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Measurements of Carotid Intima-Media Thickness and of Interadventitia Common Carotid Diameter Improve Prediction of Cardiovascular Events

Results of the IMPROVE (Carotid Intima Media Thickness [IMT] and IMT-Progression as Predictors of Vascular Events in a High Risk European Population) Study

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Objectives The goal of this study was to compare the performance of several measures of carotid intima-media thickness (C-IMT) as predictors of cardiovascular events (CVEs), and to investigate whether they add to the predictive accuracy of Framingham risk factors (FRFs).

Background Various markers of subclinical atherosclerosis have been identified as predictors of CVEs, but the most powerful variable is still under debate.

Methods A cohort study was carried out in 5 European countries. A total of 3,703 subjects (median age 64.4 years; 48% men) were followed-up for a median of 36.2 months, and 215 suffered a first CVE (incidence: 19.9/1,000 person-years).

Results All measures of C-IMT and the interadventitia common carotid artery diameter (ICCAD) were associated with the risk of CVEs, after adjustment for FRFs and therapies (all $p < 0.005$). The average of 8 maximal IMT measurements ($IMT_{mean\text{-}max}$), alone or combined with ICCAD, classified events and non-events better than the common carotid mean IMT (net reclassification improvement [NRI]: +11.6% and +19.9%, respectively; both $p < 0.01$). Compared with classification based on FRFs alone, the NRI resulting from the combination of FRFs+ICCAD+$IMT_{mean\text{-}max}$ was +12.1% ($p < 0.01$). The presence of at least 1 plaque (maximum IMT >1.5 mm) performed significantly worse than composite IMTs that incorporated plaques ($p < 0.001$). Adjusted Kaplan-Meier curves showed that individuals with a FRS = 22.6% (cohort average), and both $IMT_{mean\text{-}max}$ and ICCAD above the median, had a 6.5% risk to develop a CVE over 3 years versus a 3.4% risk for those with the same FRS, and both $IMT_{mean\text{-}max}$ and ICCAD below the median.

Conclusions A risk stratification strategy based on C-IMT and ICCAD as an adjunct to FRFs is a rational approach to prevention of cardiovascular disease. (J Am Coll Cardiol 2012;60:1489–99) © 2012 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

CI = confidence interval
C-IMT = carotid artery intima-media thickness
CVE = cardiovascular event
FRF = Framingham risk factor
FRS = Framingham risk score
HR = hazard ratio
ICCAD = interadventitia common carotid artery diameter
IDI = integrated discrimination improvement
IMT = intima-media thickness
NRI = net reclassification improvement
ROC = receiver-operating characteristic
VRF = vascular risk factor

Risk assessment in primary prevention is usually based on vascular risk factors (VRFs), but the current ability to predict new cardiovascular events (CVEs) remains limited, even using the "global risk assessment approach" (1). Carotid artery intima-media thickness (C-IMT), measured by B-mode ultrasound, is a recognized marker of carotid and coronary atherosclerosis (2), although it is still debated whether C-IMT improves the predictive capacity of VRFs (3–11).

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Other uncertainties include identification of the most informative segment (common carotid, bifurcation, or internal carotid arteries) and/or the best summary measure (mean, max, or mean–max).

Interadventitia common carotid artery diameter (ICCAD), assessed in plaque-free areas, is another variable easily measurable by B-mode ultrasound. ICCAD increases during atherogenesis (12), and this enlargement is associated with VRFs (13) and subclinical atherosclerosis (14,15). On the basis of these premises, it can be hypothesized that, like C-IMT, ICCAD may improve risk assessment in asymptomatic individuals. Studies specifically designed to assess the prognostic value of ICCAD are few (9,16–18). To the best of our knowledge, only 1 study measured the predictive capacity of the combination of C-IMT and ICCAD (9).

All the aforementioned issues have been addressed in IMPROVE (Carotid Intima Media Thickness [IMT] and IMT-Progression as Predictors of Vascular Events in a High Risk European Population), a cohort study carried out in 5 European countries (19). We performed a systematic analysis to compare the performance of 11 different C-IMT variables measured at baseline, as predictors of subsequent CVEs. In addition, we investigated: 1) whether ICCAD is a predictor of future CVEs independently of C-IMT; and 2) whether C-IMT variables, ICCAD, or their combinations significantly add to the predictive accuracy of standard models for cardiovascular risk stratification.

Methods

Participants. The design, objectives, methods, eligibility criteria, and baseline evaluation of the IMPROVE study were reported in the text and online material of Baldassarre et al. (19). Briefly, 3,711 individuals (age 54 to 79 years) with at least 3 VRFs, free from cardiovascular and cerebrovascular disease, were enrolled in 7 centers in Finland, France, Italy, the Netherlands, and Sweden (details in the Online Appendix). The measure of carotid diameter was not available for 8 individuals, so this report refers to 3,703 subjects.

Carotid ultrasound examination. Seven identical machines (Technos, Esaote, Genoa, Italy) equipped with a 5- to 10-MHz linear array probe were used. All machines were calibrated with a phantom at baseline and checked after 1 year. The far walls of the left and right common carotids, bifurcations, and internal carotid arteries were visualized at 3 scan angles (lateral, anterior, and posterior) and recorded on S-VHS videotapes. Each segment was measured in at least 3 different frames. ICCAD was measured in the second centimeter of the common carotid proximal to the bifurcation. All measurements were made in the Milan center using dedicated software (M'Ath, Metris SRL, Argenteuil, France) (20). The list of ultrasonographic variables considered, with definitions and precision metrics, are shown in Table 1. Anatomical locations are shown in Online Figure 1. Spearman correlations between ultrasonographic variables were all significant (all $p < 0.0001$) (Online Table 1).

As shown in Online Figure 1, plaques were incorporated in IMT measurements. However, to assess the potential incremental prognostic value of plaque, IMT variables were also measured after excluding plaques (defined as $IMT_{max} > 1.5$). The variable "presence of at least 1 plaque" was recorded.

Cardiovascular events. The occurrence of CVEs (myocardial infarction, sudden cardiac death, angina pectoris, ischemic stroke, transient ischemic attack, new diagnosis of intermittent claudication, heart failure, or any surgical intervention or revascularization of coronary or peripheral arteries) was assessed at months 15, 30, and at the end of follow-up. Carotid surgical or endovascular procedures were not included among endpoints, as these procedures might be directly related to the qualifying carotid ultrasound investigation at study entry or during follow-up. Angina pectoris, myocardial infarction, and ischemic stroke were diagnosed according to European Society of Cardiology guidelines (21,22). All events were validated by local specialists through medical records and death certificates. Copies of documents were sent to a designated specialist (U.d.F.), who was unaware of clinical history and C-IMT data, for adjudication.

