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Comparison of coronary artery calcification, carotid intima-media thickness and ankle-brachial index for predicting 10-year incident cardiovascular events in the general population

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Aims To compare the predictive value of coronary artery calcification (CAC), carotid intima-media thickness (CIMT) and ankle-brachial index (ABI) in a primary prevention cohort depending on risk factor profile to determine which of the three markers improves cardiovascular (CV) risk discrimination best in which risk group.

Methods and results We quantified CAC, CIMT, and ABI in 3108 subjects (mean age 59.2 ± 7.7, 47.1% male) without prevalent CV diseases from the population-based Heinz Nixdorf Recall study. Associations with incident major CV events (coronary event, stroke, CV death; $n = 223$) were assessed during a follow-up period of 10.3 ± 2.8 years with Cox proportional regressions in the total cohort and stratified by Framingham risk score (FRS) groups. Discrimination ability was evaluated with Harrell's C. All three markers were associated with CV events (hazard ratio [95% confidence interval (CI)]: CAC: 1.31 (1.23–1.39) per 1-unit increase in log(CAC + 1) vs. CIMT: 1.27 (1.13–1.43) per 1 SD vs. ABI: 1.30 (1.14–1.49) per 1 SD, in FRS adjusted models). Considering reclassification, CAC lead to highest reclassification in the total cohort, while also for CIMT and ABI significant improvement in net-reclassification was observed [NRI (95% CI): CAC: 0.55 (0.42–0.69); CIMT: 0.32 (0.19–0.45); ABI: 0.19 (0.10–0.28)].

Conclusion Coronary artery calcification provides the best discrimination of risk compared with CIMT and ABI, particularly in the intermediate risk group, whereas CIMT may be an alternative measure for reassurance in the low risk group.

Keywords CAC • CIMT • ABI • Primary prevention • Risk discrimination • Epidemiology

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Introduction

Over the last two decades, coronary artery calcification (CAC), carotid intima-media thickness (CIMT) and ankle-brachial index (ABI) have been introduced in the literature as markers of subclinical atherosclerosis and potential predictors of increased cardiovascular (CV) risk.[1–6] According to current guidelines, the use of markers of subclinical atherosclerosis can be considered for further risk stratification in the group of subjects with intermediate CV risk profile.[7,8] However, recent data suggest that the three measures may not equally redefine risk depending on risk group and outcome measure.[6,9–11] Whereas for CAC-score, there is substantial data regarding its excellent value for prediction of CV events and risk reclassification of patients, it requires low radiation exposure to the patient.[1,12] On the other hand, CIMT and ABI are quick measures, however, may not be as effective in risk stratification as CAC-scoring in certain risk groups.[6,9,5]

In the present analysis, we compared the association and the discrimination ability of CAC-score, CIMT and ABI with 10-year incident CV events in the population-based Heinz Nixdorf Recall study (HNR). By stratifying subjects with low, intermediate, and high risk for future CV events we assessed, which measure of subclinical atherosclerosis may be of greatest value for the respective patient group. Further, we investigated the difference in risk estimation using established thresholds for each measure.

Methods

Study cohort

The HNR is an ongoing population-based prospective cohort study conducted in the German Ruhr area. Residents of the cities Essen, Mülheim, and Bochum, aged 45–74 years were randomly sampled. The baseline examination (2000–03) included 4814 subjects. From these, 498 participants were excluded due to known coronary heart disease, prior stroke and 66 peripheral artery occlusive disease. Further 178 subjects were excluded due to missing CAC-score, additional 57 without ABI-measurement and 40 without at least one other covariate were excluded. Of the remaining 4041, CIMT was available in 3108 subjects. All participants provided written informed consent and the study was approved by internal institutional ethic committees.

Cardiovascular risk factors assessment

Traditional CV risk factors were measured at baseline examination as previously published.[13–15] Using risk factors, we computed the predicted 10-year risk for CV events according to the Framingham risk score (FRS) algorithm.[16]

Subclinical atherosclerosis markers assessment

Electron beam computed tomography (EBCT) was used to quantify coronary artery calcium. Electron beam computed tomography scans were performed utilizing a C-100 or C-150 scanner (GE Imatron, South San Francisco, California). CAC was defined using the Agatston method.[17]

Ultrasound images were obtained at the left and right common carotid artery (CCA) by Vivid FiVe, GE Ultrasound Europe, with a linear array 10-MHz scan head at baseline examination.[18] Trained and certified readers analysed the ultrasound images and derived side-specific CIMT medians using the semiautomatic software 'Artery Measurement System (AMS) II'.[19] For detailed information see Supplementary material online. This highly quality-assured CIMT measurements differ from manually measured values as used in Gronewald *et al.*[6]

Ankle-brachial index was assessed using an 8 MHz Doppler transducer (Kranzbühler, Logidop, Germany).[20] Ankle-brachial index was calculated per leg as ratio of the highest ankle artery pressure recorded and the highest systolic pressure measured in the right and left arm and the lower ABI of both legs was used.

