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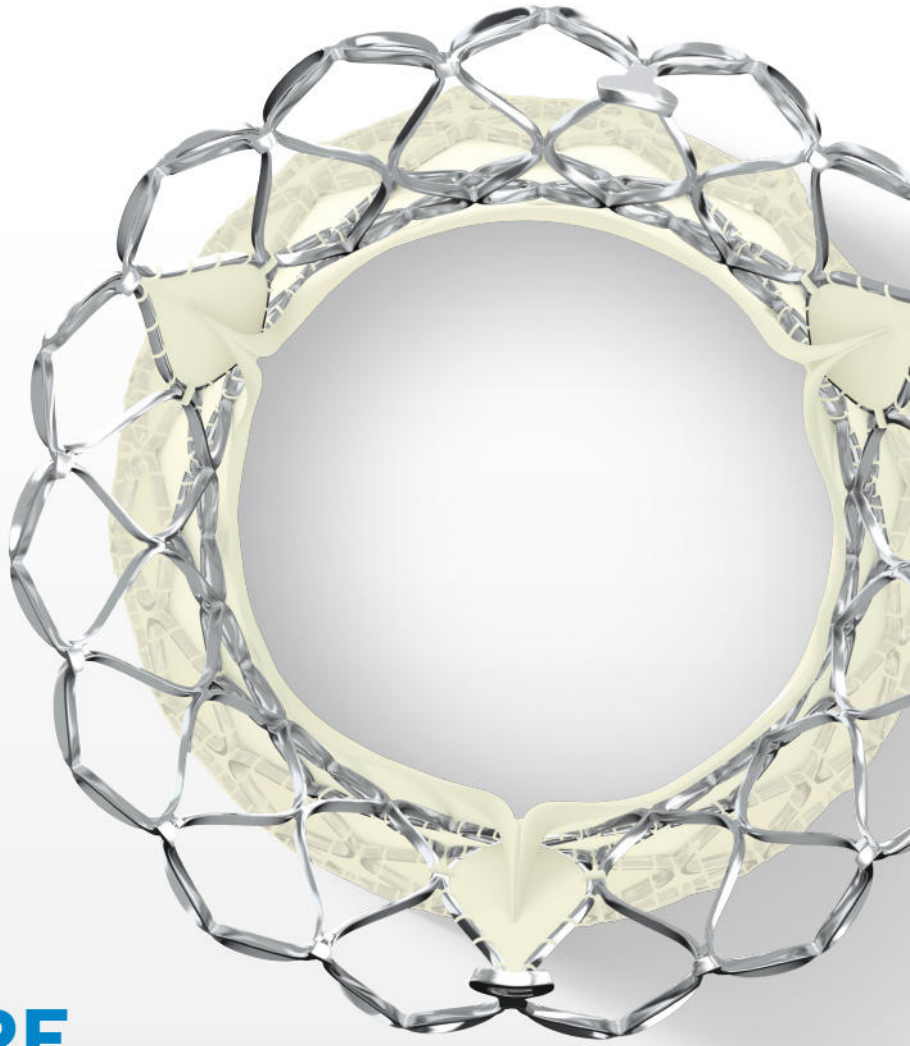

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PREVENTION WILEY CLINICAL CARDIOLOGY

CLINICAL INVESTIGATIONS

Prognostic relevance of subclinical coronary and carotid atherosclerosis in a diabetic and nondiabetic asymptomatic population

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Background: We sought to evaluate the incremental prognostic benefit of carotid artery disease and subclinical coronary artery disease (CAD) features in addition to clinical evaluation in an asymptomatic population.

Methods: Over a 6-year period, 10-year Framingham risk score together with carotid ultrasound and coronary computed tomography angiography were evaluated for prediction of major adverse cardiac events (MACE).

Results: We enrolled 517 consecutive asymptomatic patients (63% male, mean age 64 ±10 years; 17.6% with diabetes). Median (interquartile range) coronary artery calcium score (CACS) was 34 (0–100). Over a median follow-up of 4.4 (3.4–5.1) years, there were 53 MACE (10%). Patients experiencing MACE had higher CACS, incidence of carotid disease, presence of CAD ≥50%, and remodeled plaque as compared with patients without MACE. At multivariable analyses, presence of CAD ≥50% (HR: 5.14, 95% CI: 2.1–12.4) and percentage of segments with remodeled plaque (HR: 1.04, 95% CI: 1.03–1.06) independently predicted MACE ($P < 0.001$). Models adding CAD ≥50% or percentage of segments with remodeled plaque resulted in higher discrimination and reclassification ability compared with a model based on 10-year FRS, carotid disease, and CACS. Specifically, the C-statistic improved to 0.75 with addition of CAD and 0.84 when adding percentage of segments with remodeled plaque, whereas net reclassification improvement indices were 0.86 and 0.92, respectively.

Conclusions: In an asymptomatic population, CAD and plaque positive remodeling increase MACE prediction compared with a model based on 10-year FRS, carotid disease, and CACS estimation. In the diabetes subgroup, percentage of segments with remodeled plaque was the only predictor of MACE.

