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CAC Score Improves Coronary and CV Risk Assessment Above Statin Indication by ESC and AHA/ACC Primary Prevention Guidelines

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CME Objective for This Article: After reading this article the reader should understand: 1) the risk factors included in the ASCVD-Risk Score; 2) the appropriate patient population, the ASCVD-Risk Score is intended for; 3) the statin indications according to current AHA/ACC guidelines; and 4) the principles of risk estimation according to current ESC guidelines

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CAC Score Improves Coronary and CV Risk Assessment Above Statin Indication by ESC and AHA/ACC Primary Prevention Guidelines

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ABSTRACT

OBJECTIVES The aim of this study was to assess the difference in indication for statin therapy by European Society of Cardiology (ESC) versus American Heart Association/American College of Cardiology (AHA/ACC) guidelines and to quantify the potential additional role of coronary artery calcification (CAC) score over updated guidelines in a primary prevention cohort.

BACKGROUND Recently, ESC and AHA/ACC updated the guidelines regarding statin therapy in primary prevention.

METHODS In 3,745 subjects (59 ± 8 years of age, 47% men) from the population based longitudinal Heinz Nixdorf Recall cohort study without cardiovascular disease or lipid-lowering therapy at baseline CAC score was assessed between 2000 and 2003. Subjects remained unaware of their initial CAC score. Statin indication was determined according to 2012 ESC and 2013 AHA/ACC guidelines based on subjects individual baseline characteristics.

RESULTS The frequency of statin recommendation was lower according to ESC compared to AHA/ACC guidelines (34% vs. 56%; $p < 0.0001$), whereas low CAC score (<100) was common in subjects with statin indication by both guidelines (59% for ESC, 62% for AHA/ACC). During 10.4 ± 2.0 years of follow-up, 131 myocardial infarctions occurred. For ESC recommendations, CAC score differentiated risk for subjects without (1.0 [95% confidence interval (CI): 0.4 to 1.5] vs. 6.5 [95% CI: 4.1 to 8.9] coronary events per 1,000 person-years for CAC 0 vs. ≥100) and with statin indication (2.6 [95% CI: 0.6 to 4.7] vs. 9.9 [95% CI: 7.3 to 12.5] per 1,000 person-years for CAC 0 vs. ≥100). Likewise, CAC score stratified proportions experiencing events subjects with statin indication according to AHA/ACC (2.7 [95% CI: 1.1 to 4.2] vs. 9.1 [95% CI: 7.0 to 11.0] per 1,000 person-years for CAC 0 vs. ≥100), whereas event rate in subjects without statin indication was low (1.1 [95% CI: 0.65 to 1.68] per 1,000 person-years).

CONCLUSIONS Current ESC and AHA/ACC guidelines lead to markedly different recommendation regarding statin therapy in a German primary prevention cohort. Quantification of CAC score in addition to the guidelines improves stratification between subjects at high versus low risk for coronary events, indicating that CAC scoring may help to match intensified risk factor modification to atherosclerotic plaque burden as well as actual risk while avoiding therapy in subjects with low coronary atherosclerosis that have low 10-year event rate. (J Am Coll Cardiol Img 2017;10:143–53)

In 2013 and 2012 the American Heart Association (AHA) together with the American College of Cardiology (ACC) as well as the European Society of Cardiology (ESC) updated their guidelines for primary prevention including recommendations regarding cholesterol lowering therapy with statins (1,2). Although AHA/ACC guidelines widen the indication for statin therapy, recommending therapy for major parts of the U.S. population (3,4), the ESC downgrades several European countries from high- to low-risk countries, leading to an overall decrease in subjects, qualifying for statin therapy (5).

In addition to estimation of risk using traditional risk factors, coronary artery calcification (CAC) as marker of coronary atherosclerosis is an independent predictor for cardiovascular events and was demonstrated to improve risk stratification in the general population and in cohorts of varying risk, suggesting that it may identify patients qualifying for medical risk factor modification in primary prevention (6–10).

Across the spectrum of dyslipidemia, CAC discriminates the risk for future events, and improves risk discrimination among subjects without statin indication, suggesting that it may have the potential to match statin therapy to absolute cardiovascular disease (CVD) risk above cholesterol levels (11,12).

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In the present analysis we aimed to: 1) quantify the expected difference in indication for statin therapy when applying AHA/ACC versus ESC guidelines among a European general population cohort without known coronary heart disease and without statin therapy at baseline; 2) determine the event rate among subjects with different CAC scores and depending on indication for statin therapy; and 3) determine, whether quantification of CAC score may discriminate risk in subjects with and without statin indication according to both guidelines.

METHODS

STUDY PARTICIPANTS. The Heinz Nixdorf Recall study is a population-based prospective longitudinal cohort study, designed to assess the predictive value of novel markers for risk stratification in addition to traditional cardiovascular risk factors. Participants (45 to 75 years of age) were randomly selected from mandatory residence lists of 3 German cities in the Ruhr area and enrolled between December 2000 and August 2003 (recruitment efficacy 55.8%). Details for recruitment and study design were previously published (7,13). From overall 4,814 subjects, 498 subjects were excluded for known coronary heart disease, prior stroke, or prior clinical diagnosis of peripheral artery disease at baseline. Further, 365 subjects were excluded due to lipid-lowering therapy at baseline examination. CAC score was not available in 166 subjects and at least 1 risk factor was missing in additional 40 subjects, leading to a cohort of 3,745 subjects for this analysis.

