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Risk Factors for Progression of Carotid Intima-Media Thickness and Total Plaque Area

A 13-Year Follow-Up Study: The Tromsø Study

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Background and Purpose—Data on risk factors for progression of intima-media thickness (IMT) and plaque are scarce. The objective was to determine long-term risk factors for total plaque area (TPA) and IMT as well as risk factors for progression (ΔTPA and ΔIMT).

Methods—Subjects were 1307 men and 1436 women who participated in a longitudinal population-based study with ultrasound examination of the right carotid artery at baseline and after 13 years of follow-up. Total cholesterol, high-density lipoprotein cholesterol, blood pressure, body mass index, and information about smoking habits, prevalent diabetes, and cardiovascular disease were obtained at baseline. Carotid atherosclerosis was assessed as TPA and mean IMT of plaque-free segments of the common carotid artery. Associations between z-scores of risk factors and carotid atherosclerosis were assessed in multiple linear regression models.

Results—In multivariable models, total cholesterol, systolic blood pressure, and smoking were stronger predictors of follow-up TPA than of IMT, whereas sex and age were stronger predictors of IMT. Total cholesterol (standardized β=0.081), systolic blood pressure (standardized β=0.062), and smoking (standardized β=0.107) were significant predictors of ΔTPA, whereas only total cholesterol (standardized β=0.084) was an independent predictor of ΔIMT. The variance explained by traditional cardiovascular risk factors was somewhat greater for TPA than for IMT.

Conclusions—The cardiovascular risk factors total cholesterol, smoking, and systolic blood pressure were stronger long-term predictors of TPA and TPA progression than for IMT and IMT progression. **(*Stroke*. 2012;43:1818-1823.)**

Key Words: carotid atherosclerosis ■ progression ■ risk factors ■ ultrasonography

Carotid intima-media thickness (IMT) and plaque are frequently used as a proxy for cardiovascular diseases in observational and interventional studies.[1–3] However, in recent years it has been come increasingly clear that IMT and plaque show different relationships to cardiovascular risk factors as well as clinical end points. According to guidelines, IMT is preferably measured in plaque-free segments of the far wall of the distal common carotid artery (CCA-IMT).[4] CCA-IMT is strongly related to age and hypertension, and thickening of the intima-media layer mainly represents a hypertrophic adaptive response of smooth muscle cells in the tunica media to high shear stress.[5,6] Plaques usually occur at sites of low shear and nonlaminar turbulent flow such as in the carotid bulb and the proximal internal carotid artery,[6] and is rare in the distal CCA. The role of IMT as a marker of atherosclerosis has been questioned, especially when measurements include the CCA-IMT only.[7] Carotid plaque burden can be measured as a continuous variable as the sum of all plaque areas in the artery, the total plaque area (TPA). TPA has been found to be more strongly associated with traditional cardiovascular risk factors than CCA-IMT.[5,8] TPA has also been found to be a stronger predictor of coronary artery disease than CCA-IMT in both clinical and population-based studies.[9–12] In a recent publication from our group, IMT was predictive of ischemic stroke in women when assessed as an average of the mean IMT in the far and near wall of the common carotid and in the far wall of the bifurcation and with plaques included. However, CCA-IMT was not associated with future ischemic stroke after adjustment for other cardiovascular risk factors.[13] Although highly correlated, plaque and IMT may reflect different genetic and biological aspects of atherogenesis with distinctive relations to cardiovascular risk factors and to clinical vascular disease.

Data on risk factors for progression of both IMT and plaque are scarce. In the population-based Tromsø Study, we have done repeated measurements of both IMT and TPA in

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Part of the data in this study have been presented orally at the European Stroke Conference, Hamburg, May 2011.

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the same individuals, and the study is therefore well suited to assess the impact of different cardiovascular risk factors on progression of the 2 ultrasonographic phenotypes. In the present prospective study, the objective was to determine risk factors for TPA and IMT at follow-up as well as risk factors for progression (ΔTPA and ΔIMT).

