Title: Effects of Sacubitril/valsartan versus Olmesartan on central hemodynamics in the elderly with systolic hypertension: The PARAMETER* Study

Manuscript number: HYPE201608556R2

Author(s): Bryan Williams, University College London
John Cockcroft, Cardiff Metropolitan University
Kazuomi Kario, Jichi Medical University School of Medicine
Dion Zappe, Novartis Pharmaceuticals
Patrick Brunel, Novartis Clinical Development, Basle
Qian Wang, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA
Weinong Guo, Novartis Pharmaceuticals Corporation

HYPE201608556R1

Effects of Sacubitril/valsartan versus Olmesartan on central hemodynamics in the elderly with systolic hypertension: The PARAMETER* Study

Bryan Williams[1], John R Cockcroft[2], Kazuomi Kario[3], Dion H Zappe[4], Patrick C Brunel[5], Qian Wang[4], Weinong Guo[6]

Affiliations:

[1]Department of Cardiovascular Sciences, University College London (UCL), London and National Institute for Health Research University College London Hospitals Biomedical Research Centre, London, UK;
[2]Department of Cardiology, University of Cardiff, Wales, UK;
[3]Jichi Medical School, Tochigi, Japan;
[4]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA
[5]Novartis Pharma AG, Basel, Switzerland
[6]Beijing Novartis Pharma Co. Ltd. Shanghai, China

Address for correspondence:
Bryan Williams MD,
Chair of Medicine - UCL Institute of Cardiovascular Science
Maple House, First Floor Suite A,
Tottenham Court Road
London, W1T 7DN
United Kingdom
Tel: +44 (0)20 7679 6639
bryan.williams@ucl.ac.uk

*PARAMETER, Prospective comparison of Angiotensin Receptor neprilysin inhibitor with Angiotensin receptor blocker MEasuring arterial sTiffness in the eldERly study

Short title: LCZ696 vs. Olmesartan in hypertension

Word count (including references, figures and legends): 6376

Word count of the abstract: 246

Total number of figures: 4

Total number of tables: 3

ABSTRACT

Effective treatment of systolic hypertension in elderly patients remains a major therapeutic challenge. A multicenter, double-blind, randomized controlled trial with sacubitril/valsartan (LCZ696), a first-in-class angiotensin-receptor-neprilysin inhibitor, was conducted to determine its effects versus olmesartan (angiotensin receptor blocker) on central aortic pressures, in elderly patients (aged ≥60 years) with systolic hypertension and pulse pressure (PP) >60 mmHg, indicative of arterial stiffness. Patients [N=454; mean age, 67.7 years; mean seated (ms) systolic BP (SBP), 158.6 mmHg; msPP, 69.7 mmHg] were randomized to receive once-daily sacubitril/valsartan 200 mg or olmesartan 20 mg, force-titrated to double the initial doses after 4 weeks, prior to primary assessment at 12 weeks. The study extended double-blind treatment for 12−52 weeks, during which amlodipine (2.5–5 mg), subsequently hydrochlorothiazide (6.25–25 mg) were added-on for patients not achieving BP-target (<140/90). At Week-12, sacubitril/valsartan reduced central aortic systolic pressure (CASP; primary assessment) greater than olmesartan by −3.7 mmHg (P=0.010), further corroborated by secondary assessments at Week-12 (central aortic PP, −2.4 mmHg, P<0.012; mean 24-hour ambulatory brachial SBP and CASP, −4.1 mmHg and −3.6 mmHg, respectively, both P<0.001). Differences in 24-hour ambulatory pressures were pronounced during sleep. After 52 weeks, BP parameters were similar between treatments, however, (P<0.002) more patients required add-on antihypertensive therapy with olmesartan (47%), versus sacubitril/valsartan (32%) (P<0.002). Both treatments were equally well-tolerated. The PARAMETER study, for the first time, demonstrated superiority of sacubitril/valsartan versus olmesartan in reducing clinic and ambulatory central aortic and brachial pressures in elderly patients with systolic hypertension and stiff arteries.

