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Coronary calcification measures predict mortality in symptomatic women and men

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ABSTRACT

Objective To assess the prognostic value of absolute and sex-specific, age-specific and race/ethnicity-specific (Multi-Ethnic Study of Atherosclerosis, MESA) percentiles of coronary artery calcification in symptomatic women and men.

Methods The study population consisted of 4985 symptomatic patients (2793 women, 56%) visiting a diagnostic outpatient cardiology clinic between 2009 and 2018 who were referred for cardiac CT to determine Coronary Artery Calcium Score (CACS). Regular care data were used and these data were linked to the databases of Statistics Netherlands for all-cause mortality data. Kaplan-Meier curves, multivariate Cox proportional hazards regression and concordance statistics were used to evaluate the prognostic value of CACS and MESA percentiles. Women were older compared with men (60 vs 59 years).

Results Median CACS was 0 (IQR: 0–54) in women and 42 (IQR: 0–54) in men. After a median follow-up of 4.4 years (IQR: 3.1–6.3), 116 (2.3%; 53 women and 63 men) patients died. MESA percentiles did not perform better compared with absolute CACS (C-statistic 0.65, 95% CI 0.57 to 0.73, vs 0.66, 95% CI 0.58 to 0.74, in women and 0.59, 95% CI 0.51 to 0.67, vs 0.62, 95% CI 0.55 to 0.69, in men, for the percentiles and absolute CACS, respectively).

Conclusions In symptomatic individuals absolute CACS predicts mortality with a moderately good performance. MESA percentiles did not perform better compared with absolute CACS, thus there is no need to use them. Including degree of stenosis in the model might slightly improve mortality risk prediction in women, but not in men.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In asymptomatic women and men, calcification of the coronary arteries is a strong predictor for mortality.

WHAT THIS STUDY ADDS

⇒ Validation of commonly used calcification measures in a large real-word patient population.

⇒ In symptomatic patients at cardiac outpatient clinics, absolute and Multi-Ethnic Study of Atherosclerosis (MESA) percentiles of Coronary Artery Calcium Score (CACS) predict mortality equally well.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In symptomatic patients, simple absolute CACS can be used instead of additional calculation of MESA percentiles.

⇒ In this study, the hypothesis was generated that in future studies the focus should be broadened from CACS only to non-calcified plaques as well to further improve risk prediction in symptomatic women and men.

coronary artery calcification in these symptomatic individuals is not well established.[3]

Non-contrast-enhanced CT and coronary CT angiography are used to evaluate the calcification of the coronary arteries. Based on the results of this diagnostic assessment, the amount of coronary artery calcium (CAC) is quantified by the CAC Score (CACS) according to Agatston.[4] CACS, as a continuous variable, is often categorised for clinical use.[5–7]

Several studies demonstrated sex differences in the amount and type of atherosclerotic plaques in symptomatic patients. Development of coronary artery calcification is on average delayed by 10 years in symptomatic women compared with men and onset of coronary artery calcification starts at an earlier age in men than in

INTRODUCTION

In asymptomatic women and men, calcification of the coronary arteries is proven to be a strong predictor for mortality.[1] In individuals with symptoms suspicious for cardiac disease, but without coronary artery calcification, the presence of obstructive coronary artery disease (CAD) is low, and their long-term prognosis is good.[2] However, the value of

women.[5 8] Furthermore, symptomatic men mostly have calcified plaques while women predominantly have mixed or non-calcified plaques.[9 10] Therefore, use of absolute CACS to estimate mortality risk may lead to false reassurance in women with low CACS, as symptomatic women might have CAD caused by non-calcified plaques.[11] Thus, CACS may have a different prognostic value in symptomatic women compared with men,[12 13] although literature is not consistent.[14]

The presence of coronary artery calcification also differs between ethnicities[15 16] and increases with age.[5 6 8 17] Therefore, the Multi-Ethnic Study of Atherosclerosis (MESA) reported sex-specific, age-specific and race/ethnicity-specific percentiles for CACS in the general and asymptomatic population.[18 19] However, the question remains if these percentiles are a better discriminator of risk compared with absolute CACS in symptomatic patients in a real-world cardiology setting.

To address these issues, we first studied the prognostic value of coronary artery calcification measures in a symptomatic population in a sex-stratified manner, as CACS is mainly assessed and used as a risk marker in these symptomatic women and men.[20–22] Both absolute measures, as reflected by CACS, and MESA percentiles,[18] were evaluated as measures to reflect the amount of calcification. Second, we evaluated whether degree of coronary stenosis at CT angiography increases the discriminative prognostic value when added to the model based on CACS.