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Table 1 Definitions of Carotid IMT Ultrasonographic Variables

Name	Definitions	Absolute Differences (Mean ± SD)		ICCs	
		Intra	Inter	Intra	Inter
1^{st}CC-IMT_{mean}	Average of 6 mean IMT values obtained by measuring left and right CC (1-cm length) in the first centimeter proximal to the bifurcation in the 3 scan angles (lateral, anterior, and posterior)	0.031 ± 0.03	0.045 ± 0.041	0.95	0.89
1^{st}CC-IMT_{max}	The highest among all the maximal IMT values measured in each 1 of the 6 first centimeters of the CC segments	0.039 ± 0.041	0.079 ± 0.072	0.92	0.83
CC-IMT_{mean}	Average of all mean IMT values obtained from left and right CC visualized in their entire length (excluding the first centimeter) with sequential probe movements of 1-cm length, in the 3 scan angles. The total number of segments visualized ranged from 6 to 24 according to the length of the subject's neck. In each segment, the software automatically provided the maximal IMT value	0.089 ± 0.161	0.101 ± 0.081	0.92	0.95
CC-IMT_{max}	The highest of all the maximal IMT values detected in the 6–24 CC segments	0.067 ± 0.101	0.138 ± 0.307	0.96	0.52
Bif-IMT_{mean}	Average of 6 mean IMT values obtained by measuring left and right Bif (1-cm length) in the 3 scan angles (lateral, anterior, and posterior)	0.09 ± 0.114	0.139 ± 0.178	0.93	0.76
Bif-IMT_{max}	The highest maximal IMT value measured in the 6 Bif segments	0.093 ± 0.122	0.204 ± 0.26	0.84	0.68
ICA-IMT_{mean}	Average of 6 mean IMT values obtained by measuring left and right ICAs (the first cm proximal to bifurcations) in the 3 scan angles (lateral, anterior, and posterior)	0.17 ± 0.204	0.195 ± 0.153	0.95	0.94
ICA-IMT_{max}	The highest maximal IMT value measured in the 6 ICA segments	0.195 ± 0.283	0.331 ± 0.459	0.91	0.60
IMT_{mean}	Average of 1^{st}CC-IMT_{mean}, CC-IMT_{mean}, Bif-IMT_{mean}, and ICA-IMT_{mean}, left and right carotid arteries	0.038 ± 0.05	0.054 ± 0.095	0.96	0.87
IMT_{max}	Highest value out of 1^{st}CC-IMT_{max}, CC-IMT_{max}, Bif-IMT_{max}, and ICA-IMT_{max} of left and right carotid arteries	0.164 ± 0.227	0.239 ± 0.238	0.95	0.89
$IMT_{mean-max}$	Average of maximal IMT measured in 8 segments (1^{st}CC, CC, Bif, and ICA in left and right carotid arteries)	0.096 ± 0.109	0.134 ± 0.145	0.95	0.88
ICCAD	Average of left and right interadventitia common carotid artery diameters	0.037 ± 0.037	0.031 ± 0.023	0.99	0.99

Reproducibility data between 125 intrasonographer and 32 intersonographer duplicate scans are also reported. Composite variables (IMT_{mean}, IMT_{max}, and $IMT_{mean-max}$) refer to the whole carotid tree. 1^{st}CC = first centimeter of the common carotid; Bif = bifurcation; CC = common carotid; ICA = internal carotid artery; ICC = intraclass correlation coefficient; IMT = intima-medial thickness.

Ethical considerations. The study complies with the rules of good clinical practice and with the ethical principles established in the Declaration of Helsinki, and was approved by 7 independent ethics committees. All patients gave written informed consent.

Statistical analysis. Quantitative variables were reported as mean ± SD. Variables with skewed distributions were presented as median and interquartile range, and log-transformed before analysis. Categorical variables were reported as frequency and percentage. Cox models were used to estimate crude and adjusted hazard ratios (HRs) and to compute adjusted Kaplan-Meier survival curves. Integrated discrimination improvement (IDI), net reclassification improvement (NRI), and C-statistics were used to identify the best ultrasonographic variables for predictive purposes, and to assess their potential to improve risk prediction based on Framingham risk factors (FRFs) (age, sex, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, hypertension, diabetes, current smoking, and antihypertensive treatments) (details in the Online Appendix). We used FRFs instead of the Framingham risk score (FRS) as this algorithm is not specifically calibrated for a European population.

All statistical tests were 2-sided at a level of significance of 0.05 or 0.01, as indicated. The Bonferroni method was applied to account for multiple comparisons. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina). Reclassification statistics were assessed with the SAS macros published by Cook and Ridker (23).

Results

Baseline characteristics of participants with and without CVEs are shown in Table 2. Mean age was 64.2 years, and 47.9% of subjects were males. A total of 514 (13.9%) participants were free of relevant pharmacological treatments.

Follow-up and cardiovascular events. Over a median follow-up of 36.2 months (interquartile range: 35.8 to 37.4), 215 CVEs occurred (incidence per 1,000 person-years = 19.9): 125 CVEs were coronary, 73 cerebrovascular, and 17 peripheral. Number of subjects lost to follow-up was 238 (6.4%) (details of CVEs and those lost to follow-up are in the Online Appendix).

C-IMT, ICCAD, and risk of combined endpoint. All measures of C-IMT and ICCAD were significantly associated with the risk of combined CVEs (Table 3), both before (Model 1) and after (Model 2) adjustment for age and sex (all $p < 0.0042$; threshold according to Bonferroni correction for 12 comparisons). The adjusted HR for 1 SD increase ranged from 1.27 (1^{st}CC-IMT_{max}) to 1.47 ($IMT_{mean-max}$) for IMT variables, and was 1.41 for ICCAD. These associations remained significant according to Bonferroni criteria even after stratification by center and adjustment for VRFs (Model 3). Of note, the effect of the

Table 2 Baseline Characteristics of IMPROVE Study Participants With and Without Vascular Events

