7-1-2013

Progression of carotid plaque volume predicts cardiovascular events

Thapat Wannarong

Grace Parraga

Daniel Buchanan

Aaron Fenster

Andrew A House

See next page for additional authors

Progression of Carotid Plaque Volume Predicts Cardiovascular Events

Thapat Wannarong, Grace Parraga, Daniel Buchanan, Aaron Fenster, Andrew A. House, Daniel G. Hackam, and J. David Spence

2013, 44 (7), 1859-1865• DOI: 10.1161/STROKEAHA.113.001461 • Publication Date (Web): 04 Jun 2013

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

Progression of Carotid Plaque Volume Predicts Cardiovascular Events

Thapat Wannarong, MD; Grace Parraga, PhD; Daniel Buchanan, MSc; Aaron Fenster, PhD; Andrew A. House, MD; Daniel G. Hackam, MD, PhD; J. David Spence, MD

Background and Purpose—Carotid ultrasound evaluation of intima-media thickness (IMT) and plaque burden has been used for risk stratification and for evaluation of antiatherosclerotic therapies. Increasing evidence indicates that measuring plaque burden is superior to measuring IMT for both purposes. We compared progression/regression of IMT, total plaque area (TPA), and total plaque volume (TPV) as predictors of cardiovascular outcomes.

Methods—IMT, TPA, and TPV were measured at baseline in 349 patients attending vascular prevention clinics; they had TPA of 40 to 600 mm^2 at baseline to qualify for enrollment. Participants were followed up for ≤5 years (median, 3.17 years) to ascertain vascular death, myocardial infarction, stroke, and transient ischemic attacks. Follow-up measurements 1 year later were available in 323 cases for IMT and TPA, and in 306 for TPV.

Results—Progression of TPV predicted stroke, death or TIA (Kaplan-Meier logrank P=0.001), stroke/death/MI (P=0.008) and Stroke/Death/TIA/Myocardial infarction (any Cardiovascular event) (P=0.001). Progression of TPA weakly predicted Stroke/Death/TIA (P=0.097) but not stroke/death/MI (P=0.59) or any CV event (P=0.143); likewise change in IMT did not predict Stroke/Death/MI (P=0.13) or any CV event (P=0.455). In Cox regression, TPV progression remained a significant predictor of events after adjustment for coronary risk factors (P=0.001) but change in TPA did not. IMT change predicted events in an inverse manner; regression of IMT predicted events (P=0.004).

Conclusions—For assessment of response to antiatherosclerotic therapy, measurement of TPV is superior to both IMT and TPA. **(*Stroke*. 2013;44:1859-1865.)**

Key words: Carotid, Ultrasound, plaque, IMT, Stroke, Myocardial infarction, Risk

To be cost-effective, therapy to prevent cardiovascular events is best targeted to high-risk patients. Risk scores, such as the Framingham score, have been widely used for this purpose, but often misclassify risk.[1] Measurement of the burden of preclinical atherosclerosis has, therefore, been proposed as a way to improve cardiovascular prevention.[1] Although carotid intima-media thickness (IMT) has been widely used for the past 30 years, it is increasingly clear that IMT does not truly assess atherosclerosis[2,3] and is a weak predictor of cardiovascular events,[4] that it is not feasible to measure progression of IMT within individuals in clinically meaningful time frames, and in large groups IMT progression does not predict events.[5]

Quantification of plaque burden is superior to IMT for several reasons: it is a stronger predictor of cardiovascular events,[6–8] change can be reliably measured within individuals in months,[9–11] and progression of total plaque area (TPA) strongly predicts stroke, death, and myocardial infarction (MI).[12] Measurement of TPA has been used to treat arteries rather than risk factors,[10] and doing so markedly reduces cardiovascular events.[13]

Volumetric measurement of plaque burden is much more closely correlated to coronary calcium than is IMT,[14] and 3-dimensional (3D) measurement of total plaque volume (TPV) is much more sensitive to effects of therapy than TPA[11]; compared to IMT, measuring TPV reduces by two orders of magnitude the sample size and duration of followup required to study effects of new anti-atherosclerotic therapies.[11] It is expected that measurement of 3D plaque volume will be even more useful than TPA in treatment of atherosclerosis.

Here, we report results of the first study to assess prediction of cardiovascular events by progression of TPV and the first to compare progression/regression of carotid IMT, TPA, and TPV in patients attending vascular prevention clinics.

Methods

Study Population

Participants in the study were patients being followed up in the Stroke Prevention Clinic or the Premature Atherosclerosis Clinic at University Hospital, London, Ontario, Canada. Participants were screened for this study by measurement of their carotid TPA.[15] We

Received March 12, 2013; accepted April 1, 2013.