Materials and Methods

Subjects

The Tromsø Study is a population-based prospective study with repeated health surveys of inhabitants in the municipality of Tromsø, Norway.[14] In the fourth survey in 1994 to 1995 (baseline), all subjects aged 55 to 74 years and a random 5% to 10% sample in the other age groups >24 years were invited to ultrasound scanning of the carotid artery. Ultrasound of the right carotid artery was performed in 6727 subjects (77% of the eligible). Subjects who did not consent to medical research (n=40) were excluded. Representative measures of TPA and CCA-IMT were available in 6611 participants, 3271 men and 3340 women. All participants who were still living in Tromsø were invited to a new examination in the sixth survey in 2007 to 2008 (follow-up). Ultrasound examination of the right carotid artery was performed in 2975 persons who had attended both the fourth and the sixth surveys. We excluded persons without valid measures on all risk factor variables as well as the outcome variables (n=87) and 145 subjects with plaque in the distal CCA (see subsequently), leaving 2743 persons to be included in the study. The Regional Committee for Medical Research Ethics approved the study, and informed written consent was obtained from all the participants.

Cardiovascular Risk Factors

Information about smoking habits, prevalent diabetes mellitus, angina pectoris, previous myocardial infarction, stroke, and current use of antihypertensive- and lipid-lowering drugs was collected from self-administered questionnaires. Coronary heart disease was defined as previous myocardial infarction and/or prevalent angina, and cardiovascular disease as previous myocardial infarction and/or prevalent angina and/or stroke. Blood pressure was recorded 3 times at 1-minute intervals after 2 minutes of seated resting with the use of an automatic device (Dinamap Vital Signs Monitor 1846l Criticon) and by specially trained technicians. The mean of the last 2 recordings was used in the report. Standardized measurements of height, weight, nonfasting serum total cholesterol, high-density lipoprotein cholesterol, and triglycerides were performed as described previously.[13] Body mass index (BMI) was calculated as weight (kg) divided by height (m^2).

Ultrasonography

High-resolution B-mode ultrasonography of the right carotid artery was at baseline performed with a duplex scanner (Acuson Xp10 128, ART-upgraded) equipped with a 7.5-MHz linear array transducer and at follow-up with a duplex scanner GE Vivid 7 with a linear 12-MHz transducer and followed the same scanning and reading procedures and reproducibility as published previously.[15,16] Different sonographers did the baseline and follow-up scanning, and to ensure equal and standardized examination techniques and measurement procedures, all sonographers completed a 2-month prestudy training protocol.

A plaque was defined as a localized protrusion of the vessel wall into the lumen of at least 50% compared with the adjacent IMT. Six locations of the carotid artery were examined for plaque presence: the far walls and near walls of the CCA, the bifurcation (bulb), and the internal carotid artery. The area of each plaque was outlined manually with automatic calculation of plaque area. In subjects with >1 plaque, the areas of all plaques were summarized to give TPA.

Automated R-triggered measurement of IMT was performed in the far wall of the distal CCA[16] and was not limited to plaque-free segments. To ensure that the CCA-IMT measurements were done in plaque-free segments only,[4] we excluded subjects with plaque in the distal CCA (n=145). A final reading of both IMT and plaque data was done offline by the researchers. Measurements of IMT were analyzed offline by a semiautomated computerized edge-detection program.[17] The average of the mean CCA-IMT in 3 separate recordings was used in the analyses and is referred to as IMT.

Details about the inter- and intraobserver reproducibility of IMT and plaque measurements have been published previously.[15,16,18] The interequipment variability between GE Vivid 7 and Acuson XP10 was tested in 79 subjects, of whom 38 had ≥1 plaques. All subjects were examined with Acuson XP10 first. To minimize the influence of sonographer and reader variability, all examinations were performed by the same sonographer, whereas the readings of TPA and IMT were done by another person blinded to the identity of the participants. IMT values were higher when measured with GE Vivid 7 compared with Acuson XP10 with a mean arithmetic difference of 0.15 mm (95% CI, 0.14–0.17 mm). The mean absolute difference was 0.16 mm, coefficient of variation 9.1%, and the limits of agreement ±0.20 mm. For TPA, the mean absolute difference was 6.5 mm^2 and the mean arithmetic difference 2.4 mm^2 (95% CI, −0.5 to 5.4), indicating no systematic difference between machines. The coefficient of variation was 26.4% and the correlation coefficient 0.89. Limits of agreement was not calculated due to skewed distribution of the arithmetic differences. For the square root-transformed TPA values, which was used in the analyses (see subsequently), the mean arithmetic difference was 0.2 (95% CI, −0.06 to 0.50), the mean absolute difference 0.68, the coefficient of variation 13.2%, and limits of agreement ±1.7.