	Entire Sample (N = 3,703)	Without Event (n = 3488)	With Event (n = 215)	p Value
Kuopio (pooled)	1,048 (28.3)	972 (27.9)	76 (35.3)	
Stockholm	532 (14.4)	508 (14.6)	24 (11.2)	
Groningen	527 (14.2)	478 (13.7)	49 (22.8)	<0.0001
Paris	501 (13.5)	476 (13.6)	25 (11.6)	
Milan	553 (14.9)	533 (15.3)	20 (9.30)	
Perugia	542 (14.6)	521 (14.9)	21 (9.77)	
Anthropometric variables				
Male	1,774 (47.9)	1,641 (47.0)	133 (61.9)	<0.0001
Age, yrs	64.2 ± 5.4	64.1 ± 5.40	65.4 ± 5.84	0.0012
BMI, kg/m^2	27.3 ± 4.27	27.2 ± 4.25	28.0 ± 4.56	0.023
Waist/hip ratio	0.92 ± 0.09	0.92 ± 0.09	0.94 ± 0.08	<0.0001
Diastolic blood pressure, mm Hg	82.0 ± 9.8	81.9 ± 9.75	82.8 ± 10.4	0.32
Systolic blood pressure, mm Hg	142.0 ± 18.5	141.7 ± 18.3	145.8 ± 20.5	0.010
Smoking habits				
Current smokers	549 (14.8)	501 (14.4)	47 (21.9)	
Former smokers	1,371 (37.0)	1,272 (36.5)	96 (44.7)	<0.0001
Never smokers	1,783 (48.2)	1,712 (49.1)	71 (33.0)	
Pack-years*	18 (8–30)	18 (8–30)	21 (11–30)	0.06
Biochemical markers				
Total cholesterol, mmol/l	5.49 ± 1.13	5.49 ± 1.13	5.50 ± 1.05	0.75
HDL cholesterol, mmol/l	1.26 ± 0.36	1.27 ± 0.36	1.18 ± 0.30	0.0007
Triglycerides, mmol/l	1.3 (0.93, 1.89)	1.3 (0.92, 1.87)	1.48 (1.09, 2.17)	0.0001
LDL cholesterol, mmol/l	3.54 ± 1.01	3.55 ± 1.01	3.53 ± 0.94	0.75
Uric acid, μmol/l	310 (263–360)	309 (263–359)	329 (274–390)	0.0003
hs-CRP, mg/l	2.06 (0.96–3.80)	2.05 (0.95–3.75)	2.30 (1.22–4.63)	0.012
Blood glucose, mmol/l	5.92 ± 1.64	5.91 ± 1.65	6.05 ± 1.42	0.013
Creatinine, μmol/l	79 (68–91)	79 (68–90)	84 (74–97)	<0.0001
Personal history				
Hypercholesterolemia	2,581 (69.7)	2,450 (70.2)	131 (60.9)	0.004
Hypertriglyceridemia	954 (25.8)	893 (25.6)	61 (28.4)	0.37
Low HDL	488 (13.2)	449 (12.9)	39 (18.1)	0.027
Hypertension	2,552 (68.9)	2,391 (68.5)	161 (74.9)	0.053
Diabetes	913 (24.7)	846 (24.3)	67 (31.2)	0.023
Framingham risk score	22.6 (14.3–34.4)	22.2 (14.2–33.8)	30.8 (19.1–47.6)	<0.0001
≤5%	43 (1.20)	42 (1.2)	1 (0.5)	
>5, ≤10%	354 (9.6)	347 (9.9)	7 (3.3)	
>10, ≤15%	570 (15.4)	546 (15.7)	24 (11.2)	
>15, ≤20%	564 (15.2)	539 (15.5)	25 (11.6)	
>20%	2,021 (54.6)	1,875 (53.8)	146 (67.9)	<0.0001

Continued on next page

adjustment for pharmacological treatments was almost negligible (Model 4).

Figure 1 shows the FRS-adjusted Kaplan-Meier incidence curves after stratifying subjects into 4 groups according to $IMT_{mean\text{-}max}$ and ICCAD above or below their respective medians. The apparent additive effect shown in this figure was confirmed when $IMT_{mean\text{-}max}$ and ICCAD were mutually adjusted in a Cox model including age and sex. HRs for 1 SD increase of $IMT_{mean\text{-}max}$ and ICCAD were 1.36 (95% confidence interval [CI]: 1.18 to 1.58, $p < 0.001$) and 1.18 (95% CI: 1.01 to 1.38, $p = 0.03$), respectively. No significant interaction ($p = 0.63$) was found between $IMT_{mean\text{-}max}$ and ICCAD.

$IMT_{mean\text{-}max}$, ICCAD, and risk of coronary and cerebrovascular endpoints. The HRs of coronary and cerebrovascular endpoints for selected IMT variables and ICCAD, are shown in Table 4. Age- and sex-adjusted standardized HRs ranged from 1.19 to 2.51 and were generally higher for cerebrovascular endpoints. No significant interaction between ultrasonographic variables and type of vascular event was found, with p values of Model 3 ranging from 0.237 to 0.900.

Online Table 2 shows the same analysis as in Table 4, but restricted to "hard clinical events." Although no significant association with hard coronary events was detected, most of the measures of C-IMT and ICCAD remained significantly

Table 2 Continued

	Entire Sample (N = 3,703)	Without Event (n = 3488)	With Event (n = 215)	p Value
Family history				
CHD	2,315 (62.5)	2,165 (62.1)	146 (67.9)	0.062
CVD	1,322 (35.7)	1,240 (35.6)	81 (37.7)	0.53
PVD	443 (12.0)	412 (11.8)	29 (13.5)	0.42
Therapies				
Statins	1,483 (40.0)	1,408 (40.4)	75 (34.9)	0.11
Fibrates	284 (7.7)	274 (7.86)	12 (5.58)	0.23
Fish oil	125 (3.4)	120 (3.44)	5 (2.33)	0.38
Other lipid-lowering drugs	23 (0.62)	21 (0.60)	2 (0.93)	0.55
Beta blockers	878 (23.7)	815 (23.4)	64 (29.8)	0.03
Calcium antagonists	603 (16.3)	558 (16.0)	45 (20.9)	0.06
ACE inhibitors	722 (19.5)	683 (19.6)	39 (18.1)	0.60
Alpha-2 inhibitors	45 (1.22)	42 (1.20)	3 (1.40)	0.80
Sartans	562 (15.2)	529 (15.2)	33 (15.3)	0.94
Diuretics	857 (23.1)	804 (23.1)	53 (24.7)	0.59
Antiplatelet agents	618 (16.7)	561 (16.1)	57 (26.5)	<0.0001
Insulin	141 (3.81)	131 (3.76)	10 (4.65)	0.51
Estrogen supplement	226 (11.7)	220 (6.31)	6 (2.79)	0.04
Ultrasonographic variables, mm				
CC-IMT$_{mean}$	0.71 (0.65–0.80)	0.71 (0.65–0.79)	0.77 (0.69–0.88)	<0.0001
1stCC-IMT$_{mean}$	0.76 (0.69–0.87)	0.76 (0.69–0.86)	0.81 (0.73–0.96)	<0.0001
Bif-IMT$_{mean}$	1.06 (0.85–1.34)	1.05 (0.84–1.33)	1.17 (0.94–1.55)	<0.0001
ICA-IMT$_{mean}$	0.75 (0.64–1.00)	0.75 (0.63–0.98)	0.89 (0.68–1.23)	<0.0001
CC-IMT$_{max}$	1.07 (0.96–1.30)	1.06 (0.95–1.30)	1.15 (1.03–1.48)	<0.0001
1stCC-IMT$_{max}$	1.08 (0.96–1.30)	1.08 (0.96–1.27)	1.18 (1.01–1.48)	<0.0001
Bif-IMT$_{max}$	1.67 (1.30–2.22)	1.67 (1.30–2.22)	1.93 (1.45–2.59)	<0.0001
ICA-IMT$_{max}$	1.17 (0.93–1.76)	1.16 (0.92–1.74)	1.48 (1.02–2.20)	<0.0001
IMT$_{mean}$	0.85 (0.74–1.00)	0.84 (0.74–0.99)	0.95 (0.81–1.13)	<0.0001
IMT$_{max}$	1.85 (1.39–2.50)	1.85 (1.39–2.48)	2.31 (1.65–2.89)	<0.0001
IMT$_{mean-max}$	1.34 (1.12–1.65)	1.33 (1.12–1.63)	1.52 (1.28–1.89)	<0.0001
Plaque†, No.(%)	2,576 (69.5)	2,397 (68.7)	179 (83.2)	<0.0001
ICCAD	7.74 (7.22–8.32)	7.72 (7.20–8.30)	8.13 (7.53–8.66)	<0.0001