Follow-up and endpoint definition

Clinical endpoints were defined as incident coronary events, stroke or CV death with details of endpoint-definition and follow-up been previously published and described in the Supplementary material online.[21] Fatal or non-fatal myocardial infarction was defined based on symptoms, electrocardiographic signs, cardiac enzymes, and necropsy. Stroke was defined as focal neurological deficits over a period of >24 h of presumed cerebrovascular origin. In addition, CV mortality was classified by the statistical state office based on death certificate information according to the International Statistical Classification of Disease.

Statistical analyses

Subject's characteristics are reported as mean ± standard deviation (SD) or frequency (%). Median and quartiles (Q1; Q3) are reported for CAC and log(CAC + 1) was used in analyses.

Associations of CAC, CIMT and ABI (both continuous and dichotomized) with major CV events during follow-up were assessed using Cox proportional hazard regression analyses with adjustment sets as follows: (i) unadjusted, (ii) age and sex adjusted, (iii) additionally adjusted for high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, diabetes, systolic blood pressure, present smoking, and (iv) adjustment for the FRS only. Analyses stratified by sex were performed using FRS-adjusted models (see Supplementary material online). For analyses including CIMT, we adjusted for an index variable indicating if the CIMT measure was missing at one side. According to side-specific differences in number and value we conducted complete-case (both sides available) analysis for CIMT in a sensitivity analysis.

Hazard ratios were calculated for 1-unit increase in log(CAC + 1), per SD-unit increase in CIMT and per SD-unit decrease in ABI. In addition, we performed subgroup analyses, stratified by FRS categories (<10%, 10–20%, >20%) in unadjusted models and adjusted for the FRS [adjustment sets (i) and (iv)]. We used Schoenfeld residuals[22] and a Kolmogorov-type supremum test[23] to assess the proportional hazard assumption and observed no evidence for a deviation. Kaplan–Meier estimates were used to depict the CV event rate for the three dichotomized markers. Harrell's C was calculated to assess the improvement in discrimination of incident major CV events for each continuous marker alone and in combination with the FRS. Additionally, we analysed the reclassification ability of the three markers in contrast to a model including the FRS using the category-free net reclassification improvement index (NRI).[24]

All analyses were performed using SAS software (Version 9.2, SAS Institute Inc.), but Harrell's C estimation using Stata/IC version 11.2 (StataCorp LP, College Station, Texas). We applied an explorative α-significance level of 5% (two-sided) without addressing multiple testing given that our report focuses on estimation and modelling.

Results

We included 3108 subjects (mean age 59.2 years, 47.1% males) in the analyses (*Table* 1 and Supplementary material online, *Tables S1 and S2*). Subjects with incident major CV event were on average 4.8 years