All participants provided written informed consent and the study was approved by the institutional ethics committee and complies with the Declaration of Helsinki.

CARDIOVASCULAR RISK FACTOR ASSESSMENT. Cardiovascular risk factors were measured at baseline with details being previously published (14). Blood pressure was measured using an oscillometric method (Omron, Hoofddorp, the Netherlands). Standardized enzymatic methods were used to determine serum high-density lipoprotein and low-density lipoprotein (LDL) cholesterol. Glomerular filtration rate was calculated according to the Modification of Diet in Renal Disease formula. Microalbuminuria was defined as albumin levels between 30 and 300 mg/24 h. Diabetes was defined as a history of diabetes, being on medical treatment, or based on blood glucose levels (15). Smoking history was classified in current and former smokers as well as no history of smoking (16).

CARDIAC COMPUTED TOMOGRAPHY. Electron beam computed tomography (CT) scans were performed utilizing a C-100 or C-150 scanner (GE Imatron, San Francisco, California) with prospective triggering at 80% of the interval between both R-waves. Contiguous 3-mm-thick slices from the right pulmonary artery to the apex were obtained at an image acquisition time of 100 ms. CAC was defined as a focus of at least 4 contiguous pixels with a CT density >130 Hounsfield units and quantified using the Agatston method (17). Participants and overseeing physicians remained unaware of the CAC score of the baseline examination.

DEFINITION FOR STATIN INDICATION ACCORDING TO ESC AND AHA/ACC GUIDELINES. According to the 2012 ESC guidelines (1), indication for statin therapy was recommended as follows, with SCORE calculation based on the low risk country equation (as applies for Germany):

- SCORE ≥5% to <10% and LDL ≥100 mg/dl
- Diabetes mellitus without other cardiovascular risk factors or without albuminuria and LDL ≥100 mg/dl
- Glomerular filtration rate 30 to 59 ml and LDL ≥100 mg/dl
- SCORE ≥10% and LDL ≥70 mg/dl
- Diabetes mellitus and 1 or more other cardiovascular risk factors or microalbuminuria (30 to 300 mg/24 h) and LDL ≥70g/dl
- Glomerular filtration rate <30 ml and LDL ≥70 mg/dl.

According to the 2013 AHA/ACC guidelines (2), indication for statin therapy was recommended as follows:

- LDL cholesterol ≥190 mg/dl
- 40 to 75 years of age and present diabetes and LDL cholesterol 70 to 189 mg/dl
- 40 to 75 years of age and risk score ≥7.5% and LDL cholesterol 70 to 189 mg/dl

FOLLOW-UP AND ENDPOINT DEFINITION. Endpoints were defined as incident coronary events, stroke, or cardiovascular death. Annually, questionnaires on the current state of health including questions about medication, hospital admissions, and outpatient

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

AHA = American Heart Association

ASCVD = atherosclerosis cardiovascular disease

CAC = coronary artery calcification

CT = computed tomography

ESC = European Society of Cardiology

LDL = low-density lipoprotein

TABLE 1 Baseline Characteristic for the Overall Cohort as Well as Stratified by Statin Indication According to ESC and AHA/ACC Guidelines

		2012 ESC Guidelines		2013 AHA/ACC Guidelines	
	Overall	No Statin Indication	Statin Indication	No Statin Indication	Statin Indication
n	3,745	2,457 (66)	1,255 (34)	1,650 (44)	2,095 (56)
Age, yrs	59 ± 8	56 ± 7	64 ± 7	55 ± 6	62 ± 7
Male	1,760 (47)	954 (39)	787 (63)	433 (26)	1,327 (63)
Systolic blood pressure, mm Hg	132 ± 21	126 ± 18	145 ± 21	123 ± 18	140 ± 20
Diastolic blood pressure, mm Hg	82 ± 11	80 ± 10	85 ± 11	79 ± 10	84 ± 11
Antihypertensive medication	1,078 (29)	539 (22)	520 (41)	269 (16)	809 (39)
Total cholesterol, mg/dl	232 ± 39	228 ± 38	241 ± 39	220 ± 33	242 ± 40
LDL cholesterol, mg/dl	148 ± 36	143 ± 36	158 ± 34	134 ± 30	160 ± 37
HDL cholesterol, mg/dl	59 ± 17	61 ± 17	56 ± 16	65 ± 17	54 ± 16
Triglycerides, mg/dl	145 ± 97	133 ± 85	167 ± 112	117 ± 77	166 ± 105
Diabetes	426 (11.4)	10 (0.4)	416 (32)	6 (0)	420 (20)
Smoking status					
Current	867 (23)	575 (23)	292 (23)	321 (19)	546 (26)
Former	1,233 (33)	773 (31)	445 (35)	528 (32)	705 (34)
Never	1,645 (44)	1,109 (45)	518 (41)	801 (49)	844 (40)
CAC score	10 (0-95)	2 (0-43)	59 (5-244)	0 (0-15)	46 (3-200)

Values are n (%), mean ± SD, or median (interquartile range).

