91	5.28 ± 0.91	5.21 ± 0.85	<0.001
LDL-cholesterol (mmol/L)	2.82 ± 0.75	3.31 ± 0.83	3.26 ± 0.72	<0.001
HDL-cholesterol (mmol/L)	1.34 ± 0.41	1.29 ± 0.39	1.29 ± 0.36	<0.001
Triglycerides (mmol/L)	1.13 (0.80–1.67)	1.28 (0.91–1.80)	1.31 (0.94–1.83)	<0.001

Triglycerides are presented as median and quartiles and compared using the Kruskal–Wallis test.
BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

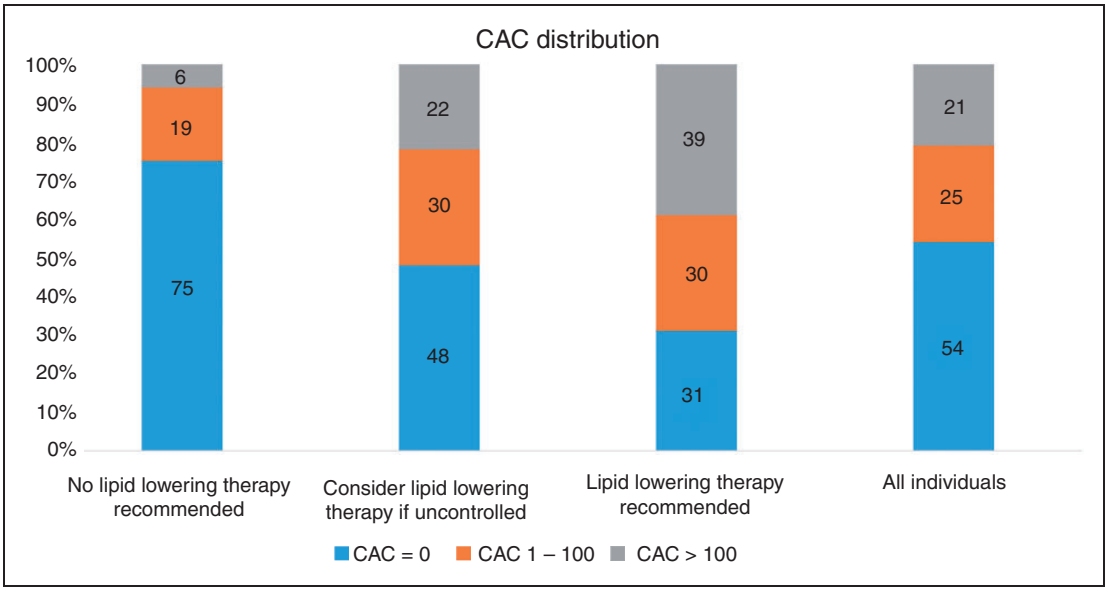

Figure 2. Coronary artery calcium (CAC) distribution as per the ESC recommended treatment groups.

had a CAC of 1–100 and 1183 (21%) had CAC greater than 100. In the recommended lipid-lowering therapy group 31% of the individuals had CAC of zero, while approximately half of those in whom lipid-lowering therapy should be considered had CAC of zero. One in every four individuals in whom no lipid-lowering therapy would be recommended had CAC greater than zero, but only 6% had CAC greater than 100 (Figure 2).

Outcomes

Over a median follow-up of 12.2 years (interquartile range 11.7–12.7 years) there were 176 (2.7%; 95% confidence interval (CI) 2.3–3.1) cardiovascular deaths. The incidence of cardiovascular death per 10 years was 0.51 (95% CI 0.30–0.86) for those to whom no lipid-lowering treatment was recommended, 1.71 (95% CI 1.22–2.40) for those to whom lipid-lowering treatment could be considered, and 5.87 (95% CI 5.88–8.31) for those to whom lipid-lowering treatment would be recommended according to the ESC guidelines. These results are also presented as Kaplan–Meier curves in Figure 3.

The absence of CAC was associated with a low rate of cardiovascular mortality in all groups. The presence of any CAC was associated with a higher cardiovascular mortality rate in individuals in whom lipid-lowering therapy was recommended upfront, but only CAC greater than 100 was associated with higher cardiovascular mortality among those in whom no lipid-lowering therapy was recommended (Figure 4). The presence of CAC greater than 100 was associated with high event rates irrespective of the treatment group recommendations. In addition, the presence of any CAC was associated with high CHD event rates in individuals in whom lipid-lowering therapy was recommended, whereas the absence of CAC was associated with low event rates in this group (Figure 5). The use of the SCORE for high-risk countries instead of the one for low-risk countries had only a minimal impact on these findings (see Supplementary Table 1).