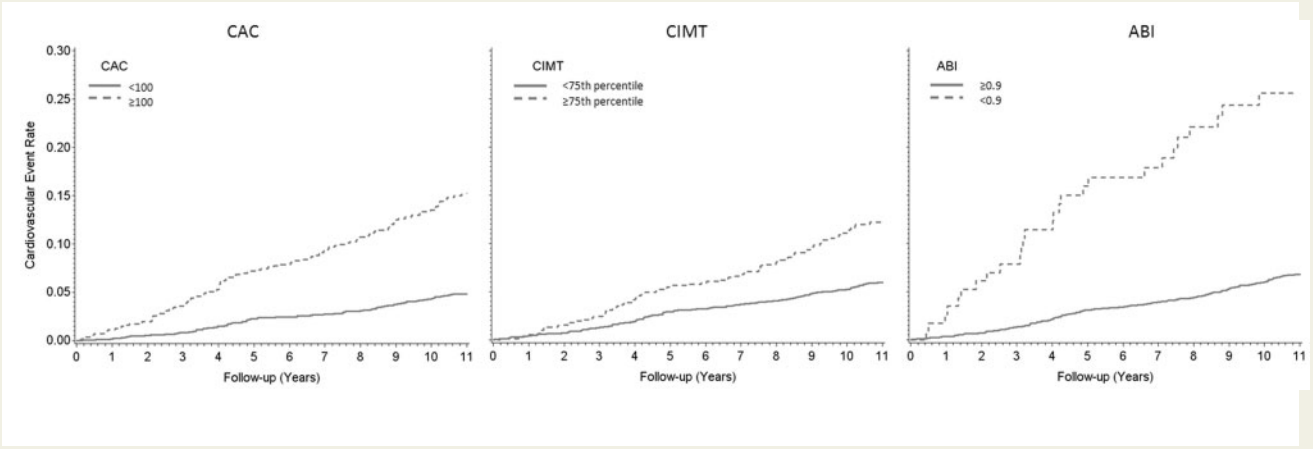

Figure 1 Event rates for the dichotomized subclinical atherosclerosis markers, stratified by Framingham risk score categories.

older than those without CV event and CAC and CIMT were, in these subjects, on average higher and ABI was lower (*Table 1*). The excluded subjects were on average older, more often male, had both a lower HDL and LDL-cholesterol level, higher systolic blood pressure and had more often diabetes mellitus (data not shown). Considering sex, men showed a higher prevalence of risk factors, an overall higher risk factor profile (FRS: men: 15.3 ± 9.0%, women: 7.6 ± 5.2%; see Supplementary material online, *Table S2*, *Figure 1*) and higher event rates than women (9.3 vs. 5.0 events/1000 person years). Detailed sex-specific analyses are provided within the supplement (Supplementary material online, *Table S3*).

Coronary artery calcification, carotid intima-media thickness and ankle-brachial index and incident major cardiovascular events

During a mean follow-up of 10.3 ± 2.8 years, 223 (7.2%) subjects developed a major CV event. 119 subjects developed a fatal or non-fatal myocardial infarction, 86 a stroke and 68 a CV death (including 28 fatal myocardial infarctions and 3 fatal strokes). Overall, 16 subjects had more than one event. In case of multiple events, time to first event was used for analysis of the combined endpoint. In subjects with incident major CV event, CAC and CIMT were on average higher and ABI was lower than in those without CV event (*Table 1*). Also, prevalence of elevated risk markers (CAC ≥ 100, CIMT ≥ 75th sex-specific percentile and ABI < 0.9) was higher in subjects with incident major CV events (*Table 1*). Descriptive analyses for dichotomized marker combinations are shown in the Supplementary material online.

Association of subclinical atherosclerosis markers with major cardiovascular events

In Cox regression analyses for major CV events, we observed a positive association for CAC [per 1-unit increase in log(CAC + 1)] in all models and also stratified by FRS categories, whereas effect sizes decreased with increasing FRS category (*Table 2*). Also, a positive association for CIMT (per SD increase) was seen in the unadjusted model (model 1), in the age- and sex-adjusted model (model 2) and in the FRS-adjusted model (model 4). The association was attenuated and non-significant when adjusting for FRS variables (model 3). Stratifying by FRS categories, the strongest association for CIMT were seen for the low FRS category (<10%) in unadjusted and FRS-adjusted models. Analysing the association of CIMT with major CV events within the subgroup of subjects with both CIMT measurements ($N = 2104$) did not substantially change the results (data not shown). Considering the entire study population, lower ABI (per SD decrease) was significantly associated with incident CV events in all models. Stratified by FRS categories, the association was strongest in the high risk FRS category (>20%) and non-significant in the low FRS category.

For dichotomized atherosclerosis markers relying on independently established clinical cut-offs, both, high CAC (≥100) and low ABI (<0.9) were significantly associated with incident major CV events using different adjustment sets. While associations were stronger for ABI in higher FRS categories, stronger associations with CAC were found in the low and intermediate FRS categories. High CIMT (≥75th sex-specific percentile) was significantly associated with major CV events in unadjusted, age- and sex- and FRS-adjusted models (*Table 2b*, *Figures 1 and 2*). The association was attenuated when adjusting for FRS variables (model 3). When ancillary adjusting for CAC-score, associations were attenuated but remained statistically significant for CIMT and ABI.

Additionally, we analysed the effect of highest vs. lowest quartile for each marker, which rendered similar results (see Supplementary material online, *Table S4*).