ACC = American College of Cardiology; AHA = American Heart Association; CAC = coronary artery calcification; ESC = European Society of Cardiology; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

diagnosis of CVD were sent to the participants. In parallel, all death certificates were regularly screened. Incident coronary events, strokes, and fatal events were validated by review of all available hospital records and records of the attending physicians, and classified by an external endpoint committee blinded to the risk factor status and the CAC score. Fatal or nonfatal myocardial infarction was defined based on symptoms, electrocardiographic signs, cardiac enzymes, and necropsy (7). Stroke was defined as focal neurological deficits over a period of >24 h of presumed cerebrovascular origin. In addition, cardiovascular mortality was classified by the statistical state office based on death certificate information according to the International Statistical Classification of Disease (18). In addition to baseline statin medication, initiation of statin therapy was assessed by annual questioners.

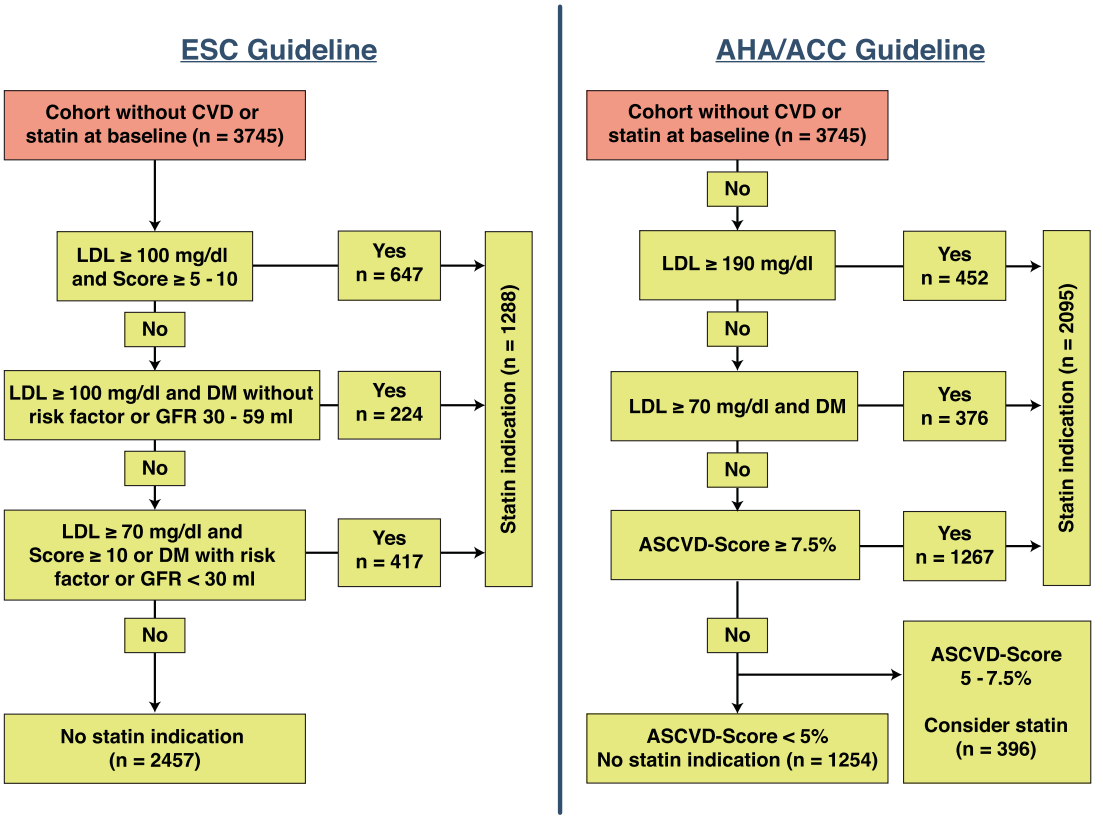
STATISTICAL ANALYSIS. Continuous variables are reported as mean ± SD or median (interquartile range). Discrete variables are given in frequency (%). For groups of statin indication according to ESC and AHA/ACC guideline and CAC groups (0, 1 to <100, ≥100 to <400, ≥400) as well as combination of statin indication and CAC group, the overall number of coronary and cardiovascular events was assessed. Chi-square test was used to assess significance in difference of event rates between CAC groups. In addition, we calculated event rates per 1,000 person-years, applying the group-specific follow-up time for groups of statin indication and CAC group (0, 1 to <100, ≥100). The number needed to scan depicts the number of CT examinations necessary to detect 1 subject with a CAC score of <100 or ≥100 in the group. For calculation of numbers needed to treat we assumed a 30% reduced risk for coronary and cardiovascular events, which we applied on the observed event rates for our cohort that was free of statin medication (19,20). In addition, standardized event ratios were calculated using indirect age- and sex specific standardization, based on the overall cohort. Further, we substratified the group of atherosclerosis cardiovascular disease (ASCVD) score <7.5% into the groups of <5.0% and 5.0% to 7.5% and calculated incidence of coronary and cardiovascular events as well as event rates per 1,000 person-years. In the subgroup of subjects with statin initiation during follow-up without prior CVD event (excluding subjects with statin medication following a CVD event), we calculated coronary and cardiovascular event rate, stratified by statin indication and CAC group. Due to the low number of events in this analysis, we only stratified CAC score by <100 versus ≥100.

