

# Effects of antihypertensive drugs on carotid intima-media thickness: Focus on angiotensin II receptor blockers. A review of randomized, controlled trials

Cesare Cuspidi<sup>1,2</sup>  
Francesca Negri<sup>1,2</sup>  
Valentina Giudici<sup>2</sup>  
Anna Capra<sup>1</sup>  
Carla Sala<sup>3</sup>

<sup>1</sup>Department of Clinical Medicine and Prevention, University of Milano-Bicocca, Milano; <sup>2</sup>Istituto Auxologico Italiano, Milano; <sup>3</sup>Thoraco-Pulmonary and Cardiocirculatory Department, University of Milano, Fondazione Policlinico di Milano, Italy

**Abstract:** Carotid intima-media thickness (IMT) and plaques have been shown to have a strong continuous relationship with cardiovascular (CV) morbidity and mortality; therefore, carotid atherosclerosis, as assessed by ultrasonography, can be regarded as a reliable surrogate end-point for therapeutic interventions. In this survey, we report the results of 16 double blind, randomized, controlled studies comparing: 1) antihypertensive drugs versus placebo/no treatment (five trials including 3,215 patients); 2) different active antihypertensive drug regimens (five trials including 4,662 patients); 3) angiotensin-II receptor blockers (ARBs) versus other antihypertensive agents (six trials including 841 patients). Our main findings can be summarized as follows: I) Long-term antihypertensive treatment has a blunting effect on carotid IMT progression, regardless of types of drugs. II) Calcium-channel blockers (CCBs) are more effective than other antihypertensive drugs including diuretics, beta-blockers, and angiotensin converting-enzyme (ACE)-inhibitors in this blunting effect; III) the effect of ARBs compared to other antihypertensive regimens (mostly based on atenolol) on carotid atherosclerosis progression needs to be further elucidated, as a protective effect was demonstrated by some, but not all studies examined. Thus, further studies are needed to clarify the role of ARBs in this therapeutic area.

**Keywords:** ultrasonography, carotid atherosclerosis, antihypertensive drugs, angiotensin II receptor blockers

## Introduction

Numerous studies based on high-definition ultrasound scanning of carotid arteries have demonstrated an association between intima-media thickness (IMT) and cardiovascular (CV) risk factors,<sup>1-3</sup> preclinical CV alterations such as left ventricular hypertrophy, cerebral white matter lesions, peripheral arterial atherosclerosis, microalbuminuria, coronary calcifications<sup>4-7</sup> and, more importantly, overt CV diseases.<sup>8</sup> In particular, high blood pressure (BP) has been shown to be a major risk factor for carotid IM thickening and plaque progression,<sup>9</sup> due to the synergistic effect of mechanical stress on the arterial wall and growth/inflammatory factors operating in hypertension.

Prospective studies in population-based samples and selected cohorts of individuals at high risk have demonstrated that diffuse and focal alterations in carotid artery walls are strong predictors of CV morbidity and mortality.<sup>10-12</sup>

Owing to the predictive power of carotid ultrasound alterations, guidelines for the management of arterial hypertension from major International scientific bodies such as the European Society of Hypertension (ESH)/European Society of Cardiology (ESC)

Correspondence: Cesare Cuspidi  
Istituto Auxologico Italiano, Clinical  
Research Unit, Viale della Resistenza  
23, 20036 Meda, Italy  
Tel +39 0362 772436  
Fax +39 0362 772416  
Email [cesare.cuspidi@unmib.it](mailto:cesare.cuspidi@unmib.it)

and World Health Organization (WHO)/International Society of Hypertension recommend carotid examination for a better stratification of total CV.<sup>13,14</sup>

Carotid IMT has been shown to be a valuable surrogate end-point for assessing the antiatherogenic effects of therapeutic interventions,<sup>15</sup> in particular in clinical trials testing the efficacy of antihypertensive and cholesterol-lowering drugs.

In this paper, we review the studies published in the last decade in which IMT was measured in order to assess the impact of antihypertensive drugs on carotid structure; focusing on the following questions in particular: 1) does antihypertensive treatment affect IMT progression? 2) do different classes of antihypertensive drugs have different antiatherogenic properties? 3) do ARBs have a role in reducing asymptomatic carotid atherosclerosis or in slowing down its progression? Before addressing this issue, however, some more general considerations on the clinical and prognostic value of carotid IMT are needed.