From the Stroke Prevention and Atherosclerosis Research Centre, Robarts Research Institute (T.W., D.G.H., J.D.S.), Imaging Research Group, Robarts Research Institute (G.P., D.B., A.F., J.D.S.), Department of Medicine (A.A.H., D.G.H.), and Department of Epidemiology and Biostatistics (D.G.H.), Western University, London, Canada; and Department of Internal Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand (T.W.).

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.113.001461/-/DC1.

Correspondence to J. David Spence, MD, Stroke Prevention and Atherosclerosis Research Centre, Robarts Research Institute, University of Western Ontario, 1400 Western Rd, London, ON, Canada N6G 2V2. E-mail dspence@robarts.ca

Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.113.001461**

recruited participants with a baseline plaque area between 40 and 600 mm^2 of TPA to ensure that participants would have measurable plaque volume and to ensure the ability to measure plaque progression or regression.

Participants gave written consent to a protocol approved by the Western University Human Ethics Research Board. They attended the research clinic at baseline and 1 year later for measurement of the ultrasound phenotypes described below, and annually for a total follow-up of 5 years for ascertainment of outcomes.

Ascertainment of Outcomes

At each annual visit, participants were queried about any events in the previous year. Any report of stroke, transient ischemic attack (TIA), MI, or revascularization (stenting, bypass, or endarterectomy of any artery) was confirmed by review of the hospital electronic record. For patients who could not be contacted to attend for follow-up because they had died, death and cause of death were confirmed by contact with the primary care physician.

Ultrasound Phenotypes

Carotid TPA, TPV, and IMT were measured at baseline and after 1 year. The observer (T.W.) was blinded to treatment and time point (baseline versus follow-up) for IMT and TPV. Measurements of TPA were performed on the ultrasound screen, not offline, so they were performed on the day of clinic visits, and, therefore, not blinded as to time. The technologists performing the plaque measurements were not aware of the treatments.

Table 1. Baseline Characteristics of Study Patients by Progression Group for Plaque Volume

Characteristics	Regression* (n=84)	Stable* (n=69)	Progression* (n=153)	*P* Value†
Age, y	70 (13)	70 (12)	70.5 (13)	0.47
SBP, mm Hg	133 (25)	135 (30)	135 (27)	0.29
DBP, mm Hg	74.5 (16)	76.5 (15)	74.5 (13)	0.60
Total plaque area, mm^2	173.5 (112.75)	136.5 (85.75)	157 (114.25)	0.08
Total plaque volume, mm^3	336.51 (308.55)	208.1 (226.3)	254.4 (249.37)	<0.001
Intima-media thickness, mm	0.96 (0.23)	0.91 (0.18)	0.89 (0.21)	0.037
Carotid stenosis, %‡	40 (10)	40 (10)	40 (0)	0.35
Total cholesterol, mmol/L	3.96 (1.19)	4.07 (1.10)	3.91 (1.28)	0.85
Triglycerides, mmol/L	1.23 (0.86)	1.22 (0.75)	1.11 (0.84)	0.57
HDL-cholesterol, mmol/L	1.31 (0.49)	1.35 (0.63)	1.345 (0.55)	0.54
LDL cholesterol, mmol/L	1.96 (1.17)	2.0 (0.82)	1.90 (0.98)	0.87
Total homocysteine, µmol/L	9.05 (4.85)	8.7 (3.9)	8.85 (5.77)	0.69
Smoking, pack-y	10 (23.63)	5.53 (27.5)	4.25 (22.19)	0.94
Smoking status				
Never smoked	36.3%	37.3%	34.3%	0.91
Quit	52.0%	52.9%	59.8%	0.47
Still smoking	11.8%	9.8%	5.9%	0.33
Female	43.1%	42.2%	43.1%	0.99
Diabetes mellitus	23.5%	19.6%	17.6%	0.57
Previous stroke	28.4%	22.5%	18.6%	0.25
Previous TIA	44.1%	50.0%	36.3%	0.14
Previous MI	14.7%	17.6%	15.7%	0.84
Previous angina pectoris	19.6%	22.5%	23.5%	0.78
Previous AF	3.9%	13.7%	9.8%	0.05
Previous heart failure	2.9%	2.9%	2.0%	0.88
Previous PAD	9.8%	14.7%	16.7%	0.34
Previous carotid endarterectomy	6.9%	3.9%	9.8%	0.25
Previous carotid angioplasty	1.0%	0%	2.9%	0.17
Previous peripheral artery angioplasty	0%	1.0%	2.9%	0.17
Previous coronary angioplasty	5.9%	9.8%	6.9%	0.54
Previous CABG	9.8%	16.7%	6.9%	0.073
Previous lower limb amputation	1.0%	0%	0%	0.37

For progression of total plaque volume (TPV); the median change in TPV was 27mm^3; regression was a reduction of TPV by >27 mm^3; progression was an increase by >27 mm^3; and stable plaque volume was a change in either direction by <27 mm^3. AF indicates atrial fibrillation; CABG, coronary artery bypass graft; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; PAD, peripheral arterial disease; SBP, systolic blood pressure; and TIA, transient ischemic attack.

