Plaque area and plaque volume rather than the degree of stenosis are suitable predictors for an increased stroke risk

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Conflicts of interest

• Philips Ultrasound: research grant
• Cook Medical: Research grant
• Bayer: consulting
• Novo Nordisk: consulting
Declining stroke risk in asymptomatic carotid stenosis – 75% reduction

Risk of Ipsilateral stroke  < 1% p.a.

Hadar N et al, Cerebrovasc Dis 2014
Does imaging of atherosclerosis improve risk prediction?

Muntendam et al: Am Heart J 2010;160:49-57
Diagnosis of carotid stenosis based on standard Doppler criteria

Sillesen et al, JACC IMG 2012
Participants were followed 3 years

Cumulative Stroke by CAS

p-value = .4532

Number at risk
- 0: 1,139
- 1 to 49: 4,515
- 50 to 100: 349

Unpublished data
Participants were followed 3 years.

Cumulative Stroke by CAS

Annual stroke rate < 0.5% in CS pt.s

Unpublished data
Optimal Medical Management Reduces Risk of Disease Progression and Ischemic Events in Asymptomatic Carotid Stenosis Patients: A Long-Term Follow-Up Study

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A total of 864 patients

1,728 carotid arteries in total

289 carotid arteries (<50 stenosis) excluded

1,439 carotid arteries studied for PSCS

79 ± 36 months mean follow-up period

4,929 carotid ultrasound studies (corresponding to an average of 3.4 ± 1.4 studies per vessel)
Guess what?
Guess what?

- I bet you that the same is happening to some extent in symptomatic carotid stenosis!
- Global stroke rate has declined by 30+%

**WHY**

- Healthier life style
- Better prevention
- Better treatment
We need better risk stratification
Ultrasonic Echolucent Carotid Plaques Predict Future Strokes

Marie-Louise M. Grønholdt, MD, PhD; Børge G. Nordestgaard, MD, DMSc; Torben V. Schroeder, MD, DMSc; Sissel Vorstrup, MD, DMSc; Henrik Sillesen, MD, DMSc

Background—We tested prospectively the hypothesis that stroke development can be predicted by echolucency of carotid atherosclerotic plaques in previously symptomatic and asymptomatic patients.

Methods and Results—We followed incidence of ipsilateral ischemic strokes for 4.4 years in 111 asymptomatic and 135 symptomatic patients with ≥50% relevant carotid artery stenosis. At inclusion, echogenicity of carotid plaques and degree of stenosis were evaluated with high-resolution B-mode ultrasound with computer-assisted image processing and Doppler ultrasound, respectively. We observed 44 ipsilateral ischemic strokes. In symptomatic patients, relative risk of ipsilateral ischemic stroke for echolucent versus echorich plaques was 3.1 (95% CI, 1.3 to 7.3), whereas for 80% to 99% versus 50% to 79% stenosis, the relative risk was 1.4 (95% CI, 0.7 to 3.0). Relative to symptomatic patients with echorich 50% to 79% stenotic plaques, those with echorich 80% to 99% stenotic plaques, echolucent 50% to 79% stenotic plaques, and echolucent 80% to 99% stenotic plaques had relative risks of ipsilateral ischemic strokes of 3.1 (95% CI, 0.7 to 14), 4.2 (95% CI, 1.2 to 15), and 7.9 (95% CI, 2.1 to 30), equivalent to absolute risk increases of 11%, 18%, and 28%. This was not observed in previously asymptomatic patients.

Conclusions—Echolucent plaques causing ≥50% diameter stenosis by Doppler ultrasound are associated with risk of future stroke in symptomatic but not asymptomatic individuals. This suggests that measurement of echolucency, together with degree of stenosis, may improve selection of patients for carotid endarterectomy. (Circulation. 2001;104:68-73.)
Figure 1. Survival free of ipsilateral ischemic strokes as a function of carotid plaque echogenicity or severity of stenosis. Echolucent is gray-scale median <74. Echorich is gray-scale median ≥74. Numbers at risk are listed below each graph.
Plaque area important for stroke risk?

Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification

Andrew N. Nicolaides, MS, FRCS, PhD (Hon), a Stavros K. Kakkos, MD, MSc, PhD, DIC, a Efstthvoulos Kyriacou, BSc, PhD, b Maura Griffin, MSc, DIC, PhD, a Michael Sabetai, MD, FRCS, PhD, a Dafydd J. Thomas, MD, PhD, c Thomas Tegos, MD, PhD, a George Geroulakos, MD, PhD, a, d Nicos Labropoulos, PhD, DIC, RVT, e Caroline J. Doré, BSc, f Tim P. Morris, MSc, f Ross Naylor, MD, FRCS, e and Anne L. Abbott, MB, BS, FRACP, PhD, h,i for the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group, London and Leicester, United Kingdom; Limassol, Cyprus; Stony Brook, NY; and Melbourne, Australia

ACSRS, JVS 2010
### Table IV

Flexible parametric proportional hazards models including significant variables from Table III with ipsilateral CORI events as the dependent variable. Selected using backward elimination on all variables with 95% CI not overlapping 1 in Table III.

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) Clinical factors only. Ipsilateral CORI events as the dependent variable. Five-year baseline hazard estimated as .886; Harrell’s C = .66; Pseudo R² = .17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis (% ECST)</td>
<td>0.028</td>
<td>1.03</td>
<td>1.01-1.04</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pack-years (&lt;10, ≥10)</td>
<td>0.429</td>
<td>1.53</td>
<td>1.07-2.18</td>
<td>.018</td>
</tr>
<tr>
<td>History of contralateral TIAs and/or stroke (Yes vs no)</td>
<td>0.858</td>
<td>2.36</td>
<td>1.61-3.46</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>(ii) Clinical factors with plaque features. Ipsilateral CORI events as the dependent variable. Five-year baseline hazard estimated as .949; Harrell’s C = .79; Pseudo R² = .55</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis (% ECST)</td>
<td>0.01696</td>
<td>1.02</td>
<td>1.00-1.03</td>
<td>.027</td>
</tr>
<tr>
<td>Log (GSM + 40)</td>
<td>-2.4519</td>
<td>0.09</td>
<td>0.04-0.17</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Plaque area$^{1/3}$ (mm²)</td>
<td>0.6539</td>
<td>1.92</td>
<td>1.50-2.46</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DWAs (Present vs absent)</td>
<td>0.7417</td>
<td>2.10</td>
<td>1.32-3.35</td>
<td>.002</td>
</tr>
<tr>
<td>History of contralateral TIAs and/or stroke (Yes vs no)</td>
<td>0.6901</td>
<td>1.99</td>
<td>1.32-2.92</td>
<td>.001</td>
</tr>
<tr>
<td>(iii) Clinical factors with plaque features. Ipsilateral hemispheric stroke as the dependent variable. Note no variable selection was performed here because of too few events. Variables were identical to those used in (ii). Five-year baseline hazard estimated as .972; Harrell’s C = .80; Pseudo R² = .61</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis (% ECST)</td>
<td>0.026</td>
<td>1.03</td>
<td>1.00-1.05</td>
<td>.024</td>
</tr>
<tr>
<td>Log (GSM + 40)</td>
<td>-2.672</td>
<td>0.07</td>
<td>0.02-0.20</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Plaque area$^{1/3}$ (mm²)</td>
<td>0.629</td>
<td>1.88</td>
<td>1.28-2.75</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>DWAs (Present vs absent)</td>
<td>0.429</td>
<td>1.54</td>
<td>0.81-2.92</td>
<td>.18</td>
</tr>
<tr>
<td>History of contralateral TIAs and/or stroke (Yes vs no)</td>
<td>0.973</td>
<td>2.65</td>
<td>1.54-4.54</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

CI, Confidence interval; CORI, cerebrovascular or retinal ischemic; DWAs, discrete white areas; ECST, European Carotid Surgery Trial; GSM, grayscale median; HR, hazard ratio; TIAs, transient ischemic attacks.
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 mm² 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.)
Table 1. Baseline Characteristics of Study Patients by Progression Group for Plaque Volume

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Regression* (n=84)</th>
<th>Stable* (n=69)</th>
<th>Progression* (n=153)</th>
<th>PValue†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70 (13)</td>
<td>70 (12)</td>
<td>70.5 (13)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Wannarong T et al, Stroke 2013
• Changes in volume was the important parameter

• NOT
  – Drug treatment
  – Cholesterol
  – Anything else!!!

Wannarong T et al, Stroke 2013
Three-Dimensional Carotid Ultrasound Plaque Texture Predicts Vascular Events

Arna van Engelen, PhD; Thapat Wannarong, MD; Grace Parraga, PhD; Wiro J. Niessen, PhD; Aaron Fenster, PhD; J. David Spence, MD; Marleen de Bruijne, PhD

Background and Purpose—Carotid ultrasound atherosclerosis measurements, including those of the arterial wall and plaque, provide a way to monitor patients at risk of vascular events. Our objective was to examine carotid ultrasound plaque texture measurements and the change in carotid plaque texture during 1 year in patients at risk of events and to compare these with measurements of plaque volume and other risk factors as predictors of vascular events.