KEYWORDS

Calcium Scoring, Cardiovascular Prevention, Carotid Disease, Computed Tomography, Coronary Artery Disease, Diabetes Mellitus, Subclinical Atherosclerosis

1 | INTRODUCTION

Prevention of cardiovascular (CV) disease is mandatory for ethical and economic reasons.[1,2] Studies have evaluated carotid and coronary atherosclerotic burden assessment in predicting CV events in healthy individuals.[3–6] Despite promising results, to date the clinical usefulness of noninvasive subclinical atherosclerosis evaluation in asymptomatic at-risk individuals is still debated. The role of coronary computed tomography angiography (CCTA) in symptomatic patients is delineated, but it is still unknown in asymptomatic individuals with significant atherosclerosis because of a paucity of data.[7–9] Accordingly, the aim of the study was to assess the prognostic benefit of carotid

artery disease by ultrasound technique and subclinical coronary artery disease (CAD) using CCTA in an asymptomatic at-risk adult population. Moreover, we analyzed the impact of each technique on improving net reclassification improvement (NRI) and integrated discrimination improvement (IDI) as compared with Framingham risk score (FRS). In addition, we sought to evaluate the prognostic impact of the comprehensive diagnostic approach in the subset of subjects with diabetes mellitus (DM).

2 | METHODS

2.1 | Study population and enrollment

We enrolled a total of 691 consecutive asymptomatic patients referred to Centro Cardiologico Monzino for carotid ultrasound (CUS) assessment and CCTA for screening between February 2004 and June 2010. Exclusion criteria included previous history of CV disease (n = 51), contraindication to CCTA (n = 102), and inadequate heart rate (>75 bpm; n = 21). Accordingly, 517 patients were included in the study and underwent a structured clinical interview, CV risk factors collection, 10-year CV risk calculation according to FRS,[10] CUS, and CCTA within 2 weeks of the enrollment. Written informed consent was obtained from all patients, and the institutional ethics committee approved the study protocol.

2.2 | Carotid ultrasound

All patients underwent CUS evaluation using Hawk 2002 grayscale ultrasound with a special multifrequency linear probe (V-K Medical Co., Chennai, India). Two experienced operators (D.C. and M.D.L.), blinded to the clinical, laboratory, and radiological findings, performed the measurements independently. Longitudinal and transverse views of the left and right carotid arteries were obtained. Carotid artery disease was defined as the presence of increased carotid intima-media thickness (CIMT >0.9 mm) and/or any carotid plaque. Measurements were obtained on the far wall of the distal common carotid artery according to the Mannheim consensus.[11] Carotid plaque was defined as a focal structure encroaching on the arterial lumen of ≥0.5 mm, 50% of the surrounding CIMT value, or demonstrating a thickness of ≥1.5 mm, as measured from the media-adventitia interface to the intima-lumen interface.

2.3 | CCTA protocol and images analysis

CCTA was performed with a 64-slice scanner (Discovery HD 750 Medical System; GE Healthcare, Milwaukee, WI). First, images were acquired for the calculation of coronary artery calcium score (CACS) and then contrast-enhanced CCTA was performed. Retrospective and prospective electrocardiographic triggering (SnapShot Pulse; GE Healthcare) was used with variable padding, tube voltage, and tube current, as previously described.[12–14] The dose-length product was recorded.[15] The CCTA images were transferred to a remote dedicated workstation (GE Healthcare). Two experienced operators evaluated the datasets (A.I.G. and G.P., both with ≥8 years of clinical experience in CCTA performance and analysis), blinded to all patient information. Consensus agreement was achieved by a third reader (D.A., with equal years of experience) in case of any disagreement. The American Heart Association (AHA) 16-segment model was used to segment coronary arteries.[16] CACS and atherosclerotic plaque showing noncalcified, mixed, calcified, and remodeled features were identified and evaluated as previously described.[14,17] Positive remodeling was defined whenever vessel diameter at the plaque site was ≥10% larger than that of the reference segment. Finally, the percentage of stenosis was derived according to the formula (diameter ref. – diameter min.) / diameter ref. × 100,[14] where "ref." is reference and "min." is minimum. A stenosis ≥50% was considered obstructive CAD.

2.4 | Follow-up

Patient follow-up was performed by checking medical records, by phone interview, and by communication with personal physicians by researchers unaware of the patients' CUS and CCTA results. All suspected new events were reviewed by 2 experienced investigators who evaluated all pertinent records. We defined MACE as a combined endpoint of coronary death, nonfatal myocardial infarction, and non–ST-segment myocardial infarction.[10,18,19] In case of multiple events in a given patient, the first event was included in the analysis.

