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Chapter 9

Carotid intima-media thickness: influence of drug treatment and clinical implications

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SUMMARY

With B-mode ultrasound measurements of the intima-media thickness (IMT) of the carotid arterial wall (asymptomatic) atherosclerosis can be detected. In this article several studies are reviewed in which IMT was used as a surrogate endpoint to assess effects of lipid-lowering or antihypertensive drugs on peripheral atherosclerosis, and the clinical implications are discussed. After one year of treatment with lipid-lowering drugs an improvement of the blood lipid profile and retarded progression of the carotid IMT was seen. No incontrovertible evidence can be provided for a correlation between induced changes in the carotid and coronary arteries. Carotid IMT appears to be of prognostic value for cardiovascular events. The range of treatment-induced changes in IMT do not support the use of IMT in an individual patient to monitor treatment effects. However, with increased IMT as independent cardiovascular risk factor, IMT measurements are valuable in risk assessment in the individual patient in clinical practice. Looking forward to some ongoing studies, there is so far insufficient evidence that treating hypertension also inhibits progression of the IMT.

INTRODUCTION

Recently, several studies have demonstrated the beneficial effects of lipid-lowering drugs on atherosclerotic alterations in coronary arteries and on cardiovascular morbidity and mortality 1. In some studies B-mode ultrasound measurements of the intima-media thickness (IMT) of the carotid arterial wall demonstrated favourable effects of lipid-lowering treatment 2-9. Principles, technique, limitations and properties of IMT measurements have been reviewed previously in this Journal 10. Briefly, high resolution B-mode ultrasound can be used for the detection of both atherosclerotic plaques and wall thickness of superficial arteries like the carotid and femoral artery. IMT is a good marker of early atherosclerotic changes and it is found to be increased in groups of patients with several (combinations of) cardiovascular risk factors 11. Furthermore, carotid IMT has proved to be an independent risk factor for myocardial infarction and stroke, as shown recently 12. The non-invasiveness, reproducibility and accuracy of the procedure makes it an appropriate research tool to evaluate the structural effects of different therapies on the vascular wall. The objective of this literature study was, to determine when the beneficial effects of therapy on carotid IMT become evident and how these effects are related to changes in coronary angiographic findings and cardiovascular events. In this article we therefore review studies in which measurement of IMT was used to evaluate especially the effects of lipid-lowering or antihypertensive drugs on atherosclerosis.
METHODS

Studies reviewed in this article were obtained after a search in WinSPIRS 2.0 (SilverPlatter International N.V.), Medline 1985 up to 1998 including, using key-words related to atherosclerosis, carotid artery, ultrasound, blood lipids, hypertension and drug therapy. Likewise, the references of the publications on these trials or editorials were checked for complementary studies. We included placebo-controlled trials in which the effects of lipid-lowering and/or antihypertensive drugs on carotid IMT were studied, both as primary or secondary endpoints. Studies were consecutively numbered to year of publication. Excluded were studies in which only quantitative carotid stenosis was used in stead of IMT, studies with merely patients with diabetes mellitus and studies describing treatment with diet and/or antioxidants without lipid-lowering or antihypertensive drugs. To compare the treatment effects of the reviewed studies, in each study the rate of change in IMT (in mm/year) of the common carotid artery (CCA) was calculated by dividing the change in IMT at the end of the study period (in mm) by the study duration (in years). Since the CCA was the only carotid segment available in all study results, we selected this segment (see also below).

