Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Continuous carotid artery MRI plaque characteristics for incident CVD analyses

Variable	Incident CVD events (n=76)	No Incident CVD events (n=324)	P-value
MRI Carotid Artery Plaque Characteristics			
Total lipid core volume, mL	0.05 (0.02, 0.11)	0.03 (0.01, 0.07)	0.03
Maximum lipid core area, mm^2	0.11 (0.05, 0.18)	0.07 (0.04, 0.13)	0.03
Mean lipid core area, mm^2	0.07 (0.04, 0.13)	0.05 (0.03, 0.09)	0.04
Total lipid core % of total wall volume, %	9.93 (3.89, 18.91)	6.70 (3.55, 12.77)	0.05
Mean fibrous cap thickness, mm	0.67 (0.40, 0.88)	0.66 (0.44, 0.86)	0.95
Mean fibrous cap thickness at max. lipid core, mm	0.62 (0.37, 0.83)	0.66 (0.44, 0.86)	0.47
Minimum fibrous cap thickness, mm	0.37 (0.19, 0.59)	0.43 (0.25, 0.66)	0.13
Mean minimum fibrous cap thickness, mm	0.44 (0.25, 0.62)	0.45 (0.27, 0.66)	0.47
Values are reported as median (25th, 75th percentiles). Continuous variables were analyzed with a two-sample Wilcoxon rank-sum test for non-normal variables. Analyses of continuous carotid artery MRI plaque characteristics are limited to those participants with a lipid core.			

eTable 2. Univariable and multivariable Cox proportional hazards models for incident CVD events for continuous carotid artery MRI plaque characteristics

Variable (per 1-unit increment in ln-transformed continuous variables*)	Univariable HR		Adj. for clinical factors: HR		Adj. for carotid thickness: HR	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Continuous Carotid Plaque Characteristics*						
Total lipid core volume	1.22 (0.92, 1.60)	0.17	0.95 (0.67, 1.34)	0.78	1.22 (0.84, 1.78)	0.29
Mean lipid core area	1.28 (0.89,1.84)	0.19	0.92 (0.58, 1.48)	0.73	1.25 (0.73, 2.14)	0.43
Max. lipid core area	1.27 (0.88, 1.83)	0.20	0.92 (0.58, 1.44)	0.70	1.26 (0.76, 2.08)	0.38
Total lipid core %-of total wall volume	1.25 (0.87, 1.78)	0.23	0.96 (0.64, 1.43)	0.84	1.21 (0.81, 1.81)	0.36
Mean fibrous cap thickness	0.72 (0.40, 1.29)	0.27	0.81 (0.47, 1.39)	0.44	0.86 (0.47, 1.57)	0.63
Min. fibrous cap thickness	0.78 (0.53, 1.15)	0.21	0.90 (0.60, 1.36)	0.63	0.91 (0.60, 1.39)	0.67

Adjusted for clinical factors: age, sex, race, and ARIC study field center, smoking, body mass index, blood glucose, diabetic status, systolic blood pressure, diastolic blood pressure, HDL cholesterol, non-HDL cholesterol, use of blood pressure-lowering medication, cholesterol lowering medication use, aspirin use, diabetes medication use, and hs-CRP

Adjusting for carotid thickness (for analyses involving lipid rich core, calcification, and fibrous cap measures only): adjusted for clinical factors + maximum carotid artery wall thickness

*Hazard ratios are per 1-unit increment in ln-transformed continuous plaque variables. All continuous carotid plaque characteristics were ln-transformed. eTable 9 shows details for the conversion between original values and ln-transformed values for continuous carotid MRI variables.
CI: confidence interval; HR: hazard ratio.
Analyses of continuous carotid artery MRI plaque characteristics are limited to those participants with a lipid core.

eTable 3. Univariable and multivariable Cox proportional hazard ratios for incident coronary heart disease events for carotid MRI plaque burden variables and categorical plaque characteristics