Assuming a 30% relative risk reduction associated with statin use, the estimated 10-year number needed to treat to reduce one cardiovascular death (NNT_{10}) in those for whom lipid-lowering therapy would be recommended was 37 for those with any CAC, and 112 for those without CAC. Interestingly, despite the low cardiovascular mortality, the presence of CAC greater than 100 was associated with a low NNT_{10} to reduce one CHD event, irrespective of the recommended treatment group. The detailed NNT_{10} estimations are presented in Table 2. The sensitivity analysis for NNT_{10} assuming a 20% and a 40% relative risk reduction with statins are provided in Supplementary Table 2.

Discussion

Our study demonstrates that there is marked variability in the presence and severity of coronary atherosclerosis, and consequently cardiovascular death events, among individuals for whom lipid-lowering therapy should be considered or recommended as per the ESC guidelines. The absence of CAC identified lower risk individuals among those who should be considered for treatment according to the guidelines. As the actual risk of such individuals would be lower than the current threshold for treatment, lipid-lowering therapy could be avoided, particularly if there is a strong preference by patients. The potential clinical implications of such a selective approach to treatment could be considerable, as almost one in every two individuals from the group in which lipid-lowering therapy should be considered and one in every three individuals in whom lipid-lowering therapy would have been recommended were reclassified to a lower risk group.

CAC has been shown to provide substantial prognostic value, which is incremental to other clinical risk scores such as the Framingham risk score or the current atherosclerotic cardiovascular disease risk calculator recommended by ACC/AHA.[4,11,12] Importantly, the enhanced discrimination and reclassification of CAC is attributable not only to its ability to identify higher risk patients, but also due to the fact that the absence of coronary artery calcification is associated with extremely low rates of events, both in US and European cohorts using those tools,[4,11,12] and even in individuals traditionally considered to be at increased risk.[13]

The lower risk of incident events in individuals with a CAC of zero has previously been demonstrated across the spectrum of risk stratification and treatment recommendation groups defined by the current US guidelines for cardiovascular risk stratification.[3] Our results expand this previous knowledge by showing similar results with the current ESC guidelines for cardiovascular risk estimation and dyslipidemia management. Among those recommended for primary prevention lipid-lowering therapy, approximately one in every three individuals will have a CAC of zero, and a low enough risk of cardiovascular mortality in a 10-year window that they could be considered part of the lower risk group. A similar finding would occur in about one in every two individuals in whom lipid-lowering therapy could be considered, who had a CAC of zero and correspondingly a low cardiovascular mortality in up to 10 years of follow-up. Comparable results for both the ACC/AHA guidelines and the previous version of the ESC guidelines from 2012 have recently been published.[4] In this study, CAC was able to improve risk assessment across the spectrum of lipid-lowering therapy recommendations from both the US and European guidelines, although the authors did not perform the analysis using cardiovascular mortality, which is the primary outcome of interest in the ESC guidelines and the SCORE risk assessment tool.

This corroboration of the findings from the US guidelines in the ESC guidelines is of interest, as those two guidelines use widely different strategies for the selection of candidates for lipid-lowering therapy. While the ESC guideline recommendations are based on both the baseline risk of cardiovascular mortality

