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ORIGINAL ARTICLE

Differential Sex-Specific Effects of Angiotensin-Converting Enzyme Inhibition and Angiotensin Receptor Blocker Therapy on Arterial Function in Hypertension: CALIBREX Trial

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Background: Increased arterial stiffness is associated with adverse cardiovascular outcomes. We studied the sex-specific impact of angiotensin antagonists on vascular function in hypertension with the hypothesis that their effects on arterial stiffness may be variable in men and women.

Methods: In 141 hypertensive participants with mild cognitive impairment (age 65.9±7.7, 57% female), candesartan (up to 32 mg, n=77) or lisinopril (up to 40 mg, n=64) were administered to achieve blood pressure <140/90 mm Hg. Pulse wave velocity, central pulse pressure, and central augmentation index were measured using applanation tonometry (SphygmoCor, Australia). Multivariate linear regression and mixed model analyses were performed using intention-to-treat and per protocol analyses for those completing the study.

Results: Blood pressure reduction was similar among candesartan and lisinopril groups. Compared with candesartan, lisinopril therapy resulted in lower pulse wave velocity (0.5±0.8 versus −0.7±0.4 m/s, respectively; *P*=0.003) and central pulse pressure (−1±3 versus −7±4 mm Hg; *P*=0.03) after 1 year. There was a significant interaction by sex whereby the improvements in pulse wave velocity and central pulse pressure with lisinopril compared with candesartan were only observed in women. In contrast, there was greater improvement in augmentation index with candesartan compared with lisinopril (−4±7% versus −1.5±8%; *P*=0.05), with no sex differences.

Conclusions: Despite equipotent antihypertensive effects, lisinopril was more effective than candesartan at lowering arterial stiffness in women. In contrast, candesartan was more effective than lisinopril in improving pulse wave reflections in both sexes. These findings demonstrate differential sex-specific effects of renin-angiotensin system antagonists on arterial function in hypertension that may contribute to long-term cardiovascular and neurocognitive outcomes in this population.

Key Words: blood pressure ■ population ■ pulse wave analysis ■ renin-angiotensin system ■ sex

Nonstandard Abbreviations and Acronyms	
ACE	angiotensin-converting enzyme

AIx	augmentation index
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ANBP-2	Second Australian National Blood Pressure
ARBs	angiotensin receptor blockers
BMI	body mass index
BP	blood pressure
CALIBREX	Candesartan Versus Lisinopril Effects on the Brain and Endothelial Function in Executive Function
CPP	central aortic pulse pressure
CVD	cardiovascular disease
DBP	diastolic blood pressure
ITT	intention to treat
PP	per protocol
PVA	pulse volume amplitude
PWV	pulse wave velocity
RHI	reactive hyperemia index
SBP	systolic blood pressure
VALUE	Valsartan Antihypertensive Long-Term Use Evaluation

Novelty and Relevance

What Is New?

- This randomized double-blinded control trial demonstrated that lisinopril and candesartan have differential effects on vascular function despite equipotent systolic and diastolic antihypertensive effects. Findings showed lisinopril therapy was associated with improved arterial stiffness in women (pulse wave velocity, central pulse pressure, and peripheral pulse pressure) after 1 year, whereas candesartan therapy was associated with improved pulsewave reflection. Furthermore, sex differences were observed such that these differences in vascular stiffness measures between the 2 agents were primarily found in women but not in men.

What Is Relevant?

- Our present findings highlight potential sex differences among common antihypertensive drug classes that may impact arterial stiffness and wave reflection changes found in hypertensive, older patients.

Clinical/Pathophysiological Implications?

In an older, hypertensive population, lisinopril appears to have more favorable effects on pulse wave velocity measures whereas candesartan has more favorable effects on the pulse wave reflection. In addition, the sex based differences noted in lisinopril but not with candesartan may suggest sex differences in the role of renin angiotensin system modulation on arterial function.

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide.[1] It is well known that aggressive treatment of elevated blood pressure (BP) is associated with reduced target organ damage, cardiovascular morbidity, and mortality.[2,3] However, BP varies in different arterial systems, and invasive and noninvasive studies have shown that changes in brachial arterial BP do not faithfully reflect changes in central aortic BP and vascular stiffness.[4] Furthermore, measures of central BP and arterial stiffness predict risk of future cardiovascular events, independent of brachial BP and their improvement has been associated with improved outcomes.[5–10]

Noninvasive and reproducible techniques allow estimation of central aortic pressure and arterial stiffness.[8,11] Aortic pulse wave velocity (PWV), an estimate of the speed of the pressure wave traveling along the aorta, is regarded as a gold standard measure of large artery stiffness.[12] The central augmentation index (AIx) is a composite measure of the magnitude of arterial wave reflections.[13,14] The central aortic pulse pressure (CPP) represents stiffness of the ascending aorta, although it is also affected by peripheral arterial wave reflections. Peripheral microvascular function can be assessed using digital pulse amplitude tonometry that measures pulse amplitude in the fingertip at rest and following the induction of reactive hyperemia.[15] A lower pulse amplitude tonometry hyperemic response correlates with the presence of CVD risk factors and with brachial arterial endothelial dysfunction.[16–18]

