Addendum

A combined examination of plaque morphology and vascularization imaging (PMVI) and the PLAC-RISK score

In light of the illustrated recent findings, the authors propose a new expanded and standardized procedure for the ultrasound examination of the ICA. Following the current research insights, the proposition would be to define “plaque morphology and vascularization imaging (PMVI)” as an innovative and comprehensive combination of B-mode and contrast-enhanced imaging. PMVI should consist of the following:

- B-mode sonography with harmonic imaging (THI) for the depiction of plaque morphology; digital saving of the image;
- qualitative analysis of GSM with the determination of the standard deviation as a grade of homogeneity;
- Color-coded duplex sonography or B-flow imaging for the determination of plaque surface integrity and possible qualitative assessment of possible ulceration;
- Color-coded duplex sonography or B-flow imaging in combination with spectral Doppler shift analysis for the qualitative assessment of the grade of stenosis;
- Contrast-enhanced imaging after, e.g., bolus application of 2.5 mL SonoVue™ for the evaluation of plaque neovascularization.

Molecular imaging techniques (see above) have not yet been implemented in clinical practice and were therefore not considered in this context. In order to achieve standardized and comparable evaluation of the examination, the authors further propose a novel score (PLAC-RISK score, Table 1) for the evaluation of the findings. The rationale of this score is the integration of different clinical and sonographic information according to the known relevance for the risk of upcoming ischemic stroke subject to the potential benefit of carotid endarterectomy or interventional stenting. The authors believe that the following components should be integrated and weighted according to the individual grade of risk:

1. Clinical neurological findings and history of focal neurological symptoms respectively: if there is evidence of ischemia downstream from the ICA stenosis either on the basis of the patient’s history, clinical findings, or imaging (CT, MRI), the stenosis can be classified as symptomatic. Depending on the time

<table>
<thead>
<tr>
<th>factor</th>
<th>definition</th>
<th>score</th>
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<tbody>
<tr>
<td>1. <strong>clinical presentation</strong></td>
<td>- symptomatic</td>
<td>0 = asymptomatic</td>
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<tr>
<td></td>
<td>- asymptomatic</td>
<td>3 = symptomatic 4 w&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>- transient</td>
<td>4 = symptomatic &lt;4w</td>
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<tr>
<td></td>
<td>- persistent</td>
<td>TIA ≥ 0</td>
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<tr>
<td></td>
<td></td>
<td>completed stroke ≥ + 1</td>
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<tr>
<td>2. <strong>clinical data</strong></td>
<td>a) sex</td>
<td>0 = female</td>
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<tr>
<td></td>
<td>b) Diabetes mellitus</td>
<td>1 = male</td>
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<tr>
<td></td>
<td>c) contralateral ICA obstruction (stenosis &gt; 50%)</td>
<td>0 = no</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = yes</td>
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<tr>
<td>3. <strong>grade of stenosis</strong></td>
<td>ECST criteria</td>
<td>0 = &lt; 50%</td>
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<tr>
<td></td>
<td></td>
<td>2 = 50 – 69%</td>
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<tr>
<td></td>
<td></td>
<td>6 = 70 – 99%</td>
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<tr>
<td>4. <strong>plaque morphology</strong></td>
<td>GSM, mean</td>
<td>0 = hyperechogenic (226 – 255)&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>1 = isoechogenic (69 – 225)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = echolucent (0 – 68)</td>
</tr>
<tr>
<td>5. <strong>plaque heterogeneity</strong></td>
<td>GSM, standard deviation SD</td>
<td>0 = homogeneous (0 – 60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = mixed (61 – 120)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = heterogeneous (121 – 255)</td>
</tr>
<tr>
<td>6. <strong>plaque surface integrity</strong></td>
<td>ulcerations</td>
<td>0 = regular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = irregular 0.4 – 2 mm</td>
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<tr>
<td></td>
<td></td>
<td>2 = ulcerated &gt; 2 mm</td>
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<tr>
<td>7. <strong>plaque neovascularization</strong></td>
<td>0 = no</td>
<td>score</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = moderate (subjective)</td>
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<tr>
<td></td>
<td></td>
<td>2 = extensive (subjective)</td>
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<tr>
<td><strong>evaluation</strong></td>
<td>best medical treatment</td>
<td>0 – 4</td>
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<tr>
<td></td>
<td>+ control after 6 – 12 weeks</td>
<td>5 – 8</td>
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<tr>
<td></td>
<td>intervention no later than 2 w</td>
<td>9 – 11</td>
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<tr>
<td></td>
<td>intervention immediately</td>
<td>12 – 22</td>
</tr>
</tbody>
</table>

<sup>1</sup> Adapted from ([48]).

