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Carotid Intima-Media Thickness and Presence or Absence of Plaque Improves Prediction of Coronary Heart Disease Risk

The ARIC (Atherosclerosis Risk In Communities) Study

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Objectives We evaluated whether carotid intima-media thickness (CIMT) and the presence or absence of plaque improved coronary heart disease (CHD) risk prediction when added to traditional risk factors (TRF).

Background Traditional CHD risk prediction schemes need further improvement as the majority of the CHD events occur in the "low" and "intermediate" risk groups. On an ultrasound scan, CIMT and presence of plaque are associated with CHD, and therefore could potentially help improve CHD risk prediction.

Methods Risk prediction models (overall, and in men and women) considered included TRF only, TRF plus CIMT, TRF plus plaque, and TRF plus CIMT plus plaque. Model predictivity was determined by calculating the area under the receiver-operating characteristic curve (AUC) adjusted for optimism. Cox proportional hazards models were used to estimate 10-year CHD risk for each model, and the number of subjects reclassified was determined. Observed events were compared with expected events, and the net reclassification index was calculated.

Results Of 13,145 eligible subjects (5,682 men, 7,463 women), ~23% were reclassified by adding CIMT plus plaque information. Overall, the CIMT plus TRF plus plaque model provided the most improvement in AUC, which increased from 0.742 (TRF only) to 0.755 (95% confidence interval for the difference in adjusted AUC: 0.008 to 0.017) in the overall sample. Similarly, the CIMT plus TRF plus plaque model had the best net reclassification index of 9.9% in the overall population. Sex-specific analyses are presented in the manuscript.

Conclusions Adding plaque and CIMT to TRF improves CHD risk prediction in the ARIC (Atherosclerosis Risk In Communities) study. (J Am Coll Cardiol 2010;55:1600–7) © 2010 by the American College of Cardiology Foundation

Traditional risk prediction scores such as the Framingham risk score have proven very useful in identifying persons at risk for coronary heart disease (CHD), but such risk scores have limitations. Biomarkers, imaging, and genotypes are being examined to try to improve CHD risk prediction (1–6).

Carotid intima-media thickness (CIMT) is a well-described surrogate marker for cardiovascular disease, and increased CIMT has been associated with prevalent and incident CHD and stroke (7,8). Further, statins, which reduce major adverse cardiovascular events (9), have been shown to stabilize and regress CIMT. Although reports (3,4) have suggested that adding CIMT, by improving the area under the receiver-operating characteristics curve

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(AUC), can improve risk prediction from a clinical decision-making standpoint, the ability of a marker to reclassify an person's risk group is critical (10).

Furthermore, plaque presence, which has been shown to be associated with CHD independent of CIMT measurements in several studies (11), has not been adequately evaluated in risk classification especially using contemporary criteria for evaluating novel cardiovascular risk markers (12). We investigated whether CIMT and information about the presence or absence of plaque improves CHD risk prediction in the ARIC (Atherosclerosis Risk In Communities) study.

Methods

Subjects. The ARIC study is an epidemiologic study of cardiovascular disease incidence that recruited a population-based cohort of 15,792 subjects between 45 and 64 years of age from 4 U.S. communities between 1987 and 1989. A complete description of the study design, objectives, and sampling strategy have been previously described (13). For this analysis, we excluded patients with prevalent CHD or prevalent stroke (n = 763), missing prevalent CHD data (n = 339), missing CIMT or plaque data (n = 909), missing information on traditional CHD risk factors (TRF) (n = 533), races other than black or white (n = 48), and black participants from the Minnesota or Washington field center (n = 55), providing us with a sample of 13,145 patients for the analysis.