ACE (Angiotensin-converting enzyme) inhibitors and ARBs (angiotensin receptor blockers) are widely prescribed for the treatment of hypertension with comparable short-term and long-term antihypertensive efficacy.[19–21] Clinical trials examining the impact of ACE inhibitor and ARBs on cardiovascular risk reduction,[22–26] have shown that both drug classes reduce systemic BP,[25,27,28] risk of stroke[25,28,29] and improve heart failure outcomes.[30–32] However, there are few trials comparing major cardiovascular outcomes with these 2 drug classes, and their findings have been inconsistent. These trials were performed largely in older and higher risk populations. Early comparative studies showed that ARBs failed to improve myocardial infarction or mortality rates in hypertension,[33–35] whereas ACE inhibitor improved both heart failure and major cardiac event rates.[36] However, recent meta-analyses suggest an equivalent cardiovascular protection with ACE inhibitor and ARBs.[37,38] Post hoc analyses of ACE inhibitor and ARB trials in hypertension revealed sex-based differences among these drug groups in preventing major cardiovascular outcomes.[39] In a subgroup analysis of the VALUE trial (Valsartan Antihypertensive Long-Term Use Evaluation), men, but not women had a lower cardiovascular event rate with the ARB, valsartan, as compared to placebo.[40] Similarly, use of ACE inhibitor in the ANBP-2 trial (Second Australian National Blood Pressure) and ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) was associated with benefit among men, but not in women, in reducing major cardiovascular events.[41,42]

We recently reported improved longitudinal neurocognitive outcomes with candesartan compared with lisinopril in the CALIBREX trial (Candesartan Versus Lisinopril Effects on the Brain and Endothelial Function in Executive Function) conducted in participants with hypertension and mild cognitive impairment.[43] In a post hoc analysis, we investigated differential effects of candesartan and lisinopril on changes in arterial stiffness, wave reflections, and microvascular function over a 1-year period in the CALIBREX trial. We hypothesized that there will be drug and sex-dependent differences between candesartan and lisinopril in the changes in arterial stiffness, wave reflections, and microvascular function, independent of changes in brachial BP.

Methods

Population

The data that support the findings of this study are available from the corresponding author upon reasonable request. Eligible participants were 55 years or older with mild cognitive impairment and a history of hypertension defined as systolic BP (SBP) ≥140 mm Hg or diastolic BP (DBP) ≥90 mm Hg or receiving antihypertensive medications. Key exclusion criteria were (1) intolerance to any ACE inhibitor or ARB, (2) SBP >200 or DBP >110 mm Hg, (3) elevated baseline serum creatinine

>1.99 mg/dL or serum potassium >5.5 mEq/dL. Measurements included the evaluation of cardiovascular risk factors, that is, BP (2 seated readings using American Heart Association guidelines) and heart rate, body mass index (BMI), smoking history, medication profiles, and cognitive function. Patient medical history of diabetes, hyperlipidemia, and heart disease were self-reported. The Emory University Institutional Review Board approved the protocols, and informed consents were obtained from all participants.

Trial Design

The CALIBREX trial was a single-center double-blind randomized controlled trial conducted in the Metro Atlanta area. Details of study design were described in the prior publication.[43,44] Briefly, study participants underwent screening, baseline, 3-, 6-, and 12-month evaluations, with vascular function measurements occurring at baseline and after 1 year (Table 2).[43,44] Additional visits included biweekly titration visits postrandomization to escalate hypertension treatment until goal or maximum drug treatment were achieved.

Eligible participants were provided a calibrated BP machine and were trained on using it during the screening visit. Systolic, diastolic, and pulse pressures, the latter, an index of arterial stiffness were measured. All those receiving prestudy antihypertensive medications were guided through a period of gradual taper and washout as per a standard protocol (Table S2). Participants were subsequently randomized in a 1:1 block randomization using a computerized random number generator and were stratified by race (White versus non-White) and number of antihypertensive medications before study enrollment (≤2 versus >2) to ensure equal distribution between treatment groups and to allow for future preplanned subgroup analyses.

All participants commenced the initial daily dosage of candesartan 8 mg or matched capsule of lisinopril 10 mg with subsequent dose titration as follows: candesartan 8 mg→16 mg→32 mg or matched lisinopril 10 mg→20 mg→40 mg. If BP was still above 140/90 mm Hg at the highest dose of the blinded medication, additional open-label antihypertensive therapy was added using this protocol: hydrochlorothiazide 12.5 mg→25 mg, amlodipine 2.5 mg→5 mg→10 mg, and metoprolol XL 12.5 mg→25 mg→50 mg, until BP control was achieved, or all classes were used (Table S4). Participants received all their antihypertensive therapy from the study site for 1 year from the Emory Investigational Drug Services. Throughout the study, participants did not receive any concomitant BP management from other sources, and all nonstudy medications were reviewed at each visit. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's research committee.

