Impact of Prehypertension on Common Carotid Artery Intima-Media Thickness and Left Ventricular Mass

Efstathios Manios, MD; Georgios Tsivgoulis, MD, FESO; Eleni Koroboki, MD; Kimon Stamatelopoulos, MD; Christos Papanichael, MD; Savas Toumanidis, MD; Elefterios Stamboulis, MD; Konstantinos Vemmos, MD; Nikolaos Zakopoulos, MD

Background and Purpose—Prehypertension has been recently introduced by JNC 7 as a new blood pressure (BP) category, associated with increased target-organ damage. Subclinical atherosclerosis by means of common artery intima-media thickness (CCA-IMT) has been incompletely investigated in prehypertensive patients. The aim of our study was to assess the extent of CCA-IMT and left ventricular mass (LVM) in prehypertensive adults in comparison to normotensive and untreated hypertensive subjects.

Methods—From a total of 5221 consecutive patients screened to our Hypertension Unit we selected 896 consecutive individuals according to prespecified inclusion criteria, who underwent 24-hour ambulatory BP monitoring, carotid artery ultrasonographic, and echocardiographic measurements. Patients who received antihypertensive treatment during the BP monitoring were excluded. According to the office BP levels, patients were divided into 3 subgroups: normotensives (office BP <120/80 mm Hg), prehypertensives (120/80 mm Hg ≤ office BP <140/90 mm Hg), and hypertensives (office BP ≥140/90 mm Hg). Statistical analyses were performed by means of 1-way ANOVA, χ² test, and ANCOVA.

Results—According to the office BP levels, the distribution of the study population was: normotensives (14.4%), prehypertensives (23.7%), and hypertensives (61.9%). Prehypertensive patients had higher CCA-IMT (P=0.038) and LVM (P=0.030) values than normotensive subjects, even after adjustment for baseline characteristics. Greater CCA-IMT values were observed in hypertensive patients in comparison to prehypertensives (P=0.002).

Conclusions—Prehypertensive patients had higher CCA-IMT and LVM than their normotensive counterparts. Prehypertension status is cross-sectionally associated with subclinical atherosclerosis and target-organ damage. (Stroke. 2009;40:1515-1518.)

Key Words: prehypertension • common carotid artery intima-media thickness • left ventricular mass

The term “prehypertension” was introduced by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) in 2003 and was defined as a systolic blood pressure (BP) of 120 to 139 mm Hg and a diastolic BP of 80 to 89 mm Hg.1 The reasoning behind this new category was that long-term epidemiological studies had indicated a progressively increasing risk of cardiovascular events as systolic BP rose above 110 mm Hg.1 However, whereas several studies have reported an increased risk of cardiovascular disease among prehypertensive individuals,2–4 others suggest that the risk of cardiovascular disease is modest and is associated with the presence of additional risk factors.5

Although recent evidence support the contention that prehypertension is associated with target-organ-damage (TOD), there is lack of information regarding the evaluation of common carotid artery intima-media thickness (CCA-IMT) in prehypertensive individuals and conflicting data concerning the association of prehypertension with increased left ventricular mass (LVM). Aim of our study was to assess the extent of CCA-IMT and LVM in prehypertensive adults in comparison to normotensive and untreated hypertensive subjects.

Subjects and Methods

Study Population

From January 1998 to January 2007, a consecutive series of 5221 subjects referred for evaluation to the Outpatient Hypertension Unit of our department. Among them 896 individuals fulfilled the following inclusion criteria: (1) absence of clinical evidence of hypertension related complications (coronary artery disease, heart failure, cerebrovascular disease, renal insufficiency, or peripheral artery disease); (2) no previous antihypertensive treatment; (3) no clinical signs or laboratory evidence of secondary causes of arterial hypertension; (4) at least three valid BP measurements per hour over...
24 hours ABPM (75% successful measurements); (5) carotid artery ultrasonographic and echocardiographic measurements. The above cohort of patients was evaluated by means of 24-hour ambulatory BP monitoring (ABPM) as previously described.6 The study was approved by the local scientific committee.

