Title

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Prognostic value of coronary artery calcium score, area, and density among individuals on statin therapy *vs*. non-users: The Coronary Artery Calcium Consortium

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Abstract

Background and aims—Statins do not decrease coronary artery calcium (CAC) and may increase existing calcification or its density. Therefore, we examined the prognostic significance of CAC among statin users at the time of CAC scanning.

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AUTHOR CONTRIBUTIONS

Michael Blaha, Mohammadhassan Mirbolouk, Albert Osei, Daniel Berman, Alan Rozanki, Michael Miedema, Matthew Budoff, John Rumberger participated in the conception and design of the study.

Zeina Dardari, Michael Blaha, Mohammadhassan Mirbolouk, Albert Osei conducted the statistical analyses, and prepared the tables and figures.

Mohammadhassan Mirbolouk, Leslee Shaw, John Rumberger, Daniel Berman, Alan Rozanki, Michael Miedema, Matthew Budoff, Khurram Nasir participated in the interpretation of the data, drafting of the manuscript and revised subsequent drafts critically for important intellectual content together with Michael Blaha, Garth Graham, Maciej Banach, Roger S. Blumenthal, Albert Osei, Omar Dzaye and Mahmoud Al Rifai.

Michael Blaha provided mentorship and supervision of the study.

All authors approved the final version.

Conflict of Interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Declaration of interests

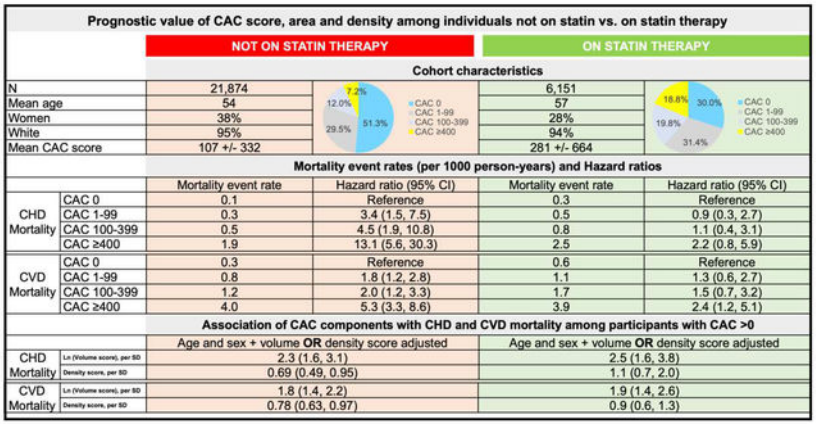
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Methods—We included 28,025 patients (6151 statin-users) aged 40–75 years from the CAC Consortium. Cox regression models were used to assess the association of CAC with coronary heart disease (CHD) and cardiovascular disease (CVD) mortality. Models were adjusted for traditional CVD risk factors. Additionally, we examined the predictive performance of CAC components including CAC area, volume, and density using an age- and sex-adjusted Cox regression model.

Results—Participants (mean age 53.9±10.3 years, 65.0% male) were followed for median 11.2 years. There were 395 CVD and 182 CHD deaths. One unit increase in log CAC score was associated with increased risk of CVD mortality (hazard ratio (HR), 1.2; 95% CI = 1.1–1.3) and CHD mortality (HR, 1.2; 95% CI = 1.1–1.4)) among statin users. There was a small but significant negative interaction between CAC score and statin use for the prediction of CHD (p-value = 0.036) CVD mortality and p-value =0.025). The volume score and CAC area were similarly associated with outcomes in statin users and non-users. Density was associated with CVD and CHD mortality in statin naïve patients, but with neither in statin users.

Conclusion—CAC scoring retains robust risk prediction in statin users, and the changing relationship of CAC density with outcomes may explain the slightly weaker relationship of CAC with outcomes in statin users.

