Assessment of Preclinical Target Organ Damage in Hypertension: Carotid Intima-Media Thickness and Plaque

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Carotid intima-media thickness and plaque
High-resolution ultrasound of the carotid arteries may allow the measurement of the intima-media complex in the arterial wall. Population studies, such as the Vobarno [1], the Rotterdam [2] and the Cardiovascular Health Study [3], have clearly demonstrated that systolic blood pressure is a major determinant of an increase in intima-media thickness (IMT) in the carotid arteries, particularly in hypertensive patients.

Methods of measurement
There are different methods for measuring IMT. The three most frequently used in clinical trials are as follows [3–6]:
1) Mean of the maximum IMT of the 4 far walls of the carotid bifurcations and distal common carotid arteries (CBMmax).
2) Mean maximum thickness (Mmax) of up to 12 different sites (right and left, near and far walls, distal common, bifurcation and proximal internal carotid), and
3) Overall single maximum IMT (Tmax). Analysis may be performed by manual cursor placement or by automated computerised edge detection. In order to optimise reproducibility with the last method, IMT measurement is restricted to the far wall of the distal segment of the common carotid artery, thus providing about 3% of relative difference between two successive measurements [7, 8].

Clinical and epidemiological studies have given useful information on the reproducibility of repeated IMT measurements. Salonen and Salonen have indicated that inter-observer and intra-observer variation coefficients of 10.5% and 8.3% respectively resulted [9]. In the ACAPS study [5] the mean replicate difference was 0.11 mm and in the MIDAS [10] 0.12 mm. In the MIDAS the arithmetic difference of the mean max IMT in replicate scans was calculated as 0.003 ± 0.156 mm. More recently the ELSA (European Lacidipine Study of Atherosclerosis) included more than 2000 patients in whom the cross-sectional reproducibility of ultrasound measurements at baseline was calculated as follows: the overall coefficient of reliability (R) was 0.859 for CBMmax, 0.872 for Mmax and 0.794 for Tmax; intra-reader and inter-reader reliability was 0.915 and 0.872 respectively [5].

Data collected in the VHAS (Verapamil in Hypertension and Atherosclerosis Study) [6] and the ELSA studies have shown a high prevalence of carotid wall structural changes in hypertensive patients. In the VHAS study 40% of the patients had a plaque (IMT > 1.5 mm) in at least one site along the carotid arteries and only 33% of patients had normal carotid arterial walls. In the ELSA study 82% of 2259 essential hypertensives had a plaque (IMT > 1.3 mm). Moreover, in the RIS study (Risk Intervention Study) patients with severe essential hypertension and high cardiovascular risk had a significantly higher prevalence of atherosclerotic lesions compared to control subjects [11].

The normal IMT values are influenced by age and sex. Normal IMT values may be defined in terms of statistical distribution within a healthy population; however, they may be better defined in terms of increased risk and available data indicate that IMT > 0.9 mm represents a risk of myocardial infarction and/or cerebrovascular disease [2, 3, 11–15].

Ultrasonic plaque morphology may add useful information about plaque stability and may correlate with symptoms. In addition to the visual judgment of plaque echolucency and homogeneity, the use of non-invasive methods that may quantify the tissue composition of the vascular wall (such as videodensitometry or the analysis of the integrated backscatter signal) has been proposed for the assessment of the cellular composition of atherosclerotic plaque, particularly of earlier lesions [16, 17]. Furthermore, plaque volume assessment by three-dimensional reconstruction of ultrasound or NMR images has been proposed to better evaluate atherosclerotic lesion changes.

Relationship to cardiovascular risk and to clinical events
Traditional risk factors, which include being of male sex, ageing, being overweight, elevated blood pressure, diabetes and smoking, are all positively associated with carotid IMT in observational and epidemiological studies. Hypertension, and particularly, high systolic blood pressure values, seems to have the greatest effect on IMT [19]. About 30% of hypertensive subjects may be mistakenly classified as at low or moderate added risk without an ultrasound for carotid arterial thickening or plaque, whereas vascular damage places them in the high-added risk group [18].

In addition, new risk factors, including various lipoproteins, plasma viscosity and hyperhomocysteinaemia, have demonstrated an association with increased IMT. Patients with metabolic syndrome have higher IMT than patients with individual metabolic risk factors. Carotid IMT has also been found to be associated with preclinical cardiovascular alterations in the heart, brain, kidney and lower-limb arteries.