Vascular Function Testing

Indices of arterial stiffness and wave reflections between the femoral and carotid arteries were estimated in the supine position after 6-hour fast using the Sphygmocor device (Atcor Medical, Australia), which records sequential high-quality pressure waveforms at peripheral pulse sites using a high-fidelity tonometer. Pulse wave analysis was performed on radial artery pressure waveforms after application of a generalized transfer function to derive the central aortic pressure waveform, from which estimates of CPP are generated. The AIx is defined as follows: (central P2−P1 or augmented pressure/central pulse pressure)×100 (Figure S1A). The SphygmoCor software incorporates an algorithm that normalizes AIx to a heart rate of 75 bpm.[45–47]

PWV measured between carotid and femoral arteries is a gold standard index of arterial stiffness.[48] Pressure waveforms at the carotid and femoral arterial sites were acquired using tonometry and electrocardiographic gating (Figure S1B). Velocity (distance/time in meters/s) was

calculated using the foot-to-foot method, measuring the interval between the R wave on the ECG and the foot of the recorded pressure waveform at each site, whereas distance between the sites was measured manually by the operator. Adequate tonometric analysis was defined as PWA derivation >80% of the operator index and PWV with <10% SD. Studies not meeting these criteria were excluded from the final analysis. Reproducibility studies in our laboratory on 9 subjects on consecutive days demonstrated a coefficient of variation of 3.8% for PWV.[49]

Pulse Amplitude Tonometry

Digital pulse amplitude tonometry was used to measure pulse volume amplitude (PVA) in the tip of the index finger, with participants resting in the supine position in a quiet, temperature-controlled environment set at 22 °C after an overnight fast (Endo-PAT; Itamar Medical) as previously described.[46] PVA was measured at rest and during reactive hyperemia, which was elicited by the release of an upper arm BP cuff inflated to suprasystolic pressure for 5 minutes. The reactive hyperemia index (RHI) was calculated as the ratio of the postocclusion to preocclusion PVA of the tested arm, divided by the postocclusion to preocclusion ratio of the control arm (the average PVA over a 1-minute interval starting 1 minute after cuff deflations divided by the average PVA measured for 1 minute before cuff inflation [baseline]; Figure S1C).[47]

Statistical Analysis

Analyses and reporting included both intention-to-treat (ITT) and per protocol (PP) analyses. Baseline characteristics were summarized by randomization group using descriptive statistics including mean, SD, and count (percentage). The χ^2 test and Student *t* test or Wilcoxon rank test were performed on categorical and continuous data, respectively. Unadjusted analyses of baseline and follow-up data using ITT and PP procedures revealed that the demographic characteristics of individuals who completed the study were statistically different from those that did not complete the study (Table S3) which precluded data imputation.

As a result, the PP procedure was selected to delineate the efficacy of drug intervention among our 2 groups. Linear mixed model regression analysis was performed to identify possible independent factor(s) associated with changes in PWV, AIx, CPP, and RHI over 1 year and least square means were derived from the model. The covariates that were significant in univariate analysis ($P<0.05$) were entered into the multivariate linear regression analyses. Risk factors were selected based on their known associations with vascular function and included age, sex, race, BMI, and SBP. Specifically, for analyses of AIx, height was entered as a covariate into each model to adjust for any inherent distance differences, primarily seen among males versus females. For completeness, analysis for the study was also performed using an ITT mixed model with repeated measures with adjustment for stratification variables (prestudy number of antihypertensive drugs and race). The treatment group was the primary factor of interest. Again, least square means were derived from these models. All tests of statistical significance were 2-tailed, and $P<0.05$ was considered significant. Finally, as CALIBREX enrolled only patients with mild cognitive impairment, preliminary models adjusting for Montreal Cognitive Assessment were performed as both a continuous variable and drug group stratified and was shown to have no significant effect on any of the tested outcome variables. Statistical analyses were performed using both SPSS, Inc, v19.0 (Chicago, IL) and SAS (Cary, NC).

Results

Of 377 individuals screened, 176 (47%) were eligible for the study, agreed to proceed with tapering of previously prescribed antihypertensive therapy, and were randomized to either candesartan or lisinopril. Of those randomized, 33 dropped out before the 6-month assessment, and an additional 2 participants dropped out after the 6-month assessment. Two participants completed the study but had their intervention discontinued after 6 months owing to hospitalization for resection of a lung mass or a persistent cough. The final sample for the ITT analysis was 176 (87 candesartan and 89 for lisinopril) and for the PP analysis was 141 (77 candesartan and 64 lisinopril) group, Figure 1.