Participants were divided into 3 subgroups according to office BP levels: (1) normotensives: SBP <120 mm Hg and DBP <80 mm Hg; (2) prehypertensives: 120 mm Hg ≤SBP <140 mm Hg and 80 mm Hg ≤DBP <90 mm Hg; (3) hypertensives: SBP ≥140 mm Hg or DBP ≥90 mm Hg.1

Office and Ambulatory BP Measurements
Office BP was measured 3 times by a physician in each arm using a mercury sphygmomanometer as previously described.6 Individuals with BP differences between the arms greater than 20 mm Hg for systolic and 10 mm Hg for diastolic BP were excluded. In each subject the 3 initial BP values provided by the sphygmomanometer were averaged to obtain a single systolic and diastolic office BP value.

All subjects underwent 24-hour ABPM on a usual working day as previously described.6 ABP was recorded using oscillometric Spacelabs 90207 equipment (SpaceLabs). The office and the ambulatory BP readings were recorded on the same day. Readings were obtained automatically at 15-minute intervals throughout the 24-hour study period. Daytime was defined as the interval between 09:00 hour and 21:00 hour, and nighttime was the interval between 01:00 hour and 06:00 hour. For each patient we computed mean daytime and nighttime systolic BP (SBP), diastolic BP (DBP), heart rate (HR).

Carotid Artery Ultrasonographic Measurements
The left and right CCA were examined in the anterolateral, postero- lateral, and mediolateral directions with a high-resolution ultrasound Doppler system (Acuson 128XP), equipped with a 7-MHz linear-array transducer. The ultrasonographic assessment of CCA-IMT by experienced sonographers blinded to all clinical data in our vascular laboratory has been previously described in detail.7

Echocardiographic Measurements
A complete M-mode 2-dimensional and color flow Doppler echocardiographic examination was performed in each patient. Studies were performed using the commercially available Hewlett Packard machine (Sonos 1000; Hewlett Packard) and a 2.5 MHz phased-array transducer. Our echocardiographic protocol in the assessment of LVM by two experienced investigators blinded to all clinical data has been previously described in detail.8 LVM was calculated using the Devereux formula according to the Penn Convention Protocol.9

Statistical Analyses
Statistical comparisons were performed between the 3 subgroups in terms of baseline characteristics, office BP values, ABPM parameters, and LVM and CCA-IMT values. Dichotomous variables were compared using the χ2 test, and continuous variables were compared using 1-way analysis of variance. Bonferroni correction for multiple comparisons was applied as appropriate. The CCA-IMT and LVM (after adjustment for baseline characteristics) were also compared among the 3 subgroups by means of ANCOVA. The covariate adjusted mean values were computed and are presented with their corresponding 95% CI. We also evaluated the potential relationship between CCA-IMT and LVM using Spearman correlation coefficient (r) and multivariate linear regression models adjusting for baseline characteristics. The Statistical Package for Social Science (SPSS Inc, version 10.0 for Windows) was used for statistical analyses.

Results
Our study population (n=896, mean age 52±16 years) consisted of 474 male and 422 female persons. According to the office BP levels, the distribution of the study population was: 129 normotensives (14.4%), 212 prehypertensives (23.7%), and 555 hypertensives (61.9%). Demographics, clinical characteristics, and BP values of the study population are presented in Table 1. Prehypertensive subjects were significantly younger than hypertensive and older than normotensive individuals. The 3 groups did not differ significantly regarding sex, prevalence of diabetes mellitus, and smoking. Body mass index and prevalence of hypercholesterolemia were significantly greater in hypertensive patients than in normotensives and prehypertensives. The use of lipid-lowering and antidiabetic medications was similar between the 3 groups (P=0.102 and P=0.574 respectively). A total of 67 patients (7.5%) had masked hypertension (normal office in the presence of elevated ambulatory BP values), while the prevalence of white-coat hypertension (elevated office in the presence of normal ambulatory BP values).

The carotid ultrasonographic and echocardiographic measurements are presented in Table 2. Higher CCA-IMT values were documented in hypertensive patients in comparison with prehypertensives (P<0.001) and normotensives (P<0.001; Table 2). Additionally, prehypertensive subjects had greater CCA-IMT values than normotensives (P=0.019; Table 2). As far as LVM is concerned, normotensive individuals had lower LVM values in comparison to prehypertensives (P=0.011) and hypertensives (P<0.001; Table 2). No statistically significant difference was observed between hypertensives and prehypertensives, regarding LVM (P=0.943; Table 2). After adjustment for baseline characteristics, prehypertensive patients had higher CCA-IMT (P=0.038) and LVM (P=0.030) val-

<table>
<thead>
<tr>
<th>Variable</th>
<th>NT (n=129)</th>
<th>PreHT (n=212)</th>
<th>HT (n=555)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>39 (23)†‡</td>
<td>51 (16)‡</td>
<td>55 (12)†‡</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>52</td>
<td>51</td>
<td>54</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25 (4)‡‡</td>
<td>27 (4)‡‡</td>
<td>28 (4)‡‡</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>8</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>26†</td>
<td>27‡</td>
<td>38‡</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>40</td>
<td>37</td>
<td>37</td>
</tr>
</tbody>
</table>

Noncontinuous variables are given as percentages. Continuous variables are presented as mean±SD.