We further evaluated, whether an increased event rate in high ABI could have diminished the performance of ABI in linear models. Using an additional group of ABI > 1.4, we did not observe an elevated event rate compared to subjects with ABI of 0.9–1.4 (CV event rate: 4.0% vs. 6.6% for subjects with ABI >1.4 vs. ABI 0.9–1.4, respectively). Likewise, including a quadratic term of ABI in the cox regression model did not lead to relevantly different results (detailed data not shown).

Table 1 Baseline characteristics of the total cohort and stratified by events

	Overall (*N* = 3108)	No events (*N* = 2885)	Events (*N* = 223)
Age	59.2 ± 7.7	58.9 ± 7.6	63.7 ± 7.6
Females/Males (%)	1643(52.9)/1465(47.1)	1557(54.0)/1328(46.0)	86(38.6)/137(61.4)
BMI (kg/m^2)	27.6 ± 4.4	27.5 ± 4.4	28.6 ± 4.0
Systolic blood pressure (mmHg)	131.8 ± 20.7	131.0 ± 20.5	142.1 ± 21.0
Diastolic blood pressure (mmHg)	81.1 ± 10.8	80.9 ± 10.8	84.0 ± 11.2
Pulse pressure (mmHg)	50.7 ± 14.4	50.2 ± 14.2	58.0 ± 15.7
Antihypertensive medication (%)	98(31.6)	878(30.4)	103(46.2)
Total cholesterol (mg/dL)	230.9 ± 38.4	230.9 ± 38.2	231.2 ± 40.7
HDL cholesterol (mg/dL)	59.2 ± 16.9	59.5 ± 16.9	55.3 ± 16.4
Lipid-lowering medication (%)	286(9.2)	256(8.9)	30(13.5)
Diabetes (%)	357(11.5)	312(10.8)	45(20.2)
Smoking			
Current	702(22.6)	651(22.6)	51(22.9)
Former	1038(33.4)	962(33.3)	76(34.1)
Never	1368(44.0)	1272(44.1)	96(43.1)
Framingham risk score (FRS)	11.2 ± 8.2	10.9 ± 8.0	15.9 ± 9.4
<10%	1694(54.5)	1629(56.5)	65(29.2)
10–20%	1022(32.9)	918(31.8)	104(46.6)
>20%	392(12.6)	338(11.7)	54(24.2)
Coronary artery calcium (CAC) Score (Agatston) [median (Q1,Q3)]	11.3(0.0;110.6)	8.8 (0.0;94.9)	116.0(17.0;420.1)
≥100 (%)	822(26.5)	706(24.5)	116(52.0)
Carotid intima-media thickness (CIMT) (mm)	0.70 ± 0.15	0.69 ± 0.15	0.76 ± 0.17
≥75th sex-specific Percentile (%)	780(25.1)	691(24.0)	89(39.9)
Ankle-brachial index (ABI)	1.14 ± 0.14	1.14 ± 0.14	1.10 ± 0.18
<0.9 (%)	116(3.7)	88(3.1)	28(12.6)

Subject's characteristics are reported as mean ± standard deviation (SD) or frequency (%).

Table 2a Cox regression for major cardiovascular events

			Coronary calcium (log (CAC+1))		Carotid intima-media thickness (per SD increase)		Ankle-brachial index (per SD decrease)	
Population	***N*/Events**	**Model**	**HR(95% CI)**	***P*-value**	**HR(95% CI)**	***P*-value**	**HR(95% CI)**	***P*-value**
All	3108/223	(1) Unadjusted	1.38(1.30; 1.46)	<0.0001	1.45(1.31; 1.62)	<0.0001	1.38(1.20; 1.59)	<0.0001
		(2) Age- and sex-adjusted	1.27(1.19; 1.35)	<0.0001	1.18(1.04; 1.33)	0.01	1.37(1.20; 1.55)	<0.0001
		(3) + Risk Factors adjusted[a]	1.24(1.16; 1.32)	<0.0001	1.10(0.97; 1.25)	0.14	1.27(1.12; 1.46)	0.0004
		(4) FRS adjusted	1.31(1.23; 1.39)	<0.0001	1.27(1.13; 1.43)	<0.0001	1.30(1.14; 1.49)	<0.0001
		(5) CAC and FRS adjusted			1.15(1.02; 1.30)	0.03	1.26(1.13; 1.43)	0.0003
Framingham risk score (FRS)								
<10%	1694/65	Unadjusted	1.41(1.28; 1.56)	<0.0001	1.58(1.22; 2.05)	0.001	1.25(0.93; 1.67)	0.14
10–20%	1022/104	Unadjusted	1.26(1.15; 1.38)	<0.0001	1.26(1.07; 1.49)	0.007	1.28(1.05; 1.57)	0.02
>20%	392/54	Unadjusted	1.20(1.03; 1.40)	0.02	1.16(0.93; 1.44)	0.19	1.47(1.19; 1.81)	0.0004
<10%	1694/65	FRS adjusted	1.34(1.20; 1.50)	<0.0001	1.39(1.07; 1.81)	0.01	1.25(0.94; 1.66)	0.13
10–20%	1022/104	FRS adjusted	1.24(1.14; 1.36)	<0.0001	1.23(1.04; 1.46)	0.02	1.26(1.03; 1.54)	0.02
>20%	392/54	FRS adjusted	1.19(1.02; 1.39)	0.02	1.13(0.91; 1.41)	0.27	1.45(1.17; 1.80)	0.001