INTIMA-MEDIA THICKNESS IN LIPID-LOWERING REGRESSION STUDIES

Study and patient characteristics
Placebo-controlled studies in which the effect of lipid-lowering drugs on IMT of the carotid arteries was evaluated, are summarized in table 1. Unfortunately, no consensus exists which IMT parameter should be used: among those studied in varying segments of the carotid artery, most frequent is the mean maximum IMT (mean max) which was defined as the mean of 12 maximum IMT measurements of the near and far wall of the common and internal carotid artery and the carotid bifurcation in both sides. Changes in IMT measurements were primary or secondary study endpoints. The Cholesterol Lowering Atherosclerosis Study (CLAS) 2 was the first study using IMT as secondary endpoint for carotid and femoral artery atherosclerosis in a subgroup of patients. The Asymptomatic Carotid Artery Progression Study (ACAPS) 3 was performed to test whether lovastatin and/or warfarin in combination with aspirin retarded the progression of early carotid atherosclerosis. From all the randomized subjects we limited the analysis to the patients randomized to either lovastatin or placebo. The Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II)4,13, the Kuopio Atherosclerosis Prevention Study (KAPS)5, and the Carotid Atherosclerosis Italian Ultrasound Study (CAIUS)7 evaluated the influence of pravastatin on IMT as the primary measure of effect on atherosclerosis of the carotid arteries. The KAPS participants were recruited from an observational study,
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the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD)\(^{14}\). In the Monitored Atherosclerosis Regression Study (MARS)\(^6\) and the Regression Growth Evaluation Statin Study (REGRESS)\(^9\) primary study end points were treatment induced changes in quantitative coronary angiography (QCA) variables, with additional IMT measurements in a subgroup of patients. Finally, the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial investigated the effects of lipid-lowering therapy on risk of death from coronary heart disease at (below) average cholesterol levels\(^{15}\) and assessed changes in carotid IMT in the LIPID Atherosclerosis Substudy\(^8\). Included participants in the IMT substudies varied from asymptomatic healthy persons (like in KAPS, although 8% of patients did have prior myocardial infarction) to patients with a history of coronary artery bypass grafting. Although inclusion ranges for lipid-profiles were different, baseline mean total cholesterol and low-density lipoprotein cholesterol (LDL-C) varied from 6.0 to 6.76 mmol/l and from 4.0 to 4.9 mmol/l, respectively. Study durations varied from 2 to 4 years with prolongation of the investigation in 74 participants to 4 years in the MARS. Except in the CLAS, varying dose of a HMG-CoA reductase inhibitor was used as lipid-lowering drug. Only the ACAPS and the CAIUS had an equal sex distribution. The other studies had a male preponderance. Age did not count as an inclusion criterium, mean ages varied from 54 to 63 years. Presented blood pressures suggest normotensive patients or well controlled hypertension, while few studies mention a history of hypertension in 25 to 33%. In the REGRESS, patients in the placebo group had more often hypertension, although this difference was not statistically significant. Merely the CLAS had no current smokers.

RESULTS

**Lipid profile.** As expected, the lipid profile was altered by lipid-lowering drugs. Except triglycerides in the CAIUS and high-density lipoprotein cholesterol (HDL-C) in the PLAC-II study and the KAPS, all changes in lipid profile were statistically significant and varied for total cholesterol between -15% and -32%, for LDL-C between -22% and -45%, for HDL-C between +3% and +38% and for triglycerides between -8% and -29%. Besides changes in lipid profile, the MARS showed a positive correlation between intermediate-density lipoprotein and IMT progression rate\(^{16}\).

**IMT.** Table 2 presents baseline values and changes in IMT of the common carotid artery (CCA) in patients with lipid-lowering treatment compared to placebo of the aforementioned studies. The IMT of the CCA was the overlapping parameter in the IMT substudies, although in the ACAPS only progression rate was available of the mean max IMT and not of the CCA separately. Although the IMT of the CCA and the mean max IMT are supposed to be the most reliable IMT parameters, more atherosclerotic changes are found in the internal carotid artery\(^{17,18}\). In the PLAC-II study the progression rate in the CCA

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was the only statistically significant difference between pravastatin and placebo. In the KAPS, the IMT progression rate was greater in patients in the placebo group with higher baseline IMT. The lovastatin treated group in the MARS had a significantly higher baseline IMT with a progression rate which was negatively correlated with the baseline IMT, in contrast to the placebo group. So, a greater decrease in IMT was found in lovastatin treated patients with high baseline (above the mean) IMT levels. In the LIPID study, after
classifying participants by tertiles of cholesterol or IMT at baseline, no differences were found of the treatment effect on IMT. The REGRESS found a significant treatment difference in IMT change of all combined measured segments during the trial of all arterial wall segments, with the largest treatment effect in the common femoral artery far wall. 

Sex. In the CAIUS, IMT progression was increased in men in the control group.

