Common Carotid Intima-Media Thickness Measurements in Cardiovascular Risk Prediction
A Meta-analysis

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Context   The evidence that measurement of the common carotid intima-media thickness (CIMT) improves the risk scores in prediction of the absolute risk of cardiovascular events is inconsistent.

Objective   To determine whether common CIMT has added value in 10-year risk prediction of first-time myocardial infarctions or strokes, above that of the Framingham Risk Score.

Data Sources   Relevant studies were identified through literature searches of databases (PubMed from 1950 to June 2012 and EMBASE from 1980 to June 2012) and expert opinion.

Study Selection   Studies were included if participants were drawn from the general population, common CIMT was measured at baseline, and individuals were followed up for first-time myocardial infarction or stroke.

Data Extraction   Individual data were combined into 1 data set and an individual participant data meta-analysis was performed on individuals without existing cardiovascular disease.

Results   We included 14 population-based cohorts contributing data for 45 828 individuals. During a median follow-up of 11 years, 4007 first-time myocardial infarctions or strokes occurred. We first refitted the risk factors of the Framingham Risk Score and then extended the model with common CIMT measurements to estimate the absolute 10-year risks to develop a first-time myocardial infarction or stroke in both models. The C statistic of both models was similar (0.757; 95% CI, 0.749-0.764; and 0.759; 95% CI, 0.752-0.766). The net reclassification improvement with the addition of common CIMT was small (0.8%; 95% CI, 0.1%-1.6%). In those at intermediate risk, the net reclassification improvement was 3.6% in all individuals (95% CI, 2.7%-4.6%) and no differences between men and women.

Conclusion   The addition of common CIMT measurements to the Framingham Risk Score was associated with small improvement in 10-year risk prediction of first-time myocardial infarction or stroke, but this improvement is unlikely to be of clinical importance.

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CARDIOVASCULAR DISEASE IS among the leading causes of morbidity and mortality worldwide. Preventive treatment of high-risk asymptomatic individuals depends on accurate prediction of a person's risk to develop a cardiovascular event. Currently, cardiovascular risk prediction in asymptomatic individuals is based on the level of cardiovascular risk factors incorporated in scoring equations.[1] Several scores are available, with the Framingham Risk Score among the most widely used.[1,2] These risk equations perform reasonably well, yet there remains considerable overlap in estimated risk between those who are affected by a cardiovascular event and those who are not.[3] Improvement in cardiovascular risk prediction is needed and may be established by including a measure of preclinical atherosclerosis in the risk prediction algorithms[4] because athero-

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sclerosis underlies the occurrence of cardiovascular events, develops over decades, and has a prolonged asymptomatic phase during which it is possible to modify the course of the disease.[5]

Measurement of carotid intima-media thickness (CIMT) has been proposed to be added to cardiovascular risk factors to improve individual risk assessment.[6,7] So far, individual studies reported on the added value of CIMT measurements in cardiovascular risk prediction, but the evidence is not consistent across studies.[8-14] Furthermore, guidelines differ in their recommendations for using CIMT measurements in primary prevention and which patients to consider, ranging from measurement in all individuals[15] to measurement in only those at intermediate risk.[4] Therefore, solid and valid evidence on this issue is needed. The USE Intima-Media Thickness (USE-IMT) collaboration is a global meta-analysis project using individual participant data from prospective cohort studies to determine the added value of the CIMT to current risk prediction models in asymptomatic individuals at risk for cardiovascular disease.

METHODS

The USE-IMT project is an ongoing meta-analysis of individual participant data. Eligible cohorts are identified through literature searches of databases and through expert suggestion (the current analysis used PubMed from 1950 to June 2012 and EMBASE from 1980 to June 2012 using the search query published elsewhere[16]). A flowchart of the search (performed on June 19, 2012) and the inclusion in USE-IMT is displayed in eFigure 1 (available at http://www.jama.com). At present, 17 cohorts participate in USE-IMT of which 14 cohorts are included in this analysis. One cohort was excluded because only maximal common CIMT values were measured.[17] The individual information from 2 other cohorts was not available yet.[18,19] The cohorts were required to have available baseline data on age, sex, cigarette smoking status, antihypertensive medication use, blood pressure, cholesterol fractions, CIMT measure-

ments, history of cardiovascular disease and diabetes mellitus, and follow-up information on occurrence of cardiovascular events. Individual data from cohorts were collected and harmonized for the statistical analyses using SPSS version 17 (SPSS).