In additional analysis, event rates for CAC of 0, 1 to 99, and ≥100 were stratified by equivalent SCORE/ASCVD score in subgroups of subjects with and without statin indication. This analysis, subjects with glomerular filtration rate <30 ml/min or diabetes using ESC guidelines and with LDL >190 mg/dl and diabetes for AHA/ACC guidelines were excluded. Identifying subgroups in which CAC score differentiated future event rate, we calculated the potential impact when applying CAC scoring in addition to ESC and AHA/ACC guidelines on medication recommendation and event rate. All analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina). A p value <0.05 indicated statistical significance.

RESULTS

Overall, 3,575 subjects (59 ± 8 years of age, 47% men) without lipid-lowering therapy or known CVD were included (Table 1). Of those, 1,288 subjects (34.4%) fulfilled criteria for statin therapy among ESC recommendations, whereas application of AHA/ACC guidelines led to a statin indication for statin therapy in 2,101 subjects (56.1%). Additionally, 897 (24.0%) subjects met statin indication based on AHA/ACC guidelines but not on ESC guidelines, whereas 84 (2.2%) were recommended taking statins according to European guidelines only. Details of

FIGURE 1 Statin Eligibility According to ESC and AHA/ACC Guidelines



Statin eligibility among the baseline study population without cardiovascular disease (CVD) and statin medication according to European Society of Cardiology (ESC) and American Heart Association/American College of Cardiology (AHA/ACC) guidelines. ASCVD = atherosclerosis cardiovascular disease; DM = diabetes mellitus; GFR = glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

classifications for meeting criteria for statin using both AHA/ACC and ESC guidelines are depicted in Figure 1.

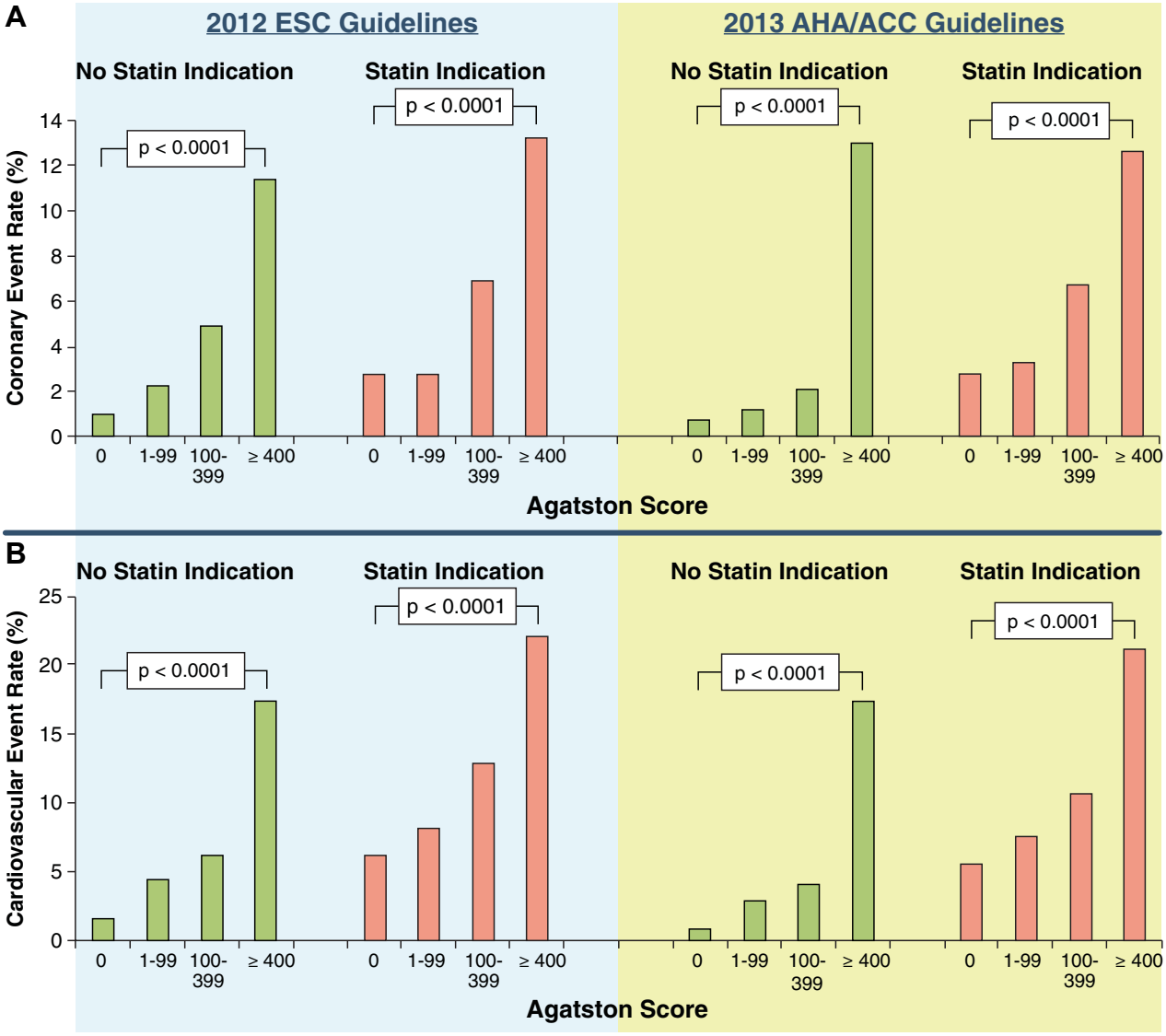
During a mean follow-up of 10.4 ± 2.0 years, a total of 131 fatal or nonfatal myocardial infarctions (event rate 3.50%), and 241 hard cardiovascular events (myocardial infarction, stroke, cardiovascular death; event rate 6.43%) occurred. As depicted in Table 2, 60 subjects (46% of all events) with coronary events did not fulfill statin indication by ESC guidelines (event rate 2.44%), whereas only 19 events (15% of all events) occurred in the group without statin indication when applying the AHA/ACC guidelines (event rate 1.15%). Although AHA/ACC guidelines identified more subjects suitable for statin treatment, event rate was comparable to ESC recommendations due to the higher absolute number of subjects with events in this group. As further