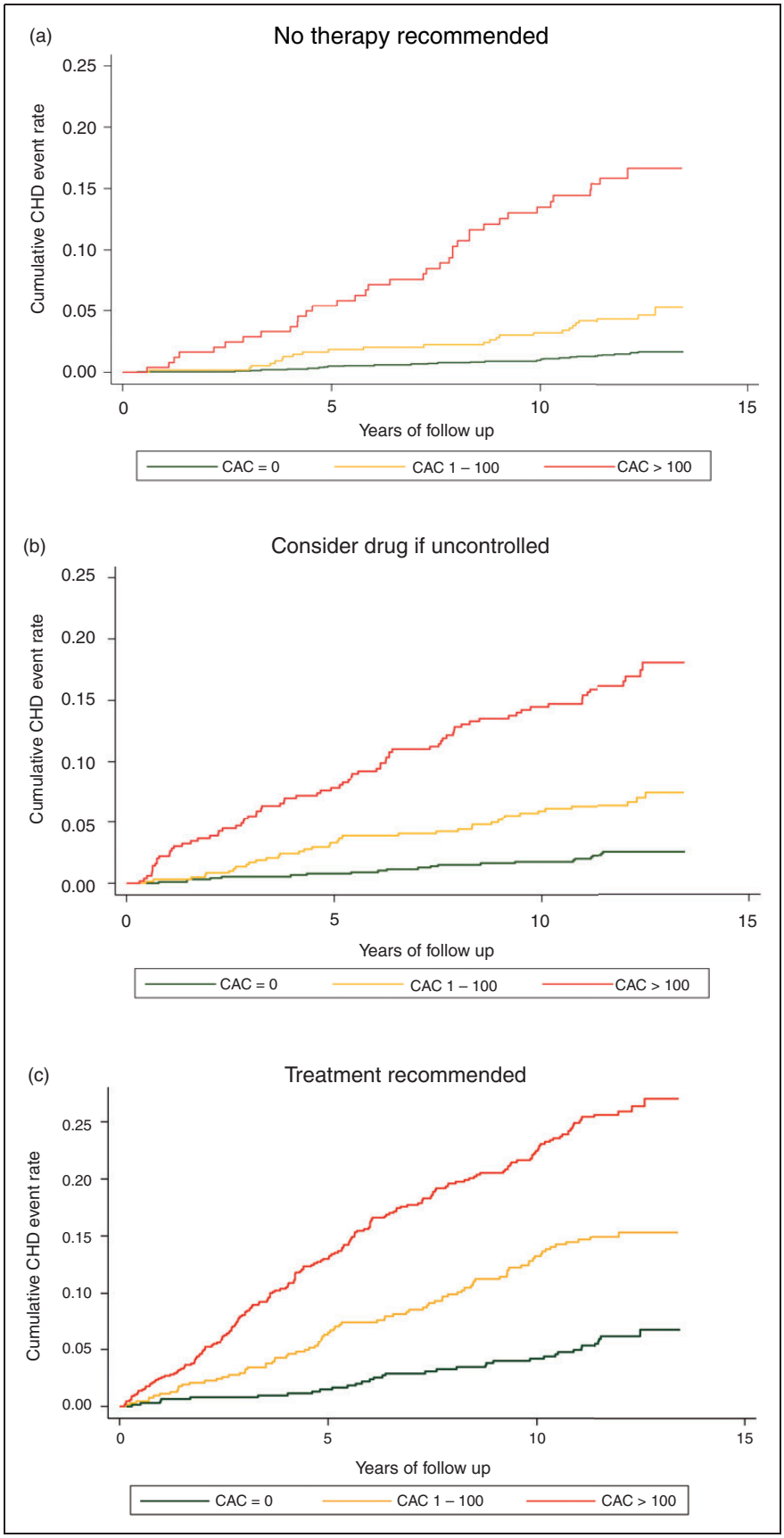

Figure 3. Kaplan–Meier survival estimates for coronary heart disease as per the coronary artery calcium (CAC) burden in each of the ESC recommended treatment groups. (a) No lipid-lowering therapy recommended; (b) lipid-lowering therapy considered if uncontrolled; (c) lipid-lowering therapy recommended upfront. $P < 0.001$ in each of the three panels.