Table 1. Characteristics* of the Study Participants Stratified by Sex: The Tromsø Study

	Men (N=1307)	Women (N=1436)	*P* Value
Age, y	55.8 (9.08)	56.6 (10.2)	0.03
BMI, kg/m^2	26.1 (3.0)	25.6 (3.91)	<0.001
Systolic blood pressure, mm Hg	139.8 (17.9)	138.4 (21.67)	0.07
Serum lipids, mmol/L			
Total cholesterol	6.51 (1.15)	6.69 (1.32)	<0.0001
HDL cholesterol	1.38 (0.37)	1.70 (0.40)	<0.0001
Triglycerides	1.79 (1.12)	1.42 (0.85)	<0.0001
Current smoking, %	28.2	27.2	0.6
Self reported disease, %			
Coronary heart disease	8.8	4.3	<0.001
Stroke	0.8	1.1	0.5
Diabetes	1.2	1.6	0.4
Use of drugs, %			
Antihypertensive medication	7.7	8.8	0.3
Lipid-lowering therapy	2.1	1.0	0.021

*Measured at baseline.
BMI indicates body mass index; HDL, high-density lipoprotein.

Statistical Analyses

Between-group differences were estimated by analysis of variance (Table 1). The distribution of TPA was skewed to the right and the square root of this variable was used in the analyses to approximate normal distribution. The independent relationship between cardiovascular risk factors (independent variables) and measurements of atherosclerosis (TPA and IMT at follow-up and ΔTPA and ΔIMT) was assessed in multiple linear regression models with all explanatory variables entered stepwise using the forward selection method. Additional adjustments were made for use of antihypertensive and lipid-lowering drugs at baseline. All variables, both dependent and independent, were standardized using z-scores to compare the

Table 2. Mean Intima-Media Thickness* and Total Plaque Area at Baseline and Progression Between Baseline and Follow-Up by Age and Sex: The Tromsø Study

				Progression			
	Baseline			ΔIMT, mm		ΔTPA, mm^2	
	No.	IMT, mm	TPA, mm^2	Total	Annual	Total	Annual
Men							
25–49 y	243	0.63	2.60	0.14	0.01	2.32	0.18
50–59 y	531	0.73	6.34	0.18	0.01	7.25	0.55
60–69 y	466	0.78	10.31	0.17	0.01	7.37	0.58
≥70 y	67	0.85	13.39	0.15	0.01	13.52	1.02
Total	1307	0.73	7.42	0.16	0.01	10.84	0.82
Women							
25–49 y	257	0.59	0.71	0.11	0.01	1.39	0.11
50–59 y	488	0.68	3.63	0.12	0.01	1.79	0.14
60–69 y	594	0.73	6.18	0.13	0.01	5.28	0.4
≥70 y	98	0.79	12.01	0.15	0.01	9.09	0.69
Total	1437	0.69	4.73	0.14	0.01	7.42	0.56

*Mean of 3 measurements in plaque-free segments in the far wall of the distal common carotid artery.
IMT indicates intima-media thickness; TPA, total plaque area.

strength of the β coefficients of each independent variable. The summarized and partial R^2 of the models were used to calculate the proportion of the explained variance associated with each independent variable. The significance level for entry into the model was set at 0.05. SAS software, Version 9, and STATA software, Version 12, were used for statistical analyses. Two-sided probability values <0.05 were considered statistically significant.

Results

The mean observation time was 13.2 years. Baseline characteristics are shown in Table 1. Men had higher BMI, higher triglyceride, and lower high-density lipoprotein levels than women and a higher proportion of men reported coronary heart disease, use of lipid-lowering drugs, and current smoking.

Plaque was present in 41.6% of men and 32.6% of women at baseline. Mean TPA was 7.41 (SD 12.60) mm^2 in men and 4.73 (SD 9.73) mm^2 in women (Table 2). Mean IMT was higher in men (mean, 0.73; SD 0.16 mm) than in women (0.69; SD 0.13 mm).

