European Heart Journal (2012) **33**, 183–190
doi:10.1093/eurheartj/ehr192

Common carotid artery intima–media thickness is as good as carotid intima–media thickness of all carotid artery segments in improving prediction of coronary heart disease risk in the Atherosclerosis Risk in Communities (ARIC) study

Vijay Nambi[1,2]*, Lloyd Chambless[3], Max He[3], Aaron R. Folsom[4], Tom Mosley[5], Eric Boerwinkle[6], and Christie M. Ballantyne[1,2]

[1]Section of Atherosclerosis and Vascular Medicine, Department of Medicine, Baylor College of Medicine, Houston, TX, USA; [2]Center for Cardiovascular Disease Prevention, Methodist DeBakey Heart and Vascular Center, Houston, TX, USA; [3]Department of Biostatistics, University of North Carolina, Chapel Hill, NC, USA; [4]Division of Epidemiology and Community Health, University of Minnesota School of Public Health, Minneapolis, MN, USA; [5]Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA; and [6]Human Genetics Center and Institute of Molecular Medicine, University of Texas–Houston Health Science Center, Houston, TX, USA

Received 2 November 2010; revised 27 April 2011; accepted 20 May 2011; online publish-ahead-of-print 11 June 2011

Aims Carotid intima–media thickness (CIMT) and plaque information can improve coronary heart disease (CHD) risk prediction when added to traditional risk factors (TRF). However, obtaining adequate images of all carotid artery segments (A-CIMT) may be difficult. Of A-CIMT, the common carotid artery intima–media thickness (CCA-IMT) is relatively more reliable and easier to measure. We evaluated whether CCA-IMT is comparable to A-CIMT when added to TRF and plaque information in improving CHD risk prediction in the Atherosclerosis Risk in Communities (ARIC) study.

Methods and results Ten-year CHD risk prediction models using TRF alone, TRF + A-CIMT + plaque, and TRF + CCA-IMT + plaque were developed for the overall cohort, men, and women. The area under the receiver operator characteristic curve (AUC), per cent individuals reclassified, net reclassification index (NRI), and model calibration by the Grønnesby–Borgan test were estimated. There were 1722 incident CHD events in 12 576 individuals over a mean follow-up of 15.2 years. The AUC for TRF only, TRF + A-CIMT + plaque, and TRF + CCA-IMT + plaque models were 0.741, 0.754, and 0.753, respectively. Although there was some discordance when the CCA-IMT + plaque- and A-CIMT + plaque-based risk estimation was compared, the NRI and clinical NRI (NRI in the intermediate-risk group) when comparing the CIMT models with TRF-only model, per cent reclassified, and test for model calibration were not significantly different.

Conclusion Coronary heart disease risk prediction can be improved by adding A-CIMT + plaque or CCA-IMT + plaque information to TRF. Therefore, evaluating the carotid artery for plaque presence and measuring CCA-IMT, which is easier and more reliable than measuring A-CIMT, provide a good alternative to measuring A-CIMT for CHD risk prediction.

Keywords CIMT • Plaque • Risk prediction

* Corresponding author: 6565 Fannin Street, M.S. A-601/ STE B160, Houston, TX 77030, USA. Tel: +1 713 798 7545; fax: +1 713 798 7885, Email: vnambi@bcm.tmc.edu

Introduction

Carotid intima–media thickness (CIMT) is a well-established surrogate of atherosclerosis and has been associated with both prevalent and incident cardiovascular disease (CVD).[1,2] Furthermore, CIMT has also been used as a surrogate endpoint to monitor the efficacy of therapy against atherosclerosis in clinical trials.[3–5]

Among the limitations frequently cited in measuring of CIMT is the difficulty to adequately image all carotid artery segments, especially the internal carotid artery (ICA). In the Atherosclerosis Risk in Communities (ARIC) study, 51.4% of the ICA segments when compared with 9% of common carotid artery (CCA) segments could not be imaged.[6,7] Similarly, in the Rotterdam study, CIMT measurements were possible in 96% of the CCA segments when compared with 31% of the ICA segments.[8] Even though one would now expect that technically adequate images of the ICA and CCA can be more frequently obtained with the advances in ultrasound technology, the ICA still remains the more difficult of the carotid artery segments to image; and therefore, it is less reliable.[9,10] There has been no carotid artery segment (i.e. comparison among the various segments) that has clearly demonstrated a more significant association with CVD; some reports suggest that the CCA may have marginally higher adjusted relative risk (RR) for stroke prediction, whereas the ICA may have marginally higher RR for coronary heart disease (CHD) risk prediction.[2]

Finally, measuring all carotid segments significantly increases the time required to complete a study. Based on all of the above, the American Society of Echocardiography and Society of Vascular Medicine and Biology concluded, in a report on the use of vascular ultrasound in cardiovascular risk stratification, that 'there does not appear to be compelling evidence to suggest that combined measurements or measurement of a specific segment is clearly superior' and recommended the use of the CCA segment for improved reproducibility.[9]

We have recently shown that adding the mean CIMT of all carotid artery segments (common, bulb, and internal carotid arteries) (A-CIMT) and plaque information to traditional risk factors (TRF) improves CHD risk prediction in the ARIC study.[11]

We tested, in the ARIC study, whether adding CCA-IMT and plaque is as good as adding A-CIMT and plaque to TRF in improving CHD risk prediction. If CCA-IMT is comparable to A-CIMT, it will have significant clinical and possible research implications by allowing the use of the more reproducible and easier measure of CIMT.