[a]Risk factors: HDL-cholesterol, LDL-cholesterol, diabetes, systolic blood pressure and present smoking.

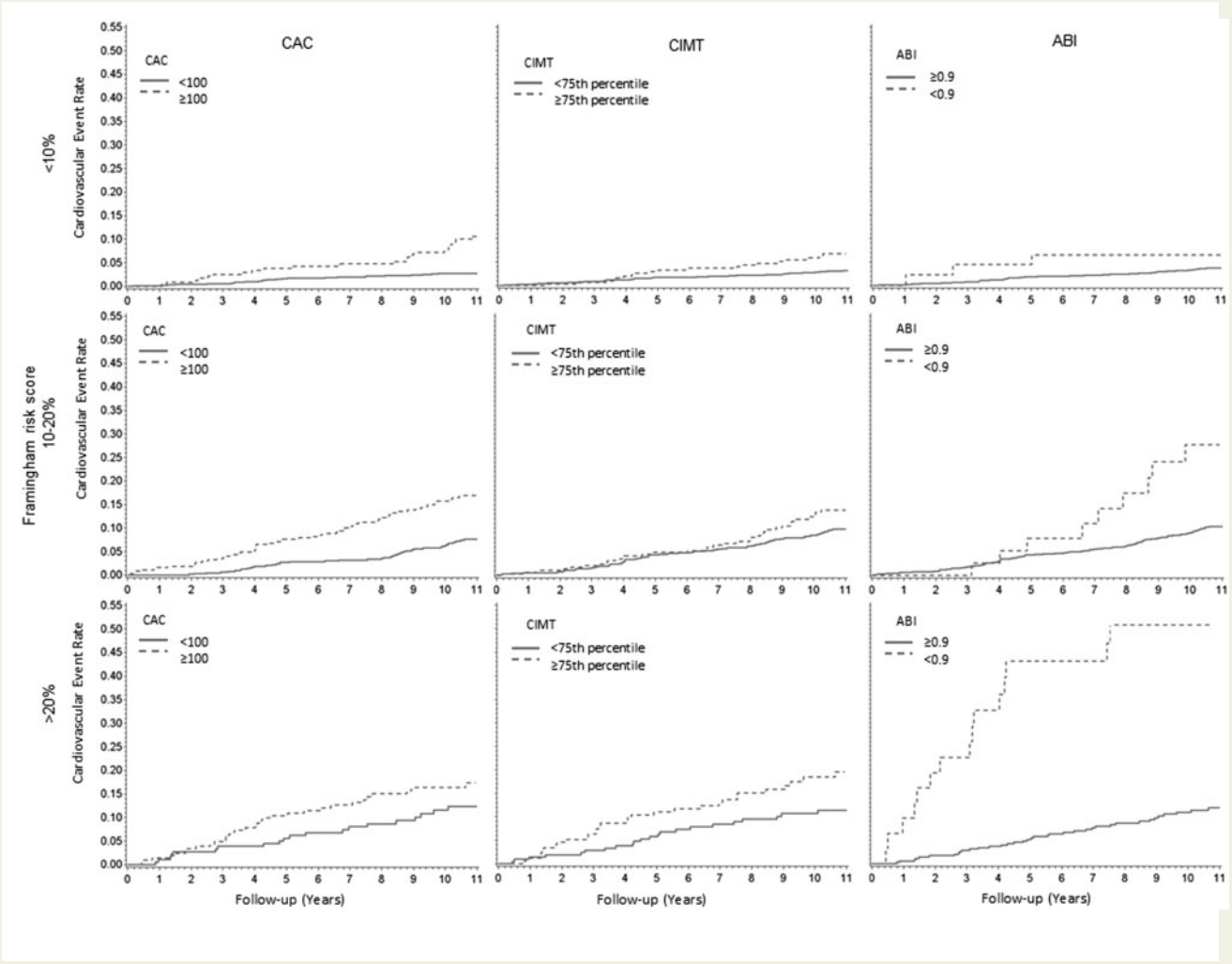

Figure 2 Event rates for the dichotomized subclinical atherosclerosis markers: coronary artery calcification, carotid intima-media thickness, ankle-brachial index.

Analysing the components of the primary endpoint, we found that for CAC the associations were comparable for the three components, whereas for CIMT associations were stronger for stroke and CV death and strongest for stroke considering ABI (Supplementary material online, *Table S4*). Finally, analysing the age at event (see Supplementary material online, *Figure S1*), no risk discrimination was seen for CIMT (≥75th sex-specific percentile) in any FRS group. In addition to FRS, we used the European HeartScore in additional analysis, which did not lead to markedly different results (detailed data not shown).

Improvement of discrimination by different atherosclerosis markers

Coronary artery calcification alone reached the highest Harrell's C compared with CIMT and ABI alone in unadjusted models (*Table 3*). For subjects within the low FRS groups, however, CIMT alone reached highest Harrell's C of the three atherosclerosis markers. In contrast, Harrell's C for ABI was comparable with CAC for subjects with high FRS.

When adding each of the three markers separately to a model including the FRS alone, only CAC led to a significant improvement in Harrell's C for the overall cohort as well as for the low and intermediate risk groups. While CIMT outperformed ABI regarding the improvement in risk discrimination within the low risk group, ABI was superior within the high risk group (*Table 3*).