TABLE 2 Myocardial Infarction and Hard Cardiovascular Event Rate, Stratified by Statin Indication and CAC Group

Category	n	Coronary Events in 10.4 Yrs	Cardiovascular Events in 10.4 Yrs
ESC guidelines			
No statin indication	2,457	60 (2.4)	97 (4.0)
Statin indication	1,288	71 (5.5)	144 (11.2)
AHA/ACC guidelines			
No statin indication	1,650	19 (1.2)	35 (2.1)
Statin indication	2,095	112 (5.3)	206 (9.8)
CAC group			
0	1,272	17 (1.3)	30 (2.4)
1-99	1,555	38 (2.4)	88 (5.7)
100-399	601	36 (6.0)	58 (9.7)
≥400	317	40 (12.6)	65 (20.5)

Values are n (%).
Abbreviations as in Table 1.

FIGURE 2 CAC-Stratified Coronary and Cardiovascular Event Rate



Coronary and cardiovascular event rate for subjects with and without statin indication according to ESC and AHA/ACC guidelines, stratified by coronary artery calcification (CAC) group, showing a distinct increase in event rates for both coronary and cardiovascular events with increasing CAC score, irrespective of statin indication according to ESC and AHA/ACC guidelines. Abbreviations as in Figure 1.

depicted in Table 2, 10-year event rate also increased with CAC group with an approximately 10-fold higher event rate for subjects with CAC ≥400 compared to subjects with CAC score of 0.

Figure 2A shows the event rate for coronary events, stratified by CAC groups for subjects with and without statin indication according to both guidelines, showing that coronary event rate increased with CAC score but not relevantly with statin indication by either guideline. In contrast, frequency of events for subjects with CAC score <100 was low (≤3.3%) in subjects with and without statin indication. Similar results were observed for hard cardiovascular events, whereas discrimination by CAC score was not as distinct as for coronary events (Figure 2B).

CAC SCORE FOR DISCRIMINATION OF RISK IN SUBJECTS WITH AND WITHOUT STATIN INDICATION ACCORDING TO ESC AND AHA/ACC GUIDELINES. Consecutively, we examined coronary event rates for subjects with and

without statin indication, stratified by CAC score of 0, 1 to 99, and ≥100 (Table 3). For subjects without statin indication according to ESC guidelines, event rate was low when CAC score was low. In contrast, it was considerably higher for those without statin indication and CAC score ≥100 (4.3 per 1,000 person-years) and even higher than the event rate for subjects, fulfilling statin indication according to ESC guidelines when not applying CAC score (3.8 per 1,000 person-years). One in 6.2 subjects without statin indication had a CAC score of ≥100. Likewise, for subjects with statin indication, event rate was comparable to the group without statin indication (2.8 vs. 2.7 per 1,000 person-years), when CAC score was <100, which was the case in nearly 60% of participants in this group. In contrast, event rate reached 8.0 per 1,000 person-years, when CAC score was ≥100. In addition, we calculated numbers needed to treat to prevent 1 event within 10 years, assuming that 30% of events could be prevented when taking a statin. We observed that the assumed 10-year numbers needed to treat was ≤100 for subjects with CAC ≥100, again irrespective of presence or absence of statin indication according to ESC guidelines (Table 3). Age and sex standardized event ratios revealed that aside from the influence of age and sex, CAC score but not statin indication group discriminated the risk for future events (Online Table 1).

Different results were observed when applying AHA/ACC guidelines. Among those without statin indication, not only event rate, but also frequency of high CAC scores was low, whereas event rate in this rare group was 3.1 per 1,000 person-years. In contrast, for the large group of subjects with statin indication according to U.S. guidelines, CAC score of 0 was associated with a very low event rate. Treating only subjects with CAC ≥100, would have the ability for improving the number needed to tread most importantly reducing the number of subjects, qualifying for intensified risk modification from 2,101 to 800 (Table 3). Again, standardized event ratios confirmed the discriminative power of CAC scoring within each statin indication group (Online Table 1).

Further stratifying the group of ASCVD score <7.5% into 0% to 5% and 5% to 7.5% did not lead to markedly different results, whereas overall event rate was very low in both groups (Online Table 2). Specifically looking at subjects with diabetes and statin indication, similar results were observed (Online Table 3).

Similar to coronary events, also for major hard cardiovascular events, CAC score discriminated event rates among subjects with and without statin indication. Especially, for the ESC guidelines, CAC score identified subjects with increased CVD event rate among those without statin indication (Table 4, Online Table 1).