During follow-up, the overall progression of TPA was 10.84 mm^2 in men and 7.42 mm^2 in women ($P<0.0001$; Table 2). In all age groups, TPA and ΔTPA were greater in men than in women (Figures 1 and 2). Regression in TPA was found in 11% of women (mean, −8.96 mm^2) and 14% of men (mean, −11.48 mm^2). Plaque growth increased by age in both men and women and more rapidly after the age of 50 years, whereas the progression rate of IMT was constant over time (Table 2; Figure 2). The annual progression rate of IMT was 0.012 mm in men and 0.011 mm in women. Regression in IMT was found in 13% of women (mean, −0.097 mm) and 13.4% of men (mean, −0.104 mm). Although IMT levels at baseline and follow-up increased by age, no correlation was found between ΔIMT and age (Table 2; Figure 2).

In a stepwise multivariable regression model, age, sex, total cholesterol, systolic blood pressure, smoking, prevalent cardiovascular disease, and use of lipid-lowering drugs were independent predictors of TPA at follow-up (Table 3). The model R^2 was 0.19. Age accounted for 53% of the explained variance, smoking and sex 11% each, total cholesterol 10%, systolic blood pressure 7%, lipid-lowering drugs 4%, and cerebrovascular disease 1% (calculated from the partial and summarized R^2; Table 3). Age, sex, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, BMI, and smoking were independent predictors of IMT at follow-up (model R^2 0.21; Table 3). Age explained 71% of the explained IMT variance, sex 19%, BMI 5%, total cholesterol 2%, and systolic blood pressure, smoking, and high-density lipoprotein cholesterol 1% each.

Age, sex, smoking, total cholesterol, systolic blood pressure, and use of lipid-lowering drugs were independent

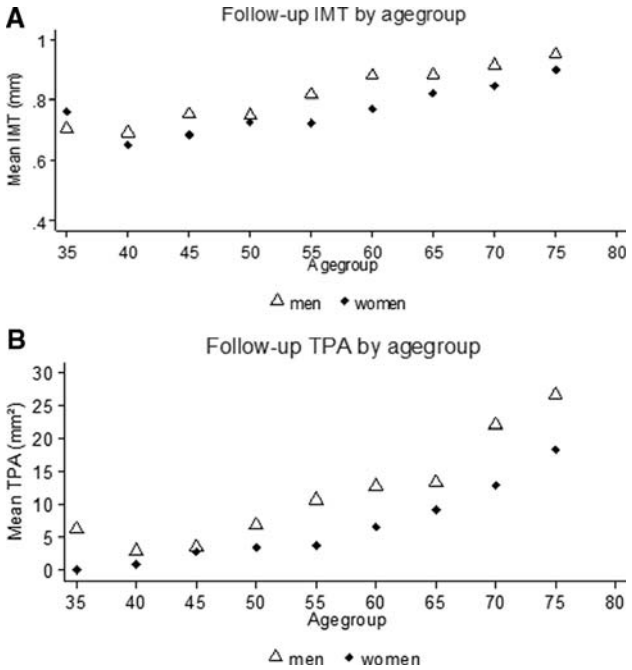

Figure 1. A–B, IMT and TPA at follow-up by sex and age group. IMT indicates intima-media thickness; TPA, total plaque area.

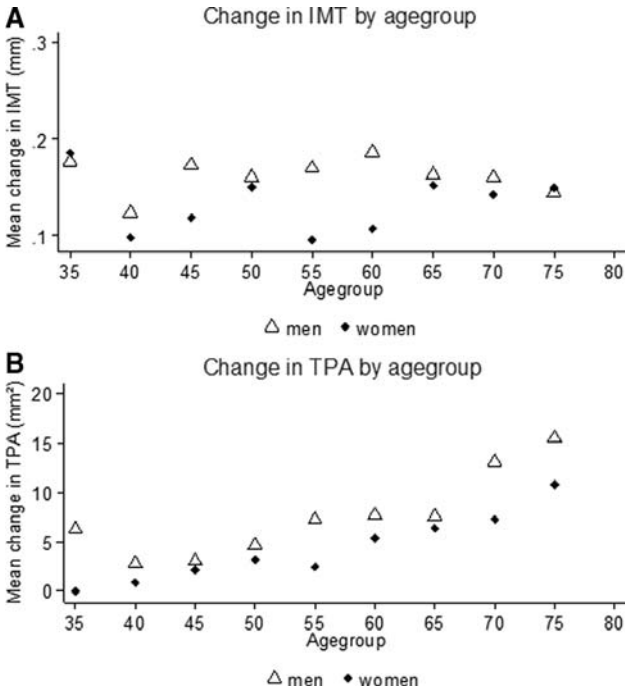

Figure 2. A–B, Change in IMT and TPA from baseline to follow-up by sex and age group. IMT indicates intima-media thickness; TPA, total plaque area.

