Approach to the Successful Selection of Antihypertensive Agents for the Patient with Atherosclerosis

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Abstract

Coronary 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

Introduction

Coronary heart disease (CHD) has become a medical and public health issue associated with multiple risk factors such as age, diet, obesity, sedentary life style, smoking, inflammatory states, shear stress, hypertension, dyslipidemia and diabetes mellitus[1].

CHD represent a modern pandemic with the higher morbidity and mortality rates worldwide; according to World Health Organization 3.8 million men and 3.4 million women die each year due to CHD[2]. In addition hypertension has shown to have a continuous, consistent, and independent association with cardiovascular events[3] also demonstrated by a consistent reduction of acute coronary events in patients receiving antihypertensive therapy[4].

Atherosclerosis explains the beginning of CHD and it is defined as a chronic vascular disease mediated by a complex immunological signaling in response to metabolic disorders like dyslipidemia[5-11]. Atherosclerosis has been extensively associated to high blood pressure which have demonstrated to exert proinflammatory effects on the artery wall resulting in diapedesis of monocytes and more atherosclerosis[12].

Hypertension can enhance atherosclerosis by inducing hypertrophy and hyperplasia of smooth muscle cells and stimulating synthesis of key extracellular matrix proteins resulting in increased arterial wall thickness and rigidity[13]. Also, there is clear evidence that reactive oxygen species production is enhanced in hypertensive models[14] contributing to lipid oxidation in LDL cholesterol molecules.

The four most widely used antihypertensive agents include angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers (CCB's), β-blockers and diuretics and their influences in atherosclerotic progression has been studied in the last 20 years. 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.

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[15]. Nonetheless, several methods have been proposed to assess atherosclerosis severity for research purposes using as principle high definition ultrasound[16,17] and computed tomography[18].

Several studies have shown that increased carotid cIMT confers risk of future coronary heart disease and stroke[19-21]. 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[22] 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[23].

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[24] possibly due to the lack of standardization.

Antihypertensive therapy and atherosclerosis

Calcium Channel Blockers (CCBs)

Table 1 shows clinical trials of calcium antagonists and atherosclerosis

Year	Study	n	Drug	Arteries or Outcome	Months	Results
1990	Montreal Heart Institute Trial[25]	383	Nicardipine	Coronaries	24	No significant diminishment on IMT
1993	Heart Trasplant[26]	106	Diltiazem	Coronaries	24	Attenuation of the usual reduction in the coronary diameter during the first year
1996	MIDAS[27]	883	Isradipina vs. hydrochlorothiazide	Carotids	36	No difference in the rate of progression. Isradipine group had higher incidence of major vascular events
1998	VHAS[28]	498	Verapamil vs. Chlorthalidone	Carotids	48	Verapamil was more effective than chlorthalidone in promoting regression of thicker carotid lesions
2000	PREVENT[29]	825	Amlodipine	Carotids and Coronary	36	Any effect on the progression of minimal coronary artery lesions, although had a significant effect on the progression of carotid artery atherosclerosis.
2001	INSIGHT[30]	439	Nifedipine vs. Hydrochlorothiazide and amiloride	Carotids	48	IMT progressed significantly on co-amilozide but not on nifedipine (P=0,001)
2002	ELSA[31]	2334	Lacidipine vs. Atenolol	Carotids	48	The yearly IMT progression rate was higher in atenolol-treated compared to lacidipine-treated patients (p=0.0073)
2003	INSIGHT[32]	6321 of whom 1302 had diabetes at baseline	Nifedipine vs. Hydrochlorothiazide and amiloride	Cardiovascular death, myocardial infarction, heart failure, and stroke	48	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)

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 chortalidone (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 chortalidone indicating that verapamil was more effective in promoting regression of thicker carotid lesions[28].

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)[29].

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/y with lacidipine and 0.0145 mm/y 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 diminishment 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 309 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 mm2; 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 independent of statin treatment. They conclude that higher intreatment 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 109 were allocated to amlodipine and 100 to candesartan treatment. The hypothesis of a mayor decrease of intima media thickness with candesartan over amlodipine 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 amlodipine 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 MMP-9 protein 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[38] 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[41] 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 intravascular ultrasound sub-analysis, amplodipine showed evidence of slowing of atherosclerosis progression[43].

Other Antihypertensive Agents

Renin inhibitors have shown to improve the risk profile in patients with CHD[44]. Imanishi et al[45] 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 century[46-52] 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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