Graphical Abstract



Prognostic value of CAC score, area and density among individuals not on statin vs. on statin therapy

		NOT ON STATIN THERAPY		ON STATIN THERAPY	
Cohort characteristics					
N		21,874		6,151	
Mean age		54		57	
Women		38%		28%	
White		95%		94%	
Mean CAC score		107 +/- 332		281 +/- 664	
Mortality event rates (per 1000 person-years) and Hazard ratios					
		Mortality event rate	Hazard ratio (95% CI)	Mortality event rate	Hazard ratio (95% CI)
CHD Mortality	CAC 0	0.1	Reference	0.3	Reference
	CAC 1-99	0.3	3.4 (1.5, 7.5)	0.5	0.9 (0.3, 2.7)
	CAC 100-399	0.5	4.5 (1.9, 10.8)	0.8	1.1 (0.4, 3.1)
	CAC ≥400	1.9	13.1 (5.6, 30.3)	2.5	2.2 (0.8, 5.9)
CVD Mortality	CAC 0	0.3	Reference	0.6	Reference
	CAC 1-99	0.8	1.8 (1.2, 2.8)	1.1	1.3 (0.6, 2.7)
	CAC 100-399	1.2	2.0 (1.2, 3.3)	1.7	1.5 (0.7, 3.2)
	CAC ≥400	4.0	5.3 (3.3, 8.6)	3.9	2.4 (1.2, 5.1)
Association of CAC components with CHD and CVD mortality among participants with CAC >0					
		Age and sex + volume **OR** density score adjusted		Age and sex + volume **OR** density score adjusted	
CHD Mortality	Ln (Volume score), per SD	2.3 (1.6, 3.1)		2.5 (1.6, 3.8)	
	Density score, per SD	0.69 (0.49, 0.95)		1.1 (0.7, 2.0)	
CVD Mortality	Ln (Volume score), per SD	1.8 (1.4, 2.2)		1.9 (1.4, 2.6)	
	Density score, per SD	0.78 (0.63, 0.97)		0.9 (0.6, 1.3)	

Keywords

Coronary artery calcium; Statins; CAC area; CAC volume; CAC density

Introduction

The 2018 American Heart Association/American College of Cardiology (AHA/ACC) Cholesterol Management Guidelines recommend selective use of coronary artery calcium (CAC) scoring in guiding the decision to initiate statins in intermediate risk individuals.[1] The guidelines also mention that there is no clinical utility for CAC scoring in statin users, citing a study by Lee et al.[2] This study showed that while the percent atheroma volume progressed slower in statin users, the progression of calcified percent atheroma volume

increased more rapidly,[2] reinforcing prior data that statins may increase the rate of CAC progression.[3,4]

While statins may increase calcification in mechanistic and imaging studies, their impact on CAC predictive value remains unclear. Additionally, there are no studies to compare the risk prediction of different CAC scoring components—area, volume, and density—which may be differentially impacted by statins. We examined the prognostic performance of CAC score and its components for coronary heart disease (CHD) and cardiovascular disease (CVD) mortality in statin users *vs.* non-users at the time of their CAC examination.

Materials and methods

Study population

We utilized data from the CAC Consortium, a multicenter cohort of 66,636 participants aged 18 years or older without baseline CVD referred for CAC scoring for clinical risk stratification.[5] The CAC Consortium consists of four institutions from three states in the US (California, Minnesota, and Ohio). Written informed consent was obtained from all participants at all study sites and institutional review board approval for coordinating center activities was obtained from Johns Hopkins University School of Medicine. Data on risk factors and laboratory test results were collated from semi-structured in-person interviews or during routine clinical visit for CAC testing.[5] Smoking was based on self-report and categorized as current, never or former smoking. Diabetes was defined as prior diagnosis of diabetes or treatment with insulin or oral hypoglycemic agent. Hypertension was defined by a prior clinical diagnosis or treatment with antihypertensive therapy. Family history of CHD was determined by the presence of a first-degree relative with a history of CHD at any age. Dyslipidemia was defined as prior diagnosis of primary hyperlipidemia, prior diagnosis of dyslipidemia (elevated triglycerides and/or low HDL-C), or treatment with any lipid-lowering drug. In participants with concomitant laboratory data, dyslipidemia was additionally considered present if LDL-C > 160 mg/dL, HDL-C < 40 mg/dL in men and <50 mg/dL in women, or fasting triglycerides >150 mg/dL. Primary outcomes were CVD and CHD mortality.[5] CVD death was defined as death from cardiovascular causes including CHD, stroke, heart failure and other circulatory diseases. Mortality data in the CAC Consortium was ascertained through linkage of patient records with the United States Social Security Administration Death Master File using a previously validated algorithm. Coded death certificates obtained from the National Death Index Cause of death were used to ascertain the cause of death. The cause of death and supporting causes of death were reported as ICD-9 and ICD-10 codes.[5]