Ultrasound measurement. The ultrasound procedure in the ARIC study has been previously described (14–17). Briefly, a Biosound 2000 (Biosound, Indianapolis, Indiana) IISA system was used and images recorded on a VHS tape. The CIMT was measured centrally by trained readers at the ARIC Ultrasound Reading Center and was assessed in 3 segments: the distal common carotid (1 cm proximal to dilation of the carotid bulb), the carotid artery bifurcation (1 cm proximal to the flow divider), and the proximal internal carotid arteries (1 cm section of the internal carotid artery immediately distal to the flow divider). At each of these segments, 11 measurements of the far wall (in 1-mm increments) were attempted. The mean of the mean measurements across these segments of both the right and the left sides was estimated. Trained readers adjudicated plaque presence or absence if 2 of the following 3 criteria were met: abnormal wall thickness (defined as CIMT >1.5 mm), abnormal shape (protrusion into the lumen, loss of alignment with adjacent arterial wall boundary), and abnormal wall texture (brighter echoes than adjacent boundaries) (11,15). The reproducibility and variation of CIMT and plaque measurements in the ARIC study have been previously published (15,18). The site-specific reliability coefficients was estimated as 0.77, 0.73, and 0.70 for the mean carotid far wall IMT at the carotid bifurcation, internal carotid arteries, and common carotid arteries, respectively. For the presence or absence of plaque, the intra-reader agreement was associated with a κ statistic of 0.76, and the inter-reader agreement was 0.56, which suggests good agreement beyond chance.

Abbreviations and Acronyms

ACRS = ARIC coronary risk score
AUC = area under the receiver-operating characteristic curve
CHD = coronary heart disease
CI = confidence interval
CIMT = carotid intima-media thickness
IDI = integrated discrimination improvement
MI = myocardial infarction
NRI = net reclassification index
TRF = traditional risk factors

Ascertainment of incident CHD events. Incident CHD events included definite or probable myocardial infarction (MI), silent MI between examinations indicated by electrocardiograms, definite CHD death, or coronary revascularization. The methods by which the incident CHD events were ascertained and classified and the details of quality assurance have been previously published (19). Briefly, participants were contacted annually, and discharge lists from local hospitals and death certificates were surveyed to look for incident CHD events. Follow-up for this analysis was until December 31, 2005.

Statistical analysis. The analyses were performed in the entire study sample and then by sex. The ARIC coronary risk score (ACRS), developed by Chambless et al. (4) in the ARIC cohort, is similar to the Framingham risk score and includes age, age^2, sex, systolic blood pressure, antihypertensive medication use, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, and smoking status. The ACRS variables were used in the "TRF only" risk prediction model in our analysis, as it would represent the best TRF-based model in the ARIC study for CHD prediction. However, we also evaluated adding CIMT and plaque to a Framingham risk score (FRS)-based TRF model because the FRS is traditionally used by most clinicians.

Several models were considered: 1) TRF plus (sex-specific) CIMT, categorized as <25th percentile, 25th to 75th percentile, and >75th percentile; 2) TRF plus plaque; and 3) TRF plus CIMT (sex-specific and categorized as previously stated) plus plaque. We described the area under the receiver-operating characteristic curve (AUC) for 10-year risk using methods that accounted for censoring (20) for each of the models to describe the model predictivity. Bootstrapping was performed to obtain confidence intervals (CI) for the differences in adjusted AUC between the models and to adjust for the overoptimism that can occur when the fit of the model is tested using the same data in which it was described (21–23).

Using Cox proportional hazards, the 10-year CHD risk for each of the models was calculated, and subjects classified into 0% to 5% risk (low risk), 5% to 10% risk (low-intermediate risk), 10% to 20% risk (intermediate-high risk), and >20% risk (high risk). The number of subjects who changed risk groups (i.e., reclassified after adding CIMT and plaque data) was then described. To test the model calibration, we compared the goodness-of-fit of the observed and expected number of events within estimated

risk decile groups using the Grønnesby-Borgan statistic (24). Large values of the test statistic (i.e., significant p values) suggest poor model fit. We then calculated the net reclassification index (NRI), which examines the net effect of adding a marker to the risk prediction scheme using a statistic described by Pencina et al. (25), except estimated by a method accounting for censoring (Dr. Lloyd Chambless, personal communication, 2009). We also described the clinical NRI, or the NRI in the groups defined as intermediate risk (5% to 10% and 10% to 20% estimated CHD risk based on the model before reclassification), namely, the groups in which the addition of a marker may be of most use. Finally, we also estimated the integrated discrimination improvement (IDI) (25) (again accounting for censoring), which is the difference in an R^2-like statistic between the traditional and expanded models. The AUC, NRI, and IDI were calculated for 10-year follow-up and, confidence intervals were furnished by bootstrapping.

