Candesartan- and Atenolol-Based Treatments Induce Different Patterns of Carotid Artery and Left Ventricular Remodeling in Hypertension

Ben Ariff, MRCP; Andrew Zambanini, MRCP; Sarita Vamadeva, MBBS, BSc; Dean Barratt, PhD; Yun Xu, PhD; Peter Sever, PhD, FRCP; Alice Stanton, PhD, FRCP; Alun Hughes, MB, PhD; Simon Thom, MD, FRCP

Background and Purpose—Angiotensin receptor blocker (ARB)–based treatment reduces cardiovascular events and stroke more than does β-blocker–based treatment despite similar blood pressure (BP) reduction. We investigated whether these treatments have different effects on cardiac and large-artery remodelling and evaluated the relation of arterial remodelling to hemodynamic changes in subjects with hypertension.

Methods—We compared the treatment effects of an ARB (candesartan cilexetil)-based regimen and a β-blocker (atenolol)–based regimen for 52 weeks on common carotid artery (CCA) and left ventricular structure in hypertensive patients in a randomized, double-blind study. Clinic brachial BP and 24-hour ambulatory BP, carotid BP, left ventricular mass index, CCA intima-media thickness, lumen diameter, intima-media area, and carotid blood flow were measured. Distensibility, circumferential tensile stress, Young’s elastic modulus (Eμ), and shear stress (γ) in the CCA were also calculated.

Results—Both candesartan and atenolol reduced intima-media thickness and intima-media area and increased distensibility to similar extents after 52 weeks of treatment. Despite similar reductions in BP, treatment with atenolol resulted in a lesser reduction in left ventricular mass index, a decrease in lumen diameter, and a reduction in carotid blood flow compared with candesartan.

Conclusions—BP-independent effects of ARB on cardiac and arterial structure may contribute to the beneficial effects of these agents on cardiovascular disease. (Stroke. 2006;37:2381-2384.)

Key Words: antihypertensive agents ■ hypertension ■ intima-media thickness

Hypertension is associated with changes in cardiovascular structure, and some treatments may cause regression through mechanisms independent of blood pressure (BP)—lowering.1 Currently, the mechanisms involved in the BP-independent effects of antihypertensive agents on cardiovascular structure are not fully understood but may contribute to differences in cardiovascular risk protection.

This study compared an angiotensin receptor blocker (ARB; candesartan cilexetil)–based regimen and a β-blocker (atenolol)–based regimen on carotid artery and left ventricular structure in hypertensive subjects after 52 weeks of treatment. Differences in hemodynamics were also explored as possible explanations of treatment differences.

Methods

Patients and Study Design

Eighty-eight patients with uncontrolled essential hypertension (>160/100 mm Hg untreated; >140/90 mm Hg on treatment plus evidence of target-organ damage) were recruited into a randomized, prospective, double-blind parallel-group study (Table 1). Details of the protocol have been published previously.2 Individuals were excluded if they had evidence of accelerated hypertension (>220/120 mm Hg), previous myocardial infarction or stroke within 6 months, diabetes mellitus, or any other condition that precluded participation.

All subjects gave informed consent, the local research committee approved the study protocol, and the research was carried out in accordance with the Helsinki Declaration of the World Medical Association (1989). After a 4-week drug-free period, patients were randomized with minimization for ethnic origin, sex, age, and left ventricular hypertrophy to receive either candesartan (8 to 16 mg once daily) or atenolol (50 to 100 mg once daily). Follow-up visits were at 2-week intervals until BP was controlled and then every 3 months. Hydrochlorothiazide (12.5 to 25 mg once daily), felodipine (5 to 10 mg once daily), and doxazosin (4 to 16 mg once daily) were added as required. Study measurements were performed at baseline, at 26 weeks, and at 52 weeks.

BP Measurements

Systolic BP and diastolic BP were measured in the right arm with an Omron HEM-705-CP. Carotid BP was measured by applanation...
Ultrasound Studies
Echocardiography and ultrasound scans of the right CCA were performed with an HDI 5000 scanner equipped with a 4- to 2-MHz and 12- to 5-MHz linear-array transducer respectively.2 Left ventricular mass index (LVMI) was determined according to the Penn convention.4 Intima-media thickness (IMT) was analyzed with a validated program.5 Average IMT and lumen diameter (LD) were measured over a 5- to 15-mm segment in the distal CCA from the anterior, anterolateral, and posterior projections.

Carotid blood flow (CBF) velocity was measured in the right CCA 2 cm proximal to the bulb by pulsed Doppler and a sample volume of 1.5 mm² located in the center of the artery, with the ultrasound beam positioned at 60° to the direction of blood flow. Analysis was performed with software written in MatLab (MatLab 6.0, Mathworks). Intima-media area (IMA), circumferential wall tension (Tm), circumferential tensile stress, distensibility coefficient, Young’s modulus (Em), and volumetric CBF (by analytical solution of the Womersley equation) were also calculated.6,7

Reproducibility
All measurements were made in a blinded manner by a single observer. Intraobserver reproducibility (mean difference±SD) was:

- 0.003±0.011 mm for CCA IMT,
- 3.85±7.91 g/m² for LVMI,
- 0.028±0.300 mm for LD.