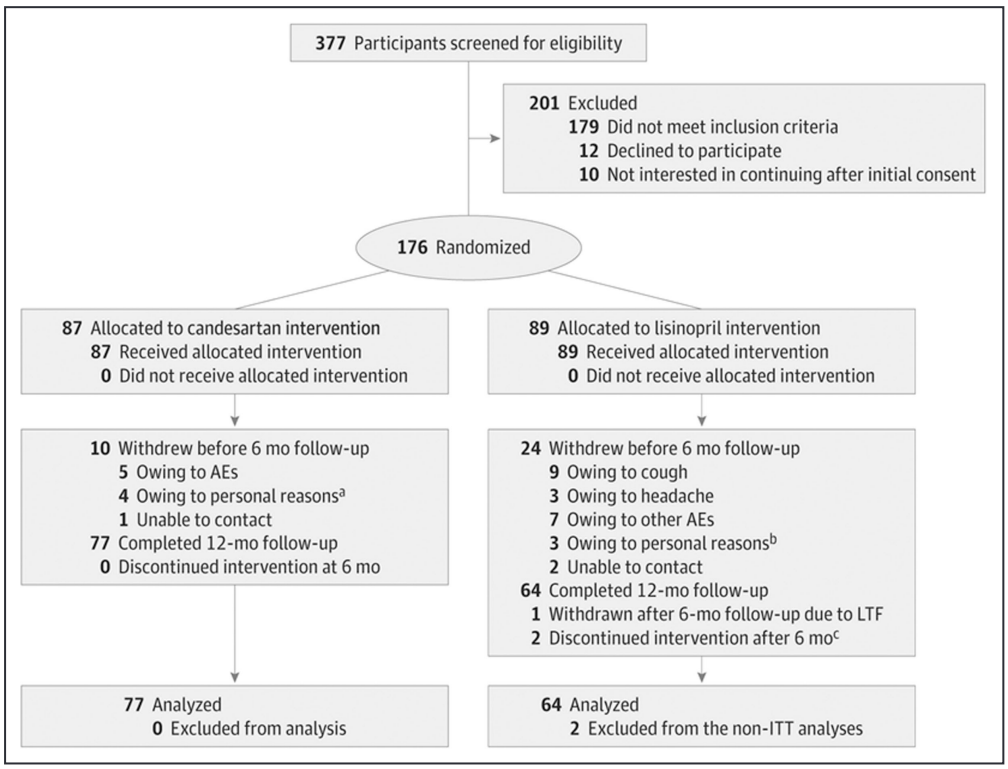

Figure 1. Study Recruitment Flow Diagram. A, Personal reasons for withdrawing from candesartan group included: 1 owing to depression, 2 owing to insufficient study compensation to continue, and 1 owing to high home blood pressure readings. B, Personal reasons for withdrawing from lisinopril group included 1 owing to relocation, 1 owing to busy life schedule, and 1 owing to insufficient study compensation. C, Two participants discontinued study intervention at 7 months owing to cough and owing to hospitalization for lung tumor resection. The latter was receiving lisinopril as part of their clinical treatment at 12 months. Both participants completed 12-month follow-up visit. AE indicates adverse event; ITT, intention-to-treat; and LTF, loss to follow-up.

Subject Characteristics

Baseline demographics, medical/medication history, and clinical characteristics of the study participants are presented in Table 1. Mean age was 65.9 years, 57% were female, and 64% were Black. All women were postmenopausal by history and only 2 of 101 women were on hormone replacement therapy. All enrolled patients had a history of hypertension and 81.3% were on at least one antihypertensive medication before enrollment (Table 1). There was no significant difference in add-on antihypertensive medications between candesartan and lisinopril treatment groups (Table S4). There were no significant differences in the demographic and clinical risk factors between the 2 study groups at baseline.

Table 1. Baseline Demographic and Clinical Characteristics of Candesartan and Lisinopril Treatment Groups (Table view)

Demographics	Candesartan, n=77	Lisinopril, n=64	*P* value
Age at enrollment	65.7±7.3	64.5±6.9	0.81

Demographics	Candesartan, n=77	Lisinopril, n=64	*P* value
BMI	32.7±6.6	31.8±7.3	0.49
Men	34 (44.1%)	29 (45.3%)	0.89
Race			0.65
White	28 (36.4%)	22 (34.4%)	
Black	48 (62.3%)	40 (62.5%)	
Other	1 (1.3%)	2 (3.1%)	
Sex/race			0.48
Men-White	19 (24.5%)	12 (18.8%)	
Men-Black	15 (19.5%)	17 (26.6%)	
Women-White	10 (13%)	12 (18.8%)	
Women-Black	33 (42.9%)	23 (35.9%)	
Baseline BP			
Systolic BP, mm Hg	134±20	130±17	0.17
Diastolic BP, mm Hg	78±12	77±11	0.52
Pulse rate, beats/min	69±11	70±12	0.61
Baseline chemistry			
Potassium, mEq	4.3±0.5	4.3±0.6	0.82
Blood urea nitrogen, mg/dL	15.4±5.2	16.6±5.4	0.16
Creatinine, mg/dL	0.96±0.21	0.97±0.26	0.71
Medical history			
Diabetes	19 (24.6%)	18 (28.1%)	0.41
Heart disease	8 (10.4%)	7 (10.9%)	0.82
High cholesterol	48 (62.3%)	33 (51.5%)	0.16
MoCA (score)	21.7±3.5	21.4±3.4	0.81
Preenrollment medications			
Antihypertensive use	65 (84.4%)	50 (78.1%)	0.42
Antidiabetic medications	17 (22.1%)	15 (23.4%)	0.88
ACE inhibitor use	19 (24.7%)	17 (26.6%)	0.69
ARB use	28 (36.3%)	23 (35.9%)	0.86

Per protocol data for individuals completing the trial. Values shown are means±SD or counts (%). ACE indicates angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BMI, body mass index; and BP, blood pressure.