*Continuous variables are reported as median (interquartile range); for categorical variables as percentages.

†Using Kruskal–Wallis *H* test for continuous variables and using Pearson χ^2 test for categorical variables.

‡Maximal internal carotid stenosis on either side.

Total Plaque Area

TPA was measured by 2 experienced registered vascular technologists, using Phillips duplex scanners (ATL 5000 HDI with a L12-5, 50 mm transducer, using Sono-CT compound imaging; Advanced Technology Laboratories, Bothel, WA). As previously described,[15,16] plaque was defined as a focal thickening of the intima-media layer, >1 mm in thickness. All plaques seen from the clavicle to the angle of the jaw, including the right subclavian artery and both common, internal and external carotid arteries, were measured. Each plaque was measured in a longitudinal view, selecting the plane in which the plaque seemed to have the largest footprint, and the cross-sectional area measured by tracing the perimeter of the plaque on the screen with a cursor driven by a trackball. The sum of the areas of all plaques seen was the TPA. Intraobserver reliability was 94% for repeated measurements; interobserver reliability on repeat scanning by the 2 technologists was 85%.[15]

Total Plaque Volume

As previously described,[17,18] TPV was measured with a software update permitting semiautomated segmentation of the lumen.[19,20] 3D US images were acquired by translating the ultrasound transducer (L12-5, 50 mm, Philips, Bothel, WA) in a transverse orientation (perpendicular to the axis of flow) along the neck of the patient for ≈8 seconds an approximate distance of 4.0 cm, whereas video frames from the duplex scanner were digitized using 3DEchotec equipment (General Electric Medical Systems, Halbergmoos, Germany) coupled to the ATL HDI 5000 scanner. Cross-sectional slices were acquired at the rate of ≈30 slices/s, and saved to a computer workstation. The orientation and speed of the transducer was adjusted so that the resulting transverse 2D images were approximately parallel to each other with a mean spatial interval of ≈0.15 mm. The acquired 2D images were reconstructed immediately into a 3D US image and displayed using 3D viewing software (3DQuantify, Robarts Imaging Laboratories, London, Canada).

A semiautomated approach that uses 2 planes was used to quantify carotid plaque volume as previously described.[20] Plaque was defined as focal thickening >1 mm of the intima-media in the longitudinal view. Briefly, a longitudinal axis was set parallel to the axis of flow in the common and internal carotid arteries. Plaques were measured in the common carotid and internal carotid, from 1.5 cm below the bifurcation to 1 cm above the bifurcation. In a longitudinal view, the plane in which the plaque seemed to have the largest footprint was selected to identify the length and end points of the plaque. Along this length the plaque boundary was identified at 25%, 50%, and 75% of the total length using a second plane perpendicular to arterial blood flow. Although the longitudinal view identified the length and end points of the plaque, the perpendicular cross-sectional view defined plaque morphology. Individual plaque volumes within the same artery were summed to generate a TPV for 1 side. Intraobserver reliability for measurement of TPV is 94%, and interobserver reliability is 93%.[9] As previously described,[18] carotid TPVs were summed from left and right carotid arteries to generate a TPV for each subject at a particular time point.

Intima-Media Thickness

As previously described,[21] IMT was measured from lateral image planes extracted from the 3D US images. Images were included for analysis only if there was a clear intima-media layer present for

Table 2. Percentage of Patients Taking Various Classes of Cardiovascular Medications

	Regression	Stable	Progression	*P* Value*
Antiplatelet agent	82.4	80.4	73.5	0.27
Anticoagulant	4.9	16.7	14.7	0.022
Antihypertensive drug	88.2	91.2	87.3	0.65
ACE inhibitor	49.0	54.9	45.1	0.37
ARB	20.6	19.6	31.4	0.091
β Blocker	29.4	39.2	36.3	0.32
CCB	33.3	30.4	51.0	0.005
Diuretic	54.9	45.1	58.8	0.13
Aliskiren	0	0	1.0	0.37
Alpha blocker	2.9	6.9	4.9	0.43
Oral DM	14.7	7.8	12.7	0.29
Insulin	2.0	4.9	4.9	0.46
Lipid-lowering drug	96.1	92.2	93.1	0.48
Statin	90.2	85.3	85.3	0.49
Low dose†	17.6	18.6	25.5	0.32
Medium dose†	60.8	47.1	46.1	0.063
High dose†	11.8	19.6	13.7	0.26
Ezetimibe	49.0	38.2	52.9	0.093
Fibrate	14.7	17.6	19.6	0.65
Niacin	7.8	4.9	8.8	0.53
NSAIDs	8.8	7.8	5.9	0.72
Vitamin B12	76.5	78.4	76.5	0.93

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; NSAIDs, nonsteroidal anti-inflammatory drugs; Oral DM, oral hypoglycemic drug; and statin, HMG CoA reductase inhibitor.