Several studies have demonstrated and confirmed the important prognostic significance of IMT, as measured by ultrasound. In their prospective study Salonen et al. [12] observed in 1288 Finnish male subjects that the risk for coronary events was exponentially related to the increase in IMT in the common carotid and in the bifurcation. In a larger sample of middle aged subjects (13,780) enrolled into the ARIC (Atherosclerotic Risk In The Communities) study [13] IMT, measured by ultrasound, was associated with an increased prevalence of cardiovascular and cerebrovascular diseases. In the Rotterdam study [2] IMT was shown to predict the risk of myocardial infarction and cerebrovascular events during a mean follow-up period of 2.7 years. The Cardiovascular Health Study [3] has prospectively evaluated 4,400 subjects aged over 65 years for a follow-up period of 6 years; the annual incidence of myocardial infarction or stroke increased in the highest quintiles of IMT measured in the common and the internal carotid arteries.

A recent metaanalysis of data collected in 8 studies in general populations, including 37,197 subjects who were followed up for a mean of 5.5 years, has demonstrated that for an absolute carotid IMT difference of 0.1 mm, the future risk of myocardial infarction increases by 10% to 15%, and the stroke risk increases by 13% to 18% [15] (Table 1).

Effect of treatment
Therapeutic double-blind trials have shown that antihypertensive drugs may have a more or less marked effect on carotid IMT progression. A recent metagression analysis [20], including 22 randomised controlled trials, has evaluated the effects of an antihypertensive agent on carotid arterial IMT. The results, which are shown in Table 1, suggest that the drug therapy has a small but consistent effect on carotid IMT.
tensive drug versus placebo or another antihypertensive agent of a different class on carotid IMT. The results have shown that compared with non-treatment, diuretics ± beta-blockers or ACE inhibitors, or calcium channel blockers attenuate the rate of progression of carotid intima-media thickening. In the prevention of carotid intima-media thickening, calcium-antagonists are more effective than ACE inhibitors, which in turn are more effective than placebo or non-treatment, but not more active than diuretics ± beta-blockers (Table 2). The odds ratio for all fatal and non-fatal cardiovascular events in trials comparing active treatment with placebo reached statistical significance (P = 0.007).

The results of the PHYLLIS study have reported that in hypertensive and hypercholesterolemic patients the administration of pravasta-
tin prevents the progression of carotid intima-media thickening, seen in patients treated with hydrochlorothiazide, but the combina-
tion of pravastatin and the ACE-inhibitor fosinopril had no additive effect [21].

Few studies including a relatively small number of patients have shown slower IMT during treatment with angiotensin II antago-
nists than in patients treated with beta-blockers [22].

An ongoing study (Multicenter Olmesartan Atherosclerosis Re-
gression Evaluation MORE) will give a more precise assessment of the effect of long-term treatment with an AT1 receptor antagonist (olmesartan) and with a beta-blocker (atenolol) on carotid atherosclerosis, even with the use of the non invasive 3-D plaque measure-
ment.

No significant changes in plaque composition were observed after 4 years of treatment with either lacidipine or atenolol in pa-
patients participating in the ELSA study, suggesting that treatment with a calcium antagonist may slow IMT progression without influ-
encing the characteristics of plaque tissue [23].

Conclusions

An ultrasound examination of the common, bifurcation and in-
ternal carotid arteries should be performed in hypertensive pa-
tients with concomitant risk factors, such as smoking, dyslipi-
daemia, diabetes or a family history of cardiovascular diseases. However, before routine measurement of IMT may be proposed in wide clinical practice for stratifying cardiovascular risk, meth-
odological standardisation for IMT measurement needs to be fur-
ther implemented.

Quantitative B-mode ultrasound of the carotid arteries re-
quires appropriate training. In the presence of increased IMT or
plaque in the carotid arteries an aggressive approach to risk-factor modification should be considered.

<table>
<thead>
<tr>
<th>Antihypertensive treatment</th>
<th>Comparison</th>
<th>Change IMT µm/year (95% confidence intervals)</th>
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<tbody>
<tr>
<td>All trials (n = 1870)</td>
<td>Placebo</td>
<td>–7 µm (–12 to –2) p = 0.01</td>
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<tr>
<td>(n = 1549)</td>
<td>ACE inhibitors (n = 1161)</td>
<td>Placebo</td>
</tr>
<tr>
<td>Beta-blockers (n = 428)</td>
<td>Placebo</td>
<td>–10 µm (–33 to 13) p = 0.02</td>
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<tr>
<td>(n = 434)</td>
<td>Calcium-antagonists (n = 1181)</td>
<td>Diuretics/beta-blockers</td>
</tr>
<tr>
<td>(n = 1808)</td>
<td>ACE inhibitors (n = 319)</td>
<td>Diuretics/beta-blockers</td>
</tr>
<tr>
<td>(n = 321)</td>
<td>ACE inhibitors (n = 142)</td>
<td>Calcium-antagonists</td>
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</tbody>
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