METHODS
Patient selection
Individual patient data from electronic health records (CardioPortal, Cardiology Centers of the Netherlands (CCN) proprietary electronic health records, EHR) was retrieved from thirteen Dutch outpatient cardiology clinics (CCN) between 2007 and 2018. A detailed description of this database has been previously published.[23] All included patients were symptomatic, that is, they had cardiovascular complaints and were referred by the general practitioner to a cardiovascular screening centre. We analysed a selection of patients that underwent cardiac CT as part of clinical care, resulting in a study population of 4985 women and men, aged between 45 and 85 years (figure 1). Standardised cardiovascular workup was performed and documented for these patients.[23]

Calcium score, MESA percentiles and degree of stenosis assessment
The cardiac CT scanning protocol consisted of a non-contrast enhanced scan to evaluate CACS and a contrast-enhanced protocol for coronary angiography. Type of CT-scanner was determined by availability in the referred centres. Results of diagnostic imaging were reported in free text, which was transformed into different features, for example, CACS and degree of stenosis in one of the main coronary arteries. Sex-specific, age-specific and race/ethnicity-specific percentiles were based on retrieved absolute CACS using the previously reported percentile tables from the MESA.[19] As race/ethnicity was not structurally reported in the database, we used Caucasian percentiles in the main analysis.

As CACS is clinically used in different categories, we categorised CACS into the following groups: zero CACS, CACS 1–100, CACS 101–400 and CACS>400. For the MESA percentiles the following categories were used: no CAC, ≤75th percentile, 75th–90th percentile and >90th percentile. In 2715 (54%) of these patients, degree of stenosis determined by CT angiography was also documented in free text. A comparison was made for baseline characteristics of the complete CT population in which CACS was reported and the CT population in whom degree of stenosis was additionally documented. The available CT angiography results were classified into grades of stenosis, namely 0%, 1%–24%, 25%–49%, 50%–70%, 71%–99% and 100% stenosis.[24] Qualitative indications of degree of stenosis were discussed with two cardiologists to enable quantification of stenosis degree. This resulted in the following conversion from qualitative to quantative; for 1%–24% any, minimal, minor, for 25–49% partial, diffuse, mild, not-significant, non-significant, for 50%–70% important, clear, significant, intermediate, for 71%–99% severe, high grade and for 100% occlusion. As (high-risk) plaque characteristics were irregularly and unstructured mentioned in free text, these features were not taken into account for analysis.

Outcome assessment
Information on a patient's country of origin, mortality and cause of death was obtained by linkage to the population registry of Statistics Netherlands. Event rates are only exactly reported when 10 or more events were included, following regulations of Statistics Netherlands to avoid risk of personal disclosure. In all other cases, the number of events and percentages were reported as '<10' with the corresponding percentage.