Variable (per 1-unit increment in ln-transformed continuous variables*, or dichotomous†)	Univariable HR		Adj. for clinical factors: HR		Adj. for carotid thickness: HR	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Carotid Plaque Burden*						
Lumen area	0.67 (0.40, 1.13)	0.13	0.59 (0.37, 0.94)	0.03		
Wall area	1.84 (1.07, 3.16)	0.03	1.15 (0.60, 2.19)	0.68		
Total wall volume	1.89 (1.04, 3.45)	0.04	1.17 (0.54, 2.55)	0.69		
Maximum carotid artery wall thickness	1.73 (1.04, 2.89)	0.03	1.36 (0.77, 2.40)	0.29		
Normalized wall index	2.20 (0.97, 5.01)	0.06	1.89 (0.80, 4.47)	0.15		
Max. stenosis	1.31 (1.13, 1.53)	<0.001	1.24 (1.04, 1.47)	0.02		
Carotid Plaque Characteristics†						
Presence of lipid core	2.54 (1.61, 3.99)	<0.001	2.05 (1.21, 3.46)	0.007	2.43 (1.25, 4.72)	0.009
Presence of lipid core in 2+ adjacent slices	2.50 (1.57, 3.99)	<0.001	1.92 (1.14, 3.25)	0.02	2.11 (1.15, 3.89)	0.02
Presence of calcification	2.15 (1.35, 3.41)	0.001	1.70 (1.02, 2.83)	0.04	1.68 (0.79, 3.57)	0.18
Presence of intra plaque hemorrhage	1.48 (0.77, 2.85)	0.24	1.16 (0.57, 2.34)	0.68		

<u>Adjusted for clinical factors:</u> age, sex, race, and ARIC study field center, smoking, body mass index, blood glucose, diabetic status, systolic blood pressure, diastolic blood pressure, HDL cholesterol, non-HDL cholesterol, use of blood pressure-lowering medication, cholesterol lowering medication use, aspirin use, diabetes medication use, and hs-CRP

<u>Adjusting for carotid thickness</u> (for analyses involving lipid rich core, calcification, and fibrous cap measures only): adjusted for clinical factors + maximum carotid artery wall thickness

*Hazard ratios are per 1-unit increment in ln-transformed continuous plaque burden variables. All plaque burden variables were ln-transformed. eTable 9 shows details for the conversion between original values and ln-transformed values for continuous carotid MRI variables.
† Hazard ratio is for presence vs. absence.
CI: confidence interval; HR: hazard ratio.

eTable 4 Univariable and multivariable Cox proportional hazard ratios for incident coronary heart disease events for continuous carotid artery MRI plaque characteristics

Variable (per 1-unit increment in ln-transformed continuous variables*)	Univariable HR		Adj. for clinical factors: HR		Adj. for carotid thickness: HR	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Carotid Plaque Characteristics*						
Total lipid core volume	1.29 (0.92, 1.79)	0.14	1.03 (0.70, 1.53)	0.88	1.24 (0.80, 1.93)	0.33
Mean lipid core area	1.35 (0.88, 2.06)	0.17	0.98 (0.57, 1.70)	0.94	1.15 (0.61, 2.19)	0.67
Max. lipid core area	1.38 (0.90, 2.11)	0.14	1.01 (0.60, 1.71)	0.98	1.27 (0.68, 2.37)	0.45
Total lipid core %-of total wall volume	1.37 (0.87, 2.14)	0.17	1.08 (0.67, 1.74)	0.74	1.32 (0.81, 2.15)	0.27
Mean fibrous cap thickness	0.64 (0.33, 1.26)	0.20	0.69 (0.39, 1.22)	0.20	0.70 (0.38, 1.28)	0.25
Min. fibrous cap thickness	0.69 (0.45, 1.08)	0.10	0.80 (0.52, 1.23)	0.30	0.80 (0.52, 1.23)	0.31

Adjusted for clinical factors: age, sex, race, and ARIC study field center, smoking, body mass index, blood glucose, diabetic status, systolic blood pressure, diastolic blood pressure, HDL cholesterol, non-HDL cholesterol, use of blood pressure-lowering medication, cholesterol lowering medication use, aspirin use, diabetes medication use, and hs-CRP

Adjusting for carotid thickness (for analyses involving lipid rich core, calcification, and fibrous cap measures only): adjusted for clinical factors + maximum carotid artery wall thickness

*Hazard ratios are per 1-unit increment in ln-transformed continuous plaque variables. All continuous carotid plaque characteristics were ln-transformed. eTable 9 shows details for the conversion between original values and ln-transformed values for continuous carotid MRI variables.
CI: confidence interval; HR: hazard ratio.