predictors of progression of TPA (Table 4). Age accounted for 39% of the explained variance, smoking 29%, total cholesterol 12%, sex 9%, systolic blood pressure 7%, and lipid-lowering therapy 5% (Table 4). Sex and total cholesterol were associated with progression of IMT (Table 4), whereas systolic blood pressure showed an inverse relationship (standardized β −0.076). None of the other cardiovascular risk factors predicted IMT progression.

Discussion

The main finding of the present study was that age, total cholesterol, systolic blood pressure, and smoking predicted progression of TPA, whereas only total cholesterol was a predictor of IMT progression. The variance explained by traditional cardiovascular risk factors was somewhat greater for TPA than for IMT.

Few studies have assessed risk factors for progression of IMT and plaque, and to the best of our knowledge, data on progression of TPA and IMT in the same individuals have not been published previously. In the Rotterdam study, current smoking was the strongest predictor of increase in plaque number.[19] Strong associations were also found for age, total cholesterol, hypertension, and systolic blood pressure, whereas only age and BMI predicted progression of IMT consistently.[19] In the Atherosclerosis Risk in Communities Study (ARIC), diabetes, current smoking, high-density lipoprotein cholesterol, pulse pressure, white blood cell count, and fibrinogen were predictors of IMT progression.[20] In a Finnish population-based study in men, age, serum low-density lipoprotein cholesterol, pack-years of smoking, blood leukocyte count, and platelet aggregability were the strongest predictors of CCA-IMT progression. Hypertension, blood pressure, and high-density lipoprotein cholesterol did not show any association with progression of IMT over 2 years.[21]

Surprisingly, systolic blood pressure was negatively associated with IMT progression despite the fact that systolic blood pressure was a strong predictor of follow-up IMT. These findings are confusing when comparing previous reports that highlight age and hypertension as major risk factors of intima media thickening. However, previous studies have failed to find significant associations between systolic blood pressure and/or hypertension and progression of IMT.[19–21] Larger within-person variance of progression of IMT than of cross-sectional IMT can be expected to result in stronger estimates for cross-sectional analyses compared with longitudinal.[20]

Increased use of statins during the follow-up period may have affected the associations between risk factors and the dependent variables. Use of statins in the population was very

Table 3. Predictors of IMT and TPA at Follow-Up in Stepwise Multivariable Regression Analysis: The Tromsø Study

	IMT			TPA*		
	β†	r^2	*P* Value	β†	r^2	*P* Value
Age, y	0.359	0.145	<0.0001	0.263	0.099	<0.0001
Male sex	0.177	0.039	<0.0001	0.136	0.020	<0.0001
Total cholesterol, mmol/L	0.066	0.004	0.0001	0.125	0.019	<0.0001
HDL cholesterol, mmol/L	−0.049	0.002	0.011	…	…	…
Systolic blood pressure, mm Hg	0.041	0.001	0.003	0.126	0.014	<0.0001
Body mass index, kg/m^2	0.081	0.011	<0.0001	…	…	…
Smoking	0.054	0.003	0.002	0.165	0.026	<0.0001
Use of lipid-lowering drugs	…	…	…	0.075	0.007	<0.0001
Cardiovascular disease	…	…	…	0.045	0.002	<0.0001
Diabetes	…	…	…	…	…	…
Summarized model R^2		0.206			0.186	

IMT indicates intima-media thickness, TPA; total plaque area; HDL, high-density lipoprotein.
*Square root transformed.
†Standardized regression β coefficients; z-scores for all independent and dependent variables.