Results

The study sample's baseline characteristics are listed in Table 1. The 25th and 75th percentile CIMT of the 5,682 men and 7,463 women (n = 13,145) were 0.65 mm and 0.84 mm for men and 0.58 mm and 0.74 mm for women, respectively. Atherosclerotic plaque presence increased from 13.6% in the overall population with a CIMT <25th percentile (17.4% in men, 10.7% in women), to 26.2% in those with a CIMT between the 25th and 75th percentile (33.5% for men and 20.7% for women), and to 65.3% in those with a CIMT >75th percentile (73.1% in men and 59.5% in women). When evaluated by risk groups, plaque prevalence increased from 24% in the 0% to 5% risk group to 34.3% in the 5% to 10% risk group, 46.5% in the 10% to 20% risk group, and 54.6% in the >20% risk group, 10-year CHD (high) risk groups.

Over a mean follow-up period of 15.1 years (men = 14.4 years, women = 15.7 years), there were 1,812 incident CHD events (867 definite or probable MI, 159 CHD deaths, 688 coronary revascularizations, and 98 silent [electrocardiography-confirmed] MI).

When examining the AUC, adding CIMT and/or plaque information (individually and together) to TRF improved the AUC significantly (even after adjustment for optimism) in both men and women, except that adding CIMT alone in women was not significant (Table 2).

Adding plaque to TRF had a more pronounced effect than adding CIMT to TRF on the AUC in women. In women, the AUC increased from 0.759 (TRF alone) to 0.762 (95% CI for the difference in adjusted AUC: −0.002 to 0.006) when CIMT was added to TRF, whereas the AUC increased to 0.770 (95% CI for the difference in adjusted AUC: 0.005 to 0.016) for plaque alone plus TRF. The TRF plus CIMT plus plaque model was associated with a similar AUC of 0.770 (95% CI: 0.005 to 0.017). Conversely, adding CIMT had a more pronounced effect than adding plaque to TRF on the AUC for men. For men, the AUC increased from 0.674 (TRF alone) to 0.690 (95% CI for the difference in adjusted AUC: 0.009 to 0.022) when CIMT was added to TRF while the AUC increased to 0.686 (95% CI: 0.005 to 0.017) for plaque alone plus TRF. The TRF plus CIMT plus plaque model was associated with the most increase in AUC, which increased to 0.694 (95% CI: 0.011 to 0.027). When we considered the

Table 1 Baseline Characteristics After Exclusions: ARIC Study, 1987 to 1989

	Men (n = 5,682)	Women (n = 7,463)	Entire Sample (n = 13,145)
Age, yrs	54.42 (5.8)	53.75 (5.7)	54.0 (5.8)
Body mass index, kg/m^2	27.23 (4.0)	27.46 (5.8)	27.36 (5.1)
Systolic blood pressure, mm Hg	122.1 (17.7)	119.7 (19.1)	120.72 (18.6)
Diastolic blood pressure, mm Hg	75.5 (11.2)	71.9 (10.9)	73.46 (11.2)
Total cholesterol, mg/dl	210.2 (39.4)	217.0 (42.1)	214.0 (41.1)
Triglycerides, mg/dl	130.4 (67.0)	117.1 (60.5)	122.9 (63.7)
HDL cholesterol, mg/dl	45.3 (13.9)	58.2 (17.2)	52.6 (17.1)
LDL cholesterol, mg/dl	138.8 (37.2)	135.4 (40.2)	136.8 (39.0)
CIMT 25th percentile (unadjusted), mm	0.65	0.58	0.61
CIMT 75th percentile (unadjusted), mm	0.84	0.74	0.78
Fasting glucose, mg/dl	106.3 (28.0)	104.1 (32.6)	105.0 (30.7)
Whites	77.7%	72.6%	74.8%
Diabetes mellitus	10.3%	10.0%	10.1%
Current tobacco use	27.6%	25.0%	26.1%
Former tobacco use	43.2%	22.48%	31.5%
Cholesterol-lowering medication use	2.3%	2.6%	2.4%
Aspirin use (%)	41.1%	49.4%	45.8%
Statin use (%)	0.3%	0.6%	0.5%