Statistics
Analyses were conducted according to the intention-to-treat principle with SAS 8.1 (SAS Institute Inc). Baseline data are mean±SD or median (range) for skewed data. Comparisons at baseline were made with an unpaired Student t test (after logarithmic transformation where appropriate) for continuous data and χ² test for categorical variables.

Results
Treatment groups were well matched at baseline (Table 1), and candesartan-based and atenolol-based treatments achieved similar reductions in BP reduction. Heart rate was reduced by both candesartan and atenolol treatment (Table 2). There was no significant difference in the use of second- or third-line agents between treatment groups.

CCA Structure
Both candesartan and atenolol caused similar regressions of IMT and IMA at 52 weeks (the Figure and Table 2).
An ARB (candesartan)-based regimen and a \( \beta \)-blocker (atenolol)-based regimen had different effects on carotid artery and LV structure, despite an equivalent lowering of BP. BP reduction was associated with regression of carotid IMT, IMA, and LVMI, but atenolol-based treatment was associated with inward remodeling of the carotid artery and lesser LVMI regression. Carotid distensibility increased with both treatments, but \( E_m \) (a measure of intrinsic elastic properties) was unaltered, suggesting that the increase in distensibility is likely to be a consequence of reduced BP.

A previous study reported that the ARB losartan reduced LVMI more than atenolol and reduced IMT to a similar extent. However, a small substudy of the LIFE trial showed a significant decrease in carotid IMT and IMA with losartan therapy, but not with atenolol therapy, after 3 years of treatment. Another study reported that 8-week treatment with irbesartan decreased radial artery wall thickness in comparison with placebo but did not affect carotid artery LD or IMT. Differences between these studies may relate to small sample sizes, the nonequivalence of BP reduction, or variable duration of therapy.

Factors influencing the LD of the carotid artery are not well understood. Carotid pulse pressure has been shown to predict carotid LD independent of brachial BP, but carotid BP did not differ between treatments in our study. However, our study may have been underpowered to detect small differences in carotid pulse pressure. Interestingly ARBs have been shown to cause outward remodeling in resistance arteries, and this may be related to vasodilation. It has been suggested that arterial remodeling acts to preserve levels of endothelial shear stress, and in our study, shear stress did not change with treatment, despite the different effects on LD and CBF. Measurement of CBF in our study also suggested that

### Discussion

An ARB (candesartan)-based regimen and a \( \beta \)-blocker (atenolol)-based regimen had different effects on carotid artery and LV structure, despite an equivalent lowering of BP. BP reduction was associated with regression of carotid IMT, IMA, and LVMI, but atenolol-based treatment was associated with inward remodeling of the carotid artery and lesser LVMI regression. Carotid distensibility increased with both treatments, but \( E_m \) (a measure of intrinsic elastic properties) was unaltered, suggesting that the increase in distensibility is likely to be a consequence of reduced BP.

A previous study reported that the ARB losartan reduced LVMI more than atenolol and reduced IMT to a similar extent. However, a small substudy of the LIFE trial showed a significant decrease in carotid IMT and IMA with losartan therapy, but not with atenolol therapy, after 3 years of treatment. Another study reported that 8-week treatment with irbesartan decreased radial artery wall thickness in comparison with placebo but did not affect carotid artery LD or IMT. Differences between these studies may relate to small sample sizes, the nonequivalence of BP reduction, or variable duration of therapy.

Factors influencing the LD of the carotid artery are not well understood. Carotid pulse pressure has been shown to predict carotid LD independent of brachial BP, but carotid BP did not differ between treatments in our study. However, our study may have been underpowered to detect small differences in carotid pulse pressure. Interestingly ARBs have been shown to cause outward remodeling in resistance arteries, and this may be related to vasodilation. It has been suggested that arterial remodeling acts to preserve levels of endothelial shear stress, and in our study, shear stress did not change with treatment, despite the different effects on LD and CBF. Measurement of CBF in our study also suggested that