Study Population

Of the 63 514 individuals included in USE-IMT, we selected 45 828 individuals to whom the cardiovascular risk scores like Framingham Risk Score apply (aged 45-75 years, systolic blood pressure <180 mm Hg, total cholesterol <300 mg/dL; no symptomatic cardiovascular disease at baseline). Using these criteria, the number of excluded individuals was 6154 because of age, 2977 for total cholesterol level, 1757 for systolic pressure, and 7740 for previous cardiovascular disease (not mutually exclusive). Incomplete data on common CIMT, cardiovascular risk factors, and (time to) events resulted in 2.2% missing data points, which were imputed using single imputation for each cohort separately (using the Multivariate Imputation by Chained Equations package of R). Predictors in our imputation model included all variables in our database including the outcome of interest, as recommended previously.[20] For a sensitivity analysis, we also performed a complete case analysis.

Common CIMT and Outcome Measure

Per cohort, we averaged all available common CIMT measurements (from the number of angles; from either the far wall, near wall, or both; and from one or both sides of the neck). This choice was based on the observation that the magnitude of the relation between common CIMT and cardiovascular events risk do not differ greatly across various measures.[21] All CIMT values were used in the analysis, including values larger than 1 mm, which are suggestive of plaque. To account for differences in absolute CIMT levels across cohorts because of differences in methodology, we also calculated cohort-specific z scores, which were created by subtracting the individual

CIMT values from the cohort mean CIMT. This value was then divided by the cohort CIMT standard deviation. First-time myocardial infarction and first-time stroke were included as a combined end point. These included both fatal and nonfatal events.

Statistical Analysis

The original variables of the 10-year Framingham Risk Score[2] (age, sex, cigarette smoking status, blood pressure, antihypertensive medication use, total cholesterol level, high-density lipoprotein cholesterol level, and presence of diabetes mellitus) were first refit using multivariable Cox proportional-hazards model. This baseline model was then extended by a log-transformed common CIMT variable. Both models included cohort as a random effect using the frailty model. Heterogeneity in CIMT and events across cohorts was tested with a likelihood ratio test for interaction between cohort and CIMT in the Cox proportional-hazards model. In addition, we also tested for heterogeneity of the hazards ratios across cohorts using a random effects meta-analysis.

The improvement of addition of mean common CIMT to the baseline model was tested with the Wald test and the likelihood ratio test. The predictive performance of both models was assessed by comparing the predicted vs the 10-year observed risk, based on the Kaplan-Meier estimate (eFigure 2). The discriminative value of both models was expressed with Harrell C index.[22] The 10-year absolute risk to develop a myocardial infarction or stroke was calculated and was used to classify individuals into risk categories of less than 5% (low risk), 5% to less than 20% (intermediate risk), or 20% or greater (high risk) according to the risk classification of the Framingham Heart Study.[12] The net reclassification improvement was calculated and quantifies the percentage of correct movement across categories for those with and without events. Correct movement is upward classification by a new marker in those with events and downward classification for those without events. Our risk prediction model was

Table 1. Baseline Characteristics of the Cohorts in USE-IMT[a]