Keywords: Systolic hypertension, elderly, sacubitril/valsartan, olmesartan, central aortic systolic pressure

INTRODUCTION

Systolic hypertension and increased pulse pressure (PP) are indicative of arterial ageing and large artery stiffening,[1, 2] which can predict incident cardiovascular (CV) disease, stroke, chronic kidney disease (CKD), and heart failure (HF).[3-10] The correlation is even stronger with 24-hour ambulatory blood pressure (BP), particularly, with elevated nocturnal BP.[11-15] Large artery stiffening with age impairs ventricular:vascular coupling by increasing characteristic impedance, the pressure required to generate blood flow. This explains the disproportionate rise in systolic pressure and PP with ageing and the increased load on the ventricle as a major risk factor for HF development, specifically HF with preserved ejection fraction (HFpEF).[16-19]

Arterial stiffening also leads to an accelerated rise in central aortic systolic and pulse pressure relative to brachial pressures leading to reduced aortic:brachial pressure pulse amplification.[20] Reducing systolic BP with antihypertensive therapies in elderly patients is associated with prominent reductions in morbidity and mortality due to CV disease, stroke and HF.[21-24] Emerging evidence suggest reductions in central aortic systolic pressure (CASP) and/or central aortic pulse pressure (CAPP) relative to brachial BP reductions could be beneficial as they are better indicators of left ventricular loading, systemic exposure to pressure and consequently, a better predictor of CV disease risk .[25-27]

However, antihypertensive therapies can have differential effects on central aortic pressures, despite similar effects on brachial BP.[28, 29] In view of the disproportionate elevation of central aortic pressures in patients with systolic hypertension and stiffened arteries, we were interested to determine whether the novel angiotensin-receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan (LCZ696) would be more effective than conventional renin-angiotensin

system (RAS) blockade with an angiotensin receptor blocker (ARB), olmesartan, in reducing CASP and CAPP.

Sacubitril/valsartan (LCZ696) combines the actions of an ARB, valsartan, with a neprilysin (NEP) inhibitor,[30] sacubitril. NEP is a neutral endopeptidase that degrades a number of potentially beneficial vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin. Inhibition of NEP potentiates the action of these peptides and we thus hypothesized, that NEP inhibition simultaneous with angiotensin receptor blockade, had the potential to counteract some of the mechanisms contributing to arterial stiffening in patients with systolic hypertension and could provide more effective lowering of central aortic pressures than an ARB alone.

This hypothesis was supported by two key observations that sacubitril/valsartan was more effective at lowering seated and ambulatory brachial BP and PP than an ARB alone,[31, 32] and greater improvements in aortic characteristic impedance and greater reductions in aortic pressures in a previous study with an angiotensin converting enzyme (ACE)/NEP inhibitor (omapatrilat) compared with enalapril.[16] Despite the clinical promise, omapatrilat was withdrawn due to safety concerns including increased risk of angioedema associated with the ACE-inhibitor component, which was seemingly potentiated by the NEP inhibition. Nevertheless, the potential benefit of dual RAS/NEP inhibition on aortic pressures and haemodynamics was suggested. More substantial support for the hypothesis came from PARADIGM-HF study, wherein sacubitril/valsartan showed superior clinical benefits to RAS blockade alone (enalapril) in reducing CV death and HF hospitalization in patients with HF and a reduced ejection fraction (HFrEF).[33]

The Prospective comparison of Angiotensin Receptor neprilysin inhibitor with Angiotensin receptor blocker MEasuring arterial sTiffness in the eldERly (PARAMETER) study was thus designed to assess both the short- and long-term effects (12 and 52 weeks) of sacubitril/valsartan in comparison with ARB, olmesartan, on CASP and other measures of central haemodynamics and arterial stiffness in elderly patients with an elevated systolic BP (SBP) and an increased PP, indicative of increased arterial stiffness.

METHODS

Study design and patients

The PARAMETER study design have been described in detail previously.[34] In brief, the PARAMETER study was a multi-center, randomized, double-blind, active-controlled, parallel-group, 52-week study conducted in 12 countries (Argentina, Colombia, France, Germany, Greece, Italy, Japan, Korea, Russia, Spain, Taiwan, and the USA) at 48 research sites (see online supplement 1 for study site details). The study comprised a screening period, a 3-4-week placebo run-in, and an initial double-blind monotherapy treatment period (sacubitril/valsartan versus olmesartan) of 12 weeks, followed by a double-blind extension of 40 weeks, during which add-on therapy was permitted for patients not yet achieving the clinic BP treatment goal of <140/90mmHg. Patients were initially randomised to receive once-daily sacubitril/valsartan 200 mg or olmesartan 20 mg for 4 weeks, followed by a forced-titration to double the initial doses for the remainder of the study. After 12 weeks, patients with uncontrolled BP (mean sitting [ms] SBP >140 mm Hg and/or ms diastolic BP [msDBP] >90 mm Hg) received open-label amlodipine (2.5–5 mg) followed by hydrochlorothiazide (6.25–25 mg), as needed, at an interval of 4 weeks up to Week 24 (on-line supplement figure S1).