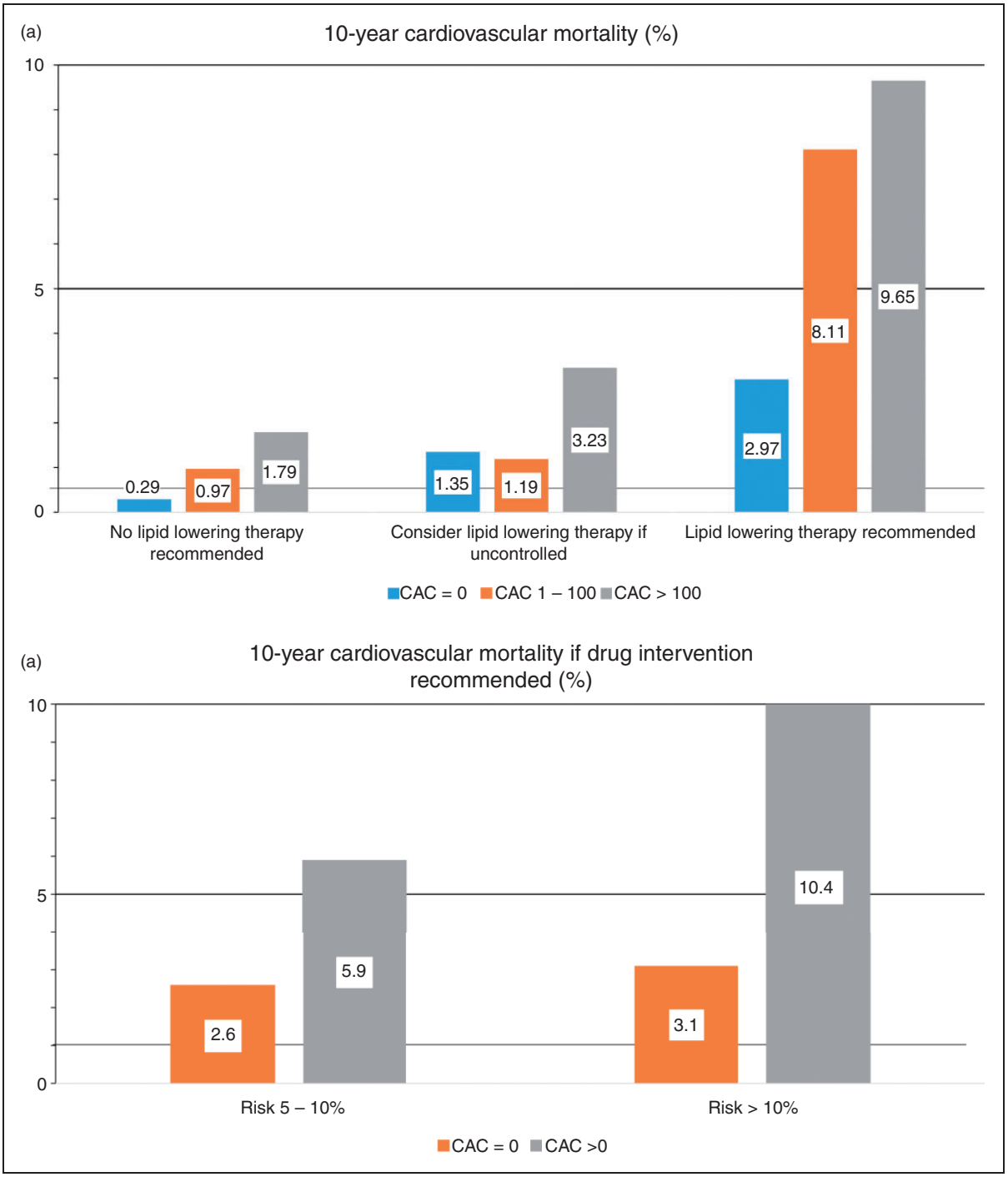

Figure 4. 10-Year cardiovascular mortality rates as per the ESC recommended treatment group (a) and stratified as per the risk category in those for whom lipid-lowering therapy is recommended upfront (b).

and LDL-cholesterol levels, the US guidelines are mostly based on estimated cardiovascular risk. In addition, while the US guidelines are based on a risk score for the prediction of global atherosclerotic events, including non-fatal events, the ESC guidelines are based on the prediction of cardiovascular mortality only. Although those differences may be perceived as small technical details, not only is the risk prediction model in the US guidelines more aggressive, and results in identifying a much larger segment of the population for consideration of lipid-lowering therapy,[4,14] but it also leads to an overestimation of risk due to miscalibration.[15] As a result, more lower risk individuals are identified as candidates for treatment. As those