Smoking. The KAPS found different progression rates for smokers and non-smokers. IMT progression rate was greater in smokers of the placebo group than in smokers of the pravastatin group versus non-smokers in these groups. Furthermore, the treatment effect of lipid-lowering drugs was greater in smokers than in non-smokers. On the contrary, the MARS and LIPID study found no significantly different progression rates between smokers and non-smokers within each treatment group.

**ONSET AND DURATION OF THERAPEUTIC BENEFIT**

Although the CLAS 19, the MARS and CAIUS found no significant difference after 6 months of treatment, all mentioned the first significant reduction in IMT and difference in IMT between treatment and placebo group after 1 year of treatment. In the MARS, the reduction of IMT with lipid-lowering drugs compared to placebo persisted for the remaining years afterwards with a slightly decreased regression rate after 2 years. This flattening in IMT regression rate after 3 years was also observed in the CLAS, as contrasted with the LIPID study. In table 2, IMT progression rates of the CCA have been expressed in mm/year to make it possible to compare studies with different years of follow-up. However, some changes in IMT are only given at the end of the study. So, if the findings of the MARS and CLAS are indeed representative, by recalculating IMT progression/regression rates differences caused by treatment effect may be underestimated during the first years of the studies and overestimated in the later years.

**INTIMA-MEDIA THICKNESS AND CORONARY ANGIOGRAPHY**

As stated in the introduction part, the favourable effect of lipid-lowering therapy on coronary atherosclerosis is well known 1. Although the relationship between carotid and coronary artery disease is strong 20, it still is a matter of debate if a change in coronary atherosclerosis may be associated with a comparable change in peripheral atherosclerosis. A fundamental problem is the difference in measurement techniques for the different sides of atherosclerosis. QCA images the lumen of the coronary arteries and not the wall, in contrast to the IMT measurements of the carotid arteries. In 3 studies, CLAS, MARS and REGRESS, IMT measurements and QCA were done concurrently to evaluate the effect of lipid-lowering therapy. In the CLAS, at baseline the IMT was significantly
correlated with the average coronary stenosis ($r=0.34$, $p<0.05$) but after 4 years of treatment this correlation disappeared. Although coronary angiographic and IMT measurements were made in all patients in the MARS, no significant correlations were found between (changes) in IMT and QCA-measurements. However, in their discussion, the authors stated that progression and treatment response are comparable in carotid and coronary atherosclerosis. In the REGRESS, the baseline correlations between mean IMT of the carotid and femoral arteries with QCA findings of mean percent stenosis varied from 0.23 to 0.36. Baseline maximal IMT was significantly correlated with baseline coronary segment and obstruction diameter ($r=-0.32$ and $r=-0.27$, respectively). No significant correlations were found between change in IMT and any of the parameters of change in coronary diameter. In conclusion, there is no incontrovertible evidence for a correlation between induced changes in carotid and coronary arteries.

Table 2. Changes of intima-media thickness (±SEM) of the common carotid artery in studies with lipid-lowering treatment versus placebo*.

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline SD</th>
<th>Lipid-lowering SD</th>
<th>Placebo SD</th>
<th>Treatment effect</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLAS</td>
<td>0.63</td>
<td>0.019</td>
<td>0.0125</td>
<td>-0.025</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACAPS</td>
<td>1.14</td>
<td>0.0063</td>
<td>0.003</td>
<td>-0.015</td>
<td>0.001</td>
</tr>
<tr>
<td>PLAC-II</td>
<td>1.01</td>
<td>0.0162</td>
<td>0.0342</td>
<td>-0.018</td>
<td>0.02</td>
</tr>
<tr>
<td>KAPS</td>
<td>1.35</td>
<td>0.0096</td>
<td>0.0285</td>
<td>-0.0189</td>
<td>0.0019</td>
</tr>
<tr>
<td>MARS</td>
<td>0.717</td>
<td>0.014</td>
<td>0.003</td>
<td>-0.043</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAIUS</td>
<td>0.88</td>
<td>0.010</td>
<td>0.0027</td>
<td>-0.0109</td>
<td>0.0047</td>
</tr>
<tr>
<td>LIPID</td>
<td>0.79</td>
<td>0.0035</td>
<td>0.012</td>
<td>-0.0155</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>REGRESS</td>
<td>0.82</td>
<td>0.0013</td>
<td>0.00175</td>
<td>+0.005</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Study acronyms see table 1.; change is defined as decrease (negative value) or increase (positive value) in IMT, given in mm/year; *treatment effect: mathematical difference in IMT changes between both groups; n.s.: not significant;
INTIMA-MEDIA THICKNESS AND CARDIOVASCULAR EVENTS