Data shown as mean (SD) or prevalence %.
CIMT = carotid intima-media thickness; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 2 Adjusted AUC for Different Models, With 95% Confidence Interval for Difference in Adjusted AUC Comparing Various Models With TRF-Only Model

Model	Overall	Men	Women
TRF only	0.742	0.674	0.759
TRF+CIMT	0.750 (0.005 to 0.012)	0.690 (0.009 to 0.022)	0.762 (−0.002 to 0.006)
TRF+plaque	0.751 (0.006 to 0.013)	0.686 (0.005 to 0.017)	0.770 (0.005 to 0.016)
TRF+CIMT+plaque	0.755 (0.008 to 0.017)	0.694 (0.011 to 0.027)	0.770 (0.005 to 0.017)
TRF+CIMT+plaque vs. TRF+IMT	(0.001 to 0.006)	(−0.001 to 0.006)	(0.003 to 0.012)
TRF+IMT+plaque vs. TRF+plaque	(0.001 to 0.005)	(0.002 to 0.011)	(−0.002 to 0.002)

AUC = area under the curve; CI = confidence interval; CIMT = carotid intima-media thickness; TRF = traditional risk factors.

addition of plaque to a model that included TRF plus CIMT, it significantly improved the AUC in women by 0.009 (95% CI: 0.003 to 0.012), whereas in men, the increase in AUC by 0.004 (95% CI: −0.001 to 0.006) was nonsignificant. Conversely, when we considered the addition of CIMT to a model that included TRF plus plaque, it improved the AUC in men by 0.008 (95% CI: 0.002 to 0.011), but in women, the increase in AUC by 0.000 (95% CI: −0.002 to 0.002) was nonsignificant.

The CHD incidence rate per 1,000 person years in the various CIMT categories taking into account the presence or absence of plaque is described in Figure 1. In all CIMT categories, the presence of plaque was associated with a higher incidence of CHD events.

Adding plaque information along with CIMT to TRF resulted in the reclassification of 8.6%, 37.5%, 38.3%, and 21.5% of the overall sample in the <5%, 5% to 10%, 10% to 20%, and >20% 10-year estimated risk groups, respectively (Table 3); and adding plaque and CIMT reclassified 17.4%, 32.8%, 36.6%, and 25.2% of the men (Table 4) and 5.1%, 40.2%, 38.4%, and 24.9% of the women (Table 5) in the same risk groups. Overall, more subjects were reclassified to a lower risk group (~12.4%) than to a higher risk group (~10.8%), and nobody was reclassified from the low-risk group (<5% estimated 10-year CHD risk) to the high-risk group (>20%, 10-year estimated CHD risk) or vice versa.

We then examined the goodness-of-fit of the various models using the Grønnesby-Borgan statistic. When the overall population was considered, although model fit improved with the addition of CIMT and/or plaque, none of the models had a good fit with the chi-square statistic (p value) being 30.0 (p = 0.0004), 23.7 (p = 0.005), and 24.3 (p = 0.004) for the TRF only model, TRF plus CIMT model, and TRF plus CIMT plus plaque model, respectively. When men and women were considered separately, the model fit improved. In men, the CIMT plus TRF model was the best fit (chi-square statistic = 14.12, p = 0.11), while the CIMT plus TRF plus plaque model and the TRF-only model were not as good fits (chi-square statistic = 17.9 [p = 0.04] and 18.7 [p = 0.028], respectively). Conversely, in women, the chi-square test statistics were 15.0 (p = 0.09), 9.1 (p = 0.43), and 8.7 (p = 0.47) for the TRF only, TRF plus CIMT and TRF plus