## Intima-media thickness as a marker of CV risk

The refined methodologies now available allow to detect and measure preclinical structural and functional alterations of the CV system. Ultrasonic assessment of the carotid artery structure has attracted considerable interest in this field and is largely applied either for clinical and research purposes.<sup>16</sup> In the mid 80's, Pioneer studies by Pignoli and colleagues<sup>17</sup> investigated the correlation of ultrasonic interfaces with anatomical components of the arterial wall; they demonstrated that IM complex, namely the lumen-intima and media-adventitia boundary, which appears as a double-line pattern at the ultrasound examination, provides a reliable measurement of the arterial based on both histological and gross pathological comparisons. Since then, hundreds of cross-sectional studies have been performed in order to assess the prevalence and distribution of carotid atherosclerosis and its association with CV risk factors.<sup>1,18</sup> In essential hypertensives, a significant increase in IMT has been reported as compared with age-matched normotensive controls, after adjustment for several confounding variables.<sup>19</sup> Studies in population and hypertensive cohorts have consistently shown that systolic and pulse pressure are significantly correlated to the degree of carotid thickness.<sup>20–22</sup>

A number of prospective trials, including the Atherosclerotic Risk in Communities (ARIC),<sup>23</sup> the Rotterdam Study,<sup>24</sup> the Cardiovascular Health Study (CHS),<sup>25</sup> the European Lacidipine Study on Atherosclerosis (ELSA)<sup>26</sup> and the

Carotid Atherosclerosis Progression Study (CAPS)<sup>27</sup> have reported that carotid IMT and/or plaques are strong predictors of coronary events and stroke.

In the ARIC study the relation of carotid IMT with the incidence of coronary heart disease (CHD) was assessed over a 4–7 years follow-up in 7,289 women and 5,552 men aged 45–64 years and free from CHD at baseline.<sup>23</sup> Incident events were 96 in women and 194 in men; in sex-specific Cox proportional hazards models, the hazard ratio for IMT values  $\geq 1$  mm versus  $< 1$  mm was 5.07 in women (95% confidence interval [CI]: 3.08–8.36) and 1.85 in men (95% CI: 1.28–2.69).

The Rotterdam Study investigated the prognostic value of carotid plaques in predicting stroke in a population-based survey including 4,217 asymptomatic subjects aged 55 years or older.<sup>24</sup> The presence of carotid plaques at six locations of the arteries was assessed at baseline; after an average follow-up of 5.2 years, 160 strokes had occurred. The presence of carotid plaques, irrespective of their location, increased by 50% the risk of stroke.

Among the 5,858 elderly participants in the CHS, the incidence of CV events, in particular the relative risk of myocardial infarction (MI) or stroke, correlated with carotid IMT ( $p < 0.001$ ).<sup>25</sup> The relative risk of MI or stroke adjusted for age and sex in the highest thickness quintile as compared with the lowest one was 3.87 (95% CI: 2.72–5.51). The association between CV events and IMT remained significant after adjusting for traditional risk factors; the results of separate analyses of MI and stroke paralleled those for the combined end point.

In the ELSA study, including 2,334 patients with uncomplicated hypertension, death, MI, major and all CV events had an increased incidence in the highest carotid IMT quintile and in groups with the greatest number of plaques at baseline.<sup>26</sup> The risk increase compared to the lowest quintile was about fivefold, when considering IMT, and threefold after adjusting for age, gender, clinical systolic blood pressure (SBP), and treatment.

In the CAPS study common carotid artery (CCA) IMT and vascular risk factors have been evaluated at baseline in 5,056 participants (mean age 50.1 years) and the incidence of stroke, MI, and death was determined prospectively over a mean follow-up period of 4.2 years.<sup>27</sup> IMT was highly predictive of all end points (eg, hazard rate ratios per 1 SD CCA-IMT increase were 1.43 [95% CI: 1.35–1.51] for MI, 1.47 [95% CI: 1.35–1.60] for stroke, and 1.45 [95% CI: 1.38–1.52] for MI, stroke, or death;  $p < 0.0001$  for all). The predictive value of IMT remained significant for MI and

the combined end point, after adjustment for age, sex, and vascular risk factors.