Statistical analyses
The baseline characteristics of the datasets were described as mean±standard deviation (SD) or median with interquartile range (IQR) when appropriate. We estimated survival functions using Kaplan-Meier curves. Cox proportional hazards regression analysis was performed to study the predictive value of coronary artery calcification (absolute CACS as calculated by the Agatston score and MESA percentiles) and mortality. For the model based on the MESA percentiles, a binary variable was added to indicate whether CACS was positive (>0) at baseline. The addition of a variable to indicate the presence or absence of CACS is needed to correct for the possible discontinuity in the MESA percentiles between individuals with a CACS of zero or any positive continuous CACS. We first constructed models including CACS or MESA percentiles as continuous variables. Subsequently, we constructed models with the previously described categorised CACS and MESA percentiles. The concordance
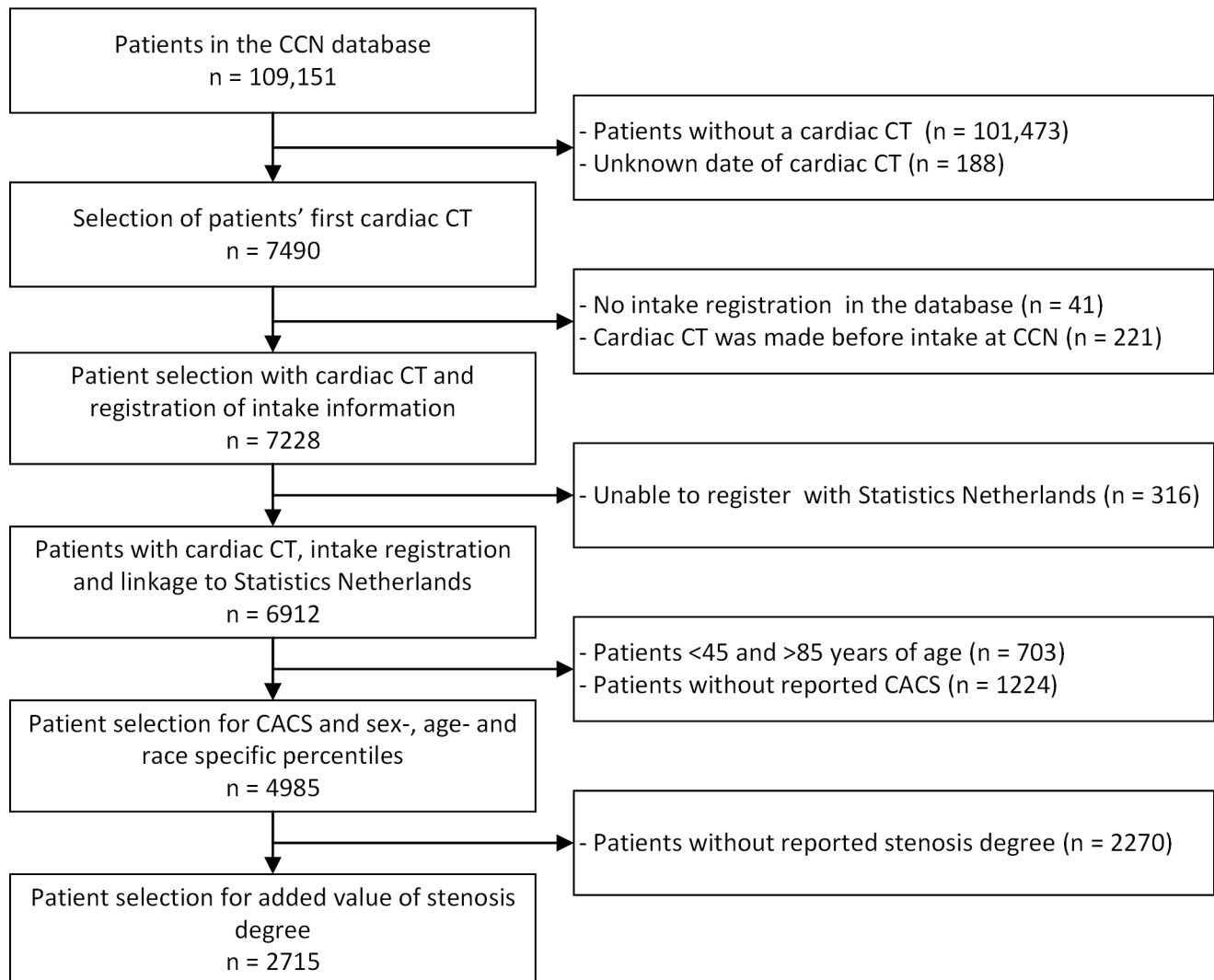
Figure 1 Patient selection for CACS and sex-specific, age-specific and race/ethnicity-specific analysis and for analysis of addition of stenosis degree. CACS, Coronary Artery Calcium Score; CCN, Cardiology Centers of the Netherlands.

statistic (C-statistic) with 95% confidence interval (CI) was used to assess the ability of these models to discriminate patients at risk for mortality. A higher C-statistic indicates a better fit and higher prognostic power. Subsequently, we evaluated whether addition of degree of stenosis on top of absolute CACS improved the prognostic power of the Cox proportional hazards model. All analyses were stratified by sex. Statistical analyses were performed in R (V.4.0.2).

Sensitivity analyses

The race groups within the MESA percentiles as defined by the MESA[19] were not transferable to a patient's country of origin as documented in the population registry of Statistics Netherlands. In our primary analyses, we calculated MESA percentiles based on the Caucasian race. In a sensitivity analysis, we excluded all patients born outside Europe, using this individual's characteristic as a surrogate for a different race.

Patient and public involvement

Patients were not involved in any stage of this research process.