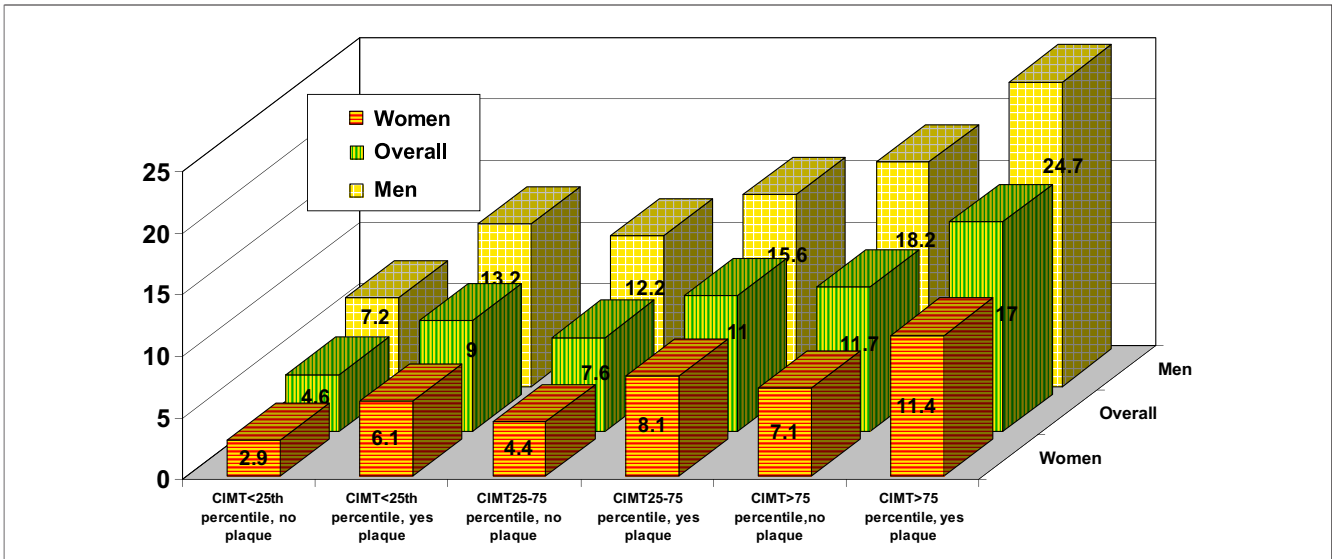

Figure 1 Adjusted Coronary Heart Disease Incidence Rate per 1,000 Person-Years Adjusted by CIMT Categories With and Without Plaque

For every carotid intima-media thickness (CIMT) category (i.e., <25th percentile, 25th to 75th percentile, and >75th percentile), for the overall group **(green bars)**, men **(yellow bars)**, or women **(orange bars)**, having carotid artery plaque is associated with a higher incidence of coronary heart disease.

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Table 3 Number and Percent Reclassified in CHD Risk Categories and Observed CHD Risk* When CIMT and Plaque Information Are Added to Traditional Risk Prediction Models (Overall Sample)

	CHD Risk by TRF + CIMT + Plaque				
CHD Risk by TRF Only	<5%	5%–10%	10%–20%	>20%	All
≤5%, low risk	5,585 (91.4)	523 (8.6)	0 (0.00)	0 (0.00)	6,108 (46.5)
	2	5	—	—	2
5%–10%, low-intermediate risk	839 (22.4)	2,340 (62.5)	563 (15.1)	0 (0.00)	3,742 (28.5)
	5	7	17	—	8
10%–20%, high-intermediate risk	0 (0.00)	627 (24.8)	1,560 (61.7)	340 (13.5)	2,527 (19.2)
	—	11	15	24	15
>20%, high risk	0 (0.00)	0 (0.00)	165 (21.5)	603 (78.5)	768 (5.8)
	—	—	14	31	27
All	6,264 (48.9)	3,490 (26.6)	2,288 (17.4)	943 (7.2)	13,145 (100.0)
	2	7	15	28	7

Values are n (%) and Kaplan-Meier 10-year risk (%). *All observed risks have been interpolated to 10-year event rates by Kaplan-Meier risk estimates using the actual observed events over a mean follow-up of 15.1 years.

CIMT plus plaque models, respectively, which suggested that the TRF plus CIMT plus plaque model had the best model fit.