Methods

Study population

The ARIC study is a population-based study of CVD incidence which enrolled 15 792 individuals in four communities in the USA between 1987 and 1989. Study details have been published previously.[12] Data collected during the baseline ARIC visit included information about the TRF for CVD and carotid artery ultrasound. For this analysis, we excluded individuals with prevalent CHD ($n = 763$), missing CIMT or CCA-IMT data ($n = 1478$), missing CHD prevalence data ($n = 339$), missing TRF data ($n = 533$), races other than 'black' or 'white' ($n = 48$), and black participants from the Minnesota or Washington field centre ($n = 55$). This provided us with a study sample of 12 576 individuals.

Ultrasound measurements

The ultrasound protocol to measure CIMT in the ARIC study has been described previously.[13–16] Briefly, measurements were made in a 1 cm segment in the distal CCA (1 cm proximal to dilation of the carotid bulb), 1 cm of the carotid artery bifurcation (1 cm proximal to the flow divider), and 1 cm in the proximal ICA (1 cm section of the ICA immediately distal to the flow divider) of both right and left sides using a Biosound 2000IISA system (8 MHz transducer, axial resolution ~0.10 mm, and an effective lateral resolution in the focal plane slightly better than 1.0 mm). Eleven far-wall mean and maximum CIMT measures were obtained at 1 mm increments. In addition, information about the presence or absence of plaque was also recorded. The presence of plaque was judged by trained readers using the presence or absence of two of the following three criteria: abnormal wall thickness (defined as CIMT >1.5 mm), abnormal shape (protrusion into the lumen and loss of alignment with adjacent arterial wall boundary), and abnormal wall texture (brighter echoes than adjacent boundaries).[14,17] For the purpose of this analysis, both the mean far-wall IMT of the right and left carotid arteries and information about the presence or absence of plaque in each subject were used. The reproducibility of CIMT and plaque measurements has been published previously.[14,15,18] Overall, of all the segments, the CCA measurements had the best coefficient of variation, although not the best reliability coefficient. However, it must be noted that ~57% of ICA measurements had to be imputed due to poor image quality, whereas only ~9% of the CCA measurements had to be imputed. We excluded those with missing CCA-IMT for our analysis, whereas imputed values (single imputation method) were used for missing ICA and bulb measurements. In secondary analyses, we used only the non-imputed (i.e. available measured values) IMT measurements for each subject. However, since IMT values at the bulb, CCA, and ICA vary, we adjusted the measurements at each segment to have a weighted mean equal to the unadjusted population mean over all sites.

Incident coronary heart disease events

Follow-up included for this analysis was until December 2005. Incident CHD events included definite or probable myocardial infarction (MI), silent MI between examinations indicated by electrocardiograms, definite CHD death, or coronary revascularization. In additional analyses, we considered only 'hard' CHD endpoints which included MI and definite CHD death only. Methods used to ascertain these events in the ARIC study and the quality control measures used have been published previously.[19]

Statistical analysis

We used SAS version 9.1 for all analyses. A *P*-value of <0.05 was considered to be statistically significant, and we used two-tailed tests to assess the *P*-values. The following models were considered: (i) TRF-only; (ii) TRF + A-CIMT + plaque; and (iii) TRF + CCA-IMT + plaque. The evaluated TRF models included the ARIC coronary risk score (ACRS) [20] and the Framingham risk score (FRS). We did this as the ACRS represents the best model to predict CHD risk in the ARIC study, whereas the FRS model is the model most used clinically. In secondary analysis, we also estimated SCORE[21] and the effect of adding the two IMT models to it. The TRF that constitute the ACRS, FRS, and SCORE are presented in Supplementary material online, *Table S1*. ACRS includes age and its quadratic form (age^2), sex, systolic blood pressure, antihypertensive medication use, total

cholesterol, HDL cholesterol, diabetes, and smoking status. The analyses were performed for the overall cohort and then by gender. Carotid intima–media thickness was classified into sex-specific percentile categories of <25th percentile, 25–75th percentile, and >75th percentile. For A-CIMT, all the segments were used to derive the percentile cut-points, whereas for CCA-IMT, only the CCA-IMT segment was used. The concordance and discordance between A-CIMT and CCA-IMT (i.e. percentile categories) and the observed and predicted risk in these various categories were described.

The area under the receiver operator characteristic curve (AUC) for 10-year risk was then calculated accounting for censoring,[22] and bootstrapping was performed to furnish 95% confidence intervals for the differences in the adjusted AUC and to correct for over optimism.[23–25]

The study population was classified into various 10-year CHD risk groups (0–5% or low risk, 5–10% or low–intermediate risk, 10–20% or intermediate–high risk, and >20% or high risk) for the different models (except SCORE) using Cox's proportional hazards models. The number of individuals reclassified (i.e. the number that changed groups when one model was compared with the other) was then described. The net reclassification index (NRI), clinical NRI, and the integrated discrimination index (IDI)[26] were described using a method accounting for censoring.[27] The 95% confidence intervals for the differences between the models were again furnished by bootstrapping.

Finally, the calibration of the various models (comparing the expected and observed events based on the Kaplan–Meier 10-year estimates) was tested using the Grønnesby–Borgan goodness-of-fit statistic.[28] Smaller values of the test statistic (i.e. non-significant *P*-values) suggested good model fit (i.e. better calibration) when the observed and expected events are compared.