Specifically looking at the subgroup of subjects with initiation of statin therapy during follow-up (n = 628), 60 subjects received statin medication

TABLE 3 Event Rate of Myocardial Infarction, NNT, and NNS for Subjects With and Without Statin Indication, Stratified by CAC Score 0, 1 to 99, and ≥100

Statin Indication	CAC Group	N (%)	Coronary Events in 10.4 Yrs	Event Rate per 1,000 Patient-Yrs (95% CI)	NNS to Detect 1 Subject With CAC <100/≥100*	Assumed 10-Yr NNT†
ESC guidelines						
No	0	1,056 (43.0)	11 (1.0)	1.0 (0.4–1.5)		344
	1–99	1,012 (41.1)	23 (2.3)	2.2 (1.3–3.1)	1.2/6.3	153
	≥100	389 (15.8)	26 (6.7)	6.5 (4.1–8.9)		52
Yes	0	216 (16.8)	6 (2.8)	2.6 (0.6–4.7)		127
	1–99	543 (42.2)	15 (2.8)	2.7 (1.4–4.1)	1.7/2.4	123
	≥100	529 (41.1)	50 (9.5)	9.9 (7.3–12.5)		34
AHA/ACC guidelines						
No	0	881 (53.3)	6 (0.7)	0.6 (0.1–1.1)		530
	1–99	650 (39.3)	8 (1.2)	1.2 (0.4–2.0)	1.1/13.9	287
	≥100	119 (7.2)	5 (4.2)	4.1 (0.6–7.6)		84
Yes	0	391 (18.7)	11 (2.8)	2.7 (1.1–4.2)		124
	1–99	905 (43.2)	30 (3.3)	3.3 (2.1–4.4)	1.6/2.6	102
	≥100	799 (38.1)	71 (8.9)	9.1 (7.0–11.0)		37

Values are n (%) unless otherwise indicated. *Number needed to scan (NNS) to detect 1 subject with a CAC score of <100 or ≥100 within each group of subjects with or without statin indication. †Ten-year number needed to treat (NNT), applying that 30% of events within the first 5 years could be prevented when treated with a statin.

CI = confidence interval; other abbreviations as in Table 1.

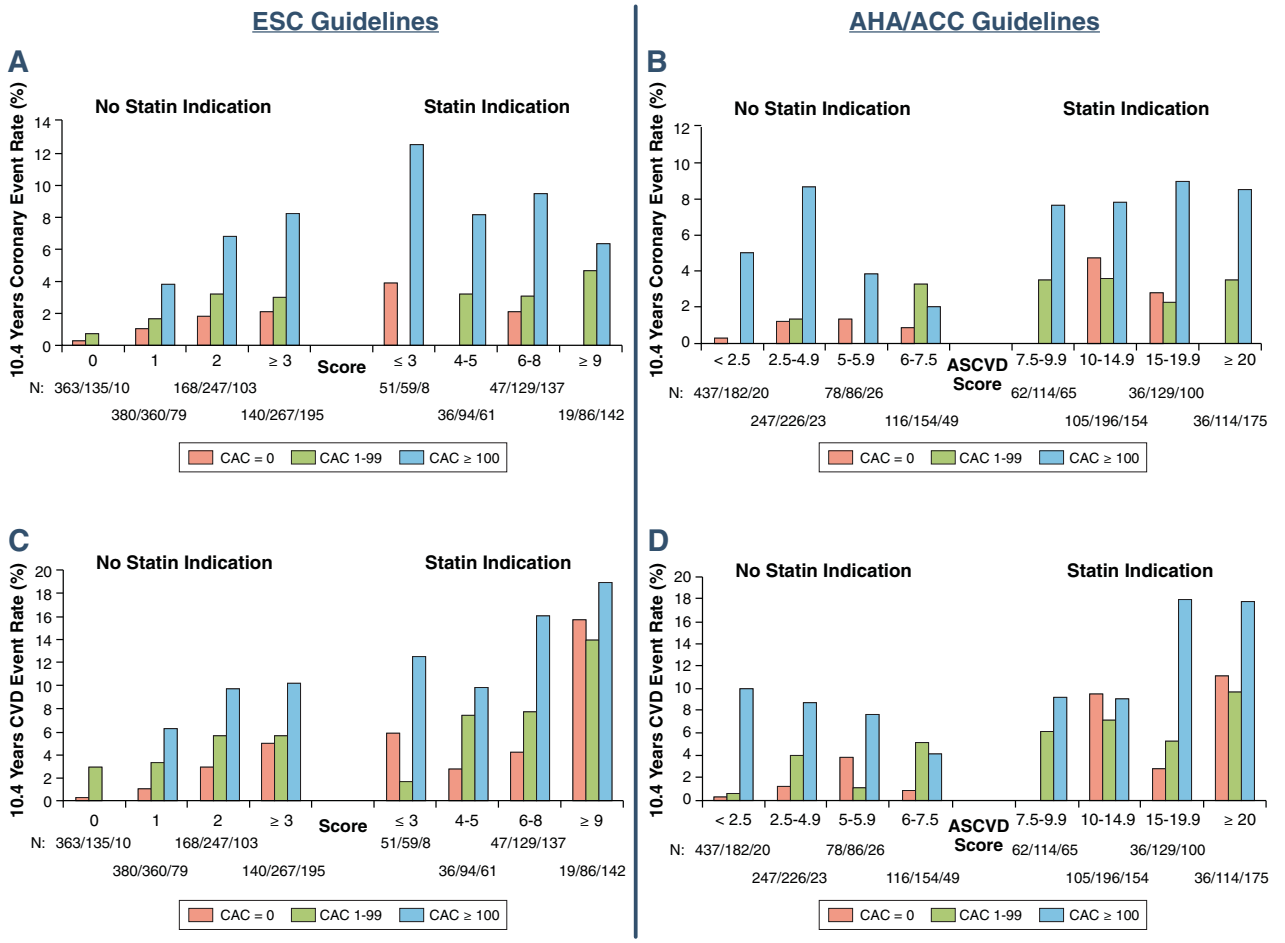
TABLE 4 Event Rate of Hard Cardiovascular Events, NNT, and NNS for Subjects With and Without Statin Indication, Stratified by CAC score 0, 1 to 99, and ≥100