NT indicates normotensives; PreHT, prehypertensives; HT, hypertensives; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

*P<0.05 vs NT; †P<0.05 vs PreHT; ‡P<0.05 vs HT.
ues than normotensive subjects. There was no difference between patients with prehypertension and masked hypertension both in CCA-IMT ($P=0.198$) and LVM ($P=0.212$). In contrast, prehypertensive patients had higher CCA-IMT values than white-coat hypertensives ($P=0.034$).

A positive correlation was identified between CCA-IMT and LVM ($r=0.248$, $P<0.001$). This relationship persisted after adjustment for baseline characteristics on multivariate linear regression models (standardized linear regression coefficient: 0.107, $P=0.001$).

### Discussion

Our study showed that prehypertensive subjects had higher CCA-IMT and LVM values than their normotensive counterparts, even after adjustment for baseline characteristics. Previous studies have demonstrated associations between biomarkers and prehypertension status related to atherosclerotic disease. The Attica study pointed out that inflammatory markers such as C-reactive protein, TNF-a, amyloid-a, and homocysteine levels were higher in prehypertensive compared with normotensive subjects. The authors concluded that prehypertension might be a proinflammatory condition, promoting subclinical atherosclerotic disease. In another study Papadopoulos et al reported that hypoadiponectinemia and hyperresistinemia were documented in prehypertensive patients compared with normotensives, which may contribute to insulin resistance and accelerated atherogenesis.

To the best of our knowledge, this is the first study investigating CCA-IMT in the new JNC-7 category of prehypertension. Our findings indicate that prehypertension may increase the risk of atherosclerosis, implying that the increase in CCA-IMT is an earlier preclinical atherosclerotic change. This finding is in line with two reports that documented an independent association between borderline hypertension and intima-media thickening.

Epidemiological data have shown that increased LVM is an independent predictor of cardiovascular events in the general population and in several clinical conditions, including arterial hypertension. The present study documented that prehypertensive and normotensive patients had significantly greater LVM values than normotensive individuals. These findings are in accordance with a recent study in 1940 young participants, which pointed out that both prehypertensive and hypertensive subjects had higher LVM values than their normotensive counterparts even after adjustment for covariates. Conversely, a smaller study reported that prehypertensive and normotensive individuals had similar LVM values.

Methodological differences between these studies (different inclusion criteria, different ABPM protocol) may account for the discrepant results, and further research is needed to elucidate the relationship of prehypertension with left ventricular thickening in a prospective fashion.

Certain limitations of the present report need to be addressed. According to the guidelines of the JNC-7, the classification of prehypertension requires two or more office visits. In this study prehypertension was classified during a single office visit, although BP was taken with caution and the average of 3 measures was used. Moreover, the cross-sectional design of the present study does not allow us to establish a cause-effect relationship between prehypertension and carotid intima-media thickening or increased LVM. Finally, another possible limitation of the present report study is the age difference between normotensive and prehypertensive subjects. As age is the major determinant of IMT, it may be argued that there may be certain bias concerning the real effect of prehypertension on IMT despite the adjustment for age using an ANCOVA model.

In conclusion, our results suggest that prehypertensive adult patients present higher CCA-IMT and LVM values than their normotensive counterparts and lend support to the current notion that prehypertension may be associated with subclinical atherosclerosis and TOD.

### Disclosures

None.
References


Impact of Prehypertension on Common Carotid Artery Intima-Media Thickness and Left Ventricular Mass
Efstatios Manios, Georgios Tsivgoulis, Eleni Korobaki, Kimon Stamatelopoulos, Christos Papamichael, Savas Toumanidis, Elefterios Stamboulis, Konstantinos Vemmos and Nikolaos Zakopoulos

Stroke. 2009;40:1515-1518; originally published online January 22, 2009;
doi: 10.1161/STROKEAHA.108.528174

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/40/4/1515

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/