Overall, these trials indicate that carotid IMT and plaques have a strong continuous relationship with MI, stroke, and CV death, the relationship remaining significant after adjustment for major traditional risk factors.

## Effects of antihypertensive drugs on IMT

Since the mid 90s, a number of trials have compared the effects of different antihypertensive drugs on carotid IMT and plaque progression in a variety of clinical conditions (ie, CHD, asymptomatic carotid artery disease, diabetes, dyslipidemia, hypertension, and preclinical renal disease). A limited fraction of these studies, however, provided reliable information. Studies evaluating drug effects on IMT progression should follow strict methodological criteria: include enough subjects (at least 100–200 per treatment arm) to detect small but clinically relevant between-treatment differences, have a long-term follow-up (at least >1 year) and apply reading protocols minimizing the regression to the mean and readers' bias.

In this review, we describe the results of 16 double-blind, randomized controlled studies divided in three groups according to the study design comparing: I) antihypertensive drugs with placebo or no treatment (five trials including 3,215 patients); II) active antihypertensive drug regimens based on diuretics, beta-blockers, CCBs and ACE inhibitors (five trials including 4,662 patients); III) ARBs

versus other antihypertensive agents (six trials including 841 patients). Studies reported in trials comparing antihypertensive drugs versus placebo and trials comparing active antihypertensive drug regimens (Tables 1 and 2) fulfill all the aforementioned criteria; this was not the case for the studies reported in ARBs versus other antihypertensive drugs (Table 3), which also included trials with >40 patients per treatment arm.

## Trials comparing antihypertensive drugs versus placebo

These trials mostly tested the protective effects of ACE-inhibitors on carotid atherosclerosis, as these drugs have been shown to reduce coronary events in various patient groups and to prevent atherosclerosis in animal models.

In the Prevention of Atherosclerosis with Ramipril (PART 2), 617 patients with coronary, cerebrovascular or peripheral vascular disease were randomized to ramipril (5–10 mg daily) or placebo.<sup>28</sup> Carotid atherosclerosis was assessed at baseline as well as after two and four treatment years: BP was reduced by 6 mmHg systolic and 4 mmHg diastolic in the ramipril compared to the placebo group ( $p < 0.001$ ); no significant difference, however, was found between groups in the changes of CCA far wall thickness or carotid plaque score from baseline to follow-up.

The Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) was a multicenter, randomized, placebo-controlled trial designed to test the slowing effect of amlodipine in the progression of early coronary

**Table 1** Randomized controlled trials comparing the effects on carotid IMT of different antihypertensive drugs versus placebo/no treatment with a minimum numerosity of 100 patients per treatment arm

Trial/Setting/Drug	Ref.	Subjects (n)	Primary outcome	Duration (years)	Results
<b>PART-2</b> CHD, cerebrovascular, and peripheral disease ramipril/no-treatment	28	617	IMT changes and plaque score	4	No difference
<b>SECURE</b> Diabetes, vascular disease, ramipril/placebo	30	732	IMT changes	4.5	Ramipril more effective
<b>PREVEND</b> Patients with microalbuminuria, fosinopril/placebo	31	642	IMT changes	4	No difference
<b>BCAPS</b> Patients with asymptomatic carotid plaque, metoprolol/placebo	32	793	IMT changes	3	Metoprolol more effective
<b>PREVENT</b> Sub-study CHD, amlodipine/placebo	29	377	IMT changes	3	Amlodipine more effective

**Abbreviations:** CHD, coronary heart disease; IMT, intima-media thickness.

**Table 2** Randomized controlled trials comparing the effects on carotid IMT of different antihypertensive drugs with a minimum numerosity of 100 patients per treatment arm

Trial/Setting/Drug	Ref.	Subjects (n)	Primary outcome	Duration (years)	Results
<b>MIDAS</b> Essential hypertension, israpidine/HCTZ	34	883	IMT changes	3	No difference
<b>VHAS</b> Essential hypertension, verapamil/ chorthalidone	35	498	IMT changes	4	Verapamil more effective
<b>INSIGHT</b> Essential hypertension, nifedipine/ co-amilozide	36	439	IMT changes	4	Nifedipine more effective
<b>ELSA</b> Essential hypertension, lacidipine/atenolol	26	2334	IMT changes and plaque progression	4	Lacidipine more effective
<b>PHYLLIS</b> Essential hypertension, dyslipidemia, fosinopril/HCTZ	37	508	IMT changes	2.6	Fosinopril more effective