As opposed to many publications concerning the relationship between IMT and cardiovascular risk factors, studies regarding the prospective relationship with cardiovascular disease are scarce. The Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) \(^{14}\), the Rotterdam Study \(^{21}\), the Atherosclerosis Risk in Communities Study (ARIC)\(^{22}\) and the Cardiovascular Health Study Collaborative Research Group \(^{12}\) have shown associated increased incidences of peripheral arterial disease, stroke and myocardial infarction with higher IMT levels at baseline. Furthermore, in the last mentioned study the IMT appeared to be an independent risk factor for cardiovascular events.

As for prognostic value, the important question remains if therapy induced IMT regression is attended by a decrease in cardiovascular morbidity and mortality. A follow-up study of the CLAS \(^{23}\) is the only study demonstrating a prospective relation between IMT progression rate and coronary events. The relative risk was 2.2 for myocardial infarction or coronary death, and 3.1 for any coronary event per IMT progression rate of 0.03mm/year (p<0.001). In the ACAPS a significantly lower incidence of major cardiovascular events and deaths was found in the lovastatin treated group. As stated in their discussion the power of this study and the duration of treatment were inadequate to correlate the changes in IMT and cardiovascular events. In the PLAC-II study a tendency was found for a lower number of clinical coronary events in the pravastatin treated patients (60% reduction, p=0.09) with a significant reduction of any coronary event and any death (p=0.04). Despite significantly fewer nonscheduled percutaneous transluminal coronary angioplasty-procedures and a smaller number of patients without clinical events in the pravastatin treated group, no correlation could be made between IMT and clinical cardiovascular events. In the KAPS the decrease in cardiovascular events in the pravastatin treated patients was not significant and not related to changes in IMT. The CAIUS found no significant difference in occurrence of cardiovascular events. The LIPID study was part of the LIPID Study Group in which the effects were determined of pravastatin induced cholesterol lowering on mortality from coronary heart disease. Unfortunately, no relations were made or reported between changes in IMT and cardiovascular events. In the REGRESS after 2 years of treatment, the clinical event-free survival, including non-cardiac events, was greater in pravastatin treated patients compared to placebo group (90% and 80%, respectively, p=0.02). No comments were made about a possible relationship between changes in IMT and clinical events.

INTIMA-MEDIA THICKNESS AND ANTIHYPERTENSIVE TREATMENT

Little is known about the effects of antihypertensive treatment on IMT. So far, few studies
are completed in which the effect of single antihypertensive treatment and the combination with lipid-lowering drugs on IMT was evaluated. In the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS) 24, 883 patients with mild-to-moderate hypertension (diastolic blood pressure 90-115 mmHg) and an inclusion IMT of 1.3-3.5mm were treated for 3 years with isradipine or hydrochlorothiazide. After 6 months, the average IMT was significantly lower in the isradipine treated group compared to hydrochlorothiazide, while the progression rate of the mean max IMT of 0.03 mm/year was similar for both treatment groups. On the contrary, in the isradipine group, the incidence of major and nonmajor cardiovascular events was increased compared to the hydrochlorothiazide group. In the Verapamil Hypertension Atherosclerosis Study (VHAS) ultrasound substudy 25, the effects of 4 years treatment with verapamil compared with chlorthalidone, was investigated in 498 hypertensive patients. The IMT progression rate was significantly lower in the verapamil compared to the chlorthalidone group (-0.082 and -0.037 mm/year, respectively),

Table 3. Some ongoing trials in which the effect of single antihypertensive drugs or the combination with lipid-lowering drugs on carotid IMT is studied.

