orronary heart disease (CHD) has become a medical and public health issue associated with multiple risk factors such as age, diet and sedentary life style. Associations between hypertension and atherosclerosis have been extensively studied and several trials have demonstrated antiatherosclerotic properties in some of the most widely used antihypertensive agents. Hence, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers have been the target for a number of controlled randomized trials studying its effect on atherosclerosis progression. Carotid intima media thickness measurement by ultrasound is used as surrogate of atherosclerosis in most of this controlled trials. This review of the literature aims to summarize the most significant controlled trials involving antihypertensive therapy and atherosclerosis regression based on the carotid intima-media thickness measurement.

**Keywords:** Atherosclerosis, Hypertension, Calcium Channel Blockers, Angiotensin Receptor Blockers
Carotid intima-media thickness (cIMT) as a surrogate for atherosclerosis

Family history of early acute coronary events and the prompt detection of risk factors are essential for the primary evaluation of patients with hypertension and the estimation of risk for CHD. Nonetheless, several methods have been proposed to assess atherosclerosis severity for research purposes using as principle high definition ultrasound and computed tomography.

Several studies have shown that increased carotid cIMT confers risk of future coronary heart disease and stroke. However, the definition of end points used in controlled clinical trials of atherosclerosis is critical for interpretation of results and comparison with other studies; the duration of the trial is also critical.

Simon et al reviewed prospective epidemiological data to determine the association of cIMT assessed by B-mode ultrasonography with cardiovascular risk. They conclude that despite cIMT independently predicts coronary events and stroke, it was slightly better predicting stroke than CHD. The coronary risk prediction was modest in this study and may add small contributions beyond conventional risk factors. In addition, it has been described that the use of mean maximum cIMT rather than mean common cIMT may be more useful to evaluate the efficacy of pharmacological and non pharmacological interventions in carotid artery atherosclerosis according to Bots et al.

cIMT as measured with quantitative B-mode ultrasound imaging is a valid surrogate of sub clinical atherosclerosis and its use in intervention studies is widespread. On the other hand, its applicability beyond research purposes has ended in an insufficient improvement on the risk classification according to recent prospective studies possibly due to the lack of standardization.

**Antihypertensive therapy and atherosclerosis**

**Calcium Channel Blockers (CCBs)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>n</th>
<th>Drug</th>
<th>Arteries</th>
<th>Months</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>Montreal Heart Institute Trial</td>
<td>383</td>
<td>Nicardipine</td>
<td>Coronaries</td>
<td>24</td>
<td>No significant diminishment on IMT</td>
</tr>
<tr>
<td>1993</td>
<td>Heart Transplant</td>
<td>106</td>
<td>Diltiazem</td>
<td>Coronaries</td>
<td>24</td>
<td>Attenuation of the usual reduction in the coronary diameter during the first year</td>
</tr>
<tr>
<td>1996</td>
<td>MIDAS</td>
<td>883</td>
<td>Isradipine vs. hydrochlorothiazide</td>
<td>Carotids</td>
<td>36</td>
<td>Verapamil was more effective than chlorthalidone in promoting regression of thicker carotid lesions</td>
</tr>
<tr>
<td>1998</td>
<td>VHAS</td>
<td>498</td>
<td>Verapamil vs. Chlorthalidone</td>
<td>Carotids</td>
<td>48</td>
<td>Any effect on the progression of minimal coronary artery lesions, although had a significant effect on the progression of carotid artery atherosclerosis.</td>
</tr>
<tr>
<td>2000</td>
<td>PREVENT</td>
<td>825</td>
<td>Amlodipine</td>
<td>Carotids and Coronary</td>
<td>36</td>
<td>The yearly IMT progression rate was higher in atenolol-treated compared to ladinipine-treated patients (P=0.0073)</td>
</tr>
<tr>
<td>2001</td>
<td>INSIGHT</td>
<td>439</td>
<td>Nifedipine vs. Hydrochlorothiazide and amiloride</td>
<td>Carotids</td>
<td>48</td>
<td>IMT progressed significantly on co-amilozide but not on nifedipine (P=0.001)</td>
</tr>
<tr>
<td>2002</td>
<td>ELSA</td>
<td>2334</td>
<td>Lacidipine vs. Atenolol</td>
<td>Carotids</td>
<td>48</td>
<td>The yearly IMT progression rate was higher in atenolol-treated compared to ladinipine-treated patients (P=0.0073)</td>
</tr>
<tr>
<td>2003</td>
<td>INSIGHT</td>
<td>6321 of whom 1302 had diabetes at baseline</td>
<td>Nifedipine vs. Hydrochlorothiazide and amiloride</td>
<td>Cardiovascular death, myocardial infarction, heart failure, and stroke</td>
<td>48</td>
<td>A significant benefit for nifedipine-treated patients was seen. Among patients without diabetes at baseline there was a significant difference in the incidence of new diabetes (nifedipine 4.3% versus co-amilozide 5.6%, P=0.023)</td>
</tr>
</tbody>
</table>