Effect on Hemodynamic Measures

In the PP analysis, there was no significant difference in the baseline SBP and DBP between the 2 treatment groups, Table 2. Treatment with candesartan and lisinopril reduced both SBP (candesartan Δ −6±2 mm Hg; *P*=0.02 and lisinopril Δ −5±4 mm Hg; *P*=0.03) and DBP (candesartan Δ −7±4 mm Hg; *P*=0.01 and lisinopril Δ −7±2 mm Hg; *P*=0.01) equally after 1 year, and there was no significant difference in the magnitude of the BP decline between the 2 groups (0.46), Table 2. Although there was no significant difference in brachial pulse pressure between the groups at baseline (*P*=0.78), it was significantly lower after 1 year only with lisinopril (Δ −7±2 mm Hg; *P*=0.02) but not candesartan (Δ −1±3 mm Hg; *P*=0.81; between group difference *P*=0.03), Table 2. Baseline and 1-year heart rate values were similar in both groups, Table 2.

Table 2. Changes in Hemodynamics, Arterial Stiffness, Wave Reflections, and RHI Per Protocol Analysis (n=141): Unadjusted Data (Table view)

	Baseline		Candesartan vs lisinopril	1 Y		Candesartan vs lisinopril
A	Candesartan	Lisinopril	*P* value	Candesartan	Lisinopril	*P* value
Systolic blood pressure, mm Hg	140±21	145±20	0.46	134±22	130±23	0.44
Diastolic blood pressure, mm Hg	84±13	85±13	0.88	77±14	78±14	0.81
Pulse pressure, mm Hg	57±13	60±19	0.78	56±17	53±17*†	0.04*
Heart rate, bpm	70±11	71±12	0.91	69±12	70±15	0.88
PWV, m/s	8.5±6.9	9.4±7.1	0.34	9.0±6.1	8.7±5.5*†	0.05*
AIx corr, %	31±15	30±15	0.87	27±12	28±13	0.9
RHI, AU	2.0±1.7	2.0±1.6	0.97	2.1±1.6	2.1±1.5	0.94
Central pulse pressure, mm Hg	48±22	50±18	0.72	47±17	43±13†	0.03*
B	Candesartan		Lisinopril			Candesartan vs lisinopril
	Δ (1 y–baseline)	*P* value	Δ (1 y–baseline)		*P* value	*P* value
Systolic blood pressure, mm Hg	−6±2†	0.02*†	−5±4†		0.03*†	0.35
Diastolic blood pressure, mm Hg	−7±4†	0.01*†	−7±2†		0.01*†	0.47
Pulse pressure, mm Hg	−1±3	0.82	−7±2†		0.04*†	0.03*†
Heart rate, bpm	−1±0.4	0.87	−1±0.9		0.92	0.79
PWV, m/s	0.5±0.8	0.21	−0.7±0.4†		0.03*†	0.003*†
AIx corr, %	−4±7†	0.03*†	−1.5±8		0.24	0.05*†
RHI, AU	0.1±0.4	0.9	0.1±0.2		0.79	0.81
Central pulse pressure, mm Hg	−1±3	0.66	−7±4†		0.01*†	0.02*†

Values are mean±SD. A: Baseline and 1-y measurements of brachial blood pressure, peripheral pulse pressure, heart rate, and measures of arterial stiffness and wave reflections in patients on either lisinopril or candesartan. B: Measurements of change over 1 y (1 y–baseline) for the above indices. AIx corr indicates central augmentation index corrected for heart rate 75 beats per minute; AIx, augmentation index; PWV, pulse wave velocity; and RHI, reactive hyperemia index.
* p value < 0.05

Effect on Vascular Function

Pulse Wave Velocity There was no significant difference in PWV at baseline between the groups (*P*=0.34), Table 2. In the PP analysis, PWV decreased with lisinopril (Δ −0.7 m/s; *P*=0.03) but remained unchanged with candesartan (Δ 0.5 m/s; *P*=0.21) after 1 year, with a significant difference between groups (*P*=0.003), Table 2. After adjustment for age, sex, race, BMI, SBP, and baseline PWV, the magnitude of decrease in PWV after 1 year remained greater with lisinopril compared with candesartan, Figure 2A. In the ITT analysis, there was a similar trend towards a difference in PWV between groups (*P*=0.08; Table S6).