Finally, we examined the NRI and the clinical NRI (NRI in the intermediate groups). We compared several models (Table 6) and found that the TRF plus CIMT plus plaque model was better than the TRF-only model in the overall sample, in men, and in women. However, adding plaque data minimally affected the TRF plus CIMT model in men, while adding CIMT information minimally affected the TRF plus plaque model in women. Overall, the TRF plus CIMT plus plaque model when compared to the TRF-only model was associated with an NRI of 9.9% (clinical NRI 21.7%) in the overall sample, 8.9% (clinical NRI 16.4%) when men were considered separately, and 9.8% (clinical NRI 25.4%) when women were considered separately, suggesting effective reclassification. The IDI showed that the model predictivity was significantly improved by adding CIMT and plaque to TRF: in the overall population, the IDI was 0.011; in women, it was 0.009; and, in men, it was 0.013 (Online Table).

When we added CIMT and plaque information to a FRS-based TRF model, the results were similar. The adjusted AUC in men and women using the FRS model alone were 0.661 and 0.741, respectively, and improved to 0.685 (95% CI for the difference in adjusted AUC: 0.014 to 0.032) and 0.751 (95% CI for the difference in adjusted AUC: 0.003 to 0.016), respectively, by adding CIMT and plaque. In men, 11.5%, 34%, 37.9%, and 32% of those in the <5%, 5% to 10%, 10% to 20%, and >20% FRS categories, respectively, were reclassified by adding CIMT and plaque, resulting in a NRI of 12.7% and a clinical NRI of 18.9%. However, in women, 6.6%, 41%, 39.8% and 36.3% of those in the <5%, 5% to 10%, 10% to 20%, and >20% FRS categories, respectively, were reclassified, resulting in a NRI of 7.7% and a clinical NRI of 21.2%. Finally, when the goodness-of-fit was tested using the Grønnesby-Borgan test statistic, the model with FRS plus CIMT plus plaque was better than the FRS-only model in both men (chi-square statistic for FRS only = 15.05, p = 0.09; chi-square statistic for FRS plus CIMT plus plaque = 10.18, p = 0.34) and women (chi-square statistic for FRS only = 8.63, p = 0.47; chi-square statistic for FRS plus CIMT plus plaque = 4.97, p = 0.84).

Table 4 Number and Percent Reclassified in CHD Risk Categories and Observed CHD Risk* When CIMT and Plaque Information Are Added to Traditional Risk Prediction Models (Men)

	CHD Risk by TRF + CIMT + Plaque				
CHD Risk by TRF Only	<5%	5%–10%	10%–20%	>20%	All
≤5%, low risk	563 (82.6)	119 (17.5)	0 (0.00)	0 (0.00)	682 (12.0)
	2	2	—	—	2
5%–10%, low-intermediate risk	338 (16.0)	1,419 (67.2)	355 (16.8)	0 (0.00)	2,112 (37.2)
	5	7	13	—	8
10%–20%, high-intermediate risk	0 (0.00)	526 (23.6)	1,413 (63.4)	290 (13.0)	2,229 (39.2)
	—	11	14	24	15
>20%, high risk	0 (0.00)	0 (0.00)	166 (25.2)	493 (74.8)	659 (11.6)
	—	—	16	31	27
All	901 (15.9)	2,064 (36.3)	1,934 (34.0)	783 (13.8)	5,682 (100.0)
	3	8	14	28	12

Values are n (%) and Kaplan-Meier 10-year risk (%). *All observed risks have been interpolated to 10-year event rates by Kaplan-Meier risk estimates using the actual observed events over a mean follow-up of 14.4 years.

Table 5 Number and Percent Reclassified in CHD Risk Categories and Observed CHD Risk* When CIMT and Plaque Information Are Added to Traditional Risk Prediction Models (Women)

	CHD Risk by TRF + CIMT + Plaque				
CHD Risk by TRF Only	<5%	5%–10%	10%–20%	>20%	All
≤5%, low risk	5,305 (94.9)	287 (5.1)	0 (0.00)	0 (0.00)	5,592 (74.9)
	2	6	—	—	2
5%–10%, low-intermediate risk	316 (26.9)	704 (59.8)	157 (13.3)	0 (0.00)	1,177 (15.8)
	5	9	12	—	8
10%–20%, high-intermediate risk	0 (0.00)	132 (25.3)	321 (61.6)	68 (13.1)	521 (7.0)
	—	6	14	32	14
>20%, high risk	0 (0.00)	0 (0.00)	43 (24.9)	130 (75.1)	173 (2.3)
	—	—	8	37	30
All	5,621 (75.3)	1,123 (15.1)	521 (7.0)	198 (2.7)	7,463 (100.0)
	2	8	3	35	4

Values are n (%) and Kaplan-Meier 10-year risk (%). *All observed risks have been interpolated to 10-year event rates by Kaplan-Meier risk estimates using the actual observed events over a mean follow-up of 15.7 years.