Results

Over a mean follow-up of ~15.1 years (median follow-up = 16.8 years, inter-quartile range = 2.5 years), there were 1722 incident CHD events (632 in women and 1090 in men) in the 12 576 (7121 women and 5455 men) individuals included in this analysis. Of the 1722 incident events, there were 153 fatal CHD events, 820 MIs, 91 additional ECG-confirmed MIs, and 658 revascularization procedures. The baseline characteristics of the study cohort are listed in *Table 1*. The 25th and 75th percentile for the mean of all CIMT (A-CIMT) segments was 0.61 and 0.78 mm, respectively, for the entire cohort, whereas it was 0.65 and 0.84 mm, respectively, for men and 0.58 and 0.74 mm, respectively, for women. On the other hand, as expected, the 25th and 75th percentiles for CCA-IMT were lower: 0.53 and 0.70 mm, 0.55 and 0.74 mm, and 0.51 and 0.67 mm, respectively, for the overall group, men, and women.

When individuals were classified into <25th, 25–75th, and >75th percentile based on their sex-specific A-CIMT and CCA-IMT values, some discordance between the classification was observed (*Table 2*). Overall, for each group, approximately two-thirds were concordant (i.e. belonged to the same percentile group) and one-third was discordant (i.e. belonged to a different percentile group). Although the majority among the discordant individuals were classified to the immediately higher or lower group (e.g. moving from <25th percentile when CCA-IMT alone was used to 25–75th percentile when A-CIMT was used), a small number of individuals were reclassified from one extreme to the other (e.g. reclassified from <25th percentile by one

Table 1 Baseline characteristics of the study population [means (SD) or prevalence %] after exclusions: ARIC study, 1987–89

Variable	Men (*n* = 5455)	Women (*n* = 7121)	Entire population (*n* = 12 576)
Age (years)	54.4 (5.8)	53.8 (5.7)	54.0 (5.8)
Body mass index (kg/m^2)	27.2 (4.0)	27.3 (5.7)	27.3 (5.1)
Systolic blood pressure (mmHg)	122.2 (17.7)	119.6 (19.2)	120.7 (18.6)
Diastolic blood pressure (mmHg)	75.5 (11.2)	71.9 (10.9)	73.5 (11.2)
Total cholesterol (mg/dL)	210.1 (39.4)	216.9 (42.1)	214.0 (41.1)
Triglycerides (mg/dL)	129.6 (66.7)	116.1 (59.8)	122.0 (63.2)
High-density lipoprotein cholesterol (mg/dL)	45.4 (13.9)	58.4 (17.2)	52.7 (17.1)
Low-density lipoprotein cholesterol (mg/dL)	138.8 (37.1)	135.3 (40.3)	136.8 (39.0)
A-CIMT 25th percentile (mm)	0.65	0.58	0.61
A-CIMT 75th percentile (mm)	0.84	0.74	0.78
CCA-IMT 25th percentile (mm)	0.55	0.51	0.53
CCA-IMT 75th percentile (mm)	0.74	0.67	0.70
Whites (%)	77.2	72.5	74.5
Diabetes (%)	10.1	9.8	9.9
Eight-hour (or more) fasting glucose (mg/dL)	106.2 (28.0)	103.8 (32.2)	104.9 (30.5)
Current tobacco use (%)	27.8	25.2	26.3
Former tobacco use (%)	43.0	22.6	31.5
Cholesterol-lowering medication use (%)	2.1	2.4	2.3
Statin use (%)	0.30	0.51	0.42
Aspirin use (%)	40.9	49.4	45.7

CIMT classification to >75th percentile by the other CIMT classification and vice versa). The 10-year observed risk based on the concordant and discordant CIMT categories is presented in Supplementary material online, *Table S2*. Overall, in general, the observed risk approximated that predicted by the higher of the discordant IMT categories.

Discrimination and reclassification

There were significant increases in the AUCs adjusted for optimism when A-CIMT+ or CCA-IMT + plaque + TRF models were compared with the TRF-only model (*Table 3*). However, there was no difference when the CCA-IMT + plaque + TRF model was compared with the A-CIMT + plaque + TRF model.

In the overall group, adding CCA-IMT + plaque and A-CIMT + plaque to the TRF (ACRS-based) model resulted in reclassification of 2826/12 576 (22.5%) individuals and 2911/12 576 (23.1%) of the individuals, respectively (see Supplementary material online, *Tables S3* and *S4*). When the CCA-IMT + plaque + TRF model was compared with the A-CIMT + plaque + TRF model, 1033/12 576 or 8.2% of the individuals were reclassified or discordant (*Table 4*; see Supplementary material online, *Tables S5A* and *B*) which suggested that the use of CCA-IMT instead of A-CIMT (or vice versa) may result in ~8% of the individuals being classified into an alternate risk category. However, all individuals were either reclassified up or down by only one risk category (i.e. no individuals were reclassified from low to high risk or vice versa). If FRS was used as the TRF model, 34.4 and 33.7% of the individuals were reclassified when A-CIMT + plaque and CCA-IMT + plaque were added to the FRS-based TRF model, respectively, whereas 1326/12 576 or 10.5% of the individuals were reclassified when the CCA-IMT + plaque + TRF model was compared with the A-CIMT + plaque + TRF model (both FRS-based). Again, all individuals were either reclassified up or down by only one risk category).