Methods—We evaluated 298 patients with carotid atherosclerosis using 3-dimensional (3D) ultrasound at baseline and after 1 year and measured carotid plaque volume and 376 measures of plaque texture. Patients were followed up to 5 years (median [range], 3.12 [0.77–4.66]) for myocardial infarction, transient ischemic attack, and stroke. Sparse Cox regression was used to select the most predictive plaque texture measurements in independent training sets using a 10-fold cross-validation, repeated 5×, to ensure unbiased results.

Results—Receiver operator curves and Kaplan–Meier analysis showed that changes in texture and total plaque volume combined provided the best predictor of vascular events. In multivariate Cox regression, changes in plaque texture (median hazard ratio, 1.4; P<0.001) and total plaque volume (median hazard ratio, 1.5 per 100 mm³; P<0.001) were both significant predictors, whereas the Framingham risk score was not.

Conclusions—Changes in both plaque texture and volume are strongly predictive of vascular events. In high-risk patients, 3D ultrasound plaque measurements should be considered for vascular event risk prediction. (Stroke. 2014;45:2695-2701.)
Table 2. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Without Event (n=271)*</th>
<th>With Event (n=27)*</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70 (64–77)</td>
<td>75 (64–80)</td>
<td>0.30</td>
</tr>
<tr>
<td>Men, %</td>
<td>58</td>
<td>52</td>
<td>0.54</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>134 (122–149)</td>
<td>131 (114–142)</td>
<td>0.11</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>74 (66–82)</td>
<td>69 (62–78)</td>
<td>0.17</td>
</tr>
<tr>
<td>IMT, mm</td>
<td>0.92 (0.82–1.04)</td>
<td>0.93 (0.84–0.98)</td>
<td>0.74</td>
</tr>
<tr>
<td>TPV, mm³</td>
<td>273 (191–437)</td>
<td>253 (119–422)</td>
<td>0.21</td>
</tr>
<tr>
<td>Stenosis, %</td>
<td>40 (40–50)</td>
<td>40 (40–40)</td>
<td>0.26</td>
</tr>
<tr>
<td>BMI</td>
<td>27.9 (25.5–31.5)</td>
<td>29.0 (25.3–31.8)</td>
<td>0.96</td>
</tr>
<tr>
<td>Smoking (never, quit, and still smoking)</td>
<td>36%, 56%, and 8%</td>
<td>33%, 48%, and 19%</td>
<td>0.74, 0.45, and 0.06</td>
</tr>
<tr>
<td>Smoking pack-years</td>
<td>5 (0–24)</td>
<td>15 (0–28)</td>
<td>0.34</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>3.9 (3.4–4.7)</td>
<td>4.1 (3.5–4.9)</td>
<td>0.35</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.3 (1.1–1.7)</td>
<td>1.3 (1.1–1.8)</td>
<td>0.85</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>1.9 (1.5–2.5)</td>
<td>2.1 (1.5–2.6)</td>
<td>0.30</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.2 (0.9–1.7)</td>
<td>1.1 (0.9–1.8)</td>
<td>0.77</td>
</tr>
<tr>
<td>Framingham risk score</td>
<td>16 (13–18)</td>
<td>15 (13–19)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

van Engelen et al, Stroke 2014
Importance of changes over time

van Engelen et al, Stroke 2014
We need better technology
Impact of Fixed Elevation Focus

Elevation "Depth of Field"

1 cm

3 cm
We need 3D US
Early 3D ultrasound work

Krasinski et al, UMB 2009
Ultrasound plaque tomography

**plaque volume**

Knowing the area of plaque in each image and the distance in between, plaque volume can be calculated.
Where does a plaque “begin and end”? 
Automated identification of max plaque thickness

1 cm slice centered on max plaque thickness
Volume Reproducibility study

- 2 investigators scanned 37 plaques
- Blinded from each others findings
- Patient standing between exams
- US Machine reset in between

Ultrasound in Med. & Biol. In press 2017
Conclusion

• 3D will be a “game changer” because plaque volume can be reliably measured

• With accurate volume assessment plaque morphology can similarly be reliably assessed

• 3D Plaque volume/morphology may be the new surrogate to assess and follow, and thereby evaluate effectiveness of treatment
Thank you for your attention