Statistical analysis

We included 28,025 participants (6,151 statin users) with available baseline data on statin use. CAC measurements were performed at each study site using a shared standardized protocol. In addition to the Agatston score, a volume score was also measured. To calculate the derivative CAC components, we used methods described by Criqui et al. (area score = volume score/appropriate slice thickness; density score = Agatston score/area score).[6]

CAC was treated both as a categorical and natural-log-transformed continuous variables. Categorical CAC groups were defined as CAC=0 (reference group), CAC=1–99, CAC=100–399, and CAC≥400. Using Cox regression models, we examined the association between CAC scoring and outcomes. We calculated interaction terms on the multiplicative scale to examine the differential impact of baseline statin use status on prognostic implication of CAC. Models were adjusted for age, sex, family history of CHD, smoking status, hypertension, and diabetes.

We examined CAC scoring components (volume, area, and density) by testing each individual component using Cox regression models first adjusted for age and sex, and then adjusted for the other CAC score components. These analyses were restricted to 14,954 participants (4,303 statin users) with a CAC >0 at baseline. The incremental value of CAC components for prediction of CHD and CVD mortality was evaluated by the increase in the area under the receiver operating characteristic curve (AUC).

Results

The mean (SD) age of statin users was higher than non-users: 56.7 (8.3) *vs.* 53.8 (8.1) years (Table-1). Statin users were more likely to be men, have hypertension, diabetes, and a family history of CHD. Among participants with CAC >0, statin users had slightly higher CAC density (3.1±0.5 *vs.* 3.0±0.5) and higher CAC area (128±240.1 *vs.* 70.7±142.1) compared to non-users (Table-2). Median total CAC score was higher in statin users [128.5 (31,435.3) *vs.* 58.3 (14,211.4)] compared to non-users. Mean total CAC score was 402.2±762.5 in statin users compared to 220.6 ± 448.7 in statin non-users.

There were 141 CVD and 128 CHD deaths over a median follow-up of 10.9 years among statin users.

In both statin-users and non-users, one SD increase in lnCAC was associated with a significantly higher risk of CVD and CHD mortality. However, hazard ratios (HR) were slightly higher in statin non-users compared to statin users (Table-3). There was a small but significant negative interaction between CAC score and statin use for CHD (p-value = 0.036) and CVD mortality (p-value =0.025).

Volume score and total CAC area exhibited similar associations that were stronger for CHD than for CVD across groups. CAC density was not associated with CHD/CVD mortality in either group in models not adjusting for other CAC components. (Table-4, upper-half)

The volume score was predictive of outcomes in statin users and non-users. Adjusted for density, the volume score remained associated with increased risk of CVD and CHD mortality. However, when adjusted for volume score, CAC density was inversely associated with CVD and CHD risk only among statin non-users. (Table-4, lower-half)

Among statin users, CAC volume score increased the AUC for CHD mortality from 0.74 to 0.77 (p = 0.03), with minimal added predictive value when additionally considering CAC density. Results were similar for CVD mortality. (Table-5)

Discussion

In this study, CAC remained a powerful predictor of cardiovascular risk among statin users. There was a negative interaction between statin use and CAC, indicating slightly weaker prognostic significance of CAC in statin users. CAC volume and area showed similar predictive implications across baseline statin use status, although peak density displayed an inverse association with outcomes only in statin non-users.

Prior studies with coronary computed tomography angiography have suggested that statins might promote coronary calcification while at the same time slowing the progression of non-calcified coronary plaque, perhaps contributing to plaque stabilization.[2] Data from the intravascular ultrasound literature also supports this potential effect of statins.[7] Thus the 2018 AHA/ACC Cholesterol Management Guidelines stated that there is no clinical utility for CAC scoring among statin users.[1] However, our findings suggest that higher CAC among statin users remains highly predictive of CVD and CHD mortality as compared to statin users with lower CAC scores.

A study by Miname et al. similarly concluded that CAC is associated with ASCVD events independent of cardiovascular risk factors in patients with familial hypercholesterolemia on established background statin therapy.[8] The authors highlighted the importance of this CAC-mediated higher risk of CVD and CHD in guiding clinicians to select the intensity of preventive efforts among statin users.