Table 2 Concordance and discordance of intima–media thickness distribution by percentiles when common carotid artery intima–media thickness is compared with intima–media thickness of all segments

A-CIMT	CCA-IMT			Total
	<25th percentile	25–75th percentile	>75th percentile	
<25th percentile	2053	1093	29	3175
Row %	64.66	34.43	0.91	
25–75th percentile	951	4238	1048	6237
Row %	15.25	67.95	16.80	
>75th percentile	139	959	2066	3164
Row %	4.39	30.31	65.30	
Total	3143	6290	3143	12 576

The NRI and clinical NRI for both A-CIMT + plaque and CCA-IMT + plaque models were significant when compared with either of the TRF-only models (ACRS- or FRS-based) in the overall group, men, and women (*Table 5*) except when adding A-CIMT + plaque to the ACRS or FRS in women and adding CCA-IMT + plaque to the FRS in women when the NRI was not significant. However, when models with CCA-IMT were compared with models with A-CIMT, there was no difference in the NRI or clinical NRI, suggesting that both models were comparable.

When the IDI was evaluated in the overall population, the IDI was 0.010 when CCA-IMT + plaque + TRF was compared with the TRF-only (ACRS-based) model, whereas the IDI was 0.011 for all other comparisons: A-CIMT + plaque + TRF (ACRS) vs. TRF-only (ACRS), A-CIMT + plaque + TRF (FRS) vs. TRF-only (FRS) and CCA-IMT + plaque + TRF (FRS) vs. TRF-only (FRS).

In secondary analyses, when we disregarded imputed IMT values and only used normalized observed IMT values, no major differences in risk prediction statistical parameters were noted between A-CIMT + plaque + TRF and CCA-IMT + plaque + TRF (ACRS- or FRS-based) models (see Supplementary material online, *Tables S6* and *S7*).

Model calibration

Finally, when the goodness-of-fit statistic was calculated, CCA-IMT and A-CIMT performed similarly by improving model fit when added to TRF, compared with TRF-only (FRS- or ACRS-based) models (see Supplementary material online, *Table S8*). The only model that was not improved (i.e. χ^2 statistic increased) was when CCA-IMT was added to ACRS in women; however, even

Table 3 Adjusted area under the curves for the various models in the overall population, men, and women and the differences in area under the curves when compared with other models: the ARIC study

Model	Overall	Men	Women
ACRS-only	0.741	0.672	0.760
ACRS + A-CIMT + plaque; comparison with ACRS alone, difference (95% CI)	0.754 0.0129 (0.0086, 0.0166)	0.692 0.0200 (0.0115, 0.0270)	0.771 0.0109 (0.0040, 0.0157)
ACRS + CCA-IMT + plaque; comparison with ACRS alone, difference (95% CI)	0.753 0.0121 (0.0078, 0.0158)	0.690 0.0179 (0.0090, 0.0242)	0.771 0.0109 (0.0040, 0.0158)
ACRS + A-CIMT + plaque vs. ACRS + CCA-IMT + plaque, difference (95% CI)	−0.0008 (−0028, 0.0013)	−0.0021 (−0068, 0.0025)	0.0000 (−0.0028, 0.0027)

Mean AUC differences were calculated as model with CIMT – ACRS-only model. For comparison of the CCA-IMT model with A-CIMT model, the mean difference was calculated as CCA-IMT – A-CIMT model.

Table 4 Reclassification when A-CIMT + plaque + TRF (ACRS-based) is compared with CCA-IMT + plaque + TRF (ACRS-based) for the entire group (those with and without events) with 10-year Kaplan–Meier risk estimates

CHD risk by TRF + A-CIMT + plaque	CHD risk by TRF + CCA-IMT + plaque				
	≤5% low risk (row %)	5–10% low-intermediate risk (row %)	10–20% intermediate-high risk (row %)	>20% high risk (row %)	All
≤5%, low risk (row %)	5967 (96.3)	229 (3.7)	0	0	6196
KM 10-year risk, %	1.9	6.2	—	—	2.1
5–10%, low–intermediate risk (row %)	229 (6.9)	2897 (87.1)	201 (6.0)	0	3327
KM 10-year risk, %	5.4	7.3	9.2	—	7.3
10–20%, intermediate-high risk (row %)	0	191 (8.7)	1919 (87.4)	85 (3.9)	2195
KM 10-year risk, %	—	13.8	15.1	22.0	15.0
>20%, high risk (row %)	0	0	98 (11.4)	760 (88.6)	858
KM 10-year risk, %	—	—	19.1	28.7	27.7
All (row %)	6196 (49.3)	3317 (26.4)	2218 (17.6)	845 (6.7)	12 576 (100)
KM 10-year risk, %	2.1	7.6	14.7	27.4	7.3

KM, Kaplan–Meier.

in this case, the model fit remained 'good'. Therefore, overall, the addition of CCA-IMT was comparable if not better than A-CIMT with respect to model fit when added to TRF.

Hard coronary heart disease endpoints

When we examined hard CHD endpoints (e.g. MI or CHD death), the results were similar; both CCA-IMT and A-CIMT improved risk prediction and were comparable to each other (see Supplementary material online, *Table S9A* and *B*).