**Abbreviations:** HCTZ, hydrochlorothiazide; IMT, intima-media thickness.

atherosclerosis in 825 patients with angiographically documented CHD.<sup>29</sup> Secondary aim of the study in a subgroup of 377 patients was to investigate the CCB impact on the rate of atherosclerosis progression in carotid arteries. Amlodipine significantly slowed-down carotid atherosclerosis progression during the 36-month study period: the placebo group, indeed, experienced a 33- $\mu$ m IMT increase, whereas a 126- $\mu$ m decrease was observed in the amlodipine group ( $p = 0.007$ ).

The Study to Evaluate Carotid Ultrasound changes in patients treated with ramipril and vitamin E (SECURE) was a prospective double-blind trial evaluating the effects

of long-term treatment (average follow-up 4.5 years) with ramipril (2.5–10 mg/day) and vitamin E on atherosclerosis progression in 732 patients aged  $\geq 55$  years, affected by vascular disease or diabetes plus, at least, another risk factor.<sup>30</sup> The progression slope of the mean maximum carotid IMT was 21.7  $\mu$ m/year in the placebo group, 18.0  $\mu$ m/year in the ramipril 2.5 mg/daily group and 13.7  $\mu$ m/year in the ramipril 10 mg/daily group ( $p = 0.033$ ), thus indicating that ramipril beneficially affects atherosclerosis progression.

The Prevention of Renal and Vascular ENDstage Intervention Trial (PREVEND) assessed fosinopril and pravastatin

**Table 3** Trials comparing the effects carotid IMT of ARBs versus other antihypertensive drugs, with a minimum numerosity of 40 patients per treatment arm

Trial/Setting/Drug	Ref.	Subjects (n)	Primary outcome	Duration (years)	Results
<b>LAARS</b> Essential hypertension, losartan/atenolol	40	280	IMT changes	2	No difference
<b>SILVHIA</b> Essential hypertension, irbesartan/atenolol	41	108	IMT changes	1	Irbesartan more effective
Ariff et al Essential hypertension, candesartan/atenolol	42	88	IMT changes	1	Candesartan more effective
Ichihara et al Essential hypertension, valsartan/amlodipine	43	100	IMT changes	1	No difference
<b>MORE</b> Essential hypertension and carotid plaque, olmesartan/atenolol	44	165	IMT and plaque changes	4	No difference
Ono et al Essential hypertension, candesartan/no ARB	45	100	IMT changes	2	Candesartan more effective

**Abbreviations:** ARB, angiotensin-receptor blockers; IMT, intima-media thickness.

effects on carotid IMT in subjects with increased urinary albumin excretion (UAE; 15 to 300 mg/24 h). Measurement of IMT was performed at baseline and after four years in 642 subjects randomized to fosinopril 20 mg or matching placebo and to pravastatin 40 mg or matching placebo;<sup>31</sup> overall IMT progression rate was  $37 \pm 6 \mu\text{m}$ , no significant differences were found among fosinopril, pravastatin, and placebo.

The Beta-blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS) compared low-dose metoprolol (25 mg daily), fluvastatin (40 mg daily) and placebo effects on carotid IM progression during a 36-month treatment period in 793 subjects with asymptomatic carotid plaques.<sup>32</sup> At the study end, IMT (mean) progression rate of common carotid was reduced by fluvastatin ( $-9 \mu\text{m}/\text{y}$ ; 95% CI:  $-15$  to  $-3$ ;  $p = 0.002$ ). At both 18 and 36 months, IMT (max) progression in the carotid bulb was reduced by metoprolol ( $-58 \mu\text{m}/\text{y}$ , 95% CI:  $-94$  to  $-23$ ;  $p = 0.004$  and  $-23 \mu\text{m}/\text{y}$ , 95% CI:  $-44$  to  $-3$ ;  $p = 0.014$ , respectively), thus reflecting a favorable beta-blocker effect on atherosclerosis progression.