<sup>2</sup> With respect to [27], where GSM values were compared to histological findings.
of symptom onset preceding the time of examination, a differ-
entiated risk value (scores 0, 3 or 4) can be defined in accor-
dance with the meta-analysis of studies on ICA stenosis [48].
If there is evidence of a completed stroke rather than a transi-
ent ischemic attack, one additional point is awarded.

2. The following clinical parameters are incorporated in the
PLAC-RISK score according to the findings of the abovementioned meta-analysis:
   a) Sex: men will benefit more by TEA than women (score 0 or 1)
   b) Diabetes mellitus: score 0 or 1
   c) Contralateral ICA obstruction (stenosis > 50%): score 0 or 1

3. Grade of ICA stenosis: the clinical risk of ischemic stroke in-
creases with the grade of vessel narrowing, which will be eval-
uated by the ECST criteria (scores 0, 2 or 6).

4. Plaque morphology: B-mode sonography depicts morphologi-
cal alterations of the vessel wall by characterizing echogenicity
with grayscale quantification. It is believed that hypoechogenic
areas determine lipid-rich areas, while hyperechogenic areas
determine calcified regions. By means of the GSM method, nor-
malization of pixel distribution is possible and correlates to his-
tological findings [27]. The grayscale median (GSM), i.e., the
median value of the pixel intensities for the entire plaque,
serves as a parameter of echogenicity and determines the sta-
bility of the plaque (score 0 – 2). The graduation can alternative-
ly be performed subjectively or by means of novel industrially
manufactured tools.

5. Heterogeneity of the plaque: the more heterogeneous it is, the
more unstable a plaque becomes. The standard deviation of
the GSM derived from B-mode imaging could serve as a mea-
sure of heterogeneity (score 0 – 2). This concept has not yet
been unanimously proven but may be derived from recent
data [27]. The heterogeneity might alternatively be derived
by other adequate methods.

6. Surface integrity of the plaque: a lack of plaque integrity is a
strong indicator of instability (score 0 – 2). The definition is
derived from a consensus from 1997 [49].

7. Neovascularization of the plaque: there is strong evidence
that the neovascularization of a carotid plaque is a strong indi-
cator of plaque instability [41] and that the depiction of this
phenomenon by contrast-enhanced ultrasound reveals simi-
lar results as histological preparation [45]. There is not yet a
unanimous procedure for quantitative assessment. However,
the authors propose a semi-quantitative, subjective score
from 0 to 2 (0 = no contrast enhancement, 1 = moderate con-
trast enhancement, 2 = extensive contrast enhancement),
where in future application the use of automated, quantitative
analysis of plaque neovascularization will provide additional
value, e.g., the changes in video intensity within the plaque
after intravenous administration of a bolus of contrast agent
or flash imaging

The single values equal the PLAC-RISK score. This score acts as
a draft for a standardized tool for the classification of carotid
stenosis and the subsequent implications for proper therapy,
be it best medical treatment or interventional/surgical repair.
The individual components of the score are presently being
evaluated in a “proof of concept” study, comparing clinical
and sonographic aspects to histological evaluation. A subse-
quent multi-center prospective study must then evaluate the
score and its therapeutic implications. The authors are aware
of the fact that the proposed score in its current version
must remain imperfect. It is our ambition to promote the de-
bate regarding a comprehensive tool for the sonographic and
clinical evaluation of atherosclerotic alterations of the internal
carotid artery. This debate should result in a formal consensus
procedure for the adequate estimation of the various current
ultrasound techniques and their impact on therapeutic strate-
gies liable to clinical course.