2.5 | Statistical analysis

Descriptive analyses were performed to characterize patients with and without MACE, and the distribution of variables within the group was evaluated using the independent *t* test or Mann–Whitney test for continuous variables and the χ^2 or Fisher exact test for categorical data. Univariable and multivariable Cox proportional hazard models were used to estimate the incidence of MACE. Covariate selection in multivariable models was done using clinical and statistical criteria, particularly to avoid overfitting in the development of multivariable models. Multicollinearity was examined in all models and proportional hazard assumption was verified by use of the Schoenfeld test. To evaluate the utility of CUS parameters, first a clinical model including the FRS was built and then CIMT >0.9 plus any carotid plaque and CACS were added incrementally to the model; the additional value of the addition of CTA data were evaluated considering 2 separated models in which CAD >50% or information on segments with remodeled plaque were included in the model with clinical and CUS data. The clinical utility of the addition of CUS and CCTA data on the clinical model was evaluated in terms of discrimination and risk reclassification ability. The Harrell C-statistic was used to evaluate discrimination ability, and risk reclassification was evaluated using continuous and categorical NRI estimated considering the survival nature of the data. Moreover, the IDI was also used to assess the incremental value of the addition of variable at each step (Figure 1).[20] Categorical NRI was evaluated adapting standard thresholds of the FRS commonly used to define low, intermediate, and high risk over 10 years (<10%, 10%–20%, and > 20%, respectively) to the time frame of the study, thus considering 4.5% and 9% as cutoffs to discriminate risk categories.

All tests were 2-tailed, and a *P* value <0.05 was considered significant. Statistical analyses were performed using Stata software release

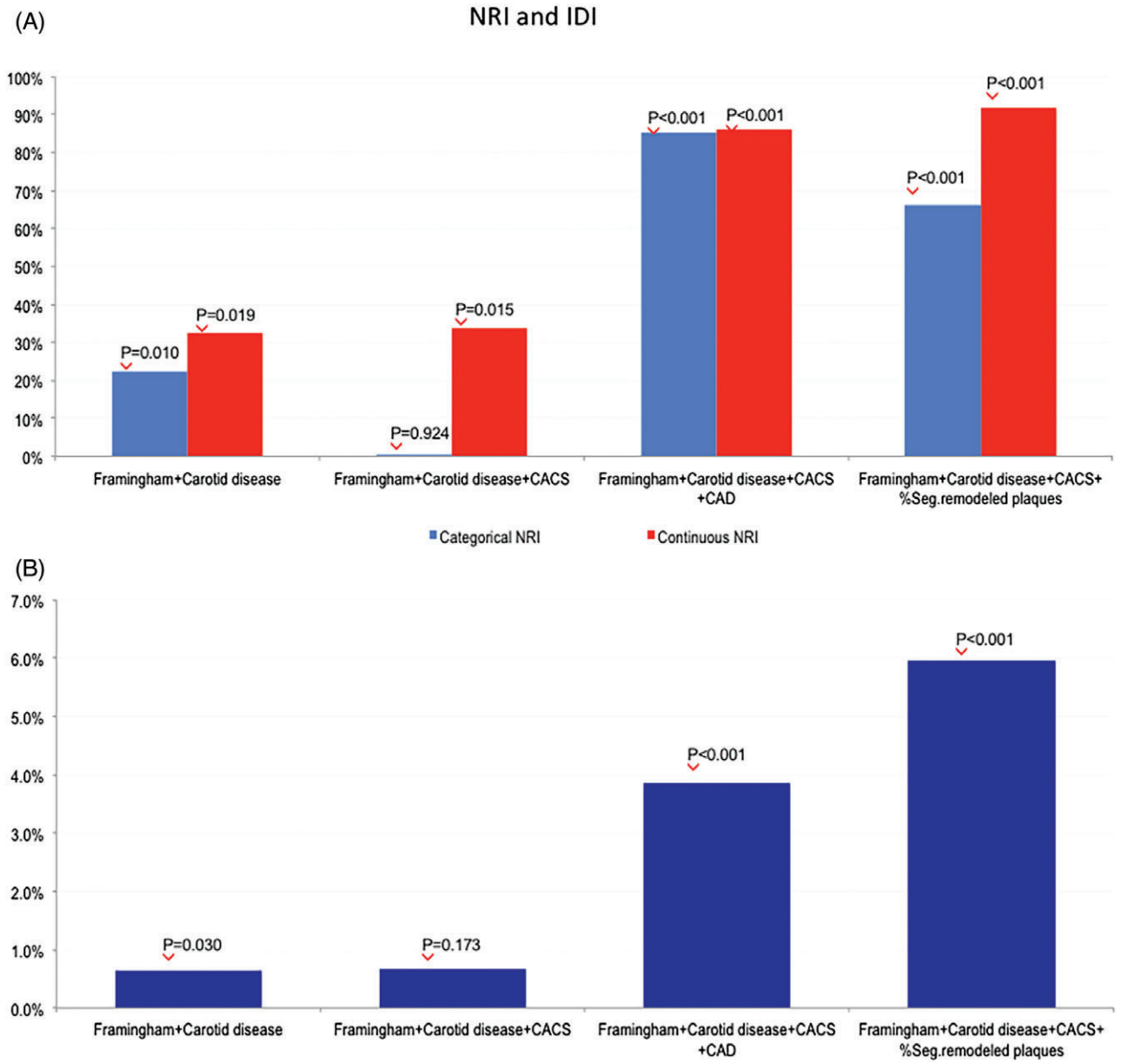


FIGURE 1 NRI and IDI. Incremental value of the incremental addition of carotid disease, CACS, CAD, and percentage of segments with remodeled plaque to the clinical model assessed by (A) categorical and continuous NRI and (B) IDI. *P* values are referred to the utility of the addition of each variable as compared with the previous step. Abbreviations: CACS, coronary artery calcium score; CAD, coronary artery disease; IDI, integrated discrimination improvement; NRI, net reclassification index

10 (StataCorp LP, College Station, TX) and R 2.11 (R Foundation, Vienna, Austria).