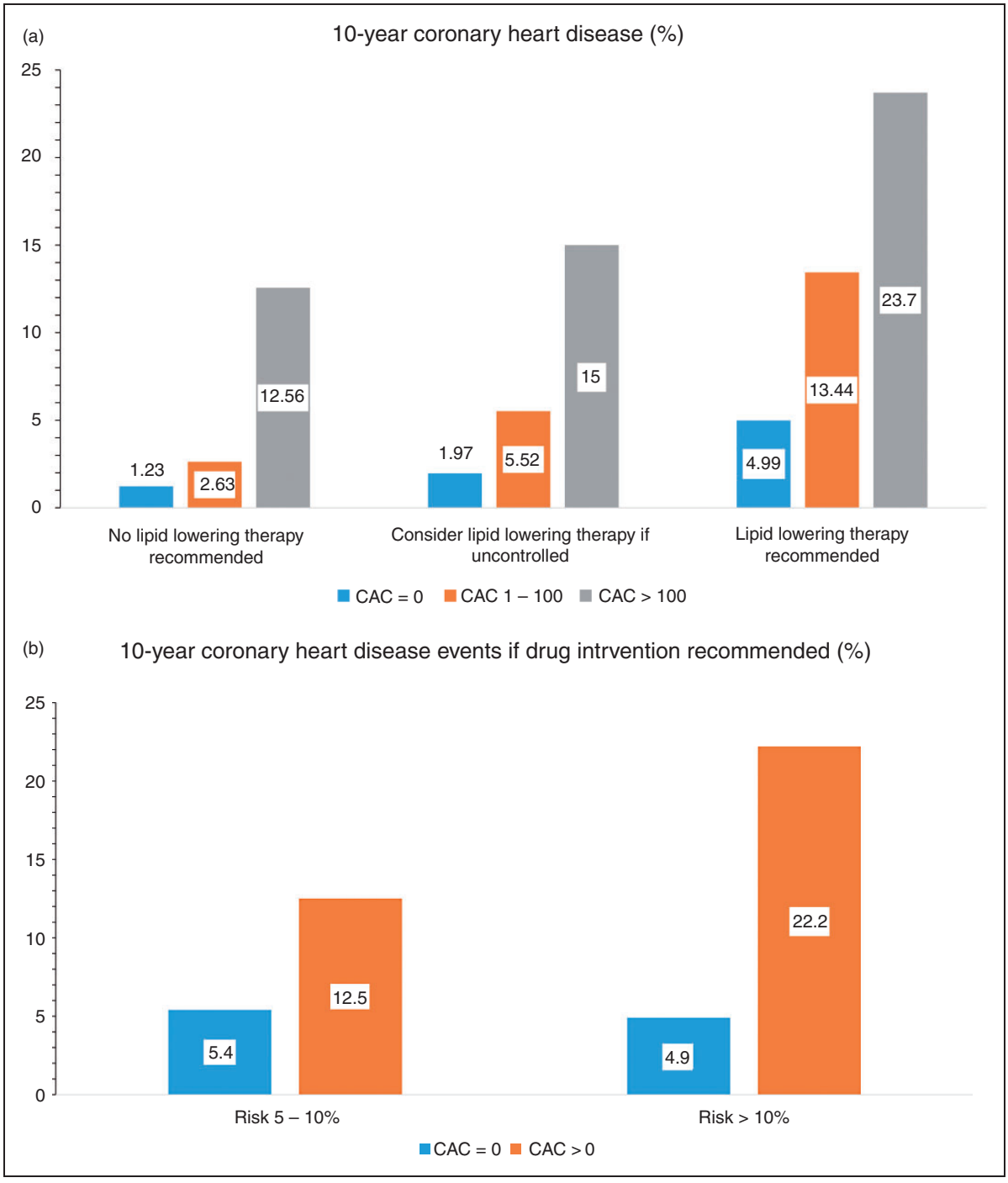

Figure 5. 10-Year coronary heart disease event rates as per the ESC recommended treatment group (a) and stratified as per the risk category in those for whom lipid-lowering therapy is recommended upfront (b).

individuals are less likely to have any coronary calcification, it would be expected that there would be a much larger proportion of individuals in whom treatment would no longer be required with the use of CAC based on the US guidelines.

Other risk stratification tools have been proposed as alternatives to evaluate the risk of selected individuals further, and some of those tools are recommended by guidelines. The comparison of various markers for additional risk stratification beyond clinical risk scores has been performed previously. Two analyses from the MESA study have already demonstrated that CAC is the best tool for discrimination of events in individuals at intermediate risk,[16] whereas a CAC of zero has been

Table 2. Estimated 10-year number needed to treat to reduce one cardiovascular death and one coronary heart disease event by CAC burden and treatment recommendation group.