Statin Indication	CAC Group	N (%)	Median SCORE/ ASCVD Score (%)	CV Events in 10.4 Yrs	Event Rate per 1,000 Patient-Yrs (95% CI)	Assumed 0-Yr NNT*
ESC guidelines						
No	0	1,056 (43.0)	1 (0, 3)	17 (1.6)	1.5 (0.8–2.2)	222
	1–99	1,012 (41.1)	2 (1, 3)	45 (4.5)	4.3 (3.1–5.5)	78
	≥100	389 (15.8)	3 (2, 3)	35 (9.0)	8.7 (6.0–11.5)	38
Yes	0	216 (16.8)	5 (2, 6)	13 (6.0)	5.7 (2.7–8.7)	59
	1–99	543 (42.2)	5 (3, 6)	43 (7.9)	7.8 (5.5–10.0)	43
	≥100	529 (41.1)	7 (5, 10)	88 (16.6)	17.4 (14.1–20.7)	19
AHA/ACC guidelines						
No	0	881 (53.3)	2.5 (1.2, 4.2)	8 (0.9)	0.8 (0.3–1.2)	396
	1–99	650 (39.3)	3.8 (2.3, 5.4)	19 (2.9)	2.8 (1.5–4.0)	121
	≥100	119 (7.2)	5.1 (3.7, 6.2)	8 (6.7)	6.5 (2.2–11.8)	51
Yes	0	391 (18.7)	10.7 (8.1, 15.5)	22 (5.6)	5.4 (3.2–7.5)	62
	1–99	905 (43.2)	13.5 (9.3, 20.0)	69 (7.6)	7.5 (5.8–10.9)	44
	≥100	799 (38.1)	17.2 (11.3, 36.0)	115 (14.4)	14.6 (12.2–17.1)	23

Values are n (%) or median (interquartile range [quartile 1, quartile 3]), unless otherwise indicated. *Ten-year NNT, applying that 30% of events within the first 5 years could be prevented when treated with a statin.

ASCVD = atherosclerosis cardiovascular disease; other abbreviations as in Tables 1 and 3.

FIGURE 3 Difference in Event Rate by CAC Score in Subjects With Potential Statin Therapy



(A and B) Coronary event rate and **(C and D)** cardiovascular event rate for subjects with and without statin indication according to **(A and C)** ESC and **(B and D)** AHA/ACC guidelines for CAC of 0, 1 to 99, and ≥100, stratified by SCORE for ESC guidelines and ASCVD score for AHA/ACC guidelines. Abbreviations as in Figures 1 and 2.

following cardiovascular events, whereas statin therapy was initiated in 568 subjects without prior CVD event. Within the group of subjects without prior event, 10 coronary (1.76%) and 21 (3.70%) cardiovascular events occurred during follow-up. Interestingly, 53% (303 of 568) of subjects with statin initiation during follow-up did not fulfill indication according to ESC guidelines whereas 77% (437 of 568) met AHA/ACC criteria. Stratifying the event rate by indication to statin therapy according to ESC and AHA/ACC guidelines revealed a trend toward higher event rate with higher CAC score independent of statin indication, confirming the results of the main analysis, whereas overall event rate was low (Online Table 4).

EVENT RATES ACCORDING TO RISK QUARTILES WHEN STRATIFYING BY CAC. Figures 3A and 3C depict the coronary and cardiovascular event rate, stratified by SCORE for subjects with and without statin indication according to ESC guidelines, by CAC of 0, 1 to 99, and ≥100. We found that for subjects with SCORE <2, CAC ≥100 was rare and did not lead to a significant differentiation of event rate. In contrast, for subjects with SCORE of ≥2 but without statin indication, CAC well discriminated the risk for events with an event rate of 7.7% for subjects with CAC ≥100 (2.7% for CAC <100), whereas overall number needed to scan to detect 1 subject with CAC ≥100 was 3.7. For subjects with statin indication, CAC score well differentiated for subjects with SCORE ≤8,

whereas for SCORE >8 event rates were not different when stratified by CAC (**Figures 3A and 3C**).

Likewise, **Figures 3B and 3D** depict the event rates for subjects with and without statin indication by American guidelines, stratified by ASCVD score. In subjects without statin indication, high CAC score was rare for all subgroups. For subjects with statin indication, event rate was significantly higher when CAC score was ≥100 (**Figures 3B and 3D**).