Analyses of continuous carotid artery MRI plaque characteristics are limited to those participants with a lipid core.

eTable 5. Univariable and multivariable Cox proportional hazard ratios for incident ischemic stroke events for carotid MRI plaque burden variables and categorical plaque characteristics

Variable (per 1-unit increment in ln-transformed continuous variables*, or dichotomous†)	Univariable HR		Adj. for clinical factors: HR		Adj. for carotid thickness: HR	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Carotid Plaque Burden*						
Lumen area	0.64 (0.35, 1.15)	0.13	0.62 (0.36, 1.07)	0.09		
Wall area	1.32 (0.58, 2.99)	0.51	0.84 (0.32, 2.23)	0.73		
Total wall volume	1.49 (0.62, 3.59)	0.37	1.11 (0.39, 3.14)	0.85		
Maximum carotid artery wall thickness	1.00 (0.52, 1.94)	0.99	0.79 (0.39, 1.60)	0.51		
Normalized wall index	1.89 (0.58, 6.18)	0.29	1.67 (0.55, 5.05)	0.37		
Max. stenosis	1.36 (1.11, 1.67)	0.003	1.29 (1.05, 1.58)	0.02		
Carotid Plaque Characteristics†						
Presence of lipid core	2.17 (1.10, 4.28)	0.03	1.84 (0.81, 4.15)	0.14	3.80 (1.13, 12.76)	0.03
Presence of lipid core in 2+ adjacent slices	2.05 (1.02, 4.09)	0.04	1.70 (0.77, 3.80)	0.19	3.14 (0.94, 10.43)	0.06
Presence of calcification	1.12 (0.54, 2.34)	0.76	0.85 (0.36, 1.99)	0.71	0.98 (0.33, 2.92)	0.97
Presence of intra plaque hemorrhage	2.45 (1.07, 5.63)	0.04	2.28 (0.87, 6.00)	0.10		

Adjusted for clinical factors: age, sex, race, and ARIC study field center, smoking, body mass index, blood glucose, diabetic status, systolic blood pressure, diastolic blood pressure, HDL cholesterol, non-HDL cholesterol, use of blood pressure-lowering medication, cholesterol lowering medication use, aspirin use, diabetes medication use, and hs-CRP

Adjusting for carotid thickness (for analyses involving lipid rich core, calcification, and fibrous cap measures only): adjusted for clinical factors + maximum carotid artery wall thickness

*Hazard ratios are per 1-unit increment in ln-transformed continuous plaque burden variables. All plaque burden variables were ln-transformed. eTable 9 shows details for the conversion between original values and ln-transformed values for continuous carotid MRI variables.
† Hazard ratio is for presence vs. absence.
CI: confidence interval; HR: hazard ratio.

eTable 6. Univariable and multivariable Cox proportional hazard ratios for incident ischemic stroke events for continuous carotid artery MRI plaque characteristics

Variable (per 1-unit increment in ln-transformed continuous variables*)	Univariable HR		Adj. for clinical factors: HR		Adj. for carotid thickness: HR	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Carotid Plaque Characteristics*						
Total lipid core volume	0.92 (0.65, 1.32)	0.66	0.69 (0.41, 1.15)	0.15	1.10 (0.62, 1.93)	0.75
Mean lipid core area	1.06 (0.66, 1.71)	0.80	0.82 (0.38, 1.77)	0.61	1.84 (0.80, 4.23)	0.15
Max. lipid core area	0.93 (0.58, 1.49)	0.77	0.67 (0.33-1.34)	0.25	1.30 (0.62, 2.72)	0.49
Total lipid core %-of total wall volume	0.89 (0.62, 1.28)	0.53	0.65 (0.38, 1.11)	0.11	0.96 (0.56, 1.65)	0.88
Mean fibrous cap thickness	1.00 (0.46, 2.20)	0.99	1.23 (0.60, 2.54)	0.57	1.92 (0.84, 4.39)	0.12
Min. fibrous cap thickness	1.04 (0.58, 1.87)	0.89	1.18 (0.62, 2.24)	0.61	1.43 (0.71, 2.87)	0.32

Adjusted for clinical factors: age, sex, race, and ARIC study field center, smoking, body mass index, blood glucose, diabetic status, systolic blood pressure, diastolic blood pressure, HDL cholesterol, non-HDL cholesterol, use of blood pressure-lowering medication, cholesterol lowering medication use, aspirin use, diabetes medication use, and hs-CRP
Adjusting for carotid thickness (for analyses involving lipid rich core, calcification, and fibrous cap measures only): adjusted for clinical factors + maximum carotid artery wall thickness

*Hazard ratios are per 1-unit increment in ln-transformed continuous plaque variables. All continuous carotid plaque characteristics were ln-transformed. eTable 9 shows details for the conversion between original values and ln-transformed values for continuous carotid MRI variables.