RESULTS

Baseline characteristics

Baseline characteristics of the selected population are displayed in table 1. Of the 4985 patients, 2793 (56%) patients were women. On average, women were 1 year older compared with men (60 vs 59). Other cardiovascular risk factors were similar between women and men. Both sexes primarily presented with chest pain or discomfort. Median CACS in women was 0 (IQR: 0–54), and 42 (IQR: 0–54) in men. CACS categories of 0, 1–100, 100–400 and >400 were, respectively, present in 1387 (50%), 899 (32%), 340 (12%) and 167 (6%) women in this study. In men, this distribution was 569 (26%), 774 (35%), 436 (20%) and 413 (19%), respectively. Higher CACS was seen in individuals with higher age and a higher prevalence of hypertension and dyslipidaemia in both sexes (online supplemental table 1).

Table 1 Baseline characteristics of study population stratified by sex

	Overall	Women	Men
n	4985	2793	2192
Age in years (mean (SD))	59 (8)	60 (8)	59 (8)
Body mass index (mean (SD))	27 (5)	27 (5)	27 (4)
Originated from Europe, n (%)	4309 (86)	2411 (86)	1898 (87)
Complaints, n (%)			
Chest pain or discomfort	2683 (54)	1585 (57)	1098 (50)
Dyspnoea	538 (11)	329 (12)	209 (10)
Fatigue	172 (4)	85 (3)	87 (4)
Palpitations	463 (9)	290 (10)	173 (8)
Collapse	27 (1)	<10	>10
Smoking status, n (%)			
Current	1476 (32)	859 (33)	617 (30)
Former	1650 (36)	875 (34)	775 (38)
Never	1504 (33)	854 (33)	650 (32)
Diabetes mellitus, n (%)	396 (8)	213 (8)	183 (8)
Hypertension, n (%)	1581 (32)	954 (34)	627 (29)
Dyslipidaemia, n (%)	850 (17)	477 (17)	373 (17)
CACS score (median (IQR))	8 (0, 121)	0 (0, 54)	42 (0, 278)
CACS category, n (%)			
0	1956 (39)	1387 (50)	569 (26)
1–100	1673 (34)	899 (32)	774 (35)
101–400	776 (16)	340 (12)	436 (20)
>400	580 (12)	167 (6)	413 (19)
Examinations during follow-up, n (%)			
At least one CAG	812 (16)	309 (11)	503 (23)
At least one PCI or CABG	307 (6)	89 (3)	218 (10)
All-cause mortality	116 (2)	53 (2)	63 (3)
Years of follow-up (median (IQR))	4.5 (3.1, 6.3)	4.5 (3.1, 6.3)	4.5 (3.1, 6.3)

Due to privacy constraints, numbers of individuals fewer than 10 are not allowed to be exported from statistics Netherlands. These numbers are represented as '<10' with the corresponding percentage.

CABG, coronary artery bypass graft; CAC, coronary artery calcium; CACS, coronary artery calcium score CAG, coronary angiography; PCI, percutaneous coronary intervention.

Figure 2 Survival of women and men by absolute CACS. CACS, Coronary Artery Calcium Score.

The predictive value of coronary calcification for all-cause mortality

After a median follow-up of 4 years (IQR: 3–6), 116 (53 women and 63 men) patients died, of which 22 were attributed to cardiovascular mortality. Mortality rate was higher in individuals who had higher CACS (women: 1%, 2%, 4% and <6%, men: <2%, 3%, 3% and 5%, for, respectively CACS categories of 0, 1–100, 100–400 and >400, online supplemental table 1). Figure 2 shows the survival over time per absolute CACS category for women and men. Survival over time for categorised MESA percentiles is shown in figure 3. Overall, women had a better survival. Individuals with higher levels of absolute CACS showed lower survival rates compared with low CACS levels. This
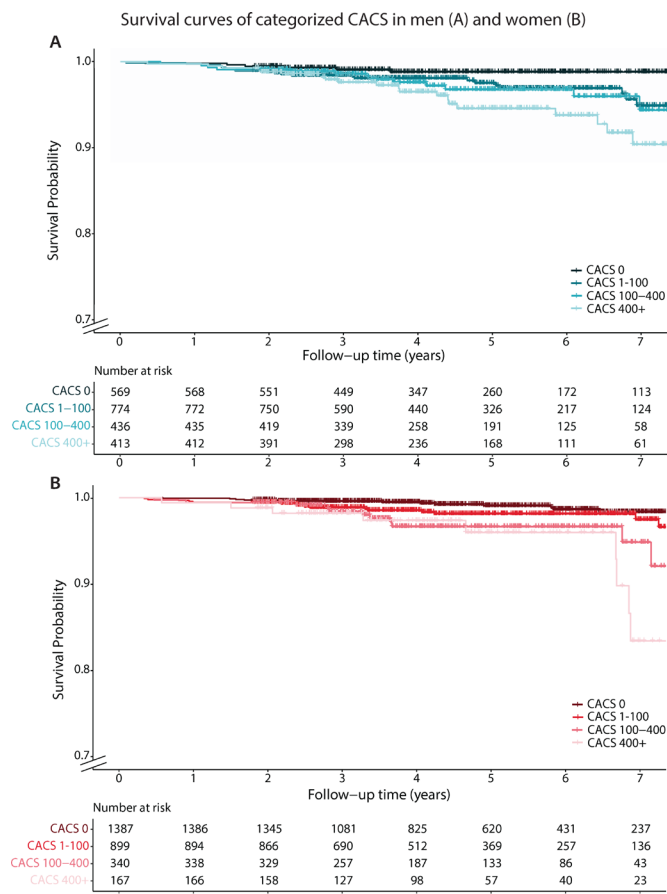
relation was also seen with higher MESA percentiles, although less strong. However, differences were small.