*Exact χ^2 test.

†Statin dose ranges: (1) low dose: atorvastatin 10 mg, simvastatin 10 to 20 mg, rosuvastatin 5 mg, fluvastatin 20 to 80 mg, and pravastatin 10 to 40 mg; (2) medium dose: atorvastatin 20 to 40 mg, rosuvastatin 10 to 20 mg, and simvastatin 40 mg; and (3) high dose: atorvastatin 80 mg and rosuvastatin 40 mg.

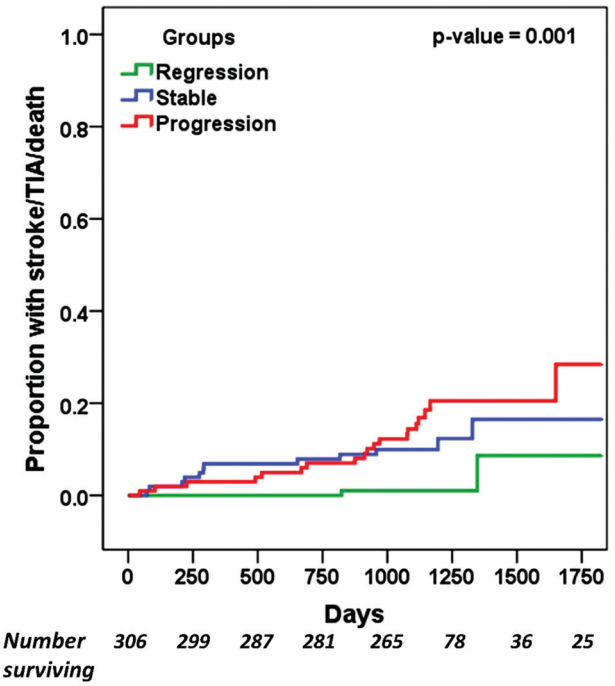

Figure 1. Risk of stroke, transient ischemic attack (TIA), or death by progression/regression of total plaque volume. Kaplan–Meier 1-survival curves of stroke, TIA, or death over 5 years in participants with regression, stable plaque, or progression (defined by the tertiles of change in plaque volume from baseline to 1 year later). Tertiles are shown in Table IV in the online-only Data Supplement. The log-rank *P* value was 0.001 across the 3 groups.

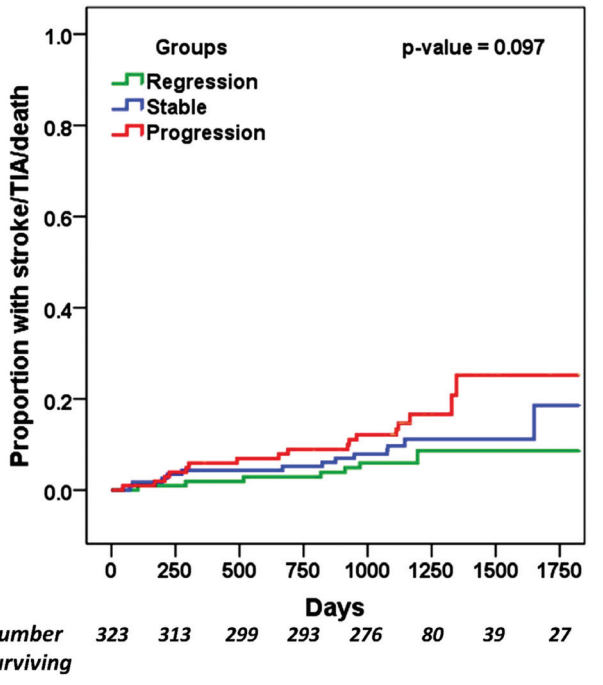

Figure 2. Risk of stroke, transient ischemic attack (TIA), or death by progression/regression of total plaque area. Kaplan–Meier 1-survival curves of stroke, TIA, or death over 5 years in participants with regression, stable plaque, or progression (defined by the tertiles of change in TPA from baseline to 1 year later). Tertiles are shown in Table IV in the online-only Data Supplement. The log-rank *P* value was 0.143 across the 3 groups.

measurement. In the 3D US image, a lateral plane parallel to the axis of the common carotid artery was selected from the location of the carotid bulb marked, and contrast and brightness optimized for viewing the intima-media layer. Calibration lines were drawn over a length of 10 mm, and a 24-bit bitmap was saved and imported into Prowin 24.0 (Medical Technologies International Inc, Palm Desert, CA). After calibration, measurements were obtained from a 10-mm segment of the far wall of the common carotid artery, 5 mm from the carotid bulb. A different segment was chosen if plaque was identified in that location (defined as focal thickening >1 mm). In some cases where there was diffuse thickening, the IMT exceeded 1 mm. A mouse-driven cursor was used to place 10 to 15 points along the media-adventitia and the intima-lumen boundary. The distance between the curves defined by the points was IMT. Measurements were repeated 3× per image, and the mean was calculated. Intraobserver reliability was 97.1%; interobserver reliability was not assessed.