Cardiovascular mortality

When we examined adding CCA-IMT + plaque or A-CIMT + plaque to SCORE in the prediction of both fatal CHD and non-CVD death in secondary analysis, there was once again no noted significant differences between the use of A-CIMT + plaque and CCA-IMT + plaque. Overall, ~87% of the men and 98% of the women were low risk (<2% 10-year risk). When either A-CIMT + plaque or CCA-IMT + plaque was added to SCORE and compared with SCORE alone, only ~1% of the women were reclassified, whereas ~20% of the men were reclassified. In men, the unadjusted AUC for SCORE-only, A-CIMT + plaque + SCORE, and CCA-IMT + plaque + SCORE were 0.591, 0.706, and 0.708, respectively, whereas in women, they were 0.619, 0.690, and 0.689, respectively. The NRI, clinical NRI, IDI, and per cent reclassified for men are provided in Supplementary material online, *Table S10*. For the women, given ~1% reclassification, we do not believe that the NRI and clinical NRI provide much information and, therefore, have not included them.

Discussion

Carotid intima–media thickness has consistently been shown to be associated with cardiovascular risk factors and incident and prevalent CHD.[9,29] The test is safe but the ability to obtain accurate and repeatable measurements has been a concern. Of all the segments of the carotid artery which have been used in CIMT measurement, the CCA is the easiest to image and has the highest reproducibility; and therefore, it has been recommended as the segment to utilize for CIMT measurements.[9]

Some investigations have compared the different carotid artery segments with respect to their association with CVD. In the Cardiovascular Health Study,[2] the combination of CCA-IMT and ICA-IMT had numerically higher RR for incident MI or stroke when compared with either CCA-IMT or ICA-IMT alone (RR: 1.36 vs. 1.27 and 1.30, respectively). When ICA-CIMT was compared with CCA-IMT, ICA-IMT had higher RR for incident CHD (1.34 vs. 1.24), whereas CCA-IMT had a higher RR for incident stroke (1.38 vs. 1.25). Overall, there has not been a clearly superior carotid artery segment associated with CVD.

Recently, we have shown that CIMT (based on the measurement of all carotid segments) and information about the presence or absence of plaque have the ability to significantly improve CHD risk prediction.[11] Few other efforts have examined the utility of CIMT in risk assessment but each with limitations.[30] Most recently, Lorenz *et al.*[31] examined the Carotid Atherosclerosis Progression Study (CAPS) and reported that CIMT did not improve CHD risk prediction and that there were no differences when individual carotid artery segments were examined for their risk predictive abilities. However, this study was limited as there were no follow-up visits to assess clinical outcomes, and clinical outcomes were ascertained primarily by ICD codes. In fact, even in the group with the highest predicted risk determined by TRF (i.e. >20% predicted 10-year risk), the Kaplan–Meier estimated observed risk was only 3.03%. Furthermore, they did not report whether CCA-IMT used alone was as good as A-CIMT in CHD risk prediction. Hence, we examined in the ARIC study whether CCA-IMT + plaque can improve CHD risk prediction similar to that obtained when A-CIMT was used and found that both measurements (i.e. CCA-IMT-only or A-CIMT) gave similar results for the most part. However, interestingly, approximately one-third of the individuals were discordant when CCA-IMT and A-CIMT categories were compared [i.e. individuals classified as

Table 5 Net reclassification index and clinical net reclassification index of various model comparisons

Model[a]	Overall				Women						Men					
	NRI %[b]			Clinical NRI %[b]			NRI %[b]			Clinical NRI %[b]			NRI %[b]			Clinical NRI %
	Overall (95% CI)	Events	No events	Overall (95% CI)	Events	No events	Overall (95% CI)	Events	No events	Overall (95% CI)	Events	No events	Overall (95% CI)	Events	No events	Overall (95% CI)	Events	No events
ACRS vs. ACRS + CCA-IMT	7.6 (2.9, 13.0)	5.5	2.2	18.7 (11.0, 26.7)	8.2	10.5	8.2 (0.8, 16.5)	8.2	0.1	24.4 (8.7, 39.3)	9.9	14.6	6.2 (1.2, 14.5)	4.8	1.4	11.6 (5.9, 22.8)	6.3	5.2
ACRS vs. ACRS + A-CIMT	8.9 (4.1, 14.4)	6.7	2.2	21.4 (13.3, 28.8)	9.9	11.4	8.1 (−0.1, 14.8)	8.1	0.0	23.0 (8.3, 37.5)	8.4	14.6	9.5 (4.4, 18.0)	3.4	6.1	16.3 (9.6, 27.6)	9.0	7.3
ACRS + A-CIMT vs. ACRS + CCA-IMT	−1.2 (−4.3, 1.6)	−1.2	−0.1	1.4 (−2.2, 6.2)	−1.4	2.7	0.09 (−3.0, 4.8)	0.0	0.1	1.27 (−3.4, 12.5)	−1.4	2.7	−3.3 (−8.0, 1.4)	−2.0	−1.4	1.28 (−4.2, 6.8)	2.4	−1.1
FRS vs. FRS + CCA-IMT	16.2 (11.2, 21.9)	12.7	3.4	24.5 (18.2, 31.9)	13.6	11.0	6.3 (−1.7, 15.0)	6.4	−0.1	19.8 (6.8, 33.7)	5.3	14.5	10.6 (4.9, 18.7)	4.7	5.8	15.6 (9.1, 25.4)	9.7	5.9
FRS vs. FRS + A-CIMT	16.5 (11.6, 23.6)	12.8	3.7	25.6 (19.0, 34.0)	13.7	11.8	6.3 (−2.3, 14.4)	6.6	−0.4	18.6 (5.2, 32.8)	4.5	14.2	12.8 (7.0, 20.6)	6.8	6.1	19. 0 (12.1, 28.1)	13.4	5.7
FRS + A-CIMT vs. FRS + CCA-IMT	−0.35 (−4.7, 2.1)	−0.1	−0.3	2.64 (−2.1, 6.0)	−1.3	4.0	0.10 (−3.8, 4.6)	−0.3	0.2	4.9 (−1.2 12.2)	−0.5	5.3	−2.27 (−7.2, 2.9)	−2.0	−0.2	1.28 (−4.4, 6.8)	2.1	−1.4

ACRS, ARIC coronary risk score using traditional risk factors; FRS, Framingham risk score using traditional risk factors; A-CIMT, CIMT using all carotid artery segments; CCA-IMT, common carotid artery IMT; NRI, net reclassification index; C-NRI, clinical NRI.