Mortality rates, hazard ratios (HR) and C-statistics are displayed in table 2 for women and men. For continuous calcification measures, the discriminative ability of absolute CACS was moderate in both women and men (C-statistic 0.66, 95% CI 0.58 to 0.74 in women, and 0.62, 95% CI 0.55 to 0.69, in men). The discriminative ability of absolute CACS was similar to models based on MESA percentiles (0.65, 95% CI 0.57 to 0.73 in women, 0.59, 95% CI 0.51 to 0.67 in men). Results were similar for the models that used categorical classifications of CACS and MESA percentiles instead of continuous measures (CACS C-statistic 0.65, 95% CI 0.57 to 0.73 and 0.60, 95% CI 0.53 to 0.67, in women and men, respectively, MESA percentiles C-statistic 0.64, 95% CI 0.57 to 0.73 and 0.61, 95% CI 0.54 to 0.67 in women and men, respectively).

The sensitivity analysis in which we excluded all patients in whom the country of birth was documented to be outside Europe (n=676, 13.5%), as a surrogate for a different race, showed similar results. The European population comprised 2411 women and 1898 men. The C-statistic for absolute CACS was comparable to MESA percentiles (in women, 0.67, 95% CI 0.59 to 0.76, vs 0.66, 95% CI 0.58 to 0.75, and in men 0.64, 95% CI 0.55 to
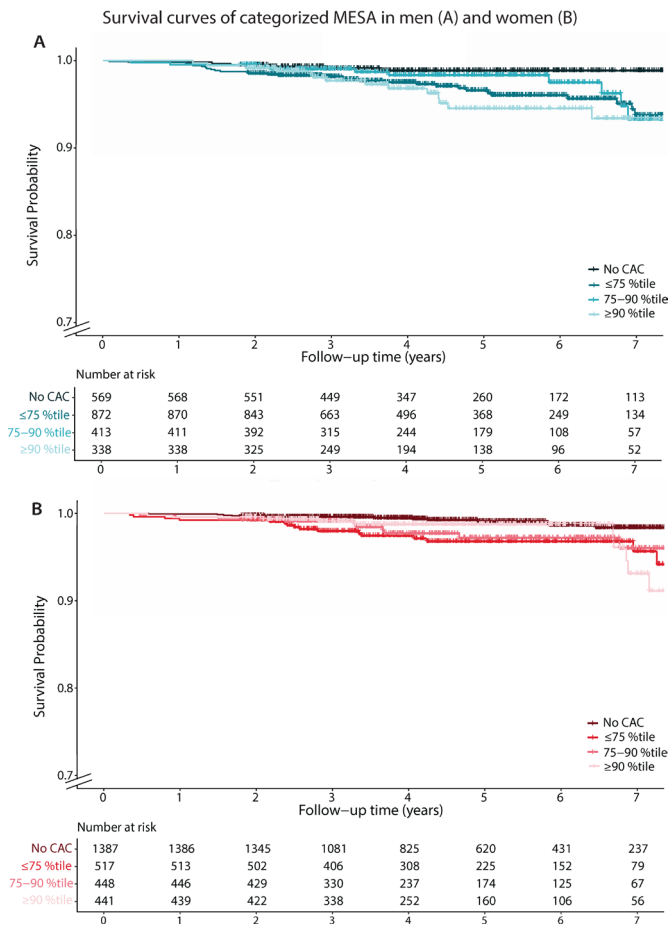
Figure 3 Survival of women and men by age-specific, sex-specific and race/ethnicity-specific percentiles (MESA). CAC, coronary artery calcium; MESA, Multi-Ethnic Study of Atherosclerosis.