<table>
<thead>
<tr>
<th>Study</th>
<th>Antihypertensive drugs</th>
<th>Lipid-lowering drugs</th>
<th>Study duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antihypertensive treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELSA</td>
<td>lacidipine vs atenolol</td>
<td></td>
<td>4 years</td>
</tr>
<tr>
<td>PROTECT</td>
<td>perindopril vs hydrochlorothiazide</td>
<td></td>
<td>2 years</td>
</tr>
<tr>
<td>ELVERA</td>
<td>amlodipine vs lisinopril</td>
<td></td>
<td>2 years</td>
</tr>
<tr>
<td><strong>Multifactorial design</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHYLLIS</td>
<td>fosinopril vs hydrochlorothiazide</td>
<td>pravastatin vs lipid</td>
<td>3 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lowering diet</td>
<td></td>
</tr>
<tr>
<td>SECURE</td>
<td>ramipril vs placebo</td>
<td>vitamin E vs placebo</td>
<td>4 years</td>
</tr>
<tr>
<td>ADORZO</td>
<td>nifedipine (open label)</td>
<td>simvastatin vs placebo</td>
<td>2 years</td>
</tr>
</tbody>
</table>

ELSA: European Lacidipine Study of Atherosclerosis 27; PROTECT: Perindopril Regression of Vascular Thickening European Community Trial 28; ELVERA: Effects of amlodipine and lisinopril in Left VEntriculaR mAss and intima-media thickness; PHYLLIS: Plaque Hypertension Lipid Lowering Italian Study 27; SECURE: Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamin E 29; ADORZO: ADalat ORos versus ZOcor/placebo; vs: versus;
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when this was related to the initial value. Moreover, less cardiovascular events were observed in the verapamil compared to the chlorthalidone treated group. In a Swedish study 26, the effects of multifactorial risk factor intervention compared to placebo on IMT progression was evaluated in 149 men. The multifactorial risk factor intervention consisted of stopping smoking, and lipid and blood pressure lowering. Lipid-lowering drugs consisted of simvastatin, cholestyramine and/or gemfibrozil, and antihypertensive drugs consisted of beta-blockers, angiotensin-converting enzyme inhibitors, calcium-channel blockers and/or diuretics. After 2 years, no significant difference was found in IMT progression rates between the intervention and control group.

In table 3, some ongoing trials are mentioned, in which the effect of antihypertensive treatment on IMT progression is studied.

CLINICAL IMPLICATIONS

The aforementioned studies demonstrate a beneficial effect of lowering blood lipids and perhaps of blood pressure on IMT. The CLAS has shown a relation between IMT progression rate and the occurrence of clinical coronary events. No evidence was found for changes in IMT as a marker for alterations of atherosclerosis in coronary arteries. The low cost and non-invasiveness of the IMT measurements make it an appropriate clinical research tool, especially in studies with moderately large numbers of participants, for instance 100 participants in a two-arm trial 2. However, this does not extend to its clinical use in monitoring treatment effects in individual patients. Presented IMT regression or progression rates are group means with considerable interindividual variation, as was the same for several correlations. Alterations in IMT must also be related to the normal increase in IMT due to ageing 30. Supported by nomograms, the annual increase in IMT for women and men are for the carotid bifurcation 0.015 and 0.018 mm, for the internal carotid artery 0.010 and 0.014 mm, and the CCA 0.010 and 0.010 mm, respectively. Therefore, IMT measurements can excellently be used as parameter and even independent risk factor 12 for cardiovascular disease, but up to the present there is insufficient evidence that changes in IMT can act as marker for changes in generalized atherosclerosis in the individual patient.

CONCLUSIONS

IMT measurement is a non-invasive diagnostic tool to detect (asymptomatic) atherosclerosis of superficial arteries. Studies in which patients were treated with lipid-lowering drugs showed the expected improvement of the blood lipid profile to be associated with regression of the IMT of the carotid artery. The beneficial therapeutic effect became
evident after one year of treatment. No incontrovertible evidence could be provided for a
correlation between induced changes in carotid IMT and changes in coronary arteries,
and only one study found a relationship between IMT progression rate and the appearance
of cardiovascular events. This, and the range of treatment-induced changes in IMT, do
not support the use of IMT in an individual patient to monitor treatment effects. However,
with increased IMT as independent cardiovascular risk factor, IMT measurements are
valuable in risk assessment in the individual patient in clinical practice. Looking forward
to some ongoing studies, there is so far insufficient evidence that treating hypertension
also inhibits progression of the IMT.
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