#### TABLE 2. Changes From Baseline (\( \Delta \)) in Variables at 52 Weeks After Candesartan- or Atenolol-Based Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Candesartan, ( n=44 )</th>
<th>Atenolol, ( n=44 )</th>
<th>( P ) (Between Treatments)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic brachial SBP, mm Hg</td>
<td>(-35 (-39, -30))</td>
<td>(-32 (-40, -26))</td>
<td>0.38</td>
</tr>
<tr>
<td>Clinic brachial DBP, mm Hg</td>
<td>(-18 (-21, -16))</td>
<td>(-20 (-22, -16))</td>
<td>0.81</td>
</tr>
<tr>
<td>Carotid SBP, mm Hg</td>
<td>(-22 (-27, -17))</td>
<td>(-18 (-26, -11))</td>
<td>0.84</td>
</tr>
<tr>
<td>Carotid pulse pressure, mm Hg</td>
<td>(-15 (-20, -9))</td>
<td>(-8 (-14, -3))</td>
<td>0.12</td>
</tr>
<tr>
<td>Systolic ABP, mm Hg</td>
<td>(-29 (-37, -21))</td>
<td>(-27 (-32, -22))</td>
<td>0.75</td>
</tr>
<tr>
<td>Diastolic ABP, mm Hg</td>
<td>(-17 (-22, -11))</td>
<td>(-19 (-22, -17))</td>
<td>0.43</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>(-1 (-3, 2))</td>
<td>(-13 (-15, -10))</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carotid IMT, mm</td>
<td>(-0.05 (-0.07, -0.03))</td>
<td>(-0.07 (-0.10, -0.03))</td>
<td>0.93</td>
</tr>
<tr>
<td>Carotid IMA, mm</td>
<td>(-1.5 (-2.0, -1.0))</td>
<td>(-2.3 (-3.2, -1.3))</td>
<td>0.53</td>
</tr>
<tr>
<td>LD, mm</td>
<td>(-0.08 (-0.2, 0.04))</td>
<td>(-0.29 (-0.41, -0.17))</td>
<td>0.02</td>
</tr>
<tr>
<td>DC, ( \times 10^5 )</td>
<td>0.5 (1.8, 2.5)</td>
<td>1.0 (1.8, 2.4)</td>
<td>0.24</td>
</tr>
<tr>
<td>( E_m ), ( \times 10^8 ) Pa</td>
<td>2.1 (0.3, 4.6)</td>
<td>2.7 (0.1, 5.5)</td>
<td>0.17</td>
</tr>
<tr>
<td>CTS, Pa</td>
<td>(-0.3 (-0.6, 0.1))</td>
<td>(-0.6 (-1.0, -0.1))</td>
<td>0.11</td>
</tr>
<tr>
<td>CBF, mL/s</td>
<td>(-0.4 (-0.5, 1.1))</td>
<td>(-1.6 (-0.5, -2.7))</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean ( \tau ), Pa</td>
<td>0.12 (-0.03, 0.27)</td>
<td>0.13 (-0.19, 0.46)</td>
<td>0.03</td>
</tr>
<tr>
<td>LVMI, g/m(^2)</td>
<td>(-15.7 (-19.3, -12.1))</td>
<td>(-7.7 (-11.3, -4.0))</td>
<td>0.002</td>
</tr>
<tr>
<td>LV internal diameter in diastole, cm</td>
<td>(-0.09 (-0.17, -0.01))</td>
<td>(-0.03 (-0.09, 0.03))</td>
<td>0.18</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>(-0.019 (-0.033, -0.006))</td>
<td>(-0.015 (-0.028, -0.003))</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Data are expressed as mean (95% CI). Statistical comparisons between treatments were made by ANCOVA after adjusting for baseline clinic brachial SBP.

In contrast, candesartan-based treatment was not associated with a reduction in carotid LD, whereas atenolol-based treatment reduced LD (the Figure and Table 2). LD was significantly greater in the candesartan group at 52 weeks (the Figure).

### LV Structure

Treatment caused regression of LVMI at 52 weeks, but there was greater reduction in LVMI in the candesartan group (the Figure). Candesartan treatment caused a significant reduction in left ventricular internal diameter (LVID), whereas atenolol did not. Regional wall thickness (RWT) was significantly reduced by both treatments (Table 2).

### Effect of Treatment on Carotid Artery Distensibility, \( E_m \), and \( T_m \)

Carotid distensibility was increased after 52 weeks of antihypertensive therapy (Table 2), and there was no difference between groups. Increased distensibility was not associated with a change in \( E_m \) or \( T_m \) (Table 2).

### Effect of Treatment on CBF and Wall Shear Stress

CBF was reduced by atenolol, but there was no change in CBF in the candesartan group. Mean wall shear stress did not change or differ between treatments (Table 2).
Conclusions

Treatment of hypertension for 1 year with candesartan-based or atenolol-based regimens has different effects on cardiac and arterial remodeling, despite an equivalent lowering of BP. BP-independent effects of ARBs on cardiac and arterial structure may contribute to the beneficial effects of these agents on cardiovascular disease.

Acknowledgment

E. Beresford assisted with the statistical analyses.

Source of Funding

This study was supported by a grant from AstraZeneca.

Disclosures

P.S. and S.T. received a research grant and honoraria from AstraZeneca. A.H. received a research grant from AstraZeneca. The other authors report no conflicts of interest.

References

Candesartan- and Atenolol-Based Treatments Induce Different Patterns of Carotid Artery and Left Ventricular Remodeling in Hypertension
Ben Ariff, Andrew Zambanini, Sarita Vamadeva, Dean Barratt, Yun Xu, Peter Sever, Alice Stanton, Alun Hughes and Simon Thom

Stroke. 2006;37:2381-2384; originally published online August 3, 2006; doi: 10.1161/01.STR.0000236839.69658.c5
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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/37/9/2381

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/