Similarly, using data from the Multi-Ethnic Study of Atherosclerosis, Al Rifai et al. also showed in multivariable analyses that CAC >0 was associated with significantly higher risk of ASCVD events, irrespective of baseline or incident statin use or after accounting for time-varying statin use. The authors concluded that the prognostic utility of CAC is not weakened by current statin use.[9]

Importantly, our finding of the negative interaction between statin use, CAC score, and CVD/CHD mortality suggests that prognostic significance of CAC is slightly less in statin users, and is possibly mediated by a shift toward more densely calcified plaque.[2] This raises important questions about the impact of statins on different components of the Agatston CAC score.

Similar to our overall results, Criqui et al. demonstrated that for a given CAC volume, CAC density is inversely associated with incident CHD and CVD,[6] suggesting that upweighting density in the Agatston method might decrease the relationship between CAC and outcome.[6] Furthermore, in our study, the prognostic significance of CAC density was not observed among statin users compared to statin non-users, while the volume score remained similarly predictive across statin use status. Why the inverse relationship between CAC density and outcome was not seen in the patients taking statins is unclear, although consideration of the direct biological effects of statins on plaque *vs.* the “natural history” of plaque evolution is a potential explanation worthy of further investigation in mechanistic studies and longitudinal studies with serial plaque imaging. Taken together, it appears that the increase in CAC among those on statin therapy may be protective against CVD events via shifting associations of CAC density and area/volume, warranting further research.[10,11]

Importantly, these findings are critical for opening the door to future detailed and specific studies on application of CAC scoring among statin users, particularly in how it can be used to guide the intensity of preventive therapies. There is an emerging literature suggesting that CAC can be used to guide intensity of LDL lowering therapies, including the potential addition of non-statin therapies.[12] In addition, recent data supports the use of CAC to select those most likely to receive net benefit from the use of low dose aspirin for primary prevention of CVD.[13] Finally, given the inclusion of risk prediction in the algorithm for treatment of stage 1 hypertension in the 2017 AHA/ACC/Multisociety blood pressure guidelines,[14] there may be a potential role for CAC driving decisions about anti-hypertensive pharmacotherapy[15] and blood pressure goals in statin treated patients.[16] The 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Guidelines for the management of dyslipidemias: lipid modification to reduce cardiovascular risk highlight the role of non-invasive cardiovascular imaging in CVD risk assessment, recommending the use of CAC scoring in low to moderate risk individuals (Class IIa) in whom LDL-C goal is not achieved with lifestyle therapy alone.[17] The guideline further acknowledges that CAC score is increased in statin users. However, it does not counsel against testing, but acknowledges that CAC scores of statin-treated patients should be interpreted with caution.[17] CAC data may provide critical information that may be useful in decision making about statin treatment intensity and, potentially, the addition of non-statins.

Our study had limitations. There was no information on intensity, duration, or the reason for statin initiation. Only baseline CAC was known; therefore, we were unable to evaluate the influence of statins on progression of the various components of calcified plaque. Additionally, we had no data to evaluate the influence of length of statin therapy on CHD and CVD mortality by categories of CAC scores. In addition, the limited race/ethnicity diversity is a limitation, as there are known to be small differences in plaque type between Whites and Blacks for example. Also, residual confounding could exist as statin users could differ from non-users in other ways not measured in our study. Despite these limitations, our analysis incorporates data from the largest sample to date, with long-term follow-up. Our data from a large clinical cohort complements prior data from prospective cohort studies of healthy volunteers,[9] providing both real-world and investigational support for the role of CAC in risk stratifying patients taking statins.

Conclusion

CAC scoring retains utility for risk prediction in statin users, and the changing relationship of CAC density with outcomes may explain the slightly weaker relationship of CAC with outcomes in statin users. There appears to be a role for CAC to guide the intensity of LDL lowering or other preventive therapies in statin users.

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Highlights

- While statins may increase calcification in mechanistic and imaging studies, their impact on CAC predictive value is unclear.
- CAC scoring retains utility for risk prediction in statin users.
- The changing relationship of CAC density with outcomes may explain the slightly weaker relationship of CAC with outcomes in statin users.