Values are n (%), mean ± SD, or median (interquartile range). p Values were calculated by Wilcoxon test or by chi-square as appropriate. To convert biochemical markers in mg/dl, divide values of total and HDL cholesterol by 0.0259016, values of triglycerides by 0.0113815, values of uric acid by 59.48, values of blood glucose by 0.0556122, and values of creatinine by 87.777778. The Framingham risk score was not calculated in 151 patients because of missing data in 1 of the variables included in the algorithm. *Calculated excluding never smokers. †Plaque = presence of at least 1 plaque.

ACE = angiotensin-converting enzyme; BMI = body mass index; CHD = coronary heart disease; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; other abbreviations as in Table 1.

associated with ischemic stroke according to Bonferroni criteria, even after adjustment for age and sex (Models 1 and 2). In Model 3, only ICCAD remained significantly associated with ischemic stroke after Bonferroni correction.

Performance of several measures of subclinical atherosclerosis as predictors of subsequent CVEs. IDI values in Table 5 show that IMT$_{mean}$ and IMT$_{mean-max}$, and their combination with ICCAD, performed better than CC-IMT$_{mean}$ (the IMT variable most widely used in ultrasonographic studies). The NRI using these variables ranged from 10.7% (IMT$_{mean}$) to 20.1% (ICCAD + IMT$_{max}$). When the analysis was repeated considering coronary or cerebrovascular endpoints, composite IMT variables performed better than CC-IMT$_{mean}$ in the reclassification of cerebrovascular events, but not in reclassification of coronary events. Regardless of the type of endpoint considered, models with the combination ICCAD + IMT$_{mean}$ or IMT$_{mean-max}$ always performed significantly better than CC-IMT$_{mean}$.

Table 6 shows that in IDI analysis, the variable "Presence of at least 1 plaque," defined as IMT$_{max}$ >1.5, performed significantly better than IMT$_{mean}$ only when the latter was measured in plaque-free areas; otherwise, the predictive value of the plaque presence alone was always significantly worse.

Incremental value of C-IMT with respect to FRFs. The combination of IMT variables or ICCAD with FRFs added little to the overall risk discrimination based on FRFs alone in receiver-operating characteristic (ROC) analyses (all p values >0.05), but performed significantly better than FRFs alone in reclassification analyses (Table 7). In most cases, IDI values reached statistical significance even after Bonferroni correction. The combination of FRFs plus composite IMTs plus ICCAD provided the highest score in risk

Table 3 HRs (95% CI) of Combined Vascular Endpoints per 1 SD Increase for Ultrasonographic Continuous (Log-Transformed) Variables

	Model 1	Model 2	Model 3	Model 4
CC-IMT$_{mean}$	1.44 (1.29–1.61)	1.33 (1.18–1.50)	1.30 (1.14–1.49)	1.31 (1.14–1.49)
1stCC-IMT$_{mean}$	1.40 (1.25–1.57)	1.30 (1.16–1.47)	1.26 (1.10–1.44)	1.26 (1.10–1.44)
Bif-IMT$_{mean}$	1.40 (1.23–1.59)	1.28 (1.12–1.47)	1.25 (1.08–1.45)	1.24 (1.08–1.44)
ICA-IMT$_{mean}$	1.43 (1.28–1.61)	1.34 (1.18–1.51)	1.26 (1.10–1.44)	1.27 (1.11–1.44)
CC-IMT$_{max}$	1.37 (1.23–1.53)	1.28 (1.14–1.44)	1.27 (1.12–1.44)	1.27 (1.12–1.44)
1stCC-IMT$_{max}$	1.35 (1.21–1.51)	1.27 (1.13–1.43)	1.22 (1.08–1.39)	1.22 (1.07–1.38)
Bif-IMT$_{max}$	1.39 (1.22–1.59)	1.29 (1.12–1.47)	1.27 (1.09–1.47)	1.26 (1.08–1.46)
ICA-IMT$_{max}$	1.46 (1.29–1.65)	1.36 (1.20–1.55)	1.30 (1.13–1.49)	1.30 (1.14–1.50)
IMT$_{mean}$	1.58 (1.40–1.78)	1.45 (1.28–1.66)	1.39 (1.21–1.61)	1.39 (1.21–1.61)
IMT$_{max}$	1.49 (1.31–1.71)	1.38 (1.20–1.58)	1.35 (1.16–1.57)	1.35 (1.16–1.57)
IMT$_{mean-max}$	1.59 (1.40–1.81)	1.47 (1.29–1.68)	1.43 (1.23–1.65)	1.43 (1.23–1.65)
ICCAD	1.54 (1.36–1.74)	1.41 (1.23–1.62)	1.28 (1.09–1.50)	1.27 (1.08–1.50)

Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, and VRFs (LDL-C, HDL-C, systolic blood pressure, personal history of diabetes and of hypertension, family history of diabetes, family history of hypertension, pack-years), and stratified by center; Model 4 as Model 3 plus pharmacological treatments (statins, beta-blockers, ACE inhibitors, diuretics, and calcium antagonists). All $p < 0.0042$; threshold according to Bonferroni correction for 12 comparisons. This threshold was selected even if some of the IMT variables were not statistically independent (for example, IMT$_{mean-max}$ and IMT$_{mean}$) in order to be conservative.

CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; VRF = vascular risk factor; other abbreviations as in Tables 1 and 2.

classification. The further inclusion of plaque presence increased NRI from 12.1% to 13.0%. The use of the FRS in place of FRFs in reclassification analyses provided similar results (data not shown).

Table 8 shows the estimated 10-year CVE risk categories according to FRFs before and after adding ICCAD and IMT$_{mean-max}$. The overall NRI was 12% ($p = 0.003$), and 35.9% of subjects at intermediate risk were reclassified.

Sex differences. Men and women differed in mean values for many baseline variables (data not shown), but no significant interactions with sex were found in any of the analyses presented.

Discussion

In this study of Europeans with at least 3 VRFs, but no overt cardiovascular or cerebrovascular disease, we found

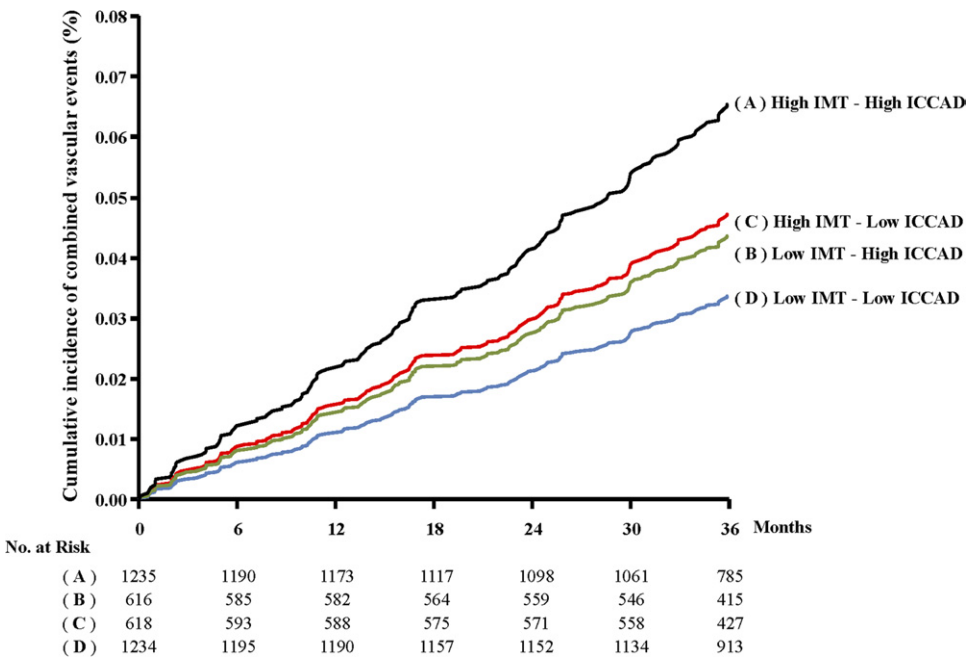

Figure 1 FRS-Adjusted Kaplan-Meier Incidence Curves

The study population was stratified according to IMT$_{mean-max}$ and ICCAD values above or below their respective medians (1.34 mm and 7.74 mm, respectively). Curves were computed for the mean value of FRS (22.6%). FRS = Framingham Risk score; ICCAD = interadventitia common carotid artery diameter; IMT$_{mean-max}$ = mean–maximum intima-media thickness.

Table 4 HRs (95% CI) of Coronary and Cerebrovascular Endpoints per 1 SD Increase for Ultrasonographic Continuous (Log-Standardized) Variables

	Model 1	Model 2	Model 3
Coronary endpoints (n = 125)			
CC-IMT$_{mean}$	**1.40 (1.22–1.62)***	**1.27 (1.09–1.49)***	**1.25 (1.05–1.49)**
CC-IMT$_{max}$	**1.30 (1.12–1.50)***	**1.19 (1.02–1.39)**	1.17 (0.99–1.39)
IMT$_{mean}$	**1.51 (1.29–1.76)***	**1.35 (1.14–1.59)***	**1.26 (1.04–1.53)**
IMT$_{max}$	**1.42 (1.20–1.68)***	**1.27 (1.07–1.52)***	1.21 (1.00–1.47)
IMT$_{mean-max}$	**1.52 (1.29–1.78)***	**1.36 (1.14–1.61)***	**1.28 (1.05–1.55)**
ICCAD	**1.48 (1.26–1.73)***	**1.30 (1.09–1.55)***	1.19 (0.96–1.46)
Cerebrovascular endpoints (n = 73)			
CC-IMT$_{mean}$	**1.46 (1.21–1.75)***	**1.38 (1.13–1.69)***	**1.36 (1.09–1.71)***
CC-IMT$_{max}$	**1.40 (1.16–1.68)***	**1.34 (1.10–1.62)***	**1.34 (1.09–1.65)***
IMT$_{mean}$	**1.70 (1.39–2.08)***	**1.63 (1.32–2.03)***	**1.58 (1.25–2.01)***
IMT$_{max}$	**1.65 (1.31–2.07)***	**1.56 (1.23–1.98)***	**1.58 (1.22–2.04)***
IMT$_{mean-max}$	**1.74 (1.41–2.15)***	**1.67 (1.33–2.09)***	**1.66 (1.30–2.13)***
ICCAD	**1.63 (1.33–2.00)***	**1.63 (1.29–2.06)***	**1.53 (1.17–2.01)***

Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, and vascular risk factors (LDL-C, HDL-C, systolic blood pressure, personal history of diabetes and of hypertension, family history of diabetes, family history of hypertension, pack-years), pharmacological treatments (statins, beta-blockers, ACE inhibitors, diuretics and calcium antagonists) and stratified by center. Hazard ratios with $p < 0.05$ are in **bold**. *$p < 0.0083$: threshold according to Bonferroni correction for 6 comparisons. This threshold was selected even if some of the IMT variables were not statistically independent (e.g., IMT$_{mean-max}$ and IMT$_{mean}$) in order to be conservative.

Abbreviations as in Tables 1 and 3.

that increased IMTs and ICCAD enlargement are independent predictors of CVEs. Importantly, the HRs of these ultrasonographic variables remained significant after adjustment for pharmacological treatment. Thus, even in the presence of effective antiatherosclerotic treatments, IMT and ICCAD provide additional information that can be used as an adjunct to FRFs to refine the estimate of cardiovascular risk. The HRs found in our study are in line with those reported in the CHS (Cardiovascular Health Study) (24), ARIC (Atherosclerosis Risk in Communities) (25,26), and Rotterdam (27) studies, despite considerable differences in ultrasound protocols and population characteristics.