Source	Men, No.	Women, No.	Age, Mean (Range), y	SBP, mm Hg, Mean (SD)	No. (%) Smoking	Diabetes	Statin Use	Hypertensive Lowering Medication	Mean (SD) Total Cholesterol, mg/dL	HDL Cholesterol, mg/dL	Common CIMT, mm
ARIC,[25] 1994	6219	8099	54 (45-64)	120 (17.4)	3691 (26)	1530 (11)	3351 (23)	3920 (27)	212 (38)	54 (17)	0.65 (0.146)
CAPS,[26] 2006	1889	2000	52 (35-75)	128 (16.1)	810 (21)	103 (3)	180 (5)	743 (19)	224 (37)	58 (17)	0.74 (0.142)
Charlottesville,[27] 2006	341	269	57 (35-75)	138 (17.2)	52 (9)	21 (3)	150 (25)	264 (43)	220 (40)	46 (15)	0.82 (0.171)
CHS,[28] 2007	1183	1942	70 (65-75)	133 (18.6)	439 (14)	413 (13)	158 (5)	1141 (37)	212 (36)	54 (16)	0.85 (0.155)
FATE,[8] 2011	1438	3	51 (35-75)	128 (16.4)	184 (13)	38 (3)	130 (9)	163 (11)	205 (35)	50 (11)	0.72 (0.176)
Hoorn Study,[29] 2003	122	126	67 (60-75)	137 (18.4)	40 (16)	43 (17)	19 (8)	61 (25)	224 (37)	54 (15)	0.83 (0.152)
KIHD,[30] 1991	879		51 (42-61)	132 (14.6)	338 (39)	30 (3)	3 (1)	98 (11)	220 (35)	50 (12)	0.75 (0.157)
Malmö,[31] 2000	1973	2794	57 (46-68)	140 (17.4)	1077 (23)	356 (8)	118 (2)	692 (15)	232 (36)	54 (14)	0.76 (0.149)
MESA,[32] 2007	2800	3095	60 (44-75)	124 (19.3)	832 (14)	708 (12)	988 (17)	2093 (36)	193 (34)	50 (15)	0.74 (0.165)
Nijmegen Study,[33] 2009	562	638	61 (50-72)	128 (14.9)	194 (16)	58 (5)	97 (8)	238 (20)	224 (36)	54 (14)	0.83 (0.108)
NOMAS,[34] 2007	458	633	65 (50-75)	137 (17.5)	186 (17)	158 (14)	150 (19)	530 (49)	201 (37)	46 (14)	0.71 (0.087)
OSACA2 Study,[35] 2007	199	204	63 (39-75)	136 (17.3)	89 (22)	50 (12)	106 (26)	220 (55)	212 (33)	58 (16)	0.85 (0.258)
Rotterdam Study,[36] 1997	1536	2189	65 (55-75)	134 (19.2)	901 (24)	108 (3)	75 (20)	314 (8)	247 (35)	54 (14)	0.75 (0.137)
Tromsø Study,[37] 2000	2129	2111	60 (35-75)	141 (18.0)	1378 (3)	108 (3)	40 (1)	356 (8)	247 (36)	62 (17)	0.78 (0.152)
USE-IMT (total)	21 730	24 098	58 (35-75)	129 (19.4)	10 211 (22)	5131 (11)	5565 (12)	10 833 (24)	220 (40)	54 (17)	0.73 (0.163)

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CAPS, Carotid Atherosclerosis Progression Study; CHS, Cardiovascular Health Study; CIMT, carotid intima-media thickness; FATE, Firefighters and Their Endothelium Study; HDL, high-density lipoprotein; KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study; Malmö, Malmö Diet and Cancer Study; MESA, Multi-Ethnic Study of Atherosclerosis; Nijmegen Study, Nijmegen Biomedical Study; NOMAS, Northern Manhattan Study; OSACA2, Osaka Follow-up Study for Carotid Atherosclerosis 2; SBP, systolic blood pressure; USE-IMT, USE Intima-Media Thickness collaboration.
SI conversion factors: To convert total and HDL cholesterol to mmol/L, multiply by 0.0259.
[a] Values are based on the individuals in the cohorts after applying the inclusion criteria as described in the "Methods" section.

based on time-to-event data, which contain not only events and nonevents but also individuals who discontinue prematurely. Therefore, the number of individuals reclassified due to a change in risk category was then described using the net reclassification improvement taking survival time into account.[23] The corresponding 95% confidence intervals were obtained with bootstrapping.

We also calculated the net reclassification improvement for 4 risk categories: less than 5% (low risk), 5% to less than 10% (low to intermediate risk), 10% to less than 20% (intermediate to high risk), and 20% or greater (high risk) because the 4-level risk category approach is still widely used outside the United States. In addition, we assessed improvement without cutoff by risk categories using the integrated discrimination improvement, which can be seen as equal to differences in discrimination slopes.[24] The relative integrated discrimination improvement was calculated by dividing the integrated discrimination improvement by the discrimination of the baseline model (based on the predicted probabilities in those with events and those without events).[24]

Finally, the net reclassification improvement and the (relative) integrated discrimination improvement were assessed separately in men and women. This sex-specific analysis was performed as the relation between CIMT and first-time myocardial infarction or stroke was different for men and women (interaction term in Cox proportional hazards model, $P = .017$). In addition, we specifically addressed individuals classified in the intermediate-risk groups (according to the baseline model and defined as a 10-year absolute risk of 5% to 20%). All analyses were performed in the statistical environment R (version 2.10.0). We did not validate our model with CIMT measurements because the aim was not to create and validate a new prediction rule, but to assess the actual improvement in risk prediction. All statistical testing was 2-sided and a $P < .05$ was considered statistically significant.