Table 1:

Baseline characteristics of participants with information on statin use

	Not on statin therapy (N=21874)	On statin therapy (N=6151)
Age	53.8 ± 8.1	56.7 ± 8.3
Sex		
Women	8247, 37.7%	1716, 27.9%
Men	13627, 62.3%	4435, 72.1%
Race		
White	18803, 94.6%	5160, 94.1%
Asian	314, 1.6%	89, 1.6%
Black	309, 1.6%	79, 1.4%
Hispanic	204, 1.0%	88, 1.6%
Other	238, 1.2%	67, 1.2%
Hypertension	5564, 25.4%	2762, 44.9%
Hyperlipidemia	9838, 45.0%	6151, 100.0%
Family history of CHD	9621, 44.0%	3102, 50.4%
Diabetes	983, 4.5%	662, 10.8%
Smokers	2172, 9.9%	607, 9.9%
Total CAC score		
Mean	107.4 ± 332.0	281.3 ± 663.8
Median	0 (0, 54.7)	39.3 (0, 257)
CAC group		
CAC 0	11223, 51.3%	1848, 30.0%
CAC 1–99	6460, 29.5%	1929, 31.4%
CAC 100–399	2612, 12.0%	1218, 19.8%
CAC ≥400	1579, 7.2%	1156, 18.8%
Mean total volume score	86.0 ± 263.1	223.8 ± 523.1

Table 2:

Baseline characteristics of participants with CAC > 0 for examination of components of CAC

CAC>0	All (N=14954)	Not on statin therapy(N=10651)	On statin therapy (N=4303)	*p*-value
Age	57.0 +/− 8.1	56.5 +/− 8.1	58.3 +/− 8.1	<0.001
Sex				<0.001
Women	3655, 24.4%	2706, 25.4%	949, 22.1%	
Men	11299, 75.6%	7945, 74.6%	3354, 78.0%	
Race				<0.001
White	12826, 94.9%	9241, 95.2%	3585, 94.0%	
Asian	183, 1.4%	117, 1.2%	66, 1.7%	
Black	179, 1.3%	127, 1.3%	52, 1.4%	
Hispanic	151, 1.1%	89, 0.9%	62, 1.6%	
Other	177, 1.3%	129, 1.3%	48, 1.3%	
Hypertension	5400, 36.1%	3297, 31.0%	2103, 48.9%	<0.001
Hyperlipidemia	9478, 63.4%	5175, 48.6%	4303, 100.0%	<0.001
Family history of CHD	6984, 46.7%	4762, 44.7%	2222, 51.6%	<0.001
Diabetes	1202, 8.0%	665, 6.2%	537, 12.5%	<0.001
Smokers	1627, 10.9%	1183, 11.1%	444, 10.3%	0.16
Total CAC score				
Mean	272.8± 563.4	220.6 ±448.7	402.2 ± 762.5	<0.001
Median	73 (17.7, 268.3)	58.3 (14, 211.4)	128.5 (31, 435.3)	
CAC Group				<0.001
CAC 1–99	8389, 56.1%	6460, 60.7%	1929, 44.8%	
CAC 100–399	3830, 25.6%	2612, 24.5%	1218, 28.3%	
CAC ≥400	2735, 18.3%	1579, 14.8%	1156, 26.9%	
Mean total volume score	217.9 ± 444.7	176.7 ± 355.2	319.9 ± 600.3	<0.001
Total area score	87.2 ± 177.9	70.7 ±142.1	128 ±240.1	<0.001
Peak density score	3.0 ±0.53	3.0 ±0.5	3.1 ± 0.5	<0.001
Volume/Agatston ratio	0.86 ± 0.23	0.87 ± 0.23	0.85 ± 0.20	<0.001

Table 3:

Hazard ratios and event rates (per 1000 person-year) for CAC score groups among participants on and not on statin therapy at baseline, CAC Consortium