Finally, in a recent meta-analysis including all the above mentioned trials plus four smaller studies, Wang and coworkers have shown that antihypertensive treatment significantly reduced IM thickening rate by  $7 \mu\text{m}/\text{year}$  compared with placebo ( $p = 0.01$ ).<sup>33</sup>

## Trials comparing active antihypertensive drug regimens

The Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS) was the first prospective trial investigating this area by comparing the effects of a twice daily dose of isradipine (2.5–5 mg) and hydrochlorothiazide (HCTZ) (12.5–25 mg) in 883 patients with mild to moderate hypertension and maximum IMT of  $1.17 \pm 0.20 \text{ mm}$  ( $=1170 \pm 200 \mu\text{m}$ ).<sup>34</sup> The study primary end point, namely the rate of mean maximum IMT progression in 12 carotid sites over three years ( $30 \mu\text{m}/\text{year}$ ), did not differ between the treatment groups ( $p = 0.68$ ). Since patients randomized to HCTZ achieved significantly lower BP levels than their counterparts, the lack of differences in IMT progression between treatment arms was considered as an indirect evidence of a protective effect of isradipine on the carotid artery wall.

In the Verapamil in Hypertension and Atherosclerosis Study (VHAS) 498 hypertensive patients, randomized to either verapamil (240 mg daily) or chlorthalidone (25 mg daily), underwent carotid ultrasound examinations at baseline and after 3, 12, 24, 36, and 48 months of treatment.<sup>35</sup>

The primary endpoint for treatment efficacy, namely the IMT change slope over four years (rate of change,  $\mu\text{m}/\text{year}$ ), was significantly different between treatment groups (verapamil  $-82 \mu\text{m}/\text{year}$  versus chlorthalidone  $-37 \mu\text{m}/\text{year}$ ;  $p < 0.02$ ). As the BP-lowering effect of the two randomized treatments was similar, these findings indicate the verapamil is more effective than chlorthalidone in promoting regression of carotid atherosclerosis.

The International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) assessed common carotid IMT progression in 439 hypertensives randomized to nifedipine 30 mg or co-amilofide (HCTZ 25 mg and amiloride 2.5 mg) for a four-year follow-up period.<sup>36</sup> Ultrasonography was performed at baseline, at four months, and subsequently every year. Primary outcome was IMT progression rate (slope of IMT-time regression): this parameter differed between treatment groups either before ( $p = 0.002$ ) as after ( $p = 0.003$ ) adjustment for baseline covariates and BP changes. In particular, nifedipine retarded the progression of carotid wall changes as compared to coamilofide, despite similar BP-lowering effects.

The European Lacidipine Study on Atherosclerosis (ELSA), a randomized double-blind trial in 2,334 hypertensive patients, tested the effects of a four-year treatment with lacidipine or atenolol on mean maximum IMT in common carotid arteries and bifurcations.<sup>26</sup> Yearly IMT progression rate was  $14.5 \mu\text{m}/\text{y}$  in atenolol-treated and  $8.7 \mu\text{m}/\text{y}$  in lacidipine-treated patients ( $p = 0.001$ ); plaque progression was significantly less common, and plaque regression was significantly more frequent in the lacidipine group. Clinic BP was similarly reduced by both treatments, whereas 24-hour ambulatory systolic/diastolic BP changes were greater in the atenolol- ( $-10/-9 \text{ mm Hg}$ ) than lacidipine-group ( $-7/-5 \text{ mm Hg}$ ). A greater efficacy of lacidipine on carotid IMT and plaque progression despite a smaller ambulatory BP reduction, supports an antiatherosclerotic action of lacidipine which is partially independent of the antihypertensive effect.

The Plaque Hypertension Lipid-Lowering Italian Study (PHYLLIS) was designed to test whether: 1) fosinopril (20 mg per day) was more effective than HCTZ (25 mg per day) on carotid atherosclerosis progression; 2) pravastatin (40 mg per day) was more effective than placebo when added to either HCTZ or fosinopril; 3) the ACE inhibitor and statin had additive antiatherosclerotic effects.<sup>37</sup>

Five hundred and eight hypertensive hypercholesterolemic patients with asymptomatic carotid atherosclerosis were randomized to the following treatments: (A) HCTZ,



(B) fosinopril, (C) HCTZ plus pravastatin, (D) fosinopril plus pravastatin and followed-up for 2.6 years. The primary outcome was the change in mean maximum IMT of far and near common carotid walls and bifurcations bilaterally ( $CBM_{max}$ ).  $CBM_{max}$  significantly progressed ( $10 \pm 4 \mu\text{m}/\text{year}$ ;  $p = 0.01$ ) in group A compared to the remaining groups;  $CBM_{max}$  changes in group B, C, and D were significantly lower than in group A. Clinic and ambulatory BP reductions were not different among groups, whereas total and low-density lipoprotein cholesterol decreased by approximately 1 mmol/L in group C and D. These results show that both fosinopril and pravastatin exert an antiatherosclerotic action, although they do not provide any evidence about an additive effect of their combination on IMT progression.