Statistical Methods

Analyses were performed using IBM SPSS Statistics version 20 (IBM, Chicago, IL). A Kolmogorov–Smirnov test of normality showed that continuous variables were not normally distributed, hence median and interquartile range were reported for descriptive statistics, and a Kruskal–Wallis test was used to test for differences among groups. Categorical variables were reported as percentages and a χ^2 test (Exact test) used to test for differences. Progression or regression of TPA, TPV, or IMT was defined by tertiles of change from baseline to 1 year later. Kaplan–Meier survival analysis was performed to assess event rate by progression, stability, or regression of the ultrasound variables; comparisons among groups were by the log-rank test pooled over strata. Cox regression, using a backward stepwise Wald approach, was used to evaluate effects of covariates: age, sex, smoking status, serum total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, systolic blood pressure, and diabetes mellitus.

Results

There were 349 patients enrolled in the study. The median duration of follow-up was 3.17 years, with a maximum of 5.0 and a minimum of 0.07 years. The timing of dropouts and events is shown in Figure IV in the online-only Data Supplement. During 5 years, there were 21 dropouts. For each case the first qualifying event was used in the survival analyses. There were 50 first events: 20 vascular deaths, 11 strokes, 13 TIAs, and 6 MIs. Timing of first events is shown in Figure IV in the online-only Data Supplement. Some participants had >1 event; Table IV in the online-only Data Supplement shows the timing of all 55 events.

Baseline characteristics are shown in Table 1, and baseline medications being taken by the participants are shown in Table 2, both grouped by regression, stability, or progression of TPV. Table V in the online-only Data Supplement shows tertiles of progression of TPV, TPA, and IMT.

The distribution of baseline IMT, TPA, and TPV, and the distribution of change from baseline to 1 year later for the 3 phenotypes are shown in Figure V in the online-only Data Supplement. Data on 1-year progression/regression were available in 323 cases for TPA and in 306 cases for TPV and IMT.

Assessed by Pearson correlation (*R*), baseline TPV was strongly correlated with TPA (*R*=0.645; *P*=0.001), but only weakly correlated with IMT (*R*=0.189; *P*=0.001). This is illustrated in Figure VI in the online-only Data Supplement. Accordingly, TPA was also weakly correlated with IMT (*R*=0.282; *P*=0.001). However, there was no significant correlation between progression/regression of TPA versus TPV

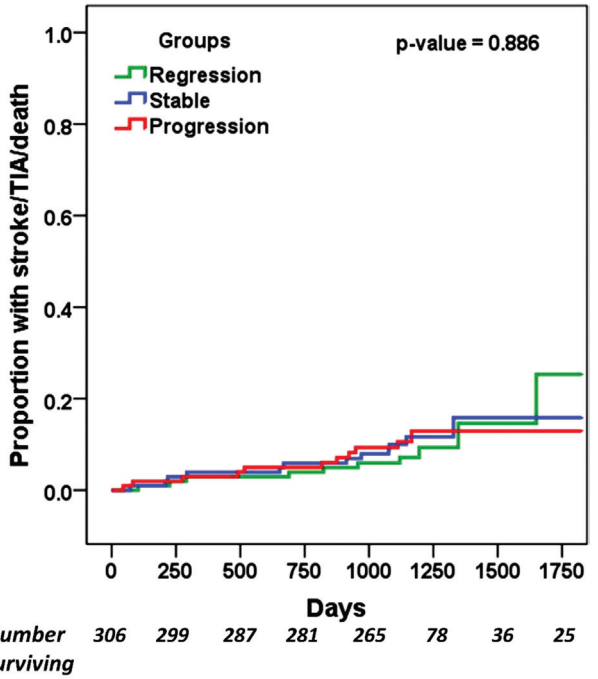

Figure 3. Risk of stroke, transient ischemic attack (TIA), or death by progression/regression of intima-media thickness. Kaplan–Meier 1-survival curves of stroke, TIA, or death >5 years in participants with regression, stable plaque, or progression (defined by the tertiles of change in IMT from baseline to 1 year later). Tertiles are shown in Table IV in the online-only Data Supplement. The log-rank *P* value was 0.886 across the 3 groups.

(*R*=–0.035; *P*=0.549), TPA versus IMT (*R*=–0.024; *P*=0.680), or TPV versus IMT (*R*=0.042; *P*=0.460).