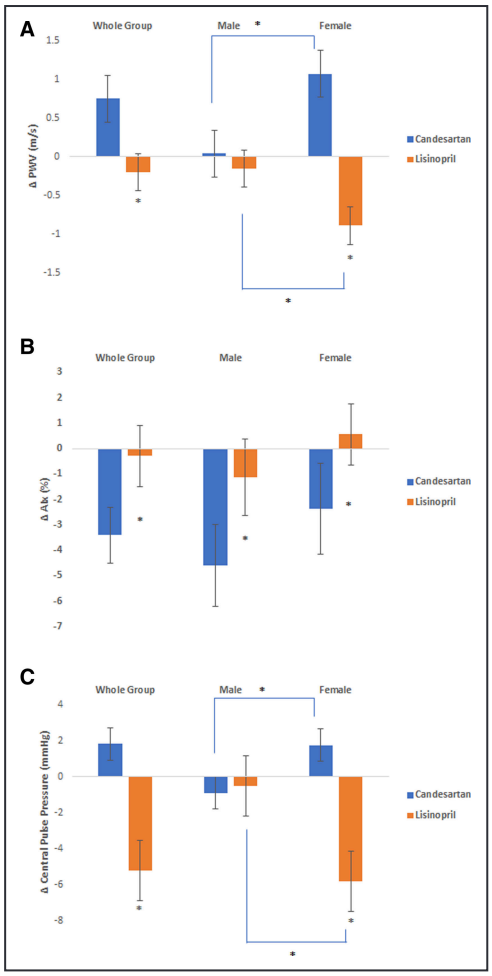

Figure 2. Analyses of arterial stiffness and wave reflections over time. Adjusted changes in pulse wave velocity (PWV) (A), augmentation index (AIx) (B) and central pulse pressure (C) in the whole population and in men and women: Per protocol analysis (n=141): Values adjusted for age, race, BMI, systolic BP and baseline PWV, error bars are standard error. * p value < 0.05

Central Pulse Pressure In the PP analysis, there was no significant difference in CPP at baseline between the 2 groups (*P*=0.72), Table 2. However, CPP decreased over 1 year with lisinopril (*P*=0.01) but remained unchanged with Candesartan (*P*=0.66), with a significant difference between groups (*P*=0.02), Table 2. After adjustment for the aforementioned covariates, this between group difference remained significant (*P*=0.04), Figure 2C. In the ITT analysis, these differences were not statistically different (Table S6).

Augmentation Index In the PP analysis, AIx was similar at baseline in the 2 groups (*P*=0.87), Table 2. Treatment with candesartan lowered AIx after 1 year (Δ −4%; *P*=0.03), but it remained unchanged with lisinopril (Δ −1.5%; *P*=0.24), with a significant difference in the change between the 2 groups (*P*=0.05), Table 2. After adjustment with the aforementioned covariates, the reduction in AIx after 1 year remained significant between the groups (*P*=0.01), Figure 2B. These differences were not present in the ITT analysis (Table S6).

Reactive Hyperemia Index For both PP and ITT analyses, RHI was similar in the 2 groups at baseline and remained unchanged after 1 year (PP, *P*=0.94 and ITT, *P*=0.88), with no significant differences in the changes after 1 year (PP, *P*=0.81 and ITT, *P*=0.72), even after adjustment (data not shown).

Determinants of the Changes in Arterial Stiffness, Wave Reflections, and RHI

Determinants of change in arterial stiffness, wave reflections, and RHI after 1 year were assessed using multivariate analyses in the entire study population. Therapy with lisinopril (*P*=0.009), male sex (*P*=0.03), lower BMI (*P*=0.001), and elevated baseline SBP (*P*=0.04) were independently associated with a greater reduction in PWV after 1 year. Therapy with lisinopril (*P*=0.02), male sex (*P*=0.04), and elevated baseline SBP (*P*=0.03) were also independently associated with a greater reduction in CPP after 1 year. Therapy with candesartan (*P*=0.03), lower baseline SBP (*P*=0.04), and lower BMI (*P*=0.01) were independent predictors of a greater reduction in AIx after 1 year.

Sex Differences

There was a significant interaction by sex in the magnitude of reduction in PWV and CPP with lisinopril compared with candesartan after 1 year (drug × sex interaction for PWV [*P*=0.006] and CPP [*P*=0.002]), Table 3. Thus, separate analyses were performed in men and women. There were no differences in the baseline (Table 4) and the change after 1 year (Table 4) in either SBP or DBP in men or women receiving either drug. Although there were no baseline sex differences, brachial pulse pressure after 1 year was significantly lower in women but not in men treated with lisinopril (Δ −9±3 versus −3±2 mm Hg, respectively), while there were no sex differences in the changes with candesartan, Table 4. There were also no sex-based differences in the heart rate at baseline (Table 4) and magnitude of change after 1 year (Table 4).

Table 3. Associations Between Participants Characteristics and Changes in Vascular Function Measures Over 1 Year: Per Protocol Multivariate Analysis (n=141) (Table view)

	Δ PWV		Δ Aix		Δ CPP		Δ RHI	
	β	*P* value	β	*P* value	β	*P* value	β	*P* value
Drug	0.65	0.004*	−0.36	0.03*	0.22	0.009*	0.03	0.83
Age	0.18	0.54	0.2	0.5	0.02	0.84	0.03	0.77
Female sex	0.43	0.01*	0.27	0.77	0.29	0.01*	0.06	0.73
Race	0.46	0.12	0.17	0.2	0.69	0.18	0.05	0.9
Drug × sex	0.71	0.006*	0.11	0.63	0.59	0.002*	0.04	0.88
Drug × race	0.35	0.39	0.19	0.2	0.41	0.11	0.06	0.71

Values shown are standardized β coefficients. Values are adjusted for all CVD risk factors displayed in the first column. AIx indicates augmentation index corrected for pulse rate 75 bpm; CPP, central pulse pressure; CVD, cardiovascular disease; drug, candesartan vs lisinopril; PWV, pulse wave velocity; and RHI, reactive hyperemia index.
* p value < 0.05

Table 4. Sex Stratified Changes in Hemodynamics, Arterial Stiffness, and Wave Reflections: Unadjusted Data (Table view)