RESULTS

Baseline characteristics of the cohorts are presented in TABLE 1. The majority of the studied population was white. Mean (SD) common CIMT in USE-IMT was 0.73 (0.16) mm. Mean CIMT increased with age in every cohort (eTable 1). The median (SD) follow-up in USE-IMT was 11 (3.7) years, during which 4007 first-time myocardial infarctions or first-time strokes occurred (TABLE 2).

Common CIMT and First-Time Myocardial Infarction or Stroke

The risk factors included in the Framingham Risk Score and increased common CIMT were all related to first-time myocardial infarction or stroke (eTable 2), and there was no evidence for heterogeneity in the relation between CIMT and outcome between studies (likelihood ratio rest for interaction, $P = .18$). Adjusted common CIMT was positively related to myocardial infarction and stroke with a hazard ratio per 0.1-mm difference of common CIMT of 1.12 (95% CI, 1.09-1.14) for women and 1.08 (95% CI, 1.05-1.11) for men. The hazard ratio per 0.1-mm difference of common CIMT was 1.08 (95% CI, 1.05-1.10) for myocardial infarction and 1.12 (95% CI, 1.10-1.15) for stroke. The study-specific hazard ratios for mean common CIMT and first-time myocardial infarction or stroke are displayed in FIGURE 1. Based on a ran-

Table 2. Baseline Risk and Follow-up Characteristics of the Cohorts in USE-IMT[a]

Source	Absolute 10-y Risk to Develop CVD Based on Framingham Risk Score Variables, % (SD)			Follow up, Median (IQR), y	MI, No.	Strokes, No.	First-Time MI or Stroke, No.
	Overall	Men	Women				
ARIC,[25] 1994	5.9 (5.2)	8.0 (5.9)	4.3 (3.8)	13.1 (12.3-13.9)	774	494	1196
CAPS,[26] 2006	4.5 (4.5)	5.8 (5.1)	3.3 (3.4)	8.1 (7.4-9.1)	59	77	130
Charlottesville,[27] 2006	5.4 (4.2)	6.5 (4.6)	4.1 (3.1)	4.1 (2.7-5.0)	5	3	8
CHS,[28] 2007	16.8 (10.0)	22.0 (11.1)	13.6 (7.7)	13.3 (8.8-14.5)	393	393	713
FATE,[8] 2011	3.8 (3.8)	3.8 (3.8)	0.5 (0.4)	8.0 (6.9-8.9)	23	10	33
Hoorn Study,[29] 2003	8.2 (5.8)	9.6 (5.6)	6.9 (5.7)	7.7 (7.5-8.2)	8	4	12
KIHD,[30] 1991	9.6 (5.8)	9.6 (5.8)		14.2 (13.2-15.2)	108	54	152
Malmö,[31] 2000	6.0 (4.9)	8.3 (5.8)	4.4 (3.4)	10.9 (10.2-11.6)	162	168	315
MESA,[32] 2007	5.5 (5.0)	7.1 (5.6)	4.2 (3.8)	6.5 (6.2-6.7)	98	72	167
Nijmegen Study,[33] 2009	5.5 (4.0)	7.2 (4.5)	4.0 (2.7)	3.9 (3.0-4.4)	12	5	17
NOMAS,[34] 2007	6.9 (5.1)	9.0 (6.0)	5.4 (3.7)	8.7 (5.7-10.3)	29	31	57
OSACA2 Study,[35] 2007	11.3 (8.3)	14.9 (9.1)	7.8 (5.7)	4.6 (3.3-6.1)	2	17	19
Rotterdam Study,[36] 1997	11.0 (7.3)	14.3 (8.1)	8.6 (5.6)	13.9 (10.6-14.8)	245	415	630
Tromsø Study,[37] 2000	11.9 (9.0)	14.7 (9.9)	9.0 (6.8)	10.7 (10.4-11.0)	366	228	558
USE-IMT (total)	7.5 (7.0)	9.4 (7.9)	5.8 (5.5)	10.8 (6.9-13.2)	2284	1971	4007