In this population chosen by the presence of substantial plaque, the baseline burden of IMT, TPA, or TPV did not predict events. Survival free of any cardiovascular event (stroke, vascular death, TIA, or MI) and survival free of stroke, TIA, or vascular death were significantly predicted by progression/regression of TPV, as shown in Figure 1. In Cox regression analysis (backward stepwise Wald), at the final step (step 9), the only remaining predictors were baseline systolic blood pressure (*P*=0.086) and progression/regression of TPV (*P*=0.001).

Participants with progression of TPA from baseline to 1 year later had more events; this approached significance for stroke/death/TIA (*P*=0.097), as shown in Figure 2, but not for any CV event (*P*=0.143). Prediction of any CV event by progression/regression of TPA was intermediate between prediction by TPV and IMT, as shown in Figures VII to IX in the online-only Data Supplement. In Cox regression with TPA change and baseline covariates, only age (*P*=0.034) and smoking status (*P*=0.031) remained in the model at the final step (step 7). Similarly, as shown in online supplementary figures 10-12, progression of TPV predicted stroke/death/myocardial infarction (*P*=0.007), progression of TPA did not (*P*-0.59), nor did progression of IMT (*P*=0.13).

However, progression/regression of IMT did not predict stroke/TIA/death as shown in Figure 3 nor did it predict any cardiovascular event (Figure IX in the online-only Data Supplement). In Cox regression with baseline covariates as listed in Methods, smoking status (*P*=0.021), triglycerides (*P*=0.009), high-density lipoprotein cholesterol (*P*=0.044), and IMT change (*P*=0.004) were significant predictors of events, but as shown in Figure 3 and Figure IX in the online-only Data Supplement, the relationship to IMT change was inverse because IMT regression was associated with a higher risk of events.

Discussion

To our knowledge, this is the first study of TPV progression as a predictor of cardiovascular outcomes, and the first to compare progression of IMT, TPA, and TPV in the same participants. The Tromsø study[22] compared progression of IMT and TPA with regard to coronary risk factors, but did not measure TPV, and to date have not reported on prediction of events by progression of IMT and TPA. Sillesen et al[14] showed that plaque burden measured by a 3D probe (but not strictly plaque volume, as the probe was moved along the artery) was much more strongly correlated with coronary calcium score than was IMT; they did not measure TPA.

We found that progression of TPV strongly predicted cardiovascular events, and the prediction remained significant after adjustment for coronary risk factors in Cox regression. Surprisingly, it was regression of IMT rather than progression that predicted events, a finding that strengthens the growing consensus that IMT measured in the far wall of the common carotid at a site where there is no plaque should not be regarded as truly representing atherosclerosis.[2,3,22–24] Possible reasons for this finding, and for the weak correlation between IMT and plaque, have been discussed previously[25,26]; IMT is a different phenotype that probably represents mainly hypertensive medial hypertrophy, and probably does not truly represent atherosclerosis.[2] Another possible reason is that for technical reasons we measured different segments of the carotid arteries with the 3 methods. Progression of TPA weakly predicted stroke/TIA/death but not the all cardiovascular events, and prediction of risk was not significant after adjustment for coronary risk factors.

A limitation of the study was the relatively small sample, which was determined by the funding available. The a priori sample size calculation had been that 350 participants followed for a mean of 4.7 years would give an adequate sample size to show differences among the ultrasound phenotypes with regard to prediction of cardiovascular events. This was based on data from our 2002 report[15] and was consistent with the sample in a study of TPA, IMT, and endothelial function as predictors of events in patients with coronary artery disease by Chan et al.[27] However, the finding that progression of TPV significantly predicted events in such a small sample supports the contention that measurement of TPV is a powerful tool for assessing clinically relevant effects of therapy.

It should be noted that the study population was powerful, despite its small size, because all participants had substantial carotid plaque, and the number of events was relatively high. In our 2002 study[15] of TPA and TPA progression, in which approximately half the participants had little or no plaque at baseline, there were 166 vascular events among 1686 participants (9.8%) followed for an average of 2.5 years (about as many events as in the first 10 years of the Framingham Heart Study); in this study population, there were first vascular events in 15.8% of participants during a median follow-up of 3.17 years.

In 2012, the Rotterdam study[28] and the MESA study[29] both showed that coronary artery calcium, but not IMT, improved risk prediction and risk reclassification beyond a Framingham risk score. Although a single coronary artery calcium might be useful for reclassifying patients to higher risk so that they can be appropriately chosen for more intensive therapy, concern about radiation with repeated scans precludes its use for management of patients. Carotid TPA has been used successfully to treat arteries instead of risk factors,[10] and this approach markedly reduced risk among high-risk patients with asymptomatic carotid stenosis.[30] Brook et al[31] found that TPA was more closely related to coronary stenosis than IMT, coronary calcium, or CRP, and Johri et al[32] found that plaque volume was more sensitive than plaque thickness for prediction of coronary stenosis. Our findings suggest that measurement of TPV will be a useful approach to treating high-risk patients; this hypothesis will need to be tested in a clinical trial. It should be noted that our management of patients was not protocol-based but was based on our previously reported approach[10] to treating arteries instead of treating risk factors.