3 | RESULTS

Five-hundred-seventy consecutive patients were enrolled in the study, including 328 (63%) males, with a mean age of 64 ±10 years. Subjects with DM numbered 91 (17.6%), and those without DM numbered 426 (82.4%). The baseline clinical characteristics are listed in Table 1. The overall evaluability of coronary segments imaged by CCTA was 89%. Patients with carotid disease, including both CIMT >0.9 mm and carotid plaque, showed a higher rate of CAD ≥50% when compared with those without carotid disease (58% and 28%, respectively, $P < 0.001$; see Supporting Information, Table S1, in the online version of this article).

Patients in whom CCTA showed ≥1 segment with noncalcified plaque, calcified plaque, mixed plaque, and remodeled plaque were more represented in the carotid disease group when compared with those without carotid disease (42% vs 32%, $P = 0.018$; 43% vs 22%, $P < 0.001$; 54% vs 30%, $P < 0.001$; and 54% vs 31%, $P < 0.001$, respectively). Moreover, CACS was significantly higher in patients with carotid disease (59 [0 min–132 max] vs 0 [0 min–65 max]; $P < 0.001$) as compared with patients without carotid disease.

Over a median follow-up of 4.4 years (interquartile range [IQR], 3.4–5.1 years), there were a total of 53 MACE (10%) including 6 cardiac deaths (1%), 13 nonfatal myocardial infarction (4%), and 34 non–ST-segment myocardial infarction (7%). No patients were lost to

TABLE 1 Baseline characteristics

	All Patients	CHD Events	No CHD Events	*P* Value
N (%)	517 (100)	53 (10.3)	464 (89.8)	NS
Age, y	64 ± 10	65 ±10	63 ±10	NS
Male sex	328 (63.4)	36 (67.9)	292 (62.9)	NS
Risk factors				
HTN	368 (71.2)	43 (81.1)	325 (70)	NS
Smoking	155 (30)	17 (32)	138 (30)	NS
Hyperlipidemia	324 (63)	40 (75)	284 (61)	0.042
DM	91 (18)	16 (30)	75 (16)	0.011
Family history of CAD	153 (30)	16 (30)	137 (30)	NS
Medical therapy				
β-Blockers	144 (28)	16 (30)	128 (28)	NS
ACEIs	238 (46)	29 (55)	209 (45)	NS
ASA	229 (64)	34 (64)	195 (42)	0.002
Nitrates	77 (15)	17 (32)	60 (13)	<0.001
Statins	181 (35)	25 (47)	156 (34)	NS
Ca antagonists	116 (22)	16 (30)	100 (22)	NS
Antihypertensives	349 (68)	41 (77)	308 (66)	NS
FRS	12 (7–21)	16 (8–23)	12 (6–20)	NS
FRS categories				
Low, <10%	226 (44)	19 (36)	207 (45)	NS
Intermediate, 10%–20%	168 (33)	19 (36)	149 (32)	
High, >20%	123 (24)	15 (28)	108 (23)	
CUS				
CIMT >0.9 mm	389 (75)	45 (85)	344 (74)	NS
Carotid plaque	295 (57)	39 (74)	256 (55)	0.011
CCTA characteristics				
CACS	34 (0–100)	87 (52–157)	15 (0–91)	<0.001
CAD ≥50%	226 (44)	46 (87)	180 (39)	<0.001
1 vessel ≥50%	112 (22)	22 (42)	90 (19)	<0.001
2 vessels ≥50%	72 (14)	14 (26)	58 (13)	
3 vessels ≥50%	41 (8)	10 (19)	31 (7)	
LM ≥50%	2 (0.3)	1 (2)	1 (0.2)	NS
Segments with stenosis	0 (0–8)	1 (0–7)	0 (0–8)	<0.001
≥1 segment with noncalcific plaque	191 (37)	28 (53)	163 (35)	0.016
≥1 segment with calcific plaque	172 (33)	22 (42)	150 (32)	NS
≥1 segment with mixed plaque	220 (43)	46 (87)	174 (37)	<0.001
≥1 segment with remodeled plaque	223 (43)	49 (92)	174 (37)	<0.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ASA, acetylsalicylic acid (aspirin); Ca, calcium; CACS, coronary artery calcium score; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CHD, coronary heart disease; CIMT, carotid intima-media thickness; CUS, carotid ultrasound; DM, diabetes mellitus; FRS, Framingham risk score; HTN, hypertension; IQR, interquartile range; LM, left main artery; NS, not significant; SD, standard deviation. Data are presented as n (%), mean ± SD, or median (IQR).

follow-up. The mean 10-year FRS for CVD events was intermediate (12%) without statistically significant differences between the 2 groups (Table 1).