CHD = coronary heart disease; other abbreviations as in Table 2.

Discussion

Although CHD risk prediction models based on "traditional risk factors" have formed the basis for the clinical practice of CHD prevention, they are far from optimal (26). Several efforts have looked at adding biomarkers to improve cardiovascular risk prediction (1,2), and other recent efforts have examined the use of genetic markers as well (5). Of these, high-sensitivity C-reactive protein has shown the most promise.

Imaging tests such as carotid artery ultrasonography and coronary calcium score offer another marker that could be used in improving CHD risk prediction by directly visualizing atherosclerosis. Although several efforts have examined the use of these imaging modalities, there are limited data using contemporary statistical methodology that have evaluated whether the addition of imaging markers to risk models can improve risk prediction. Furthermore, most of the studies examining CIMT have had limited CHD events in follow-up and did not utilize information about plaque presence or absence.

We now show that, for the 13,145 ARIC participants followed up for ~15 years, using CIMT and plaque information can improve CHD risk prediction. Adding CIMT and plaque information resulted in the reclassification of ~23% of the subjects, with a net reclassification improvement of ~9.9%. However, it must be noted that more subjects were reclassified to a lower risk group than to a higher risk group. Almost 61.9% of those reclassified from the intermediate risk group (5% to 20% estimated 10-year CHD risk) were reclassified to lower risk. Furthermore, nobody from the low-risk group was reclassified to a high-risk group, and nobody from the high-risk group was reclassified to the low-risk group.

Plaque presence seemed to have a more profound effect on improving risk prediction in women than in men, and it is not completely clear why. There are likely several possible explanations. One possible explanation, perhaps, is that since middle-aged women have a relatively low prevalence of atherosclerosis, plaque presence, which reflects a definite area of atherosclerosis, was more powerful than using a sex-specific percentile "thickness" (CIMT). Similarly, given the overall lower prevalence of atherosclerosis in women, it is possible that a CIMT >75th percentile misclassifies subjects without atherosclerosis as higher risk, and a specific CIMT cutpoint may be better in women. However, it is clear that when one considers the intermediate risk groups, the groups for which one would advocate further risk stratification, adding plaque and CIMT data best improved risk prediction in men and women.

Overall, the NRI and clinical NRI (9.9% and 21.7%, respectively, in the overall sample population when the TRF plus CIMT plus plaque model was compared to the TRF-only model) was similar to other recent strategies that have been used in improving risk prediction (2,25).

Coronary calcium score is another imaging test used in clinical practice to identify higher risk subjects. A recent

Table 6 NRI Using Various Comparison Models in Overall Sample, Men, and Women

	Overall		Men		Women	
Model	NRI	Clinical NRI	NRI	Clinical NRI	NRI	Clinical NRI
TRF vs. TRF + CIMT	7.1 (2.2 to 10.6)	16.7 (9.3 to 22.4)	8.9 (3.4 to 15.1)	15.8 (8.6 to 24.6)	6.1 (−2.3 to 9.4)	15.9 (1 to 23.3)
TRF vs. TRF + plaque	7.7 (2.3 to 11.4)	17.7 (10.9 to 24.7)	4.2 (0.2 to 12.2)	10.5 (4.5 to 20.5)	10.2 (0.7 to 15.4)	25.6 (7.8 to 37.6)
TRF vs. TRF + CIMT + plaque	9.9 (3.8 to 13.5)	21.7 (13.4 to 28.2)	8.9 (4.1 to 17.1)	16.4 (9.5 to 27)	9.8 (1.1 to 15.4)	25.4 (9 to 37)
TRF + CIMT vs. TRF + CIMT + plaque	2.8 (−1.2 to 6.4)	10.6 (3.8 to 16.5)	0.03 (−2.6 to 6.3)	5.1 (0.3 to 13.2)	3.6 (−1.7 to 11.6)	12.8 (2.5 to 28.6)
TRF + plaque vs. TRF + CIMT + plaque	2.1 (−1.1 to 5.3)	7.9 (2.6 to 13.3)	4.8 (−0 to 10)	10.7 (4.3 to 19)	−0.3 (−3.7 to 3.6)	2.5 (−3.5 to 10.3)

Values are % (95% confidence interval).