Table 4. Predictors of Change in IMT and TPA in Stepwise Multivariable Regression Analysis: The Tromsø Study

	ΔIMT			ΔTPA*		
	β†	r^2	*P* Value	β†	R^2	*P* Value
Age, y	…	…	…	0.103	0.015	<0.0001
Male, sex	0.067	0.004	0.0002	0.054	0.004	0.002
Total cholesterol, mmol/l	0.050	0.002	0.0002	0.067	0.005	0.0003
HDL cholesterol, mmol/L	…	…	…	…	…	…
Systolic blood pressure, mm Hg	−0.076	0.004	0.002	0.056	0.003	0.0006
BMI, kg/m^2	…	…	…	…	…	…
Smoking	…	…	…	0.106	0.011	<0.0001
Use of lipid-lowering drugs	…	…	…	0.041	0.002	0.03
Cardiovascular disease	…	…	…	…	…	…
Diabetes	…	…	…	…	…	…
Summarized model R^2		0.010			0.038	

IMT indicates intima-media thickness, TPA; total plaque area; HDL, high-density lipoprotein; BMI, body mass index.
*Square root transformed.
†Standardized regression β coefficients; z-scores for all independent and dependent variables.

low (<2%) at baseline but increased to 11.8% during follow-up. Lipid-lowering therapy at baseline was positively associated with progression of TPA, and this variable probably acts as a marker of increased cardiovascular risk.

In our study, the annual progression of IMT was 0.012 mm in men and 0.011 mm in women, which is somewhat less than the progression of mean IMT of approximately 0.015 mm in previous reports.[22] Regression of IMT was found in approximately 13% of the study group. Interestingly, the progression rate of TPA increased by age, whereas progression of IMT was constant over age groups. This may explain why age was a significant risk factor for progression of TPA but not for IMT.

Plaque and IMT may represent different phenotypes of atherosclerosis with differential relations to cardiovascular risk factors and to clinical vascular disease.[5,9,23] Both autopsy studies and ultrasonographic studies have demonstrated that carotid plaque is more strongly correlated to atherosclerosis in other vascular beds than is IMT.[24–30] This probably reflects differences in the pathological processes leading to intima-media thickening of the distal part of CCA and plaque formation in other arteries, whereas plaque formation in the carotid artery and other arterial beds is more closely related.[7,8] Thickening of the intima-media layer in CCA is usually caused by hypertrophy of the smooth muscle cells in the media layer, whereas the atherosclerotic process, particularly in its early phase, is restricted to the intimal layer. Atherosclerotic plaque formation represents a later stage of atherogenesis related to oxidation of lipids, transmigration and infiltration of monocytes, and lymphocytes, inflammation, and smooth muscle cell proliferation.[5] Longitudinally plaque growth along the carotid axis of flow is >2 times faster than thickening toward the lumen.[31] Thus, TPA provides more detailed information of the atherosclerotic burden than IMT. Measuring plaque on a continuous scale increases the ability to quantify the effect of and interaction among risk factors compared with categorical classification.[32]

Measuring progression of atherosclerosis is more difficult than single measurements because random measurement errors at baseline and follow-up are accumulated, tending to attenuate the differences aimed to be detected. In the Asymptomatic Carotid Artery Progression Study, variance component analyses revealed that 11% of the total variance of IMT was attributable to systematic differences among readers, nonvisualization contributed <7%, whereas the predominant source of error was random, including any drift, nonlinearity, and sonographer differences.[33] From an imaging technology perspective, it should be emphasized that IMT is a very small structure, usually a fraction of a millimeter, and changes over time represents only tenths of millimeter, that is, the resolution of the B-mode image is below the quantities being measured. This makes the method less suitable for longitudinal measurements at an individual level. Although the large number of readings will tend to counteract the inherent measurement errors, it may still be questioned whether IMT progression at a group level can be reliably measured in epidemiological studies. Reproducibility in observational studies not a priori set up to assess IMT change over time has usually been much lower (intraclass correlation of repeated measurement of 0.59–0.75) than in trials (intraclass correlation >0.90).[34] In our study, measurements were performed on the right carotid artery only, and examination of both carotid arteries could have yielded more precise estimates of the individual's IMT and total carotid plaque burden. Furthermore, different sonographers, readers, and ultrasound equipment at baseline and follow-up represent methodological weaknesses, which may have affected the precision and reproducibility of the IMT and TPA measurements. This could result in imprecise estimation of the true relationship between risk factors and ΔIMT and ΔTPA. We found that IMT was thicker when measured by Vivid 7 compared with Acuson XP10, indicating that lack of association between risk factors and ΔIMT was not due to underestimation of the true ΔIMT levels. No systematic bias was found for TPA mea-

surements. Both the fact that plaques are larger structures and the increasing progression rate of TPA by age may make plaques more robust against this kind of measurement variability.

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Disclosures

None.

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