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CAPS, Carotid Atherosclerosis Progression Study; CHS, Cardiovascular Health Study; CIMT, carotid intima-media thickness; CVD, cardiovascular disease; FATE, Firefighters and Their Endothelium Study; HDL, high-density lipoprotein; IQR, interquartile range; KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study; Malmö, Malmö Diet and Cancer Study; MI, myocardial infarction; MESA, Multi-Ethnic Study of Atherosclerosis; Nijmegen Study, Nijmegen Biomedical Study; NOMAS, Northern Manhattan Study; OSACA2, Osaka Follow-up Study for Carotid Atherosclerosis 2; USE-IMT, USE Intima-Media Thickness collaboration.
[a] Values are based on the individuals in the cohorts after applying the inclusion criteria as described in the methods section.

dom-effects meta-analysis on the study-specific hazard ratios, there was no evidence for heterogeneity in CIMT and outcome between studies (Q test of heterogeneity P value, 0.24; I^2, 12.30%).
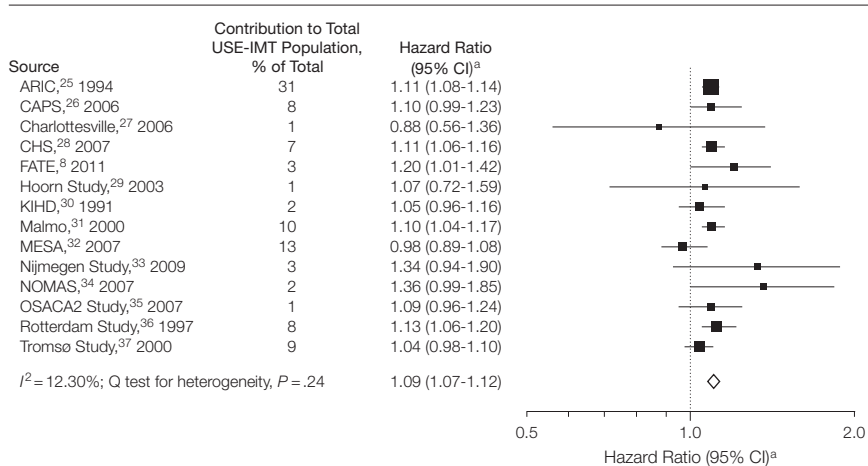
Calibration and Discrimination

The addition of mean common CIMT improved the baseline model (Wald test and likelihood ratio test, both $P < .001$). For both models, the 10-year predicted risk was closely in agreement with the 10-year cardiovascular disease risk as estimated with Kaplan-Meier (eFigure 2). Harrell C index for the baseline model was 0.757 (95% CI, 0.749-0.764) and 0.759 (95% CI, 0.752-0.766) with addition of common CIMT.

Net Reclassification

FIGURE 2A shows the distribution of the number of individuals without and with events across risk categories based on the Framingham Risk Score and the distribution of individuals after the addition of the common CIMT. More than 90% of the individuals remained in the same risk category. The numbers of individuals shifting downward or upward without and with events were similar.

Figure 1. Relation of Common Carotid Intima-Media Thickness With First-Time Myocardial Infarction or Stroke Across Studies

Source	Contribution to Total USE-IMT Population, % of Total	Hazard Ratio (95% CI)[a]
ARIC,[25] 1994	31	1.11 (1.08-1.14)
CAPS,[26] 2006	8	1.10 (0.99-1.23)
Charlottesville,[27] 2006	1	0.88 (0.56-1.36)
CHS,[28] 2007	7	1.11 (1.06-1.16)
FATE,[8] 2011	3	1.20 (1.01-1.42)
Hoorn Study,[29] 2003	1	1.07 (0.72-1.59)
KIHD,[30] 1991	2	1.05 (0.96-1.16)
Malmo,[31] 2000	10	1.10 (1.04-1.17)
MESA,[32] 2007	13	0.98 (0.89-1.08)
Nijmegen Study,[33] 2009	3	1.34 (0.94-1.90)
NOMAS,[34] 2007	2	1.36 (0.99-1.85)
OSACA2 Study,[35] 2007	1	1.09 (0.96-1.24)
Rotterdam Study,[36] 1997	8	1.13 (1.06-1.20)
Tromsø Study,[37] 2000	9	1.04 (0.98-1.10)
$I^2 = 12.30\%$; Q test for heterogeneity, $P = .24$		1.09 (1.07-1.12)

Study-specific hazard ratios (HRs) and the pooled hazard ratio based on a random-effects meta-analysis. Error bars indicate 95% CI; data marker sizes indicate the sample sizes of the cohorts.
[a] Hazard ratios are per 0.1-mm increase in common carotid intima-media thickness.