### ARBs versus other antihypertensive drugs

Experimental and clinical studies indicate that ARBs exert antiatherogenic antiproliferative effects over and beyond their antihypertensive action.<sup>38,39</sup> Scarce evidence, however, is available about the properties of these drugs in preventing carotid atherosclerosis progression. Due to the limited number of studies available, also trials with a numerosity of at least 40 patients per treatment-arm and a follow-up of at least one year have been included in this section.

The Losartan Vascular Regression Study (LAARS) investigated the effects of losartan (50 mg once daily) and atenolol (50 mg once daily) on CCA IMT in 280 patients with mild to moderate essential hypertension and right or left CCA IMT between 0.8 and 1.5 mm at baseline.<sup>40</sup> Primary end point of the study was the yearly rate of change (YRC) of mean IMT in CCA (CCA-IMT<sub>mean</sub>) from baseline over two years treatment. Target BP (SBP/diastolic blood pressure [DBP] < 140/90 mm Hg) was achieved by sequentially adding HCTZ 12.5 mg once daily, doubling the dose of the study drug, or adding an open-label CCB, as needed.

Both losartan and atenolol induced comparable reductions in SBP/DBP and CCA-IMT mean over the 24 months period compared to baseline; average YRC was  $-38 \pm 04 \mu\text{m}/\text{y}$  for losartan ( $p < 0.001$ ) and  $-37 \pm 4 \mu\text{m}/\text{y}$  for atenolol ( $p < 0.001$ ).

In the Swedish Irbesartan Left Ventricular Hypertrophy Investigations versus Atenolol (SILVHIA) study 108 hypertensive patients with LV hypertrophy were randomized double-blind to irbesartan ( $n = 52$ ) or atenolol ( $n = 56$ ) treatment for 48 weeks.<sup>41</sup> Ultrasonographic CCA and echocardiographic examinations were performed at baseline and at the study end. In front of similar blood pressure reductions, CCA IMT tended to decrease with irbesartan ( $-10 \pm 100 \mu\text{m}$

from  $920 \pm 140 \mu\text{m}$ , NS), whereas it increased with atenolol ( $+30 \pm 120 \mu\text{m}$  from  $940 \pm 210 \mu\text{m}$ ;  $p = 0.018$ ; with  $p = 0.002$  between groups).

Ariff and colleagues compared the effects of a 52-week candesartan-based (8–16 mg daily) and atenolol-based (50–100 mg daily) regimen on CCA and LV structure in 88 hypertensive patients in a randomized, double-blind study. HCTZ (12.5–25 mg/day), felodipine (5–10 mg/day), and doxazosin (4–16 mg/day) were added as required.<sup>42</sup> Clinic and 24-hour ambulatory BP, left ventricular (LV) mass index, CCA IMT, lumen diameter, IM area, carotid blood flow and distensibility were measured at baseline, at 26 and 52 weeks of treatment. Both candesartan and atenolol similarly reduced IMT and IM area and increased carotid distensibility after 52 weeks. Atenolol-based treatment, however, but not candesartan-based treatment was associated with CCA inward remodeling, as reflected by a reduction of lumen diameter.

Ichihara and colleagues investigated the long-term effects of 24-h ambulatory BP control with amlodipine versus valsartan on vascular damage in untreated hypertensive patients.<sup>43</sup> Pulse wave velocity (PWV), carotid arteries IMT, and 24-h ambulatory BP were determined in 100 untreated hypertensive patients before and after a 12-month treatment.

Amlodipine and valsartan similarly decreased ambulatory BP and PWV; neither drug altered maximum carotid artery IMT, which averaged  $920 \pm 50$  and  $880 \pm 40 \mu\text{m}$ , respectively, at baseline.