Calcium Channel Blockers have demonstrated beneficial effects regarding atherosclerotic patients when compared to placebo and other antihypertensive agents.

The Verapamil in Hypertension and Atherosclerosis study compared verapamil (240 mg once a day) in 244 patients to chlorthalidone (25 mg once a day) in 254 patients; both groups were comparable in terms of baseline characteristics. Patients were followed for four years and B-mode ultrasound scan was performed after 3, 12, 24, 36 and 48 months of treatment. In this study the regression slope was better and statistically different for verapamil faced to chlorthalidone indicating that verapamil was more effective in promoting regression of thicker carotid lesions.

In terms of CCBs, the INSIGHT study compared treatment with nifedipine GITS and Co-amilozide following a group of 439 hypertensive patients for 4 years and studying the...
progression of early carotid wall changes by ultrasound. IMT progression rate and Cross sectional Area of IMT, was measured showing that IMT and CSA-IMT increased on co-amilozide (P=0.001) but not on nifedipine group\(^{30}\).

The Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) was carried out in a group of 825 patients with angiographically documented coronary artery disease treated with amlodipine or placebo. Patients were followed for 3 years and the outcome was changes in coronary artery diameter and IMT. Average reductions in the minimal diameter were nearly identical in placebo and amlodipine groups (0.084 vs. 0.095 mm respectively; P=0.38), hence, amlodipine did not show any significant effect for each of the other angiographic outcomes. Nevertheless, amlodipine had a significant effect on the progression of carotid atherosclerosis; placebo participants had a 0.033mm increase and amlodipine participants had a 0.013mm decrease (P=0.007)\(^{39}\).

In another controlled trial, the European Lacidipine Study on Atheroclerosis (ELSA) carried out by Zanchetti et al\(^{31}\) in 410 clinics around 7 European countries followed a group of 2,259 hypertensive patients during four years. Patients received either Lacidipine 4 to 6 mg/daily or atenolol 50 to 100 mg/daily.

Lacidipine demonstrated to reduce the incidence of stroke all major cardiovascular events and deaths after the 4 years follow up. In this study the yearly IMT progression rate was 0.0087 mm\(\text{y}^{-1}\) with lacidipine and 0.0145 mm\(\text{y}^{-1}\) with atenolol and reduction in Intima Media Thickness was 40\% with lacidipine, being highly significantly statistically (P=0.0073) and clinically.

Angiotensin Receptor Blockers (ARBs) and Angiotensin-Converting Enzyme Inhibitors (ACEis)

In the Losartan intervention for endpoint reduction in hypertension study (LIFE) a randomized parallel-group trial carried out in 9193 hypertensive participants, losartan demonstrated significant diminishmend in morbidity and mortality rates when compared against atenolol. In terms of losartan and atenolol groups, 204 and 234 patients died from cardiovascular disease without significant differences (P=0.206) 232 and 305 had fatal or non-fatal stroke (P=0.001) respectively. Dahlöf et al\(^{33}\) concluded that losartan prevents more cardiovascular morbidity and death than atenolol with similar reduction in blood pressure.

Later in 2005 Olsen et al\(^{34}\) recruited 45 patients from LIFE Study with stage II-III hypertension and ECG left ventricular (LV) hypertrophy. They also found the same reduction rates in systolic and diastolic blood pressures in patients treated with losartan and atenolol. Nonetheless, intima-media cross-sectional area significantly decreased only in patients treated with losartan (19.2 vs 17.6 mm\(^2\); P=0.001) and the average relative decrease in intima-media cross-sectional area during the 3 years of treatment was higher in patients treated with losartan as compared to atenolol (-7.4 vs -2.0\%; P<0.05).