NRI = net reclassification index; other abbreviations as in Table 2.

study reported that coronary calcium score was a better predictor of incident cardiovascular events, especially CHD events, when compared to CIMT (6). However, this study did not consider plaque presence or absence. Furthermore, the overall number of incident cardiovascular disease events was only 222, including angina, and the follow-up was shorter. Other reports comparing the 2 modalities have yielded mixed results (27,28). Hence, a more long term comparison of coronary calcium scores with CIMT plus plaque in the prediction of cardiovascular risk will be instructive. In addition, several other factors including cost-effectiveness and safety and feasibility of testing will all need to be considered in identifying the role these imaging tests may have in risk stratification.

Finally, although current guidelines (29) suggest that subjects with a 0% to 10% predicted 10-year risk should be considered "low" in risk, reports suggest that there is a spectrum of risk in the 0% to 10% risk group, and therefore 5% to 20% 10-year estimated risk should be considered the "intermediate" risk group (1,30,31). Therefore, we divided the 0% to 10% risk group into 0% to 5% (low risk) and 5% to 10% (low-intermediate risk) estimated risk groups. Plaque prevalence was almost ~10% higher in the 5% to 10% risk group (34% prevalence) when compared to the 0% to 5% predicted risk group (24% prevalence).

In summary, our data suggest that CIMT and plaque information can be used to improve CHD risk prediction, and that the improvement in risk prediction may be equivalent or superior to other contemporary markers.

In the future, further improvement in our ability to stratify CHD risk may be possible through reliable quantification of plaque volume, as the mere presence of plaque without any quantification helped improve overall CHD risk prediction in our analysis.

The strengths of our study include the use of contemporary statistical methodology (12), the long-term follow-up, and the number of incident CHD events accrued over the period. Furthermore, we examined the ability of CIMT and plaque to improve risk prediction when added to both the ACRS- and FRS-based TRF models. Finally, diabetes is included in the ACRS-based TRF model; although this is considered a CHD risk equivalent, we chose to include diabetes in the model to evaluate whether adding CIMT and plaque can improve the best CHD prediction model in the ARIC study.

Study limitations. We used data from the ARIC study's baseline visit for this analysis. We have not accounted for changes in the risk factors over the period of this analysis or changes in the medications during this time. However, this is similar to any risk prediction scheme that has been described. Recent data (32) suggest that persons with an increased lifetime risk may have a higher burden of subclinical atherosclerosis. We did not consider lifetime risk, but adding CIMT and plaque data helped to better identify people at short-term risk and, hence, may have additional value over the estimation of lifetime risk. We did not account for the potential difference between plaque presence in 1 artery alone versus in multiple arteries. It is possible that plaque presence in multiple carotid artery segments may be associated with a higher risk. Several subjects (n = 909) had missing CIMT data, and we do not know how their presence in the study would have impacted the results. Finally, at this time, there is no clinical study evidence that shows whether treating subjects by this strategy based on the identification of higher risk will prevent incident cardiovascular events, although one would expect that to be the case.

Conclusions

Carotid ultrasound-based CIMT measurement and identification of plaque presence or absence improves CHD risk prediction in the ARIC study and should be considered in the intermediate risk group (5% to 20% estimated 10-year CHD risk). Ultrasound-based risk stratification strategies should be tested in clinical trials to evaluate whether improved prevention of cardiovascular events is possible. A CHD risk calculator based on adding CIMT and plaque to TRF as described in this manuscript is available online at www.ARICnews.net.

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Key Words: CIMT ■ plaque ■ risk prediction.

APPENDIX

For a supplementary table of results, please see the online version of this article.