CI: confidence interval; HR: hazard ratio. Analyses of continuous carotid artery MRI plaque characteristics are limited to those participants with a lipid core.

eTable 7. Receiver operating characteristics (ROC) analyses and area under curve (AUC) values for discriminating incident CVD events using MRI plaque burden variables and characteristics, and traditional CVD risk factors

Model	C-Statistic (95% CI)		P-value for model comparisons[†]
Models of MRI Carotid Artery Plaque Characteristics			
Model 1: Total wall volume, NWI, maximum wall thickness (n=1256)	0.578 (0.531, 0.626)		-
Model 2: Total lipid core volume, minimum fibrous cap thickness, calcification present (n=400)	0.590 (0.519, 0.661)		-
Model 3: Total wall volume, NWI, maximum wall thickness, total lipid core volume, minimum fibrous cap thickness, calcification present (Model 1 + Model 2) (n=400)	0.643 (0.577, 0.710)		-
Models with Traditional CVD Risk Factors			
Model 4: Age, gender (n=1256)	0.622 (0.578, 0.666)		-
Model 5: Age, gender, CVD risk factors[‡] (n=1256)	0.670 (0.629, 0.711)		-
Models of MRI Carotid Artery Plaque Characteristics with Traditional CVD Risk Factors			
	AUC **(95% CI) for traditional CVD model**[*]	AUC **(95% CI) for combined model**	
Model 6: MRI measures of plaque burden with traditional risk factors (Model 1 + Model 5) (n=1256)	0.670 (0.629, 0.711)	0.685 (0.645, 0.726)	0.10
Model 7: MRI measures of plaque characteristics with traditional risk factors (Model 2 + Model 5) (n=400)	0.625 (0.556, 0.695)	0.648 (0.581, 0.715)	0.19
Model 8: MRI measures of plaque burden and plaque characteristics with traditional risk factors (Model 3 + Model 5) (n=400)	0.625 (0.556, 0.695)	0.691 (0.630, 0.753)	0.02
Values are reported as c-statistic (area under curve [AUC]) from the ROC curve. CI: confidence interval; ROC: receiver operating characteristics. Model 1 includes only plaque burden variables and model 2 includes only plaque characteristics variables. ‡ CVD risk factors: total cholesterol, HDL cholesterol, SBP, antihypertensive medication use, diabetes, and smoking (current or former) † P-values for the difference in the AUC value compared with traditional CVD risk factors listed in model 5. *The AUC comparisons with traditional CVD risk factors are limited to those ARIC participants with presence of carotid plaque burden and or plaque characteristics variables (model 1, 4, 5, 6: n= 1256; model 2, 3, 7, 8: n= 400).			

eTable 8. Comparison of 10-year risk prediction for incident CVD events using traditional CVD risk factors alone (basic model) and CVD risk factors plus MRI plaque characteristics and plaque burden variables (extended model)

	AUC basic model (95% CI)	AUC extended model (95% CI)	Δ AUC (95% CI)	NRI (95% CI)	Continuous NRI (95% CI)	IDI (95% CI)
Total wall volume (N=1256)	0.678 (0.654, 0.727)	0.680 (0.655, 0.729)	0.002 (-0.0001, 0.013)	0.011 (-0.040, 0.080)	0.125 (-0.067, 0.289)	0.002 (-0.00004, 0.011)
NWI (N=1256)	0.678 (0.654, 0.727)	0.684 (0.659, 0.732)	0.006 (0.00002, 0.024)	0.059 (-0.035, 0.135)	0.161 (-0.009, 0.337)	0.005 (0.0001, 0.020)
Maximum wall thickness (N=1256)	0.678 (0.654, 0.727)	0.680 (0.656, 0.729)	0.002 (-0.0001, 0.013)	0.016 (-0.045, 0.098)	0.117 (-0.051, 0.255)	0.002 (-0.00002, 0.011)
Lipid core present (N=1256)	0.678 (0.654, 0.727)	0.688 (0.663, 0.736)	0.010 (0.001, 0.028)	0.102 (-0.037, 0.161)	0.275 (0.121, 0.431)	0.008 (0.001, 0.024)
Calcification present (N=1256)	0.678 (0.654, 0.727)	0.683 (0.658, 0.731)	0.005 (0.00002, 0.019)	0.053 (-0.053, 0.120)	0.270 (-0.071, 0.429)	0.004 (0.00003, 0.016)
Total lipid core volume (N=400)	0.646 (0.620, 0.744)	0.660 (0.634, 0.749)	0.014 (-0.00003, 0.047)	0.107 (-0.061, 0.202)	0.235 (-0.093, 0.483)	0.008 (-0.0001, 0.036)
Minimum fibrous cap thickness (N=400)	0.646 (0.620, 0.744)	0.660 (0.636, 0.750)	0.014 (0.00002, 0.040)	0.069 (-0.051, 0.178)	0.144 (-0.059, 0.478)	0.009 (0.00004, 0.038)