Figure 2B shows the observed risks of all the individuals in the categories. The observed risks of the individuals that remained in the same risk categories corresponded well to their allocated risk categories. Individuals reclassified to a higher risk category indeed had a significantly higher observed risk compared than those not reclassified. Also, individuals reclassified to a lower risk category indeed had a lower observed risk than those not reclassified. Yet the confidence intervals indicate some overlap in observed risk in categories of those reclassified.

The net reclassification improvement indicated that the added value of mean common CIMT was 0.8% (95% CI, 0.1%-1.6%) with no differences between men and women (TABLE 3). The sex-specific reclassification tables are displayed in eFigures 3 and 4. The integrated discrimination improvement was 0.0024 (Table 3). The discrimination of the baseline model based on the predicted probabilities in those with and without events was 0.067. Thus, the relative integrated discrimination improvement was 3.6% and similar in men and women (Table 3).
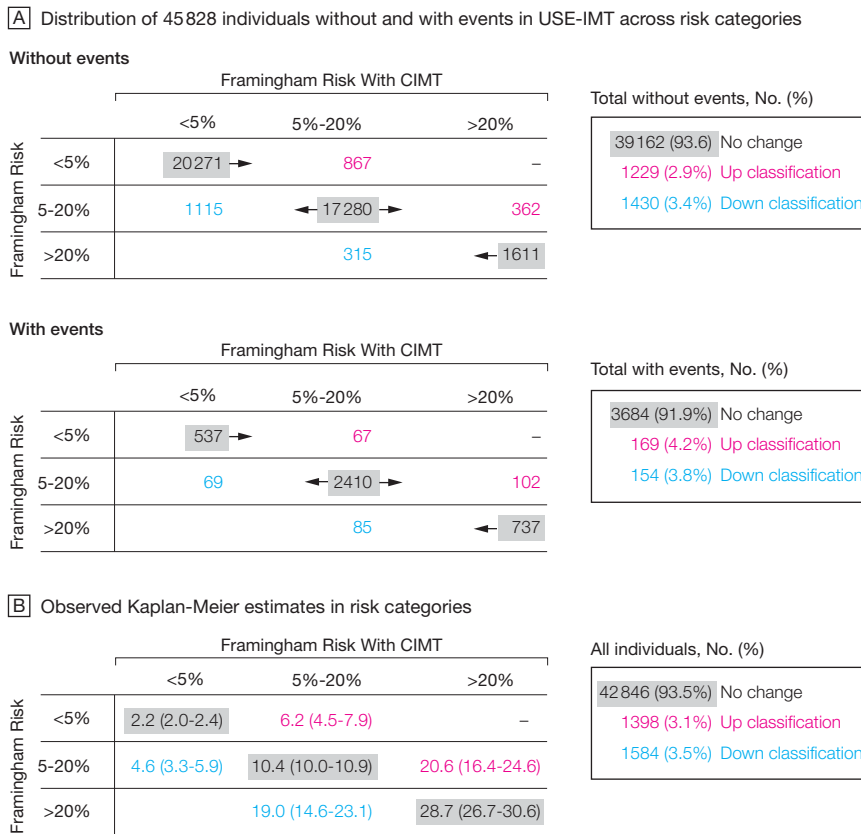
Of the individuals at intermediate risk, 88% remained in the same risk category after addition of CIMT to the Framingham Risk Score (Figure 2A). The reclassification was slightly more favorable than in the whole population with more individuals without events reclassified to a lower risk category and more individuals with events reclassified to a higher risk category.

Individuals classified to a higher risk category by CIMT had an observed risk above 20% and those classified to a lower risk category by CIMT had an observed risk less than 5%. The net reclassification improvement for the intermediate-risk group was 3.6% (95% CI, 2.7%-4.6%) with no differences between men and women (Table 3). The relative integrated discrimination improvement indicated that the improvement in the prediction model was 3.6% (Table 3).