[a]All IMT models also include plaque information.

[b]'Events' = NRI or C-NRI among those who had an event and 'No events' = NRI or C-NRI among those who did not have an event.

<25th , 25–75th, and >75th percentile with one CIMT schema (A-CIMT or CCA-IMT) were in another category when the other CIMT schema was used], whereas ~8–10% of the individuals were discordant when risk categories after risk estimation were compared using CIMT (CCA-IMT vs. A-CIMT) + plaque + TRF. This suggests that the majority of the discordance in the CIMT categories did not affect risk estimation (approximately one-third discordant by CIMT categories compared with 1/10th by risk stratification categories) which is likely because most discordance reclassified individuals to the CIMT category that was immediately above or below, thereby resulting only in limited changes in the contribution of CIMT in risk estimation, and because the presence/absence of plaque was factored in estimating risk in both CIMT (CCA-IMT and A-CIMT) risk prediction schemes. However, although ~8–10% of the individuals were classified into different risk categories depending on whether CCA-IMT or A-CIMT was added to the risk prediction scheme, there were no major statistical differences when these two CIMT strategies were compared, suggesting that correct and incorrect reclassifications by these two strategies (CCA-IMT vs. A-CIMT) 'evened' out. Furthermore, when observed risk was evaluated in the discordant IMT categories (see Supplementary material online, *Table S2*), in general, the risk remained in step with the higher of the two discordant CIMT strategies (i.e. CCA-IMT vs. A-CIMT). Overall, based on our results, it is evident that adding A-CIMT + plaque or CCA-IMT + plaque to TRF can both improve CHD risk prediction, and neither strategy is superior to the other.

Our analysis has clinical and potential research significance. In a clinical setting, it would not be possible for the practitioner to impute values for missing CIMT segments as in our analyses. Even though current-day technological advancements will result in significantly lesser poor-quality/missing images, the CCA still remains the most reliable and easiest segment to image. Furthermore, optimal image acquisition is critical in the measurement of CIMT as small changes in values can be clinically important and meaningful. For example, the difference in the mean CCA-IMT between the 25th and 75th percentile for a 45-year-old man is ~0.16 mm in the ARIC study. Changes in the angle of image acquisition can clearly affect IMT measurements. The ICA may branch off at an angle, and the bifurcation of the carotid artery may occur high in the neck, all of which can make ICA imaging a challenge even in this day and age. Therefore, one could recommend that clinicians who use CIMT in their practice for CHD risk estimation use a protocol that measures CCA-IMT and a sweep of the carotid arteries for the presence/absence of plaque given that: (i) CCA-IMT is the CIMT segment least likely to be missing, (ii) CCA-IMT is the most reproducible and easiest to image the various CIMT measurements, and (iii) our analysis now shows that a sweep of the entire carotid artery for the presence/absence of atherosclerotic plaque in concert with measurement of CCA-IMT or A-CIMT are comparable.

Similarly, in atherosclerosis research, CIMT is a commonly used and accepted surrogate endpoint in clinical trials.[32,33] However, most often, IMT of all carotid segments is used as the primary endpoint. Whether the use of CCA-IMT alone will perform as well as the use of all IMT segments in clinical trials will need to be further

explored. If CCA-IMT is comparable to the use of all IMT segments, this will again improve repeatability of the study and will allow for easier and more efficient protocols. However, other factors, including that atherosclerosis tends to occur more frequently in the bulb and internal carotid arteries, will need to be considered.

Limitations

We used data only from the baseline (1987–89) ARIC visit (CIMT and TRF) to perform our current analysis. Whether using information (including TRF and CIMT) from subsequent ARIC visits could change the results is not clear. Furthermore, we have not accounted for changes in medications (e.g. new medications being prescribed) over the course of the study period. Subsequent use of medications that decrease CHD events (such as statins) could alter the observed outcomes and therefore have impacted on the risk predictive abilities of CIMT; however, this would have been similar when A-CIMT was compared with CCA-IMT. Our data used CIMT measurements from only one time point. Given that data have suggested that CIMT progression in the various carotid segments may vary, it is unclear whether similar results will be found if one factored in the change in CCA-IMT vs. A-CIMT over time. We used imputed values for missing CIMT segments using a technique that has been validated[7]; however, it is not clear whether there would have been a difference had actual measurements been available. Finally, it is not clear whether the use of more contemporary ultrasound technology with lesser variability and improved resolution would have led to different results when CCA-IMT and A-CIMT are compared in CHD risk prediction.

Conclusions

A strategy of measuring CCA-IMT alone in concert with plaque information improves CHD risk prediction and is comparable to using all CIMT segments in the ARIC study. Whether a strategy of making therapeutic decisions using CIMT in addition to TRF when compared with using TRF alone in CHD risk prediction will prevent CHD events will need to be studied in clinical trials.