NRI was calculated using cut-points for 10-year risk set at 7.5% and 15%. CVD risk factors: total cholesterol, high-density-lipoprotein (HDL) cholesterol , systolic blood pressure, antihypertensive medication use, diabetes, and smoking (current or former). Continuous MRI plaque characteristics were analyzed in natural log transformation form. Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; NRI, net reclassification improvement; IDI, integrated discrimination index; CVD, cardiovascular disease.

eTable 9. Details on the conversion between original values and ln-transformed values for continuous carotid MRI plaque burden variables and plaque characteristics for the ARIC incident CVD population.

Variables	N	Unit	Range of the original scale	Range of natural log-transformation	Mean (SD) on natural log-transformation	Conversion of natural log-transformation to the original scale (not linear)
Total wall volume	1256	mL	0.139, 1.615	-1.975, 0.480	-0.89±0.356	Exp(-2) = 0.14 mL, exp(-1) = 0.37 mL, exp(0) = 1 mL, exp(1) = 2.72 mL, exp(2) = 7.39 mL
CA lumen area	1256	mm^2	0.027, 1.576	-3.612, 0.455	-0.92±0.501	Exp(-2) = 0.14 mm^2, exp(-1) = 0.37 mm^2, exp(0) = 1 mm^2, exp(1) = 2.72 mm^2, exp(2) = 7.39 mm^2
CA wall area	1256	mm^2	0.089, 1.484	-2.419, 0.395	-1.09±0.411	Exp(-2) = 0.14 mm^2, exp(-1) = 0.37 mm^2, exp(0) = 1 mm^2, exp(1) = 2.72 mm^2, exp(2) = 7.39 mm^2
Normalized wall index	1256	NA	0.148, 0.933	-1.908, -0.070	-0.84±0.333	Exp(-2) = 0.14, exp(-1) = 0.37, exp(0) = 1, exp(1) = 2.72, exp(2) = 7.39
Maximum carotid artery wall thickness	1256	mm	0.53, 10.02	-0.635, 2.305	0.68±0.504	Exp(-2) = 0.14 mm, exp(-1) = 0.37 mm, exp(0) = 1 mm, exp(1) = 2.72 mm, exp(2) = 7.39 mm
Maximum stenosis*	1256	NA	0, 100	0, 4.615	1.18±1.510	Exp(0) = 1, exp(1) = 2.72, exp(2) = 7.39, exp(3) = 20.09, exp(4) = 54.60
Total lipid core volume	400	mL	0.0014, 0.675	-6.571, -0.393	-3.40±1.147	Exp(-2) = 0.14 mL, exp(-1) = 0.37 mL, exp(0) = 1 mL, exp(1) = 2.72 mL, exp(2) = 7.39 mL
Maximum lipid core area	400	mm^2	0.007, 0.834	-4.962, -0.182	-2.57±0.869	Exp(-2) = 0.14 mm^2, exp(-1) = 0.37 mm^2, exp(0) = 1 mm^2, exp(1) = 2.72 mm^2, exp(2) = 7.39 mm^2
Mean lipid core area	400	mm^2	0.007, 0.482	-4.962, -0.730	-2.89±0.809	Exp(-2) = 0.14 mm^2, exp(-1) = 0.37 mm^2, exp(0) = 1 mm^2, exp(1) = 2.72 mm^2, exp(2) = 7.39 mm^2
Total lipid core % of total wall volume	400	%	0.276, 59.989	-1.286, 4.094	1.91±0.976	Exp(-2) = 0.14%, exp(-1) = 0.37%, exp(0) = 1%, exp(1) = 2.72%, exp(2) = 7.39%, exp(3) = 20.09%, , exp(4) = 54.60%
Mean fibrous cap thickness	400	mm	0.07, 1.895	-2.659, 0.639	-0.52±0.540	Exp(-2) = 0.14 mm, exp(-1) = 0.37 mm, exp(0) = 1 mm, exp(1) = 2.72 mm, exp(2) = 7.39 mm
Minimum fibrous cap thickness	400	mm	0.02, 1.56	-3.912, 0.445	-0.97±0.680	Exp(-2) = 0.14 mm, exp(-1) = 0.37 mm, exp(0) = 1 mm, exp(1) = 2.72 mm, exp(2) = 7.39 mm

*natural log-transformation = ln(1+ maximum stenosis). ln: natural log.