At carotid ultrasound evaluation, patients with carotid plaque were 74% in the MACE group and 55% in the no-MACE group, respectively ($P = 0.011$). Mean CACS was 87 (IQR, 52–157) in the MACE group and 15 (IQR, 0–91) in the no-MACE group ($P < 0.001$). At CCTA analysis, the presence of CAD ≥50% was 46 (87%) in the MACE group and 180 (39%) in the no-MACE group ($P < 0.001$). The number of patients with noncalcific, mixed, and remodeled plaque was significantly higher in the MACE group as compared with the no-MACE group ($P = 0.016$, $P < 0.001$, and $P < 0.001$, respectively). The mean radiation dose during CCTA was 4.3 ±1.0 mSv, with no difference between the 2 groups. Interobserver agreement for the detection of carotid disease, CACS, coronary artery stenosis, and plaque features was good (κ value of 0.81, 0.92, 0.78, and 0.85, respectively), whereas intraobserver agreement was very good in all situations (κ value of 0.92, 0.96, 0.90, and 0.93, respectively).

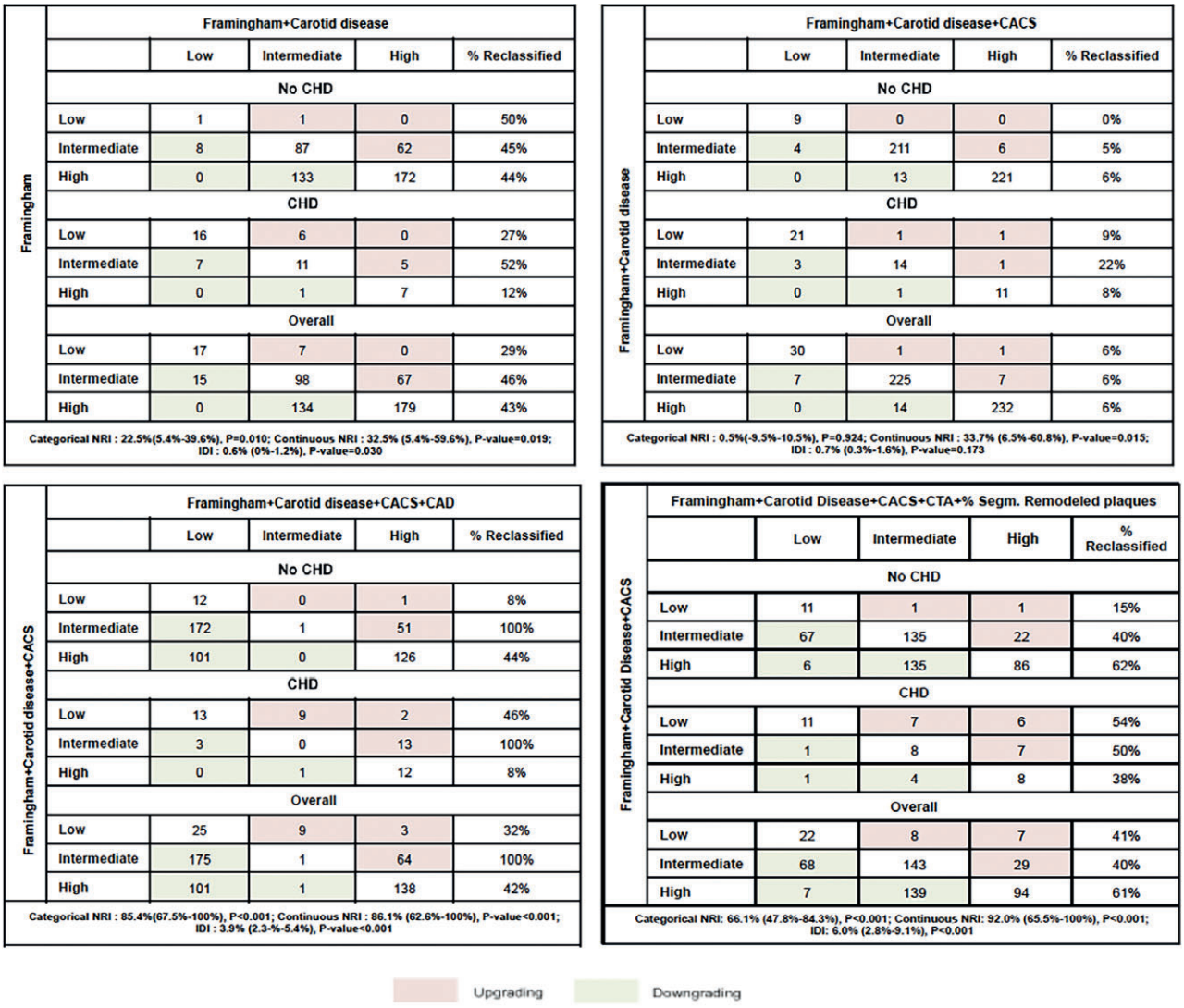
The univariate analysis (Table 2) showed that carotid plaque, but not only CIMT, was a significant predictor of MACE ($P = 0.007$).