These findings were also supported by the NRI (*Table 4*). Using dichotomized markers, NRI was highest for the CAC-score in the overall cohort, while also significant improvement in reclassification was observed for CIMT and ABI. Stratifying by risk group, CIMT was again superior to ABI in the lowest FRS category, while ABI was superior to CIMT in the higher FRS categories (*Table 4*). *Table 4* also shows that for the low risk group CAC and CIMT reached slightly higher negative predictive value than ABI while no relevant difference between the markers was observed for the high risk group.

Table 2b Cox regression for major cardiovascular events

Subgroup	Model	Coronary calcium ≥100 HR(95% CI)	*P*-value	Carotid intima media thickness ≥ 75th sex-specific percentile HR(95% CI)	*P*-value	Ankle-brachial index <0.9 HR(95% CI)	*P*-value
All	(1) Unadjusted	3.38(2.60; 4.40)	<0.0001	2.14(1.63; 2.78)	<0.0001	4.52(3.04; 6.71)	<0.0001
	(2) Age and gender adjusted	2.15(1.61; 2.86)	<0.0001	1.42(1.07; 1.89)	0.01	3.84(2.74; 5.72)	<0.0001
	(3) + RF adjusted[a]	1.94(1.45; 2.58)	<0.0001	1.27(0.95; 1.69)	0.12	3.26(2.17; 4.90)	<0.0001
	(4) FRS adjusted	2.57(1.94; 3.39)	<0.0001	1.63(1.23; 2.17)	0.001	3.89(2.61; 5.79)	<0.0001
	(5) CAC and FRS adjusted			1.41(1.07; 1.88)	0.02	3.93(2.63; 5.85)	<0.0001
Framingham risk score (FRS):							
<10%	Unadjusted	3.79(2.29; 6.28)	<0.0001	2.15(1.27; 3.64)	0.005	1.93(0.61; 6.15)	0.27
10–20%	Unadjusted	2.51(1.70; 3.70)	<0.0001	1.50(1.01; 2.24)	0.047	3.01(1.57; 5.78)	0.001
>20%	Unadjusted	1.49(0.86; 2.58)	0.15	1.75(1.02; 3.01)	0.04	6.62(3.64; 12.04)	<0.0001
<10%	FRS adjusted	2.85(1.69; 4.80)	<0.0001	1.71(1.00; 2.92)	0.049	1.68(0.53; 5.37)	0.38
10–20%	FRS adjusted	2.41(1.63; 3.56)	<0.0001	1.46(0.98; 2.17)	0.07	2.94(1.53; 5.64)	0.001
>20%	FRS adjusted	1.46(0.84; 2.52)	0.18	1.66(0.96; 2.89)	0.07	6.62(3.63; 12.05)	<0.0001

[a]Risk factors: HDL-cholesterol, LDL-cholesterol, diabetes, systolic blood pressure and present smoking.