Are composite IMT measurements better predictors than CC-IMT? Consistently with other studies (4,24–26,28,29), we found that the 11 IMT variables considered were all significantly associated with combined CVEs. However, using reclassification analyses, we showed that there is a significant advantage in using IMT$_{mean}$ or IMT$_{mean-max}$ over CC-IMT—but this is true only when combined CVEs

Table 5 Reclassification Statistics for Ultrasonographic Variables as Compared With Classification Based on CC-IMT$_{mean}$ Only in Risk Models With Combined, Coronary, or Cerebrovascular Endpoints

	NRI (%) (95% CI)			IDI (99% CI)		
New Model	Combined Endpoints	Cerebrovascular Endpoints	Coronary Endpoints	Combined Endpoints	Cerebrovascular Endpoints	Coronary Endpoints
1stCC-IMT$_{mean}$	−0.1 (−7.9 to 7.6)	1.4 (−12.4 to 15.2)	2.1 (−9.6 to 13.8)	−0.004 (−0.013 to 0.005)	−0.004 (−0.011 to 0.003)	−0.003 (−0.011 to 0.005)
Bif-IMT$_{mean}$	−2.0 (−14.3 to 10.3)	−3.1 (−21.4 to 15.1)	−6.9 (−22.5 to 8.6)	−0.009 (−0.022 to 0.005)	−0.004 (−0.014 to 0.006)	−0.009 (−0.02 to 0.002)
ICA-IMT$_{mean}$	−0.7 (−13.1 to 11.8)	16.6 (−3.9 to 37.1)	−3.2 (−19.9 to 13.5)	−0.003 (−0.018 to 0.011)	0.013 (0.0003 to 0.027)	−0.009 (−0.021 to 0.002)
CC-IMT$_{max}$	−3.9 (−11.5 to 3.6)	2.1 (−8.5 to 12.6)	−6.6 (−16.9 to 3.7)	−0.006 (−0.013 to 0.003)	−0.002 (−0.007 to 0.004)	−0.008 (−0.013 to 0.003)
1stCC-IMT$_{max}$	−2.4 (−11.6 to 6.7)	−3.4 (−17.2 to 10.4)	0.9 (−12.5 to 14.3)	−0.009 (−0.019 to 0.001)	−0.006 (−0.014 to 0.002)	−0.006 (−0.015 to 0.002)
Bif-IMT$_{max}$	−1.5 (−13.6 to 10.5)	−0.8 (−20.3 to 18.7)	−5.7 (−21.7 to 10.4)	−0.010 (−0.024 to 0.003)	−0.001 (−0.011 to 0.011)	−0.012 (−0.023 to 0.001)
ICA-IMT$_{max}$	−2.9 (−16.1 to 10.2)	15.1 (−4.6 to 34.8)	0.1 (−17.2 to 17.4)	−0.004 (−0.018 to 0.011)	0.008 (−0.005 to 0.021)	−0.007 (−0.019 to 0.005)
ICCAD	4.9 (−7.7 to 17.5)	3.3 (−13.6 to 20.2)	1.7 (−13.7 to 17.1)	0.008 (−0.005 to 0.02)	0.007 (−0.003 to 0.018)	0.0002 (−0.01 to 0.01)
IMT$_{max}$	9.2 (−3.0 to 21.3)	6.8 (−12.3 to 25.9)	0.9 (−14.7 to 16.5)	**0.015 (0.003 to 0.027)***	0.009 (−0.003 to 0.020)	−0.005 (−0.016 to 0.006)
IMT$_{mean}$	10.7 (−0.6 to 22.1)	8.7 (−8.6 to 26.1)	3.3 (−11.1 to 17.6)	0.0004 (−0.013 to 0.014)	**0.015 (0.005 to 0.025)***	0.005 (−0.005 to 0.014)
IMT$_{mean-max}$	**11.6 (0.1 to 23.1)**	11.6 (−5.7 to 29.0)	6.0 (−9.7 to 21.7)	**0.014 (0.002 to 0.026)**	**0.018 (0.007 to 0.028)***	0.003 (−0.007 to 0.012)
ICCAD + CC-IMT$_{mean}$	**11.0 (1.6 to 20.4)**	11.5 (−3.4 to 26.4)	5.1 (−8.3 to 18.4)	**0.015 (0.006 to 0.023)***	**0.010 (0.002 to 0.018)***	0.006 (−0.0004 to 0.012)
ICCAD + IMT$_{max}$	**20.1 (7.1 to 33.1)***	19.8 (−0.1 to 39.7)	6.0 (−9.7 to 21.7)	**0.023 (0.009 to 0.036)***	**0.022 (0.010 to 0.034)***	0.007 (−0.003 to 0.018)
ICCAD + IMT$_{mean}$	**17.8 (6.1 to 29.5)***	15.1 (−3.5 to 33.8)	9.9 (−4.8 to 24.6)	**0.028 (0.016 to 0.039)***	**0.023 (0.012 to 0.034)***	**0.011 (0.002 to 0.021)**
ICCAD + IMT$_{mean-max}$	**19.9 (7.5 to 32.3)***	**19.4 (1.2 to 37.7)**	**9.8 (−5.1 to 24.7)**	**0.028 (0.016 to 0.04)***	**0.026 (0.015 to 0.037)***	**0.010 (0.001 to 0.020)**

When NRI and/or IDI values are positive with a $p < 0.01$ (in bold), then the new model (first column) is better than the model that includes CC-IMT$_{mean}$ only and vice versa. Hazard ratios with $p < 0.05$ are in **bold**. *$p < 0.0033$: threshold according to Bonferroni correction for 15 comparisons. This threshold was selected even if some of IMT variables were not statistically independent (for example, IMT$_{mean-max}$ and IMT$_{mean}$) in order to be conservative.

IDI = integrated discrimination improvement; NRI = net reclassification improvement; other abbreviations as in Tables 1 and 3.

Table 6 Reclassification Statistics Comparing Ultrasonographic Variables and Plaque Information (Presence of at Least 1 Plaque) in Risk Models With Combined Vascular Endpoints

New Model	Reference Model	NRI (95% CI)	p Value	IDI (99% CI)	p Value
Plaque	IMT_{mean} measured in plaque-free areas	0.8% (−9.6 to 11.2)	0.88	0.017 (0.004 to 0.03)	<0.001
Plaque	IMT_{mean} measured in all areas (including plaque)	−8.5% (−19.0 to 1.9)	0.11	−0.029 (−0.041 to −0.017)	<0.001
Plaque	IMT_{max}	−7.9% (−18.0 to 2.2)	0.13	−0.014 (−0.023 to −0.006)	<0.0001
Plaque	$IMT_{mean\text{-}max}$	−10.4% (−20.5 to −0.3)	0.04	−0.028 (−0.04 to −0.017)	<0.001

When NRI and/or IDI values are positive with a $p < 0.05$ and $p < 0.01$, respectively then the new model is better than the reference model and vice versa.
Abbreviations as in Tables 1, 3, and 5.

or cerebrovascular events are considered. In line with the ARIC study (30), CC-IMT was as good as composite IMT variables in improving the prediction of coronary events (Tables 4 and 5). A possible explanation is that the presence of atherosclerosis in the bifurcation or in the internal carotid may actually *cause* cerebrovascular events, whereas it is merely a *marker* of coronary atherosclerosis. Interestingly, in reclassification analyses, composite IMTs that incorporate plaques in their measurement performed significantly better than the presence of plaque.