TABLE 2 Univariate and multivariate Cox models

	HR	95% CI	*P* Value
Univariate models			
Male sex	1.252	(0.703–2.230)	NS
Age	1.018	(0.989–1.047)	NS
Smoker	1.111	(0.624–1.978)	NS
DM	2.152	(1.197–3.869)	0.010
HTN	1.824	(0.916–3.629)	NS
Hyperlipidemia	1.899	(1.016–3.550)	0.045
Family history of CAD	1.044	(0.581–1.877)	NS
Antihypertensives	1.697	(0.892–3.228)	NS
ACEIs	1.468	(0.854–2.521)	NS
Nitrates	2.990	(1.679–5.325)	<0.001
β-Blockers	1.112	(0.619–1.999)	NS
Ca antagonists	1.554	(0.864–2.793)	NS
ASA	2.349	(1.340–4.119)	0.003
Statins	1.705	(0.994–2.925)	NS
FRS	6.878	(0.810–58.434)	NS
CIMT >0.9 mm	1.964	(0.926–4.168)	NS
Carotid plaque	2.180	(1.184–4.016)	0.012
Carotid disease[a]	2.231	(1.241–4.010)	0.007
CACS	1.001	(1.0–1.002)	0.001
CAD ≥50%	9.702	(4.378–21.502)	<0.001
1 vessel ≥50%	6.314	(3.061–13.028)	<0.001
2 vessels ≥50%	5.277	(2.286–12.181)	<0.001
3 vessels ≥50%	10.649	(4.409–25.718)	<0.001
LM ≥50%	7.166	(0.988–51.96)	NS
Segment with stenosis	1.278	(1.136–1.437)	<0.001
% Segments with noncalcific plaque	1.038	(1.015–1.062)	0.001
% Segments with calcific plaque	1.010	(0.991–1.029)	NS
% Segments with mixed plaque	1.047	(1.033–1.062)	<0.001
% Segments with remodeled plaque	1.063	(1.049–1.077)	<0.001
Multivariate models			
FRS	3.444	(0.373–31.769)	NS
Carotid disease[a]	2.082	(1.141–3.801)	0.017
FRS	2.809	(0.294–26.830)	NS
Carotid disease[a]	1.908	(1.036–3.516)	0.038
CACS	1.001	(1.001–1.002)	0.018
FRS	0.614	(0.051–7.429)	NS
Carotid disease[a]	1.293	(0.706–2.367)	NS
CACS	1.000	(0.999–1.001)	NS
CAD	9.079	(3.916–21.047)	<0.001
FRS	0.626	(0.053–7.253)	NS
Carotid disease[a]	1.267	(0.671–2.396)	NS
CACS	1.000	(0.999–1.001)	NS
% Segments with remodeled plaque	1.061	(1.044–1.077)	<0.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ASA, acetylsalicylic acid (aspirin); Ca, calcium; CACS, coronary artery calcium score; CAD, coronary artery disease; CI, confidence interval; CIMT, carotid intima-media thickness; DM, diabetes mellitus; FRS, Framingham risk score; HR, hazard ratio; HTN, hypertension; LM, left main artery; NS, not significant.

[a] Carotid disease refers to CIMT >0.9 mm + carotid plaque.



Framingham | Framingham+Carotid disease

	Low	Intermediate	High	% Reclassified
No CHD				
Low	1	1	0	50%
Intermediate	8	87	62	45%
High	0	133	172	44%
CHD				
Low	16	6	0	27%
Intermediate	7	11	5	52%
High	0	1	7	12%
Overall				
Low	17	7	0	29%
Intermediate	15	98	67	46%
High	0	134	179	43%

Categorical NRI : 22.5%(5.4%-39.6%), P=0.010; Continuous NRI : 32.5% (5.4%-59.6%), P-value=0.019; IDI : 0.6% (0%-1.2%), P-value=0.030

Framingham+Carotid disease | Framingham+Carotid disease+CACS

	Low	Intermediate	High	% Reclassified
No CHD				
Low	9	0	0	0%
Intermediate	4	211	6	5%
High	0	13	221	6%
CHD				
Low	21	1	1	9%
Intermediate	3	14	1	22%
High	0	1	11	8%
Overall				
Low	30	1	1	6%
Intermediate	7	225	7	6%
High	0	14	232	6%

Categorical NRI : 0.5%(-9.5%-10.5%), P=0.924; Continuous NRI : 33.7% (6.5%-60.8%), P-value=0.015; IDI : 0.7% (0.3%-1.6%), P-value=0.173

Framingham+Carotid disease+CACS | Framingham+Carotid disease+CACS+CAD

	Low	Intermediate	High	% Reclassified
No CHD				
Low	12	0	1	8%
Intermediate	172	1	51	100%
High	101	0	126	44%
CHD				
Low	13	9	2	46%
Intermediate	3	0	13	100%
High	0	1	12	8%
Overall				
Low	25	9	3	32%
Intermediate	175	1	64	100%
High	101	1	138	42%

Categorical NRI : 85.4%(67.5%-100%), P<0.001; Continuous NRI : 86.1% (62.6%-100%), P-value<0.001; IDI : 3.9% (2.3-%-5.4%), P-value<0.001

Framingham+Carotid Disease+CACS | Framingham+Carotid Disease+CACS+CTA+% Segm. Remodeled plaques