The net reclassification improvements in all individuals for myocardial infarction and stroke separately were 0.6% and 1.0%, respectively. When 4 risk categories were applied (<5%, 5%-<10%, 10%-<20%, ≥20%), the net reclassification improvement in the overall population was 1.2% (95% CI, 0.1%-2.2%) with no differences between men and women (eFigure 5). In individuals at intermediate risk, the net reclassification improvement was 4.6% (95% CI, 3.1%-6.1%) with no differences between men (3.9%; 95% CI, 2.3%-5.9%) and women (5.5%; 95% CI, 3.0%-6.9%). Results from the complete case analysis and from the analysis with the cohort-specific z scores were similar to the results presented here.

Figure 2. Reclassification With CIMT Added to Framingham Risk Score

A Distribution of 45 828 individuals without and with events in USE-IMT across risk categories

Without events

Framingham Risk	Framingham Risk With CIMT			
	<5%	5%-20%	>20%	
<5%	20 271 →	867	–	
5-20%	1115	← 17 280 →	362	
>20%		315	← 1611	

Total without events, No. (%)

39 162 (93.6)	No change
1229 (2.9%)	Up classification
1430 (3.4%)	Down classification

With events

Framingham Risk	Framingham Risk With CIMT			
	<5%	5%-20%	>20%	
<5%	537 →	67	–	
5-20%	69	← 2410 →	102	
>20%		85	← 737	

Total with events, No. (%)

3684 (91.9%)	No change
169 (4.2%)	Up classification
154 (3.8%)	Down classification

B Observed Kaplan-Meier estimates in risk categories

Framingham Risk	Framingham Risk With CIMT		
	<5%	5%-20%	>20%
<5%	2.2 (2.0-2.4)	6.2 (4.5-7.9)	–
5-20%	4.6 (3.3-5.9)	10.4 (10.0-10.9)	20.6 (16.4-24.6)
>20%		19.0 (14.6-23.1)	28.7 (26.7-30.6)

All individuals, No. (%)

42 846 (93.5%)	No change
1398 (3.1%)	Up classification
1584 (3.5%)	Down classification

A, Individuals without and with events classified according to their 10-year absolute risk to develop a myocardial infarction or stroke predicted with the Framingham Risk Score variables or classified according to their 10-year absolute risk to develop a first-time myocardial infarction or stroke predicted with the Framingham Risk Score and a common carotid intima-media thickness (CIMT) measurement. B, Observed Kaplan-Meier absolute risk estimates for all individuals (with and without events). The observed risk in reclassified individuals is significantly different from the observed risk of the individuals in the gray cells.

Table 3. Summary of the Indices of Added Value in the Total USE-IMT Cohort and in the Intermediate-Risk Categories, by Sex

	All	Men	Women
USE-IMT			
NRI, % (95% CI)	0.8 (0.1 to 1.6)	0.9 (−0.2 to 1.9)	0.8 (−0.2 to 1.6)
IDI (95% CI)	0.0024 (0.0012 to 0.0036)	0.0024 (0.0004 to 0.0041)	0.0025 (0.0009 to 0.0040)
Relative IDI, %	3.6	3.6	3.7
USE-IMT, Intermediate-Risk Group (5% to <20%)			
NRI, % (95% CI)	3.6 (2.7 to 4.6)	3.2 (2.3 to 4.4)	3.9 (2.7 to 4.9)
IDI (95% CI)	0.0024 (0.0012 to 0.0036)	0.0019 (0.0003 to 0.0034)	0.0031 (0.0013 to 0.0048)
Relative IDI, %	3.6	2.7	4.6

Abbreviations: IDI, integrated discrimination improvement; NRI, net reclassification improvement; USE-IMT, USE Intima-Media Thickness collaboration.

COMMENT

In this meta-analysis based on participant data of 45 828 individuals from 14 cohort studies worldwide, the added value of common CIMT measurements to the Framingham Risk Score in the general population was small (0.8% were correctly reclassified). In individuals at intermediate risk, the added value was 3.2% in men and 3.9% in women. Our results suggest that common CIMT measurements should not routinely be performed in the general population because the overall added value is small and unlikely to be of clinical importance.