Supplementary material

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

Acknowledgements

The authors thank the staff and participants of the ARIC study for their important contributions and Joanna Brooks, BA, for editorial assistance.

Funding

V.N. is supported by an NIH grant (5K23HL096893-02). The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022.

Conflict of interest: V.N. has research collaboration (no financial support) with General Electric (GE).

References

1. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, Clegg LX. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. *Am J Epidemiol* 1997;**146**:483–494.
2. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr, Cardiovascular Health Study Collaborative Research Group. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med* 1999;**340**:14–22.
3. Taylor AJ, Kent SM, Flaherty PJ, Coyle LC, Markwood TT, Vernalis MN. ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness. *Circulation* 2002;**106**:2055–2060.
4. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, Visseren FL, Sijbrands EJ, Trip MD, Stein EA, Gaudet D, Duivenvoorden R, Veltri EP, Marais AD, de Groot E. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008;**358**:1431–1443.
5. Crouse JR 3rd, Raichlen JS, Riley WA, Evans GW, Palmer MK, O'Leary DH, Grobbee DE, Bots ML. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. *JAMA* 2007;**297**:1344–1353.
6. Howard G, Sharrett AR, Heiss G, Evans GW, Chambless LE, Riley WA, Burke GL. Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound. ARIC Investigators. *Stroke* 1993;**24**:1297–1304.
7. Espeland MA, Byington RP, Hire D, Davis VG, Hartwell T, Probstfield J. Analysis strategies for serial multivariate ultrasonographic data that are incomplete. *Stat Med* 1992;**11**:1041–1056.
8. del Sol AI, Moons KG, Hollander M, Hofman A, Koudstaal PJ, Grobbee DE, Breteler MM, Witteman JC, Bots ML. Is carotid intima-media thickness useful in CVD risk assessment? The Rotterdam Study. *Stroke* 2001;**32**:1532–1538.
9. Roman MJ, Naqvi TZ, Gardin JM, Gerhard-Herman M, Jaff M, Mohler E. Clinical application of noninvasive vascular ultrasound in cardiovascular risk stratification: a report from the American Society of Echocardiography and the Society of Vascular Medicine and Biology. *J Am Soc Echocardiogr* 2006;**19**:943–954.
10. Dogan S, Duivenvoorden R, Grobbee DE, Kastelein JJ, Shear CL, Evans GW, Visseren FL, Bots ML. Completeness of carotid intima media thickness measurements depends on body composition: the RADIANCE 1 and 2 trials. *J Atheroscler Thromb* 2010;**17**:526–535.
11. Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, Volcik K, Boerwinkle E, Ballantyne CM. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. *J Am Coll Cardiol* 2010;**55**:1600–1607.
12. ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. *Am J Epidemiol* 1989;**129**:687–702.
13. Li R, Cai J, Tegeler C, Sorlie P, Metcalf PA, Heiss G. Reproducibility of extracranial carotid atherosclerotic lesions assessed by B-mode ultrasound: the Atherosclerosis Risk in Communities Study. *Ultrasound Med Biol* 1996;**22**:791–799.
14. Li R, Duncan BB, Metcalf PA, Crouse JR 3rd, Sharrett AR, Tyroler HA, Barnes R, Heiss G. B-mode-detected carotid artery plaque in a general population. Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Stroke* 1994;**25**:2377–2383.
15. High-resolution B-mode ultrasound reading methods in the Atherosclerosis Risk in Communities (ARIC) cohort. The ARIC Study Group. *J Neuroimaging* 1991;**1**:168–172.
16. National Heart, Lung, and Blood Institute. *Atherosclerosis Risk in Communities Study Operations Manual: Number 7: Ultrasound Reading Methods, Version 1.0*. Chapel Hill, NC: ARIC Coordinating Center; 1987.
17. Hunt KJ, Sharrett AR, Chambless LE, Folsom AR, Evans GW, Heiss G. Acoustic shadowing on B-mode ultrasound of the carotid artery predicts CHD. *Ultrasound Med Biol* 2001;**27**:357–365.
18. Chambless LE, Zhong MM, Arnett D, Folsom AR, Riley WA, Heiss G. Variability in B-mode ultrasound measurements in the atherosclerosis risk in communities (ARIC) study. *Ultrasound Med Biol* 1996;**22**:545–554.
19. White AD, Folsom AR, Chambless LE, Sharret AR, Yang K, Conwill D, Higgins M, Williams OD, Tyroler HA. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: methods and initial two years' experience. *J Clin Epidemiol* 1996;**49**:223–233.
20. Chambless LE, Folsom AR, Sharrett AR, Sorlie P, Couper D, Szklo M, Nieto FJ. Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) study. *J Clin Epidemiol* 2003;**56**:880–890.
21. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetiere P, Jousilahti P, Keil U, Njolstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM. Estimation of ten-year risk of fatal CVD in Europe: the SCORE project. *Eur Heart J* 2003;**24**:987–1003.