0.72, vs 0.59, 95% CI 0.51 to 0.67). Results of the sensitivity analysis are displayed in online supplemental table 2.

Stenosis degree and the relation between coronary calcification and mortality

Stenosis severity by CT angiography was documented for 1330 (60.7%) men and 1385 (49.6%) women. Baseline characteristics of these women and men are depicted in table 3. Online supplemental table 3 shows the baseline characteristics of the CT population in which CACS was reported and the CT population in whom degree of stenosis was additionally documented. During a median follow-up of 5 years (IQR: 3–6 years), 46 (3.5%) men and 22 (1.5%) women died. Compared with the population in which only CACS was available, these women and men did not differ in baseline characteristics (for direct comparison and baseline characteristics per CACS category, see online supplemental tables 3,4, respectively). In the population in whom both CACS and information on stenosis degree was available, the relation between calcification measures and mortality was comparable to the relation found in the total population (table 4). In men, the discriminative power of the model did not improve

when degree of stenosis was added (C-statistic changed from 0.63, 95% CI 0.55 to 0.71 based on CACS to 0.59, 95% CI 0.51 to 0.67 after addition of stenosis to the model). In women, the performance to predict mortality improved slightly (C-statistic 0.68, 95% CI 0.58 to 0.78 and 0.72, 95% CI 0.61 to 0.83, respectively). However, this improvement was not significant, and thus, no hard conclusions can be drawn.

DISCUSSION

Our data showed that absolute CACS and MESA percentiles perform equally well in predicting mortality in symptomatic women and men who visit outpatient cardiology clinics in a real-world setting. Hence, for discrimination of mortality in symptomatic individuals, there is no need for MESA percentiles to quantify coronary artery calcification. Absolute CACS predicts mortality with moderate performance, comparable to performance in asymptomatic inidivuals.[19] Finally, the data hint that in women, the discriminative power of CACS for mortality might be higher when degree of stenosis was included in the model. However, these results should be interpreted with caution, as improvement was not significant. In men, addition of degree of stenosis did not result in better prediction of mortality. This subtle sex-difference might be due to the presence of non-calcified plaques causing symptoms in women.[9] This type of plaques remains (partly) unappreciated when using CACS only for mortality prediction.

When comparing the results of the result of the prognostic value of CACS to other publications, a similar result was presented by Engbers et al[14] in which they sought to evaluate gender-specific (n=3705, 61% women) prognostic value of CACS on top of SPECT myocardial perfusion imaging. No gender-specific differences were found and the HRs described in this study are similar to the HRs for the CACS categories in both sexes in our study. Another study that focused on symptomatic individuals (n=3840, 51% women) suspected of CAD showed that a high prognostic value of CACS, which further increased after addition of stenosis degree.[3] More variables, that is, degree of stenosis, specific (high risk) plaque characteristics, were incorporated in prognostic models. However, their analysis was not stratified by sex, hampering any comparison to our data and impeding analysis of sex differences. They also showed that the recently developed CAD Reporting and Data System[24] classification provides the highest prognostic value for cardiovascular events.[3]

Our results in symptomatic women and men are in line with results of the MESA, which was conducted in nonsymptomatic individuals from the general population. The MESA demonstrated that absolute CACS outperforms MESA percentiles for event prediction.[19] We also found that the discriminative capacity remains intact when categorising CACS. This finding is valuable for clinical use, as HRs derived from categories are easier to interpret than continuous values. Furthermore, studies in asymptomatic individuals concluded that CACS predicted mortality

Table 2 Mortality prediction as a function of absolute and age-specific, sex-specific and race/ethnicity-specific percentiles of CACS in women (above) and men (below)