In a posterior analysis Olsen et al\(^{35}\) examined lipid levels in the LIFE study and their impact on the primary outcome of cardiovascular death, myocardial infarction, or stroke; total cholesterol decreased significantly but equally in losartan (n=4321) and atenolol (n=4290) groups, although HDL cholesterol decreased less during the first 2 years in losartan compared with atenolol group (-0.13 ± 0.24 vs. -0.19 ± 0.25 mmol/l) and remained higher each year in both groups dependent of statin treatment. They conclude that higher intensity statin treatment HDL cholesterol was associated with fewer composite endpoints and may partly explain the better outcome of losartan-based treatment.

The Media Intima Thickness Evaluation with Candesartan Cilexetil (MITEC) Study\(^{36}\) recruited 254 Type 2 Diabetes patients from 131 sites and were enrolled in a 4-week, single blind study; 209 were randomly selected and 105 were allocated to amiodipine and 100 to candesartan treatment. The hypothesis of a mayor decrease of intima-media thickness with candesartan over amiodipine could no be proved due to the number of patients discontinuing the study. Nevertheless, carotid intima-media thickness median showed a continued decrease during the first year with both antihypertensive drugs (-0.001 mm per year and -0.027 mm per year for candesartan and amiodipine respectively; P = 0.425).

Schieffer et al\(^{37}\) compared the effects of 20mg of enalapril vs. 300 mg of irbesartan in Interleukin-6 (IL-6), high sensitivity C-reactive protein (hsCRP), metalloprotease 9 (MMP-9), and interleukin 10 (IL-10) levels in 48 patients with coronary artery disease. Both treatments reduced hsCRP levels significantly (Irbesartan P<0.001; Enalapril P<0.05) but only irbesartan reduced serum IL-6 and hsCRP levels in a significant manner compared with baseline (P<0.01). Also, platelet aggregation was only reduced by irbesartan (P<0.001). These findings suggest that ARBs as irbesartan might have better antiatherosclerotic effects than ACEis.

Despite this study suggests that ARBs might have better antiatherosclerotic effects than ACEis, McMurray et al demonstrated in the VALIANT trial that angiotensin receptor blockers appear to be as effective as ACE inhibitors in reducing atherosclerotic events by comparing the effects of captopril, valsartan, and their combination on atherosclerotic events in 14,703 patients followed for 24 months.

In another trial Hirohata et al\(^{39}\) studied atherosclerosis progression through intravascular ultrasound in 247 stable angina pectoris patients receiving 10 to 40 mg of olmesartan (OLIVUS Trial). They observed a significant reduction in total atheroma volume in the olmesartan group compared to control (5.4\% vs. 0.6\% P<0.05) after a follow up of 14 months. Additionally, the Multicentre Olmesartan atherosclerosis Regression Evaluation (MORE) study\(^{40}\) demonstrated that CIMT was similarly decreased in olmesartan and atenolol groups, but only olmesartan was able to reduce the volume of larger atherosclerotic plaques.

These results might be based on the inhibition of VCAM-1 molecules, TNF-alpha levels and a reactive oxygen species diminishment as seen in some studies with irbesartan which has demonstrated to suppress diabetes-associated atherosclerosis in mice\(^{42}\).
In order to compare the effects of CCBs (amlodipine) vs. ACEIs (enalapril) on cardio-vascular events in patients with CHD the CAMELOT study was carried out from April 1999 to April 2002. In this study cardiovascular events occurred in 151 (23.1%) placebo-treated patients, in 110 (16.6%) amlodipine-treated patients, and in 136 (20.2%) enalapril-treated patients, although, primary end point comparison for enalapril vs. amlodipine was not significant (HR, 0.81; 95% CI, 0.63-1.04 [P = .10]). In spite if this in an intra-vascular ultrasound sub-analysis, amlodipine showed evidence of slowing of atherosclerosis progression.

Other Antihypertensive Agents

Renin inhibitors have shown to improve the risk profile in patients with CHD44. Imanishi et al45 demonstrated that Aliskiren improved heritable hyperlipidemic rabbits and enhanced endothelial dependent relaxation in thoracic aortic segments.

Concluding Remarks

Interactions among hypertension and atherosclerosis have been studied since middle 20th century46-48 and recent antihypertensive drugs may considerably benefit patients with atherosclerosis specially calcium channel blockers and angiotensin receptor II blockers. Atherosclerosis’ pro-inflammatory and pro-oxidant vascular mechanisms could be an important target of the future antihypertensive therapy.

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