The Multicentre Olmesartan atherosclerosis Regression Evaluation (MORE) study, a double-blind trial in hypertensive patients at increased CV risk due to carotid wall thickening and atherosclerotic plaques, compared the effects of a two-year treatment based on either olmesartan or atenolol on CCA IMT and plaque volume (PV) determined by two- and three-dimensional (3D) ultrasound examinations.<sup>44</sup> A total of 165 patients randomized to either olmesartan (20–40 mg/day) or atenolol (50–100 mg/day) underwent carotid ultrasonography at baseline, 28, 52, and 104 weeks of treatment. The primary efficacy outcome was the change from baseline (Delta) in CC-IMT assessed by 2D ultrasound examination; secondary outcomes included Delta in PV assessed by 3D ultrasound and in BP. Olmesartan and atenolol produced comparable significant reductions in CC-IMT; mean Delta IMT was  $-90 \pm 15 \mu\text{m}$  for olmesartan and  $-82 \pm 14 \mu\text{m}$  for atenolol. Mean Delta PV was  $-4.4 \pm 2.3 \mu\text{L}$  and  $0.1 \pm 1.5 \mu\text{L}$  in the olmesartan and atenolol group, respectively, without significant between-treatment differences. In the subgroup of patients with baseline PV greater than or equal to median value (33.7  $\mu\text{L}$ ),

significant between-treatment differences existed in Delta PV ( $p = 0.023$ ), as PV regressed with olmesartan ( $-11.5 \pm 4.4 \mu\text{L}$ ) and was unchanged with atenolol ( $0.6 \pm 2.5 \mu\text{L}$ ), thus suggesting that olmesartan exerts a more protective effect in advanced carotid atherosclerosis. Ono and colleagues evaluated the effects of antihypertensive therapy on NO production, oxidative stress and carotid IMT in 100 hypertensive patients randomized to candesartan 8 mg (plus CCBs, ACE inhibitors, and/or beta-blockers, when needed) or to treatment with all drugs above mentioned other than ARB.<sup>45</sup> Carotid IMT was assessed before and after 12 and 24 months of treatment. Urine levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG), an oxidative stress indicator, and serum levels of NOx, as a marker of NO were measured. BP similarly decreased below 140/90 mmHg in both groups.

Carotid IMT significantly decreased after 12 and 24 months of treatment in the ARB group, but not in the non-ARB group; this decrement was associated with a parallel decrease of 8-OHdG and an increase of NOx levels.

## Conclusions

A solid body of evidence indicates that carotid IM thickening and plaques are important added risks for CV events in different clinical settings, regardless of BP and conventional risk factors. Thus, carotid atherosclerosis can be regarded as a reliable surrogate end-point for therapeutic interventions. The main findings of our review may be summarized as follows. I) Carotid IMT progression is blunted by long-term antihypertensive treatment: compared with placebo or no treatment, an ACE-inhibitor,<sup>28</sup> a beta-blocker,<sup>31</sup> and a CCB<sup>29</sup> slightly reduced IMT progression rate in high risk patients with type 2 diabetes, CHD, and vascular disease. II) CCBs are more effective than other antihypertensive drugs in this respect: actively controlled studies show that CCBs retarded IMT progression more effectively than diuretics,<sup>34,35</sup> beta-blocker,<sup>26</sup> and ACE-inhibitor.<sup>37</sup> The antiatherosclerotic effect of CCBs, shown in these clinical trials, is also supported by the demonstrated efficacy of these agents in various animal models of atherosclerosis.<sup>46,47</sup> Possible specific mechanisms for the antiatherosclerotic effect of CCBs are inhibited production of reactive oxygen species and reduced expression of adhesion molecules in endothelial cells, and restoration of endothelial function.<sup>48</sup> III) Limited evidence is available, so far, for ARBs and further studies are needed to clarify role of these drugs in this therapeutic area. In fact, an ARB protective effect against the progression of carotid atherosclerosis was shown by three out of six studies examined, comparing irbesartan versus atenolol,<sup>41</sup> candesartan versus atenolol,<sup>42</sup> and

no-ARB antihypertensive therapy.<sup>45</sup> Minor protective effects favoring ARBs over the beta-blocker atenolol has been also demonstrated in the LAARS<sup>40</sup> and MORE<sup>44</sup> studies.

## Disclosure

The authors report no conflicts of interest in this work.

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