		Not on statin therapy			On statin therapy	
		N = 21,874			N = 6,151	
		Hazard ratio (95% CI)	Mortality event rates		Hazard ratio (95% CI)	Mortality event rates
CHD mortality[a]	CAC 0	Ref	0.1 (0.0, 0.2)		Ref	0.3 (0.2, 0.7)
	CAC 1–99	3.4 (1.5, 7.5)	0.3 (0.2, 0.5)		0.9 (0.3, 2.7)	0.5 (0.3, 0.9)
	CAC 100399	4.5 (1.9, 10.8)	0.5 (0.3, 0.9)		1.1 (0.4, 3.1)	0.8 (0.4, 1.5)
	CAC 400+	13.1 (5.6, 30.3)	1.9 (1.3, 2.7)		2.2 (0.8, 5.9)	2.5 (1.7, 3.7)
	Ln(CAC+1)	1.4 (1.3, 1.6)	-		1.2 (1.1, 1.4)	-
CVD mortality[a]	CAC 0	Ref	0.3 (0.2, 0.4)		Ref	0.6 (0.3, 1.1)
	CAC 1–99	1.8 (1.2, 2.8)	0.8 (0.6, 1.0)		1.3 (0.6, 2.7)	1.1 (0.7, 1.7)
	CAC 100399	2.0 (1.2, 3.3)	1.2 (0.8, 1.6)		1.5 (0.7, 3.2)	1.7 (1.1, 2.6)
	CAC 400+	5.3 (3.3, 8.6)	4.0 (3.1, 5.0)		2.4 (1.2, 5.1)	3.9 (2.9, 5.3)
	Ln(CAC+1)	1.2 (1.2, 1.3)	-		1.2 (1.1, 1.3)	-

Interaction term Total Score X Statin Therapy p= 0.036 for CHD mortality, and 0.025 for CVD mortality

[a]Models are adjusted for age, sex, hypertension, hyperlipidemia, diabetes, and smoking status. Note: all those on statin therapy have hyperlipidemia; therefore, hyperlipidemia is not adjusted for in the statin users.

Table 4:

Association of different scores of CAC with cardiovascular and coronary heart disease mortality among those with CAC >0

		CHD death		CVD death	
		Not on statin therapy	**On statin therapy**	**Not on statin therapy**	**On statin therapy**
Age and sex adjusted[a]	Ln (Agatston score), per SD	2.0 (1.5, 2.6)	2.5 (1.6, 3.9)	1.6 (1.3, 2.0)	1.9 (1.4, 2.5)
	Ln (volume score), per SD	2.0 (1.5, 2.7)	2.5 (1.6, 3.8)	1.7 (1.4, 2.0)	1.9 (1.4, 2.5)
	Ln (area score), per SD	2.0 (1.5, 2.7)	2.5 (1.6, 3.8)	1.7 (1.4, 2.0)	1.9 (1.4, 2.5)
	Density score, per SD	0.9 (0.7, 1.2)	1.3 (0.9, 1.9)	0.9 (0.8, 1.1)	1.1 (0.8, 1.4)
Density, volume score, age and sex in same model[b]	Ln (volume score), per SD	2.3 (1.6, 3.1)	2.5 (1.6, 3.8)	1.8 (1.4, 2.2)	1.9 (1.4, 2.6)
	Density score, per SD	0.69 (0.49, 0.95)	1.1 (0.7, 2.0)	0.78 (0.63, 0.97)	0.9 (0.6, 1.3)

[a]Estimates in the upper half of the table represent risk estimates of the association of individual CAC score components with CHD and CVD mortality adjusted for age and sex stratified by baseline statin-use status.

[b]Estimates in the lower half of the table, represent results of models extended to include volume score **OR** density score in order to model respective independent effects of density and volume scores.

Table 5:

Area under the ROC curve for the base model and various CAC measures

CVD mortality	**Not on statin therapy**			**On statin therapy**		
	Risk factors	Risk factors + volume score	*p*-value	Risk factors	Risk factors + volume score	*p*-value
	0.72	0.74	0.007	0.72	0.75	0.01
	Risk factors	Risk factors + density score	*p*-value	Risk factors	Risk factors + density score	*p*-value
	0.72	0.72	0.79	0.72	0.72	0.81
	Risk factors	Risk factors + volume score + density score	*p*-value	Risk factors	Risk factors + volume score + density score	*p*-value
	0.72	0.74	0.008	0.72	0.75	0.01
CHD mortality	Risk factors	Risk factors + volume score	*p*-value	Risk factors	Risk factors + volume score	*p*-value
	0.67	0.71	0.003	0.74	0.77	0.03
	Risk factors	Risk factors + density score	*p*-value	Risk factors	Risk factors + density score	*p*-value
	0.67	0.67	0.89	0.74	0.75	0.29
	Risk factors	Risk factors + volume score + density score	*p*-value	Risk factors	Risk factors + volume score + density score	*p*-value
	0.67	0.71	0.008	0.74	0.78	0.02