Measurement of TPV progression will also be useful for computing quantitative traits of atherosclerosis for genetic studies because as previously discussed,[33] age accounts for most of the explained variance in baseline plaque phenotypes, but is only a weak predictor of progression.

As genetic approaches identify new therapeutic targets for atherosclerosis,[34,35] it will be important to have methods to study effects of new therapies on atherosclerosis as proof-of-principle, before going on to very large and costly studies on the basis of reduction of events. Our findings support the recommendation[3] that measurement of TPV is a cost-effective way to assess new therapies for atherosclerosis.

Acknowledgments

Carotid imaging was performed by Maria DiCicco, RVT, and Janine DesRoches, RVT, who have a combined experience of measurement of TPA in >30 000 patients; measurement of TPA was first developed by Ms DiCicco in 1990. Joan Fleming was the study coordinator and maintained the database. Staff in the Robarts Imaging core laboratory who assisted Dr Wannarong with the measurements of IMT and TPV included Shayna McKay and Igor Gyacskov.

Sources of Funding

The study was funded by the Heart and Stroke Foundation of Canada (Ontario), grant number NA5912.

Disclosures

Dr Spence is a principal of Vascularis Inc. The other authors have no conflict to report.

References

1. Sillesen H, Falk E. Why not screen for subclinical atherosclerosis? *Lancet*. 2011;378:645–646.
2. Finn AV, Kolodgie FD, Virmani R. Correlation between carotid intimal/medial thickness and atherosclerosis: a point of view from pathology. *Arterioscler Thromb Vasc Biol*. 2010;30:177–181.
3. Spence JD. Carotid plaque measurement is superior to IMT Invited editorial comment on: carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis-Yoichi Inaba, M.D., Jennifer A. Chen M.D., Steven R. Bergmann M.D., Ph.D. *Atherosclerosis*. 2012;220:34–35.
4. Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. *JAMA*. 2012;308:796–803.
5. Lorenz MW, Polak JF, Kavousi M, Mathiesen EB, Völzke H, Tuomainen TP, et al; PROG-IMT Study Group. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. *Lancet*. 2012;379:2053–2062.
6. Inaba Y, Chen JA, Bergmann SR. Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis. *Atherosclerosis*. 2012;220:128–133.
7. Johnsen SH, Mathiesen EB, Joakimsen O, Stensland E, Wilsgaard T, Løchen ML, et al. Carotid atherosclerosis is a stronger predictor of myocardial infarction in women than in men: a 6-year follow-up study of 6226 persons: the Tromsø Study. *Stroke*. 2007;38:2873–2880.
8. Mathiesen EB, Johnsen SH, Wilsgaard T, Bønaa KH, Løchen ML, Njølstad I. Carotid plaque area and intima-media thickness in prediction of first-ever ischemic stroke: a 10-year follow-up of 6584 men and women: the Tromsø Study. *Stroke*. 2011;42:972–978.
9. Landry A, Spence JD, Fenster A. Measurement of carotid plaque volume by 3-dimensional ultrasound. *Stroke*. 2004;35:864–869.
10. Spence JD, Hackam DG. Treating arteries instead of risk factors: a paradigm change in management of atherosclerosis. *Stroke*. 2010;41:1193–1199.
11. Ainsworth CD, Blake CC, Tamayo A, Beletsky V, Fenster A, Spence JD. 3D ultrasound measurement of change in carotid plaque volume: a tool for rapid evaluation of new therapies. *Stroke*. 2005;36:1904–1909.
12. Spence JD, Eliasziw M, DiCicco M, Hackam DG, Galil R, Lohmann T. Carotid plaque area: a tool for targeting and evaluating vascular preventive therapy. *Stroke*. 2002;33:2916–2922.
13. Spence JD, Coates V, Li H, Tamayo A, Muñoz C, Hackam DG, et al. Effects of intensive medical therapy on microemboli and cardiovascular risk in asymptomatic carotid stenosis. *Arch Neurol*. 2010;67:180–186.
14. Sillesen H, Muntendam P, Adourian A, Entrekin R, Garcia M, Falk E, et al. Carotid plaque burden as a measure of subclinical atherosclerosis: comparison with other tests for subclinical arterial disease in the High Risk Plaque BioImage study. *J Am Coll Cardiol Cardiovasc Imaging*. 2012;5:681–689.
15. Spence JD, Eliasziw M, DiCicco M, Hackam DG, Galil R, Lohmann T. Carotid plaque area: a tool for targeting and evaluating vascular preventive therapy. *Stroke*. 2002;33:2916–2922.
16. Barnett PA, Spence JD, Manuck SB, Jennings JR. Psychological stress and the progression of carotid atherosclerosis. *J Hypertension*. 1997;15:49–55.
17. Landry A, Fenster A. Theoretical and experimental quantification of carotid plaque volume measurements made by three-dimensional ultrasound using test phantoms. *Med Phys*. 2002;29:2319–2327.
18. Landry A, Spence JD, Fenster A. Measurement of carotid plaque volume by 3-dimensional ultrasound. *Stroke*. 2004;35:864–869.
19. Ukwatta E, Awad J, Ward AD, Buchanan D, Samarabandu J, Parraga A et al. 3D ultrasound of carotid atherosclerosis: Semiautomated segmentation using a level set-based method. *Med Phys*. 2011;38:2479–93.
20. Buchanan D, Gyacskov I, Ukwatta E, Lindenmaier T, Fenster A, Parraga G. Semi-automated segmentation of carotid artery plaque volume from three-dimensional ultrasound carotid imaging. *Proc. SPIE* 8317, Medical Imaging 2012: Biomedical Applications in Molecular, Structural, and Functional Imaging, 83170I (March 23, 2012); doi:10.1117/12.912880; http://dx.doi.org/10.1117/12.912880.
21. Shai I, Spence JD, Schwarzfuchs D, Henkin Y, Parraga G, Rudich A, et al; DIRECT Group. Dietary intervention to reverse carotid atherosclerosis. *Circulation*. 2010;121:1200–1208.
22. Herder M, Johnsen SH, Arntzen KA, Mathiesen EB. Risk factors for progression of carotid intima-media thickness and total plaque area: a 13-year follow-up study: the Tromsø Study. *Stroke*. 2012;43:1818–1823.
23. Spence JD, Hegele RA. Noninvasive phenotypes of atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2004;24:e188; author reply e188–e188; author reply e189.
24. Spence JD, Rundek T. Toward clinical applications of carotid ultrasound: intima-media thickness, plaque area, and three-dimensional phenotypes. In: Nicolaides AN, Beach KW, Kiriacou E, Pattichis CS, eds. *Ultrasound*