	Low	Intermediate	High	% Reclassified
No CHD				
Low	11	1	1	15%
Intermediate	67	135	22	40%
High	6	135	86	62%
CHD				
Low	11	7	6	54%
Intermediate	1	8	7	50%
High	1	4	8	38%
Overall				
Low	22	8	7	41%
Intermediate	68	143	29	40%
High	7	139	94	61%

Categorical NRI: 66.1% (47.8%-84.3%), P<0.001; Continuous NRI: 92.0% (65.5%-100%), P<0.001; IDI: 6.0% (2.8%-9.1%), P<0.001

FIGURE 2 Risk reclassification showing number of subjects and percentage of subjects reclassified when the clinical model was updated, adding incrementally (A) carotid disease, (B), CACS, (C) CAD, and (D) percentage of segments with remodeled plaque. For each section, categorical and continuous NRI as well as IDI are reported with their 95% CI. Abbreviations: CACS, coronary artery calcium score; CAD, coronary artery disease; CHD, coronary heart disease; CI, confidence interval; CTA, computed tomography angiography; IDI, integrated discrimination improvement; NRI, net reclassification index

Notably, CIMT alone was not significantly associated with the risk of cardiac events. The presence of significant CAD; the number of vessels with stenosis ≥50%; the number of segments with noncalcific, mixed, and remodeled plaque; and CACS were significant predictors of MACE. The number of segments with calcified plaque was not a significant predictor of MACE.

On multivariate analysis (Table 2), carotid disease was a significant independent predictor of MACE when added to FRS, and both carotid disease and CACS were independent predictors when added to FRS. CUS data were no more significant when CCTA parameters were included in the model, with the latter being the only significant independent predictors.

The C-statistic for the FRS model was 0.57 (95% CI: 0.50–0.65). Although the addition of carotid disease did not improve discrimination ability of the model (C-statistic: 0.62, 95% CI: 0.56–0.69, $P = 0.126$), the further addition of CACS (C-statistic: 0.66, 95% CI: 0.59–0.72, $P = 0.026$), and CCTA data (C-statistic: 0.75, 95% CI: 0.69–0.80, $P = 0.003$) for CAD (C-statistic: 0.84, 95% CI: 0.80–0.88, $P < 0.001$ for the percentage of segments with remodeled plaque) significantly improved model performance in terms of discriminatory power.

In terms of risk reclassification (Figure 2), the addition of CUS and CCTA data progressively improved model performance at each step according to both continuous and categorical NRI. According to categorical NRI and IDI, the addition of CACS to the model including FRS and carotid disease did not significantly improve risk reclassification, whereas the inclusion of the presence of CAD ≥50% to the model including FRS, carotid disease, and CACS correctly reclassified 85.4% of subjects with an IDI of 3.9%. Finally, the model adding the percentage of segments with remodeled plaque allowed for a correct reclassification 66.1% of subjects with an IDI of 6.0% as compared with the model including FRS, CUS, and CACS data.

TABLE 3 Univariate and multivariate Cox models in DM population

			Multivariate Cox Model		
Univariate Cox Models	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**	**Harrell's C-statistic**
Male sex	3.030 (0.862–10.651)	NS			
Age	1.001 (0.946–1.059)	NS			
Smoker	1.282 (0.445–3.694)	NS			
HTN	1.454 (0.330–6.404)	NS			
Hyperlipidemia	1.098 (0.381–3.163)	NS			
Family history	0.966 (0.336–2.781)	NS			
Antihypertensives	0.690 (0.222–2.140)	NS			
ACEIs	0.699 (0.262–1.865)	NS			
β-Blockers	1.294 (0.450–3.725)	NS			
Ca antagonists	1.793 (0.665–4.832)	NS			
ASA	1.558 (0.502–4.834)	NS			
Statins	3.454 (1.143–10.997)	0.028			
FRS	4.275 (0.119–153.302)	NS	1.512 (1.028–1.078)	NS	0.827 (0.777–0.878)
CIMT >0.9 mm	4.653 (0.614–35.259)	NS			
Carotid plaque	1.980 (0.638–6.150)	NS			
Carotid disease[a]	2.188 (0.705–6.796)	NS			
CAD ≥50%	1.230 (0.458–3.308)	NS			
% Segments with noncalcific plaque	1.026 (0.992–1.061)	NS			
% Segments with calcific plaque	1.013 (0.983–1.044)	NS			
% Segments with mixed plaque	1.026 (1.000–1.053)	0.050			
% Segments with remodeled plaque	1.053 (1.029–1.078)	<0.001	1.053 (1.028–1.078)	<0.001	
CACS	1.001 (0.999–1.003)	NS			

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ASA, acetylsalicylic acid (aspirin); Ca, calcium; CACS, coronary artery calcium score; CAD, coronary artery disease; CI, confidence interval; CIMT, carotid intima-media thickness; DM, diabetes mellitus; FRS, Framingham risk score; HR, hazard ratio; HTN, hypertension; NS, not significant.

[a] Carotid disease refers to CIMT >0.9 mm + carotid plaque.

Considering the subset of the population with DM, the univariate analysis showed that statins and the percentage of segments with remodeled plaque were the only predictors of MACE (Table 3). The C-statistic for the model including FRS and the percentage of segments with remodeled plaque was 0.83.