22. Chambless LE, Diao G. Estimation of time-dependent area under the ROC curve for long-term risk prediction. *Stat Med* 2006;**25**:3474–3486.
23. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;**15**:361–387.
24. Efron B, Tibshirani RJ. *An Introduction to the Bootstrap*. New York: Chapman and Hall; 1993.
25. Steyerberg EW, Harrell FE Jr, Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *J Clin Epidemiol* 2001;**54**:774–781.
26. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008;**27**:157–172; discussion 207–112.
27. Chambless L, Cummiskey C, Cui G. Several methods to assess improvement in risk prediction models: extension to survival analysis. *Stat Med* 2010;**30**:22–38.
28. May S, Hosmer DW. A simplified method of calculating an overall goodness-of-fit test for the Cox proportional hazards model. *Lifetime Data Anal* 1998;**4**:109–120.
29. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, Najjar SS, Rembold CM, Post WS. Use of carotid ultrasound to identify subclinical vascular disease and evaluate CVD risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr* 2008;**21**:93–111; quiz 189–190.
30. Rundek T, Arif H, Boden-Albala B, Elkind MS, Paik MC, Sacco RL. Carotid plaque, a subclinical precursor of vascular events: the Northern Manhattan Study. *Neurology* 2008;**70**:1200–1207.
31. Lorenz MW, Schaefer C, Steinmetz H, Sitzer M. Is carotid intima media thickness useful for individual prediction of cardiovascular risk? Ten-year results from the Carotid Atherosclerosis Progression Study (CAPS). *Eur Heart J* 2010;**31**:2041–2048.
32. Espeland MA, O'Leary DH, Terry JG, Morgan T, Evans G, Mudra H. Carotid intimal-media thickness as a surrogate for CVD events in trials of HMG-CoA reductase inhibitors. *Curr Control Trials Cardiovasc Med* 2005;**6**:3.
33. Bots ML. Carotid intima-media thickness as a surrogate marker for CVD in intervention studies. *Curr Med Res Opin* 2006;**22**:2181–2190.

CARDIOVASCULAR FLASHLIGHT

doi:10.1093/eurheartj/ehr197
Online publish-ahead-of-print 30 June 2011

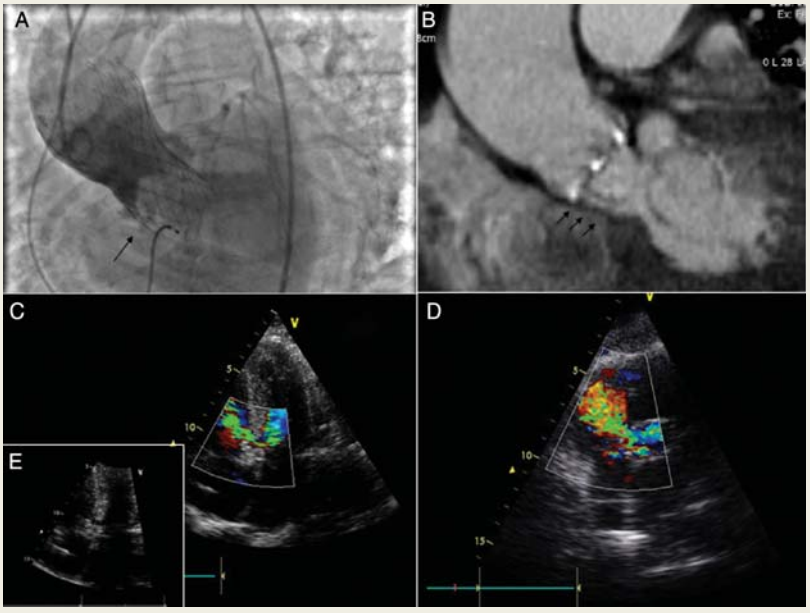
Interventricular septum rupture after transcatheter aortic valve implantation

Marina I. Revilla Martínez*, Hipólito Gutiérrez García, and José Alberto San Román Calvar

Institute of Heart Sciences (ICICOR), Cardiology Department, University Clinical Hospital, Avda. Ramón y Cajal 3, 47005 Valladolid, Spain

* Corresponding author. Tel: +34 679 64 80 41, Fax: +34 983 25 53 05, Email: marinarema@hotmail.com

A 76-year-old woman with hypertension, severe chronic obstructive pulmonary disease, and severe aortic valve stenosis with preserved left-ventricular ejection fraction was referred by dyspnoea. High surgical risk was calculated (EuroSCORE: 17%); therefore, transcatheter aortic valve implantation (TAVI) was planned.



Aortic valve was dilated with a 22 mm Nucleus® balloon and a 26 mm CoreValve® prosthesis was implanted. Aortography revealed residual severe aortic regurgitation owing to incomplete valve expansion. Therefore, a 25 mm Nucleus® balloon dilatation was performed. A new aortogram showed grade 1 aortic regurgitation and a tiny contrast pass from left to right ventricle (*Figure A*, arrow).

The patient developed symptoms of heart failure. Transthoracic echocardiography showed interventricular septum rupture (ISR) at the level of membranous septum, in apical (*Figure C*) and short-axis views (*Figure D*). Defect size was 6 mm (*Figure E*). Interventricular septum rupture surgical repair was refused because of high risk. The patient improved clinically and was discharged asymptomatic on Day 12.

Interventricular septum rupture contributing factors after TAVI are unknown. In our series of 50 patients, 6 required postdilatation with balloon and only one ISR occurred. Computed tomography in our patient showed calcification extending from aortic valve to the beginning of the membranous septum. Membranous septum size was 8.7 mm (*Figure B*, arrows), which is longer than the median length in our patients (3 mm). It is too early to determine the predisposing factors for ISR post-TAVI; however, a severely calcified membranous septum longer than usual and overdilatation of the prosthesis could contribute to this complication.