ICCAD as predictor of vascular events. Compared with CC-IMT alone, the best reclassification was obtained by combining $IMT_{mean\text{-}max}$ and ICCAD. The NRI using this combination was >19% for combined and cerebrovascular events and 9.8% for coronary events.

Although prospective studies (31) suggest a role for IMT as a predictor of myocardial infarction and stroke, evidence on the predictive capacities of ICCAD is sparse. Two studies reported that IMT is a predictor of CVEs independently of lumen diameter (32,33). Only 1 large population study (9) showed that even after adjusting for IMT and VRFs, right ICCAD was significantly associated with incident cardiac events. We also found the highest estimated cumulative incidence of events in subjects having both diameter enlargement and increased IMT. Despite this, Eigenbrodt et al. (9) reported that on the basis of ROC analyses, carotid diameter measures added little to overall risk discrimination, especially after VRF adjustment (9). Our own ROC curve analysis (Table 7) agrees with this finding, but using IDI statistics, the inclusion of ICCAD into a model based on FRFs significantly added to the overall risk discrimination.

C-IMTs and ICCAD are independent biomarkers of atherosclerosis. The fact that C-IMTs and ICCAD predict the risk of CVEs independently of each other, together with the finding that these variables are associated with different VRFs (14,34), suggests that IMTs and ICCAD represent independent arterial responses to different pathophysiological mechanisms. C-IMT assesses atherosclerosis, depending on whether atherosclerotic plaques are incorporated in IMT measurements or not. When plaques are incorporated, as in our case, IMT reflects atherosclerosis (27,35). Arterial diameter enlargement reflects at least 2 processes. The first is vascular remodeling in response to the

Table 7 Reclassification Statistics for the Added Value of Ultrasonographic Variables in Risk Models With Combined Endpoints, Carotid Segments, and Carotid Outcomes as Compared With a Reference Model Based on FRFs Only

New Model	AUC (New Model)	Total, n	Reclassified, n	Correctly Reclassified, n (%)	NRI % (95% CI)	p Value	IDI (99% CI)	p Value	p Bonferroni Holm
FRFs + CC-IMT_{mean}	0.687	3,381	622	380 (61)	4.8 (−1.5 to 11.2)	0.14	0.009 (0.002 to 0.016)	<0.01	<0.05
FRFs + 1^{st}CC-IMT_{mean}	0.690	3,384	548	331 (60)	5.2 (−1.0 to 11.5)	0.10	0.007 (0.001 to 0.014)	<0.01	0.06
FRFs + Bif-IMT_{mean}	0.686	3,364	568	318 (56)	2.7 (−2.7 to 8)	0.33	0.008 (0.002 to 0.013)	<0.001	<0.05
FRFs + ICA-IMT_{mean}	0.699	3,356	675	405 (60)	6.4 (−1.0 to 13.7)	0.09	0.011 (0.004 to 0.019)	<0.001	<0.01
FRFs + CC-IMT_{max}	0.686	3,381	539	335 (62)	8.2 (2 to 14.4)	0.01	0.008 (0.001 to 0.014)	<0.01	0.05
FRFs + 1^{st}CC-IMT_{max}	0.690	3,384	503	306 (61)	7.6 (1.8 to 13.4)	0.01	0.006 (0.001 to 0.012)	<0.01	0.13
FRFs + Bif-IMT_{max}	0.687	3,364	611	363 (59)	4.1 (−1.8 to 10.1)	0.17	0.008 (0.002 to 0.015)	<0.001	<0.05
FRFs + ICA-IMT_{max}	0.704	3,356	788	483 (61)	9.3 (1.6 to 16.9)	0.02	0.013 (0.005 to 0.021)	<0.0001	<0.01
FRFs + IMT_{max}	0.697	3,384	787	476 (60)	6.2 (−0.8 to 13.1)	0.08	0.013 (0.006 to 0.02)	<0.0001	<0.001
FRFs + IMT_{mean}	0.702	3,384	857	528 (62)	11.3 (3.6 to 19.1)	<0.01	0.016 (0.008 to 0.025)	<0.0001	<0.0001
FRFs + $IMT_{mean\text{-}max}$	0.708	3,384	915	568 (62)	10.5 (2.4 to 18.6)	0.01	0.018 (0.009 to 0.028)	<0.0001	<0.0001
FRFs + ICCAD	0.692	3,384	663	397 (60)	6.7 (0 to 13.3)	0.05	0.010 (0.003 to 0.018)	<0.001	<0.05
FRFs + ICCAD + IMT_{max}	0.705	3,384	924	572 (62)	5.9 (−1.9 to 13.6)	0.14	0.020 (0.01 to 0.029)	<0.0001	<0.0001
FRFs+ ICCAD + IMT_{mean}	0.706	3,384	935	601 (64)	11.4 (3.8 to 19)	<0.01	0.021 (0.011 to 0.031)	<0.0001	<0.0001
FRFs + ICCAD + $IMT_{mean\text{-}max}$	0.711	3,384	986	637 (65)	12.1 (4.0 to 20.1)	<0.01	0.023 (0.013 to 0.033)	<0.0001	<0.0001
FRFs + ICCAD + $IMT_{mean\text{-}max}$ + Plaque	0.710	3,384	1,010	647 (64)	13.0 (4.8 to 21.2)	<0.01	0.023 (0.013 to 0.034)	<0.0001	<0.0001

AUC of reference model = 0.674. When NRI and/or IDI values are positive with a $p < 0.05$ and $p < 0.01$, respectively, then the new model (first column) is better than the reference model (FRFs) and vice versa. Plaque = presence of at least 1 plaque, defined as IMT_{max} >1.5 mm.
AUC = area under the curve; FRF = Framingham risk factor; other abbreviations as in Tables 1, 3, and 5.