Table 3 Harrell's C for the continuous atherosclerosis markers for the total cohort and stratified by Framingham risk score (FRS) categories

	All		Framingham risk score					
			<10%		10–20%		>20%	
Model	Harrell's C	*P*-value[a]	Harrell's C	*P*-value[a]	Harrell's C	*P*-value[a]	Harrell's C	*P*-value[a]
Coronary calcium (CAC)	0.703(0.700; 0.738)		0.573(0.502; 0.644)		0.653(0.597; 0.710)		0.603(0.518; 0.689)	
Carotid intima-media thickness (CIMT)	0.618(0.580; 0.656)		0.609(0.535; 0.683)		0.540(0.482; 0.597)		0.573(0.502; 0.644)	
Ankle-brachial index (ABI)	0.558(0.517; 0.599)		0.540(0.472; 0.609)		0.556(0.497; 0.614)		0.604(0.516; 0.691)	
Framingham risk score (FRS)	0.693(0.661; 0.726)		0.658(0.602; 0.713)		0.575(0.520; 0.629)		0.556(0.482; 0.629)	
FRS + CAC	0.731(0.699; 0.763)	0.02	0.738(0.684; 0.792)	0.01	0.665(0.610; 0.720)	0.004	0.617(0.534; 0.700)	0.18
FRS + CIMT	0.695(0 .662; 0.727)	0.88	0.681(0.626; 0.737)	0.13	0.582(0.527; 0.638)	0.66	0.580(0.506; 0.654)	0.39
FRS + ABI	0.687(0.653; 0.721)	0.54	0.666(0.608; 0.724)	0.45	0.596(0.541; 0.651)	0.32	0.608(0.521; 0.694)	0.28

[a]Compared with model with the FRS alone.

Discussion

In the present study, we showed that all three markers of subclinical atherosclerosis (CAC, CIMT, and ABI) were associated with incident major CV events in the population-based HNR study. Only CAC led to a significant improvement in risk prediction for subjects in the low and intermediate risk group. Comparing the other two measures, CIMT had a higher discriminative value for subjects with low risk, while ABI provided better discrimination for subjects with high risk according to traditional risk factors. Our results confirmed that CAC-scoring outperforms CIMT and ABI in its overall predictive ability. Ankle-brachial index may be of additional value when identifying subjects at very high risk, especially indicated by the ABI < 0.9-threshold. While CIMT was associated with future events in the low risk group, no risk discrimination was seen when analysing age at event. Whereas this observation diminishes the overall value of CIMT-quantification, it might be partly attributed to the categorized parametrization.

Our results are in line with a recent study of Gepner *et al.*[10] who showed that CAC is a better predictor of future CV events compared with carotid plaque and CIMT in a multi-ethnic cohort. However, our study focused on the evaluation of different CV risk profile groups and also includes ABI as risk marker. Kavousi *et al.*[11] also showed the superior risk prediction and stratification benefit of CAC in an European prospective population-based study with older subjects (mean age 69.1 years) and a considerably shorter follow-up time (median follow-up of 6.8 years). Finally, Yeboah *et al.*[9] also investigated the prediction and discrimination ability of novel risk factors, but the considered population was limited to an intermediate risk. Besides the association of different atherosclerosis markers as

Table 4 Category-free net reclassification improvement index (NRI) and negative predictive value (NPV) for the dichotomized atherosclerosis markers on top of the model with the Framingham Risk score (FRS) for the total cohort and stratified by FRS categories