	Model	n	Events	HR (95% CI)	C-statistic (95% CI)
Women	Absolute CACS				
	Continuous	2793	53	1.0 (1.0 to 1.0)	0.66 (0.58 to 0.74)
	Categorised				
	CACS 0	1387	14	Reference	0.65 (0.57 to 0.73)
	CACS 1–100	899	18	2.1 (1.0 to 2.1)	
	CACS 101–400	340	12	4.0 (1.8 to 8.6)	
	CACS >400	167	<10	5.7 (2.5 to 13.2)	
	MESA percentiles				
	Continuous, adjusted for any calcification				
	MESA percentile	2793	53	0.4 (0.1 to 1.5)	0.65 (0.57 to 0.73)
	Any calcification			6.1 (1.9 to 19.1)	
	Categorised				
	No calcification	1387	14	Reference	0.64 (0.57 to 0.72)
	<75th percentile	517	18	3.5 (1.8 to 7.1)	
	75th–90th percentile	448	11	2.7 (1.2 to 5.9)	
	>90th percentile	441	10	2.5 (1.1 to 5.6)	
Men	Absolute CACS				
	Continuous	2192	63	1.0 (1.0 to 1.0)	0.62 (0.55 to 0.69)
	Categorised				
	CACS 0	569	<10	Reference	0.60 (0.53 to 0.67)
	CACS 1–100	774	23	3.0 (1.2 to 7.5)	
	CACS 101–400	436	14	3.3 (1.3 to 8.7)	
	CACS >400	413	20	5.1 (2.0 to 12.7)	
	MESA percentiles				
	Continuous, adjusted for any calcification				
	MESA percentile	2192	63	0.5 (0.2 to 1.5)	0.59 (0.51 to 0.67)
	Any calcification			5.7 (1.9 to 16.8)	
	Categorised				
	No calcification	569	<10	Reference	0.61 (0.54 to 0.67)
	<75th percentile	872	33	3.9 (1.6 to 9.3)	
	75th–90th percentile	413	10	2.5 (0.9 to 7.0)	
	>90th percentile	338	14	4.3 (1.6 to 11.1)	

CACS, Coronary Artery Calcium Score; MESA, Multi-Ethnic Study of Atherosclerosis.

risk equally well for both sexes,[1 12] despite the findings that women had lower CACS compared with men[1] and that significant sex differences were present in cumulative mortality.[12] Most studies reported that CACS may be a better predictor for mortality in women compared with men.[12 21 22] This suggestion is in line with the slightly higher C-statistic for the CACS-model we described in women. In addition, sex-specific CACS percentiles tend to better stratify risk in women than men as opposed to absolute scores.[21] The reason for discrepancy between results might be the inclusion of an asymptomatic older population in the study by Wang *et al*.[21]

Strengths and limitations

A strength of the presented study is the use of a real-world population in whom cardiac CT is often used as a primary diagnostic, yet its power is not often studied. This population is best described as a symptomatic population, referred to a specialised cardiac screening centre, which is positioned between general practitioners and hospital care. Furthermore, linkage to the database of Statistics Netherlands provided long-term follow-up data on mortality and information on country of birth.

Table 3 Baseline characteristics of women and men that underwent cardiac CT angiography

	Overall	Women	Men
n	2715	1385	1330
Age in years (mean (SD))	60 (8)	60 (8)	59 (8)
Body mass index (mean (SD))	27 (4)	27 (5)	27 (4)
Complaints, n (%)			
Chest pain or discomfort	1499 (55)	801 (58)	698 (53)
Dyspnoea	295 (11)	167 (12)	128 (10)
Fatigue	93 (3)	47 (3)	46 (4)
Palpitations	272 (10)	163 (12)	109 (8)
Collapse	18 (1)	<10	>10
Smoking status, n (%)			
Current	809 (32)	428 (34)	381 (31)
Former	936 (37)	461 (36)	475 (38)
Never	765 (31)	380 (30)	385 (31)
Diabetes mellitus, n (%)	211 (8)	97 (7)	114 (9)
Hypertension, n (%)	885 (33)	518 (38)	367 (28)
Dyslipidaemia, n (%)	497 (18)	263 (19)	234 (18)
CACS score (median (IQR))	34 (0–162)	14 (0–92)	67 (6–267)
CACS category, n (%)			
0	682 (25)	472 (34)	210 (16)
1–100	1150 (42)	585 (42)	565 (43)
101–400	598 (22)	251 (18)	347 (26)
>400	285 (11)	77 (6)	208 (16)
Degree of stenosis, n (%)			
0 %	792 (29)	527 (38)	265 (20)
1%–49%	1114 (41)	563 (41)	551 (41)
50%–70%	431 (16)	168 (12)	263 (20)
>70%	378 (14)	127 (9)	251 (19)
Examinations during follow-up, n (%)			
At least one CAG	553 (20)	205 (15)	348 (26)
At least one PCI or CABG	234 (9)	66 (5)	168 (13)
All-cause mortality	68 (3)	22 (2)	46 (4)
Cardiovascular mortality	10 (0.4)	<10	<10
Years of follow-up (median (IQR))	4.6 (3.2–6.3)	4.6 (3.2–6.3)	4.7 (3.2–6.4)