Table 8 Risk Reclassification Comparing the Extrapolated 10-Year Risk According to FRFs Before and After Adding ICCAD and $IMT_{mean-max}$ in the Prediction of Combined Vascular Events

	10-Year Risk Categories for FRFs Plus ICCAD Plus $IMT_{mean-max}$			
10-Year Risk Categories for FRFs	<10%	10%–20%	>20%	Reclassified, n (%)
<10%*				
n = 680 (20%)	571 (84%)	109 (16%)	0 (0%)	109 (16.0%)
Observed risk (95% CI)	8 (4.3–12.9)	9.7 (2–23.3)	NA	
10%–20%*				
n = 1,697 (50%)	364 (21.4%)	1087 (64.1%)	246 (14.5%)	610 (35.9%)
Observed risk (95% CI)	7.7 (3.3–13.9)	12.1 (8.5–16.3)	40.6 (26.8–57.4)	
>20%*				
n = 1,007 (30%)	2 (0.2%)	265 (26.3%)	740 (73.5%)	267 (26.5%)
Observed risk (95% CI)	NA	21.7 (12.4–33.6)	39.7 (31.5–48.9)	
NRI: 12.1%; p = 0.003				

*To be noticed, these categories differ from those predicted by the Framingham risk score (see Table 2) due to a recalibration of the risk estimation in our cohort.
NA = not applicable; other abbreviations as in Tables 1, 3, 5, and 7.

growth of local atherosclerotic plaques (36). The second, as measured in our study, is independent of the presence of focal atherosclerosis (being measured in plaque-free areas); this occurs as a compensatory response to VRFs (13,14) and associates fairly well with the coronary artery disease status (17). On this basis, it can be concluded that IMTs and ICCAD provide additional information on atherosclerotic burden, thus supporting the concept of their potential usefulness as independent biomarkers of this multifactorial disease. Our observation that individuals with an average FRS have a 6.5% risk of developing a first CVE over 3 years if their $IMT_{mean-max}$ and ICCAD are high, versus a 3.4% risk if these variables are low (Fig. 1), supports this concept.

C-IMTs, plaque, and ICCAD add predictive value to FRFs. It is also important to know whether C-IMT and/or ICCAD provide prognostic information for individuals over and above that provided by FRFs: the fact that these variables are significant and independent predictors of CVEs does not necessarily mean they will be useful in the clinic. This may be 1 reason for the reluctance of the medical community to adopt C-IMT as a clinical tool (18). Most of the authors using the ROC metric to address this topic (3–9) have concluded that the magnitude of any improvement is insufficient to change current clinical and public health efforts to reduce the burden of vascular diseases (3,6–8). Our own data based on ROC analyses are in line with such statements, as the addition of IMT and ICCAD to the risk models built on FRFs had marginal, nonsignificant effects on C-statistics (Table 7). However, the C-statistic is insensitive to small changes in predictive accuracy, and even well-established VRFs may be discarded as nonsignificant in some circumstances (37,38). Consequently, there is general agreement that newer methods such as reclassification statistics (IDI and NRI) must be applied (37,39). To the best of our knowledge, only 4 studies have so far used reclassification analyses to evaluate whether ultrasound measures add prognostic information over and above traditional VRFs (10,11,30,40). The first (10) concluded that, in subjects from the general population, models that included C-IMT do not consistently improve individual risk stratification over those including only traditional VRFs. The second and the third (11,30), using data from the ARIC cohort, showed that compared with a model that includes FRFs only, the model including FRFs plus C-IMT plus information on the presence of carotid plaques provided a modest improvement in the area under the curve and a significant NRI. The last study (40) showed that the addition of C-IMT to FRFs significantly improved risk classification in women, but not in men. Our results show that substantial improvements over FRFs alone can be obtained when IMT variables are used, especially when combined with ICCAD. Therefore, our findings provide new evidence to support the use of IMT variables and ICCAD, in addition to VRFs, for cardiovascular risk stratification in clinical practice, with a NRI of 12.1%. The difference from the conclusions of the previous studies (10,11) may be due to the characteristics of the IMPROVE subjects, who were chosen to have ≥3 VRFs instead of the lower-risk general population, and the use of composite IMT variables instead of only CC-IMT. Clearly, the individual assessment of composite IMT variables and ICCAD is time consuming compared with CC-IMT assessment alone (15 to 20 vs. 8 to 10 min). However, we believe that the benefits provided by a better risk classification may easily offset the additional costs.

We have shown that, focusing on the intermediate (10% to 20%) risk category, which represents the real gray decision area for many clinicians, the addition of ICCAD and $IMT_{mean-max}$ to a model based on FRFs allows, on average, the reclassification of 14.5% of subjects in the high-risk category (Table 8). Improving the predictability for this group would have significant clinical implications, because it means shifting subjects with the highest chance of developing a CVE to the risk category qualified for pharmacological treatment. The cost of such strategy can be roughly estimated from the number needed to screen to prevent 1 CVE. Table 8 also shows that, of the 1,697 subjects classified at intermediate risk by FRFs, 246 moved

to a higher-risk category, thus qualifying for pharmacological treatment, and in this group, the extrapolated 10-year incidence was 40.6% (100 events). Thus, assuming a treatment efficacy of 20% to 30% (41), from 20 to 30 events could be prevented, yielding a needed to screen ranging from 57 to 85 (i.e., 1,697/30 and 1,697/20). It has to be noticed that 26.3% of the high-risk subjects were downgraded to a lower-risk category, but this does not imply that these subjects should lose their qualification for pharmacological treatments. We believe, in fact, that the use of IMT for cardiovascular risk reclassification should be applied only to patients at intermediate risk.

Strengths and limitations. The IMPROVE study has several strengths. It examined a large number of ultrasonographic variables, which allowed us to identify the most informative segment and/or the best IMT summary measure to be used for predictive purposes. The study was conducted across 5 European countries. Methods of carotid image acquisition and measurement of C-IMT were standardized across centers (all sonographers were trained and certified, and all scans were analyzed blindly in the same reading center). With follow-up data obtained on 93.7% of patients, our results were minimally affected by "loss to follow-up" bias. Finally, the analyses were adjusted for many potential confounders not considered in previous studies, for example, pharmacological treatments.

There are also potential limitations. The findings can only be extrapolated cautiously to the general European population or to patients with fewer than 3 VRFs. However, the HRs we observed are similar to those reported in other large population studies (24–27). Also, it remains possible that systematic differences existed between recruiting centers (19). Finally, the low number of CVEs will have constrained the precision of estimates in the subgroups (coronary events and cerebrovascular events).

Conclusions

We conclude that C-IMT and ICCAD are independent predictors of CVEs in European high-risk individuals; these markers contribute significant incremental prediction beyond FRFs alone. A risk stratification strategy based on C-IMT and ICCAD as an adjunct to FRFs would seem to be a rational approach to the prevention of cardiovascular disease.

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Key Words: cardiovascular disease ■ carotid artery intima-media thickness ■ carotid diameter ■ reclassification analyses ■ risk prediction.

APPENDIX

For supplementary methods, tables, and a figure, as well as a list of the IMPROVE Study Group members, please see the online version of this article.