If CT imaging of the heart would be performed in subjects without statin indication according to ESC guidelines if SCORE was ≥2 as well as in subjects with statin indication but SCORE ≤8, overall 2,102 subjects (56.1%) in our population-based cohort would receive CT imaging. If further among those with CT only subjects with CAC ≥100 or SCORE ≥8 received statins, the 10-year event rate in the group of statin appropriate subjects would increase to 8.2% compared to 5.6% in subjects with statin indication by ESC guidelines. At the same time, event rate in subjects without statins would decrease from 2.5% (ESC guidelines) to 1.9% (ESC + CAC) while decreasing the number for subjects suitable for statin therapy from 1,255 to 957.

DISCUSSION

In this manuscript we demonstrate that: 1) application of ESC and AHA/ACC guidelines leads to markedly different recommendations regarding statin therapy in the general population; 2) among subjects with and without statin indication, CAC score well differentiates the risk for future events; and 3) when CAC score is applied to appropriate subgroups it may lead to significant improvement of risk prediction, especially in addition to European recommendations.

The finding of event rates of subjects with statin indication but low CAC score being in the range of subjects without statin indication demonstrates the ability of CAC scoring to avoid lifelong medical lipid-lowering therapy for subjects with low observed subsequent event rates. In fact, a majority of subjects, recommended for statin therapy especially following AHA/ACC guidelines had a low CAC score and a low 10-year event rate. Although following AHA/ACC guidelines, more subjects with events are suggested to take a statin, this goes in hand with a higher number of subjects without events in this group. Taking into account the low event rate in this group when CAC score is low, our results suggest that CAC quantification can overcome this challenge, avoiding therapy in major parts of the population. In contrary, following the ESC guidelines led to more subjects without statin recommendation but subsequent events. Although in this group event rate increased with CAC score, CAC quantification can justify statin therapy in subjects with moderate risk but without statin recommendation according to current ESC guidelines. Taken together, our results suggest that CAC scoring may help to match intensified risk factor modification to atherosclerotic plaque burden as well as actual risk while simultaneously justifying avoidance of lifelong intensified risk factor modification via medical treatment in primary prevention for major parts of the population.

Statin therapy is established in primary prevention as reducing cholesterol levels, having anti-inflammatory effects, and being suggested to stabilize plaque morphology (21,22). Although overall statin therapy is safe, side effects such as myopathy and increased incidence of diabetes are known (23,24). Recent literature suggests that CAC scoring is the currently best noninvasive test for improvement of prediction of future coronary and cardiovascular events over established algorithms, enabling improved stratification of risk (25–27). Recently, Nasir et al. (28) investigated the value of CAC scoring for candidates for statin therapy according to AHA/ACC guidelines and found comparable results. These findings underline pervious reports of a robust value of CAC score in primary prevention, independent of ethnicity and cohort.

The contrary approach in recent updates in ESC and AHA/ACC guidelines not only leads to markedly different recommendation regarding statin therapy, but also implies different potential for the additional value of CAC scoring. For ESC recommendations, CAC scoring identifies subjects at increased risk among those without statin indication as well as subjects at low risk among those with statin indication.

In contrast, when applying AHA/ACC recommendations, we observed a very low event rate in the group of subjects without statin indication, which may not justify additional testing. However, as was recently demonstrated, among the U.S. population between 60 and 75 years of age, 87% of men and 54% of women would be eligible for statin therapy (76% of men and 39% of women among our population 45 to 75 years of age), there is huge potential for optimization by implementation of CAC score in this group to more specifically limiting therapy for those at increased risk (3).

STUDY LIMITATIONS. Strengths of our study include the population-based study design without selection of subjects due to any clinical conditions and the highly standardized measurement of risk factors and CAC score as part of the study. As a further strength,

participants and physicians remained unaware of CAC scores of the baseline examination. A limitation is that our results are based on a single European cohort with Caucasian participants. Therefore, generalization to other ethnic groups remains uncertain. Furthermore, SCORE and ASCVD score were validated for different endpoints, which may influence the performance for our combined endpoint. Additionally, as part of our study no intervention was performed. Therefore, we can only assume an effect on risk reduction by statin therapy.

CONCLUSIONS

Current ESC and AHA/ACC guidelines lead to markedly different recommendation regarding statin therapy in a German primary prevention cohort while low CAC score is common in subjects with statin indication according to both guidelines. Quantification of CAC score in addition to the guidelines improves stratification between subjects at high versus low risk for coronary events, indicating that CAC scoring may help to match intensified risk factor modification to atherosclerotic plaque burden as well as actual risk while avoiding therapy in subjects with low coronary atherosclerosis that have low 10-year event rate.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: CAC scoring differentiates risk for future coronary and cardiovascular events in subjects with and without statin indication by current American and European primary prevention guidelines.

TRANSLATIONAL OUTLOOK: Quantification of CAC has the ability to reduce recommendation to medical lipid-lowering therapy to those subjects with high coronary plaque burden and high 10-year mortality risk. Although observational studies clearly underline the ability of CAC scoring to improve risk prediction of future cardiovascular events, randomized controlled trials are needed to establish the value of noncontrast cardiac CT to actually reduce event rate.

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KEY WORDS coronary artery calcification, guidelines, Heinz Nixdorf Recall study, primary prevention, statin indication

APPENDIX For supplemental tables, please see the online version of this article.

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