	Male (n=63)					Female (n=78)				
	Candesartan, n=34		Lisinopril, n=29		Candesartan vs lisinopril	Candesartan, n=43		Lisinopril, n=35		Car vs li
	Δ (1 y–baseline)	*P* value	Δ (1 y–baseline)	*P* value	*P* value	Δ (1 y–baseline)	*P* value	Δ (1 y–baseline)	*P* value	*P* va
Systolic blood pressure, mm Hg	−6±2*	0.02*†	−5±4*	0.03*†	0.5	−6±3*	0.02*†	−7±4*	0.02*†	0.7
Diastolic blood pressure, mm Hg	−7±4*	0.01*†	−7±2*	0.01*†	0.47	−5±5*	0.01*†	−7±3*	0.01*†	0.4

	Male (n=63)					Female (n=78)				
	Candesartan, n=34		Lisinopril, n=29		Candesartan vs lisinopril	Candesartan, n=43		Lisinopril, n=35		Car vs li
	Δ (1 y–baseline)	*P* value	Δ (1 y–baseline)	*P* value	*P* value	Δ (1 y–baseline)	*P* value	Δ (1 y–baseline)	*P* value	*P* va
Pulse pressure, mm Hg	−1±3	0.82	−3±2	0.18	0.18	0±2	0.92	−9±3*	0.01*†	0.0
Heart rate, bpm	−1±0.4	0.87	−1±0.9	0.92	0.79	0±0.4	0.91	1±0.9	0.88	0.7
PWV, m/s	0.5±0.8	0.51	−0.2±0.5	0.68	0.41	0.7±0.6	0.19	−0.9±0.5*	0.01*†	0.0
AIx corr, %	−4.6±7	0.36	−1.4±8	0.24	0.11	−3.1±5	0.14	−0.3±2	0.48	0.0
RHI, AU	0.1±0.4	0.9	0.1±0.2	0.79	0.81	0.1±0.2	0.94	0±0.3	0.89	0.8
Central pulse pressure, mm Hg	−1±3	0.66	−0.2±2	0.47	0.67	0.4±4	0.96	−9±3*	0.01*†	0.0

Values are mean±SD. Per protocol analysis (n=141): change over 1 y measurements of brachial blood pressure, peripheral pulse pressure, heart rate and measures of arterial stiffness and wave reflections in males and females taking ARBs vs ACE inhibitor. ACE indicates angiotensin-converting enzyme; AIx, augmentation index; ARBs, angiotensin receptor blockers; PWV, pulse wave velocity; and RHI, reactive hyperemia index.
* p value < 0.05

Pulse Wave Velocity Although there were no sex differences at baseline, women had a significant decrease in PWV over 1 year (Δ −0.9±0.5 m/s; *P*=0.01) with lisinopril, while there was no significant change in men (*P*=0.68). There were no significant changes with candesartan in either sex after 1 year, Table 4. In mixed models stratified by sex and adjusted for the aforementioned covariates, in women, PWV after 1 year was significantly lower with lisinopril (Δ −0.9±0.4 m/s; *P*=0.005) and significantly higher with candesartan (Δ 1.1±0.3 m/s; *P*=0.02) treatment (*P*=0.01 between groups), Figure 2A. No differences were observed in men with either drug, Figure 2A.

Central Pulse Pressure Although there were no sex differences at baseline, women had a significant decrease in CPP over 1 year with lisinopril, whereas there was no significant change in men (Table 4). These changes with lisinopril (Δ −5.8±1.3 mm Hg; *P*=0.016) in women compared with men remained significant after adjustment (*P*=0.02 between sexes), Figure 2C. There were no significant changes with candesartan in either sex after 1 year, Table 4.

Augmentation Index After adjustment, candesartan, compared with lisinopril therapy resulted in a significantly greater reduction in AIx after 1 year in both men (*P*=0.02) and women (*P*=0.04), Figure 2B.

Reactive Hyperemia Index There were no sex-based differences in the change in RHI with either drug after 1 year, Table 4.

Discussion

In a cohort of older patients with hypertension, we demonstrate that lisinopril and candesartan have differential sex-based effects on vascular function despite equipotent systolic and diastolic antihypertensive effects. Lisinopril therapy was associated with improved arterial stiffness (PWV, CPP, and peripheral pulse pressure) after 1 year, whereas candesartan did not have the same effect. Furthermore, there was a significant interaction in the magnitude of these changes between sexes, such that these differences in vascular stiffness measures between the 2 agents were primarily observed in women and not in men. Conversely, there was a greater reduction in pulse wave reflections, measured as the reduction in AIx with candesartan compared with lisinopril, a change that was similar in women and men. Microvascular function, measured as the RHI, remained unchanged in both sexes over 1 year with both ACE inhibitor and ARB therapy.