Recently, conflicting results have been published on the added value of CIMT measurements in cardiovascular risk prediction. These differences may be attributed to differences across studies in CIMT measurement (eg, carotid segments [common, bifurcation, internal], including or excluding carotid plaques), individuals' characteristics, cutoff values for risk categories, number of events (small numbers, especially in those that are shifting risk categories), and end-point definition. Within USE-IMT, we were able to summarize the majority of the existing evidence using uniform definitions of common CIMT, study population, risk categories, and cardiovascular events. We used only data on common CIMT and included only individuals to whom the risk scores apply. Also, as fatal and nonfatal myocardial infarction and stroke compose the majority of the cardiovascular events, we used these outcomes, which were available in all cohorts in USE-IMT. We used state-of-the-art statistical methods such as the net reclassification improvement, which incorporates time to event by Kaplan-Meier estimates rather than only distinguishing between events and nonevents. In addition, because the populations in USE-IMT may be very different from that in Framingham,[38] we refitted the cardiovascular risk factors and also fitted the common CIMT measurements, which may be the most straightforward method to assess the added value of common CIMT mea-

surements. Finally, to evaluate the robustness of our results, we also performed a complete-case analysis and used cohort-specific z scores of CIMT. These results were not different from our main analysis. Our results indicate no improvement in risk stratification through common CIMT measurements for the general population, neither for men nor for women.

We based our analysis on measurements of the mean common CIMT. We restricted to common CIMT measurements because they were available in all studies, they are generally feasible to use in routine clinical practice, and their use has been recommended.[15,39] Measurements of CIMT obtained from other carotid segments and the inclusion of a separate measure of carotid plaque may be important in risk prediction. Recently, the Framingham investigators showed that the maximal CIMT of the internal carotid artery has added value in risk prediction whereas the common CIMT of the mean common carotid artery did not.[12]

Our results are very similar to those of the Framingham cohort, a study that was not included in this meta-analysis. A recent meta-analysis suggested that carotid plaque was better than CIMT in predicting coronary events.[40] In several cohorts included in that meta-analysis, plaque was defined based on a certain arbitrary CIMT cutoff, and results were not presented for different definitions of plaque. In addition, others found the opposite for risk of stroke.[41] The ARIC investigators reported that plaque information, in addition to CIMT, resulted in a net reclassification improvement of 9.9% in the overall population.[11] In our study, we included all the reported CIMT values, even the thicker CIMT values suggestive of plaque. However, we did not separate plaque analysis, because separate information on plaque presence or absence was not available in USE-IMT. Furthermore, the reproducibility of plaque assessment is far less than that of CIMT (κ for plaques, 0.60-0.70, vs intraclass correlation coefficients for CIMT, 0.90-0.95).[42,43] The

added value of CIMT measurements from other sites than the common carotid segment (eg, maximal CIMT) obtainable by carotid ultrasound is yet to be determined.

Our results suggest that common CIMT measurements should not routinely be performed in the general population, as the overall added value may be too limited to result in health benefits. In individuals classified as being at intermediate risk by the Framingham Risk Score, information on the common CIMT measurements showed a slightly higher yield (net reclassification improvement of 3.2% in men and 3.9% in women). Yet, as described by Cook and Paynter,[44] the net reclassification improvement for useless markers may not be zero in the intermediate-risk group, and one should be cautious in overinterpreting the net reclassification improvement in the intermediate-risk group. Therefore, the added value of mean common CIMT in 10-year risk prediction for cardiovascular disease, even in the intermediate-risk category, is most likely too small to result in health benefit. However, as the interest in risk prediction is currently shifting from a 10-year risk to lifetime risk, the added value of a CIMT measurement and its cost-effectiveness using a horizon of 20 to 30 years may be worthwhile to explore.

Our study has several limitations. The cohorts included in USE-IMT showed variation in statin use because they were studied across different decades. Yet there was no heterogeneity in the relation between common CIMT measurements and cardiovascular events, suggesting that differences in statin use did not affect the relationship between CIMT and events. There are differences in the adjudication of events across studies. Although we do not think that these differences are related to CIMT measurement (so nondifferential misclassification), we included hard end points such as myocardial infarction and stroke as these were least likely to be affected. It is well established that ethnicity is an important determinant of CIMT.[45] Because

most individuals in USE-IMT were derived from a white population, our findings on the added value of CIMT in risk prediction may not necessarily apply to other ethnicities.

In conclusion, the added value of common CIMT in 10-year risk prediction of cardiovascular events, in addition to the Framingham Risk Score, was small and unlikely to be of clinical importance.

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