and Carotid Bifurcation Atherosclerosis. London, UK: Springer-Verlag; 2012:431–448.
25. Spence JD, Hegele RA. Noninvasive phenotypes of atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2004;24:e188; author reply e188–e188; author reply e189.
26. Al-Shali K, House AA, Hanley AJ, Khan HM, Harris SB, Mamakeesick M, et al. Differences between carotid wall morphological phenotypes measured by ultrasound in one, two and three dimensions. *Atherosclerosis*. 2005;178:319–325.
27. Chan SY, Mancini GB, Kuramoto L, Schulzer M, Frohlich J, Ignaszewski A. The prognostic importance of endothelial dysfunction and carotid atheroma burden in patients with coronary artery disease. *J Am Coll Cardiol*. 2003;42:1037–1043.
28. Kavousi M, Elias-Smale S, Rutten JH, Leening MJ, Vliegenthart R, Verwoert GC, et al. Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. *Ann Intern Med*. 2012;156:438–444.
29. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA*. 2012;308:788–795.
30. Spence JD, Coates V, Li H, Tamayo A, Muñoz C, Hackam DG, et al. Effects of intensive medical therapy on microemboli and cardiovascular risk in asymptomatic carotid stenosis. *Arch Neurol*. 2010;67:180–186.
31. Brook RD, Bard RL, Patel S, Rubenfire M, Clarke NS, Kazerooni EA, et al. A negative carotid plaque area test is superior to other noninvasive atherosclerosis studies for reducing the likelihood of having underlying significant coronary artery disease. *Arterioscler Thromb Vasc Biol*. 2006;26:656–662.
32. Johri AM, Chitty DW, Matangi M, Malik P, Mousavi P, Day A, et al. Can carotid bulb plaque assessment rule out significant coronary artery disease? A comparison of plaque quantification by two- and three-dimensional ultrasound. *J Am Soc Echocardiogr*. 2013;26:86–95.
33. Spence JD. Genetics of atherosclerosis: the power of plaque burden and progression. Invited Commentary on:Dong C, Beecham A, Wang L, Blanton SH, Rundek T, Sacco RL. Follow-Up Association Study of Linkage Regions Reveals Multiple Candidate Genes for Carotid Plaque in Dominicans. *Atherosclerosis*. 2012;223:98–101.
34. Prins BP, Lagou V, Asselbergs FW, Snieder H, Fu J. Genetics of coronary artery disease: genome-wide association studies and beyond. *Atherosclerosis*. 2012;225:1–10.
35. Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, Thompson JR et al. Large-scale association analysis identifies new risk loci for coronary artery disease. *Nat Genet*. 2013;45:25–33.