4 | DISCUSSION

The main findings of this study in an asymptomatic adult population are the following: (1) carotid disease assessment is able to predict MACE occurrence more accurately than traditional 10-year FRS; (2) CACS allows slightly better event prediction as compared with clinical plus CUS evaluation and loses its signal when coronary stenosis information or plaque features by CCTA are considered; (3) significant coronary stenosis and positive plaque remodeling represent the most powerful tool of reclassification of patient risk who experienced a MACE, which was most pronounced when a starting model including clinical risk and carotid and coronary stenosis placed them in an intermediate-risk category; and (4) in the subgroup of subjects with DM, the percentage of segments with remodeled plaque is the only predictor of MACE.

Today, carotid artery disease is used as a surrogate marker of preclinical coronary atherosclerosis.[21–24] Studies showed that the combination of CIMT and carotid plaque assessment improves the ability to identify subclinical coronary disease,[3,25] and, hence, the prediction of ischemic CVD. Accordingly, the results of our study reinforce the concept that carotid artery disease information incrementally predicts MACE occurrence with respect to FRS. In fact, it reclassifies almost half of subjects from intermediate to high or low risk. Coronary calcium scoring is a powerful marker of coronary atherosclerosis[26–28] and has also demonstrated the ability to reclassify a portion of patients in the intermediate-risk group by traditional risk factors. The BioImage Study[4] prospectively enrolled 5808 asymptomatic adults and showed that detection of subclinical carotid or coronary atherosclerosis improves 3-year risk prediction of MACE occurrence and reclassification compared with conventional risk factors, with comparable results for either modality. In the present study, we demonstrate that CACS modestly improves prediction of clinical event occurrence and very weakly reclassifies individuals to a model including FRS and carotid disease. On the other hand, CCTA allows for the direct and noninvasive assessment of CAD and has proven to be an accurate test to evaluate the degree of stenosis as compared with invasive coronary angiography.[29–31] Compared with the case of symptomatic patients where the indication of CCTA has been established,[32,33] few studies have aimed to evaluate the appropriateness of CCTA in asymptomatic patients to substantiate the clinical value and prognostic usefulness over traditional strategies.[6,34] In our study the presence of significant CAD independently predicted MACE in an at-risk asymptomatic population. Importantly, adding CAD to a model including FRS, carotid

diseases, and CACS produced a wide reclassification of patient risk. In particular, 81% of patients who experienced MACE initially included in the intermediate-risk group were reclassified as high risk and, on the contrary, 76% who did not experience cardiac events and were initially included in the intermediate-risk group were reclassified as lower risk.

The unique ability of CCTA to identify adverse plaque features such as low-density noncalcified plaque and positive remodeling of the vessel is of great clinical value.[35–39] Despite the power of coronary stenosis information in predicting event occurrence and correctly reclassifying most patients, the present analysis shows that the characterization of plaque and, specifically, the presence of positive remodeling, are able to further improve risk stratification, particularly lowering the risk of patients who do not show this feature.

Interestingly, the separate analysis of the subjects with DM in this population has shown that the assessment of carotid disease and CACS as risk-prediction markers is not useful. The only significant parameter is represented by the percentage of segments with remodeled plaque (the presence of mixed plaque reaches the limit of statistical significance). These findings could find a conceptual explanation based on the fact that patients with DM have a condition of high coronary risk per se,[40,41] such that standard risk stratification does not generate any additional prognostic information. Recently, the American Diabetes Association (ADA) and AHA issued a joint statement urging the identification of asymptomatic patients with subclinical CAD in whom more aggressive lifestyle or treatment changes would prevent progression of the disease and the reduction of future clinical events.[42] Because it is currently difficult to hypothesize a stratification with the use of CCTA of all DM patients for economic reasons, a useful strategy could be to screen patients when DM has been present for >10 years.[43]

4.1 | Study limitations

Some limitations are present in this study. First, the study enrolled a relatively low number of patients, and its results need to be confirmed in a larger population. Second, our population is highly selected, mainly due to the limitations of the use of CCTA. Moreover, we decided to include common IMT in the analysis, as the existing literature demonstrated the added predictive value of its measurement to carotid plaque burden. However, it should be mentioned that this assumption cannot hold true for carotid bifurcation and internal IMT, whose data have not been analyzed to date. Further studies are warranted to confirm the preliminary evidence emerging from this investigation. It is highly probable that other features, such as the napkin-ring sign, local and systemic inflammation, and plaque attenuation values will be able to add important information for the purpose of MACE prediction.

5 | CONCLUSION

In an asymptomatic at-risk population, carotid disease assessment is able to predict MACE occurrence more accurately than traditional clinical scores and with comparable accuracy to the coronary calcium score. Coronary artery stenosis and plaque positive remodeling represent the most powerful tools of risk reclassification in this wide subset of patients. In the subgroup of subjects with DM, the percentage of segments with remodeled plaque was the only predictor of MACE.

Conflicts of interest

G. Pontone has served on the speakers bureau and as a consultant for General Electric and has served as a consultant for HeartFlow, Medtronic, and Bayer. *D. andreini* has served on the speakers bureau for General Electric. F. Cademartiri has served as a consultant for Guerbet and Siemens. The authors declare no other potential conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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