Several randomized trials and meta-analyses have examined the effectiveness of ARBs and ACE inhibitor in reducing arterial BP and improving adverse cardiovascular outcomes. To our knowledge, this is the first study comparing the comprehensive vascular function effects of long-term treatment with ARB and ACE inhibitor on changes in large arterial stiffness, wave reflections and peripheral microvascular function in hypertension. We show that lisinopril but not candesartan effectively improved indices of arterial stiffness, measured as PWV and CPP and peripheral pulse pressure in hypertension, findings similar to some of the previous studies.[50,51] However, the female sex-specificity of the observed improvement has not been reported, probably because previous studies have been relatively small in size and enrolled younger and more heterogenous populations with and without hypertension. Previous trials with ARBs have shown either improvement[52,53] or no difference[54,55] in arterial stiffness. Despite significant reduction in BP, we also did not observe changes in PWV or CPP with candesartan. PWV and CPP both increase with age and the lack of increases in PWV and CPP over 1 year in the candesartan may also be a favorable effect. However, given we did not have a placebo arm, this conclusion is speculative at this time.

Meta-analyses have shown mixed results in the effectiveness of both ARBs and ACE inhibitor at reducing arterial wave reflections.[50] Several placebo controlled trials showed ARBs and ACE inhibitor to lower AIx over time,[56–58] while others have found no significant difference in change in AIx over time with ARBs and ACE inhibitor. Furthermore, in a direct head-to-head study of ARBs versus ACE inhibitor, Mahmud and Feely[59] found no significant difference between the 2 drugs in lowering of AIx. Compared with previous trials in patients with hypertension, our study was comparatively larger in size, enrolled more women and was conducted over a significantly longer time period. Last, our findings showed no change in RHI over 1 year with both drugs, findings similar to a previous 8-week study comparing ramipril with telmisartan.[60]

Neurocognitive changes with ACE inhibitor and ARBs have been investigated previously. Elevated AIx has been linked to the presence and severity of white matter lesions[61] and measures of mild cognitive impairment, exclusive of brachial BP differences.[62] The presence/progression of white matter lesions,[63] stroke risk,[64] and cognitive decline[65] are lower with ARB therapy, an effect that is independent of their BP lowering ability. ARBs also appear to be superior to ACE inhibitor with respect to their effects on neurovascular outcomes. For example, the ONTARGET trial reported a 9% lower risk of stroke with the ARB, telmisartan, compared with the ACE inhibitor, ramipril.[66] We previously reported superior neurocognitive outcomes with candesartan as compared to lisinopril in this CALIBREX cohort.[43] Our current findings show that candesartan, but

not lisinopril improved AIx over time, suggesting that improvements in wave reflections and not arterial stiffness measures correlate with improved neurocognitive function.

Sex-Specific Differences in the Arterial Stiffness Responses to Candesartan and Lisinopril

There are well known sex differences in the pathophysiology of hypertension.[67,68] For example, women tend to develop hypertension and CVD later in life compared with men.[69–71] Furthermore, women have lower arterial stiffness than age-matched men between puberty and menopause, after which postmenopausal women develop stiffer arteries than aged-matched men, despite similar mean arterial pressure values.[72–76] The renin-angiotensin-aldosterone pathways are also differentially regulated by gonadal hormones, where androgens upregulate these pathways and accentuate vasopressor activity, while estrogens reduce renin-angiotensin activity.[39,77] Our findings indicate a differential sex-based response with ACE inhibitor and ARB therapies on arterial stiffness. We found that postmenopausal women, the majority not on hormone replacement therapy, had significant improvement of arterial stiffness with an ACE inhibitor, but not with an ARB, while no change in arterial stiffness was observed among men with either agent. These findings may partially be explained by the observations that a loss of estrogen in the postmenopausal period increases AT-1 receptor expression and angiotensin II levels and may make ARBs less effective in postmenopausal women.[39,77,78] Additionally, physiological differences in the age-related progression, where older men and not women may have been well-established arterial stiffening, may partially account for the lack of vascular function changes among men compared with women.[72]

Study Limitations

The 1-year duration of the study may have limited evaluation of longer-term effects of these agents. While women participants were well represented, our findings about sex differences need to be confirmed in larger studies. The cohort consists of older participants with mild-moderate hypertension and MCI and will need to be confirmed in a younger population without MCI to be more widely generalizable. The sex stratified data presented within represent a post hoc analysis of a trial that was not originally designed to delineate sex differences among drug group classes. As such, future trials powered and appropriately matched for male/female sex would be beneficial. Additionally, while the study used commonly prescribed ACE inhibitor lisinopril and ARB candesartan, interpretation of these results may be limited to specific drug effects rather than whole class effects. A significantly greater number of lisinopril patients dropped out of the study (presumably from adverse events). Last, the CALIBREX study did not have a placebo comparative arm, so the comparisons are limited to the 2 agents used. It would however be unethical to treat hypertensive patients with placebo for 6 months.

Perspectives

Our findings of selective improvement in arterial stiffness with lisinopril rather than candesartan in women may explain the lack of benefit on CVD events with ARBs as compared to ACE inhibitor observed in some clinical trials.[39–42] Whether women derive greater benefit from CVD events with ACE inhibitor compared with ARBs need to be studied further. We also found a greater benefit of candesartan on pulse wave reflections in both sexes, a finding that correlates with the selective improvement in neurocognitive outcomes with ARBs.[43] Further clinical trials designed to study sex

differences among these 2 drug classes would be of use in determining any true benefit in sex-specific hypertension therapy.

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