Due to privacy constraints, numbers of individuals fewer than 10 are not allowed to be exported from statistics Netherlands. These numbers are represented as '<10' with the corresponding percentage.
CABG, coronary artery bypass graft; CAC, coronary artery calcium; CACS, Coronary Artery Calcium Score; CAG, coronary angiography; PCI, percutaneous coronary intervention.

Use of EHR data also has inherent limitations. First, data were not primarily collected for study purposes. Therefore, part of the population that underwent cardiac CT could not be included, due to insufficient documentation of CT results. Second, as CT angiography was only performed based on referral by the cardiologist and/or local scan protocol, not all patients underwent CT angiography. Thus, the subanalysis focusing on degree of stenosis, based on CT angiography results, was only performed in a subset of patients. This significantly reduced the power of our statistical analysis and might have led to selection bias. To evaluate this bias, we compared the overall and subpopulation and repeated the analyses in the subpopulation. The populations were comparable on known baseline characteristics. Moreover, the results of the use of CACS and MESA percentiles for risk stratification did not significantly differ. This suggests that increased discriminative power of CACS when degree of stenosis was added to the model is generalisable. Third, as stenosis severity was retrieved from text reports in which the degree of stenosis was not always quantified, the interpretation of the grade of stenosis could lead to uncertainty in our data. Fourth, we did not take treatment differences into account between different groups. These differences may explain the decreasing HR with an increasing degree of coronary stenosis, although this decrease was not significant. Finally, as we have used country of origin as a surrogate for race/ethnicity, the categories used in the original MESA calculations and our study population were not identical. To assess whether this has influenced our results, we performed a sensitivity analysis in which we included women and men who originated from Europe, assuming they all have the Caucasian race. These results were not significantly different from the main analyses. Moreover, as our population was primarily coming from Europe, our results might not be applicable to individuals of other ethnic populations.

We found that adding degree of stenosis to the survival model slightly improved the discriminative power in women, but not in men. However, this improvement in women was not statistically significant and confidence intervals largely overlapped. Even though we showed a moderate prognostic value of CACS in both symptomatic women and men, our results warrant evaluation beyond CACS alone for optimal risk prediction as C-statistics were below 0.70. This might be especially relevant in women, in whom information on the degree of stenosis potentially has added value due to presence of non-calcified plaques. We were unable to assess the added value of degree of stenosis properly due to incomplete data. Nevertheless, the difference between women and men we found after degree of stenosis was added to the model stresses the importance of a sex-specific view on CAD. Replication of this study in larger trials or populations is going to contribute to confirm these hypotheses, regarding the importance of non-calcified plaques in women for mortality risk.

CONCLUSION

In symptomatic individuals, absolute CACS predicts mortality with a moderately good performance. MESA percentiles did not perform better compared with

Table 4 Mortality prediction as a function of absolute CACS and degree of stenosis in women (above) and men (below)

	Model	n	Events	HR (95% CI)	C-statistic (95% CI)
Women	Absolute CACS				
	Continuous	1385	22	1.0 (1.0 to 1.0)	0.68 (0.58 to 0.78)
	+ Degree of stenosis				0.72 (0.61 to 0.83)
	0%	527	<10	Reference	
	1%–49%	563	14	6.9 (1.6 to 30.6)	
	50%–70%	168	<10	4.9 (0.9 to 28.6)	
	>70%	127	<10	2.8 (0.3 to 22.4)	
Men	Absolute CACS				
	Continuous	1330	46	1.0 (1.0 to 1.0)	0.63 (0.55 to 0.71)
	+ Degree of stenosis				0.59 (0.51 to 0.67)
	0%	265	<10	Reference	
	1%–49%	551	22	4.5 (1.3 to 15.3)	
	50%–70%	263	10	3.9 (1.1 to 14.7)	
	>70%	251	11	4.2 (1.1 to 16.3)	

CACS, Coronary Artery Calcium Score.

absolute CACS, thus, there is no need to use them. Including degree of stenosis in the model might slightly improve mortality risk prediction in women, but not in men.

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