10-year NNT	Cardiovascular death 10-Year NNT (30% RR)[a]	Coronary heart disease event 10-Year NNT (30% RR)[a]
Lipid-lowering therapy recommended ($n = 1688$)		
CAC = 0 ($n = 527$)	112	67
CAC 1–100 ($n = 499$)	41	25
CAC > 100 ($n = 662$)	35	14
Any CAC present ($n = 1162$)	37	18
Consider lipid-lowering therapy if uncontrolled ($n = 1686$)		
CAC = 0 ($n = 804$)	247	168
CAC 1–100 ($n = 501$)	280	60
CAC > 100 ($n = 381$)	103	22
Any CAC present ($n = 882$)	163	35
No lipid-lowering therapy recommended (n = 2294)		
CAC = 0 ($n = 1965$)	1149	271
CAC 1–100 ($n = 440$)	344	127
CAC > 100 ($n = 159$)	186	27
Any CAC present ($n = 599$)	287	67

[a]30% relative risk reduction from a Cochrane meta-analysis of statin therapy in primary prevention.
CAC: coronary artery calcium.

demonstrated to be the best marker to reclassify individuals as low risk,[17] supporting the strategy used in the current analysis.

The SCORE risk prediction tool used in our study was adequately calibrated for the MESA population, as demonstrated in Supplementary Figure 1. Moreover, the ESC guidelines are more restrictive on the selection of candidates for lipid-lowering medication, leading to a smaller yet higher risk group of individuals who are deemed candidates for lipid-lowering therapies. Interestingly, even in this more selective higher risk population, the absence of CAC still holds a powerful negative predictive value for incident coronary events and cardiovascular mortality. Although the proportion of individuals reclassified to lower risk in the models based on the ESC guidelines was smaller than using the estimates from the US guidelines (31% vs. 41%), the changes in management for individuals clinically considered for lipid-lowering therapy has significant implications at a population level. Our results suggest that the selective use of CAC should be considered as part of the routine evaluation of candidates for lipid-lowering therapy for primary prevention, regardless of whether the US or ESC guidelines are being used.[3]

Our results also provide evidence against the routine use of CAC in individuals who are not considered for lipid-lowering therapy. Although a CAC of over 100 could identify individuals with an increased risk of 10-year cardiovascular mortality, the prevalence of such findings was only 6% in this subgroup. That means only one in every 20 lower risk individuals might be reclassified to the higher risk groups. However, this may provide incremental benefit to selected individuals, such as those with a family history of premature atherosclerotic CVD or those with the metabolic syndrome, although this might not be cost-effective for lower risk individuals.[18]

Our study must, however, be read within the context of its design. First, the MESA study is a US multi-ethnic cohort, and the use of a European designed risk score may lead to poorer performance of the risk stratification, although our analysis suggests the SCORE used in the study fitted the data adequately. Second, MESA subjects may not be fully representative of the actual US or European population, as its sample is geographically dispersed, and community based by a not fully representative population. In addition, the results of CAC may also be influenced by other aspects such as high levels of physical activity.[19] Moreover, limited CAC results were reported to each participant, and their physicians might have changed management based on its results, which could have attenuated our results because those with high CAC scores may have been more likely to adhere to better lifestyle habits and pharmacotherapy, and the real estimation of events in individuals with CAC could have been even higher. Also, our number needed to treat calculations are based on fixed estimates across the CAC levels, although this has not been evaluated in any of the statin trials. It is also worth noting that our definition

of diabetes did not include the measurement of hemoglobin A1C. This fact might have led to a small underestimation of diabetes prevalence, which could have some impact on the final results. Finally, our results are limited to a 10-year horizon, as most guidelines are. However, lipid-lowering therapy may be beneficial in a longer-term perspective even in lower risk individuals. Thus, the treatment decision should ultimately be a shared decision between physicians and patients.

In conclusion, coronary artery calcium testing may identify lower risk individuals with CAC of zero among one third of the individuals in whom lipid-lowering therapy is recommended and in one in every two individuals in whom lipid-lowering therapy should be considered according to the current ESC guidelines.

Author contribution

MSB, RB, MJB, MJB, RB and KN contributed to the conception or design of the work. MSB, MJB, VS, ASA, MJB, HMK and KN contributed to the acquisition, analysis, or interpretation of data for the work. MSB, MJB, MJB, RSB, KN drafted the manuscript. MSB, RB, MJB, VS, ASA, MJB, HMK and KN critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

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Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: KN is on the advisory board for Quest Diagnostic. RB serves on a scientific advisory board for Amgen Inc. and receives research support from Amgen Inc. and Gilead Inc. MJB is on the speaker's bureau for General Electric. HMK is the recipient of a research grant from Medtronic, Inc. through Yale University and is chair of a cardiac scientific advisory board for UnitedHealth. MSB has received research funding from Sanofi and speaker fees from Boston Scientific. No other potential conflicts of interest relevant to this article were reported.

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