	All		Framingham risk score					
			<10%		10–20%		>20%	
Model	Category-free NRI	*P*-value[a]	Category-free NRI	*P*-value[a]	Category-free NRI	*P*-value[a]	Category-free NRI	*P*-value[a]
FRS+CAC	0.551(0.416; 0.686)	<0.0001	0.414(0.177, 0.652)	0.001	0.446(0.246, 0.646)	<0.0001	0.181(-0.100, 0.462)	0.22
FRS+CIMT	0.319(0.187; 0.451)	<0.0001	0.261(0.033, 0.488)	0.04	0.177(-0.017, 0.371)	0.09	0.272(-0.012, 0.557)	0.06
FRS+ABI	0.190(0.102, 0.278)	0.006	0.041(-0.062, 0.144)	0.75	0.129(0.014, 0.245)	0.21	0.455(0.212, 0.698)	0.0002
Event-free rate	0.928		0.962		0.898		0.862	
NPV								
CAC	0.953		0.972		0.930		0.885	
CIMT	0.942		0.968		0.910		0.892	
ABI	0.935		0.962		0.904		0.892	

[a]Compared to model with the FRS alone.

continuous variables with events, we also investigated the value of frequently used cut-off values for each marker, underlying the relevant difference in risk assessment when applied. Using these cut-off values resulted in only a few individuals for ABI < 0.9 ($n = 116$, 3.7%) compared with far more individuals for CAC ≥ 100 ($n = 822$, 26.5%) and CIMT ≥ 75th percentile ($n = 505$, 24.0%). Likewise, only 28 events (12.6% of all events) occurred in subjects with ABI < 0.9, which represented 24.1% of subjects with ABI below the threshold. In contrast, 116 events occurred (52.0%) in subjects with CAC ≥ 100, underlining the lack in comparability of risk prediction using established cut-offs values for these risk factors.

According to current ACC/AHA guidelines, assessment of CIMT is no longer recommended for risk estimation in the primary prevention. Our results confirm that in the intermediate and high risk cohort, CIMT is inferior to CAC and ABI.

Implications

Our results demonstrate relevant differences of three measures of subclinical atherosclerosis (CAC-scoring, CIMT and ABI) regarding risk prediction. These differences were enhanced when using established clinical cut-offs values for each marker. Only CAC-score improves risk prediction in the intermediate risk group. In contrast, ABI < 0.9 detects subjects with very high risk, but is a rare finding in subjects within the low or intermediate risk group. Whereas assessment of CAC and ABI are highly reproducible, assessment of CIMT is prone to measurement errors which may limit its value in clinical practice, especially when performed by less experienced hands. Despite the ability of markers of subclinical atherosclerosis to differentiate CV risk, absence of these markers in high risk patients according to FRS does not rule out elevated risk when using established thresholds, indicating that assessment of subclinical atherosclerosis in high risk population may be of limited clinical value. In contrast, in intermediate risk cohorts, the implementation of subclinical atherosclerosis markers, especially CAC, may help to avoid lipid lowering therapy in subjects without CAC-Score that in fact have low future event rate.[12,25]

Limitations

We constrain our analyses to a subgroup which represents a primary prevention cohort, thus, a healthy selection bias might be introduced. However, this selected subgroup likely represents persons who are willing and motivated to determine their own CV risk. Our results are based on a predominant European population; hence, generalization of our results to other ethnic groups remains uncertain. As a further limitation, no measurements of carotid plaque were available for this analysis. Thus, since studies[10,26] suggest that the presence of plaque improves carotid ultrasound prognostic value, our results considering CIMT are likely biased towards the null. Further studies including plaque measurements are needed.

Next to varying implications of the thresholds also pathophysiology relevantly differentiates between the three markers. While CAC reflects CAC as anatomical information of plaque, ABI reflects hemodynamic effects of atherosclerosis of peripheral arteries. Lastly, increased CIMT does not necessarily mean elevated subclinical atherosclerosis and can also be altered by media layer increase as seen in hypertension.[27]

Conclusion

Coronary artery calcification, CIMT, and ABI lead to relevantly different risk stratifications in a primary prevention cohort, especially when using established clinical cut-offs values. Our findings are additive to the current literature as we compare the predictive value of CAC, CIMT, and ABI not only in the intermediate, but also in the low and high risk group. We found that while only CAC-score improves risk prediction in the intermediate risk group, CIMT may be an alternative measure for re-assuring low risk, as it does not require radiation exposure to the patient. In contrast, ABI is of greatest value in subjects with high risk for future major CV events. We found that while only CAC-score improves risk prediction in the intermediate risk group, the value of CIMT in low risk cohorts as measure, not requiring radiation exposure to the patient, was limited when taking the age at event into account. Our results may improve the understanding of the clinical value of the three markers of subclinical atherosclerosis on the basis of patient's risk factor profile.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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