Study participants

The PARAMETER study recruited elderly patients (aged ≥60 years) with systolic hypertension (either untreated or treated with antihypertensive agents). Untreated patients (newly diagnosed or not treated with antihypertensive drugs for ≥4 weeks prior to screening) had an msSBP ≥150 mm Hg and <180 mm Hg at screening and randomization. Patients previously treated with antihypertensive agents prior to screening, had an msSBP ≥140 mm Hg and <180 mm Hg prior to 3 or 4 weeks of washout/placebo run-in and ≥150 mm Hg and <180 mm Hg at randomization. In addition, all patients had a PP>60 mm Hg at randomization. Patients with malignant or severe hypertension (msDBP ≥110 mm Hg and/or msSBP ≥ 180 mm Hg), secondary causes of hypertension, history of atrial fibrillation or atrial flutter during the 3 months prior to screening, or active atrial fibrillation or atrial flutter on electrocardiogram (ECG), history of CV disease (e.g., myocardial infarction) during 12 months prior to screening, and evidence of severe renal impairment (e.g., estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2) were excluded.

All patients provided written informed consent before starting any study-related procedure and the study protocol was approved by independent ethics committees or institutional review boards for every treatment centre and was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study was registered as EUDract number 2012-002899-14 and ClinicalTrials.gov under the code NCT01692301.

Efficacy assessments

The primary assessment of the PARAMETER study was to demonstrate the superiority of sacubitril/valsartan monotherapy versus olmesartan monotherapy in reducing mean CASP after 12 weeks of treatment. Superiority testing was also pre-specified for key secondary efficacy outcomes, including the reduction in mean CAPP and mean ambulatory (ma) CASP and maSBP after 12 weeks of treatment.

Additional secondary assessments tested the superiority of the sacubitril/valsartan-based regimen over the olmesartan-based regimen for reductions in mean CASP and CAPP from baseline to Week 52 endpoint and for reductions in mean aortic pulse wave velocity (PWV) from baseline to Week 12 and 52 endpoints. The ms central aortic diastolic BP (CADP) and mean central arterial pressure (CMAP), brachial pressures (msSBP, msDBP, msPP, msMAP), and 24-hour ma central (maCASP, maCADP, maCAPP, maCMAP) and brachial pressures (maSBP, maDBP, maPP, and maMAP) were also assessed at Weeks12 and 52 endpoints**.** Exploratory analyses include changes in N-terminal-pro brain natriuretic peptides (NT-proBNP) and urinary cyclic guanosine monophosphate (cGMP)/creatinine ratio from baseline and Week 12 and baseline and Week 52 endpoints.

Haemodynamic measurements

Seated brachial and central aortic pressure

Brachial BP, non-invasive central aortic pressures and carotid-femoral PWV (cf-PWV) were measured using the SphygmoCor XCEL System (AtCor Medical, Sydney, Australia). An appropriately sized brachial pressure cuff, integral to the device, was placed on the patient's arm, over the brachial artery and the seated brachial SBP and DBP were recorded, and patient's

brachial arterial waveform was simultaneously captured. The brachial waveform was automatically analyzed by the SphygmoCor brachial generalized transfer function (GTF) to generate a central aortic pressure waveform, and central aortic pressure indices, including CASP and CAPP.

Carotid-femoral Pulse Wave Velocity

The SphygmoCor XCEL system was also used to measure cf-PWV which is recognized as a clinical index of large artery stiffness.[34]

Ambulatory brachial and central aortic pressures

The 24-hour ma brachial and central aortic pressures were measured using a specialised oscillometric device, Mobil-O-Graph (IEM, Stolberg, Germany).[35]

Plasma NT-proBNP and urinary cGMP measurements

Biomarkers were analyzed at baseline, and Weeks 12 and 52 and expressed as change from baseline. Plasma NT-proBNP was measured using the Roche Elecsys proBNP assay (Roche Diagnostics GmbH, Germany); urinary cGMP/creatinine ratio was measured from the first morning-void urine using an enzyme-linked immunosorbent assay for cGMP (R & D Systems, USA) and creatinine was measured using an enzymatic method.

Safety assessments

Safety and drug tolerability assessments were performed throughout the study and included regular monitoring and recording of all adverse events (AEs) and concomitant medications or significant non-drug therapies. Evaluations of routine blood chemistries, blood counts with white

cell differential and urine analyses, physical examinations, ECGs, and monitoring of vital signs were also performed at regular intervals.

Sample size estimation

A sample size of 183 patients per group, completing the first phase of the study (12 weeks) was estimated to be required, based on the primary assessment that is the change from baseline in mean CASP at 12 weeks, under the alternative hypothesis, a treatment difference of 6.5 mmHg, assuming a standard deviation of 19 mmHg (based on previous data). This generated a sample size of 432 patients (216 per group, assuming a 15% drop-out rate) to provide 90% power to detect statistical significance (P<0.05, 2-sided) comparing sacubitril/valsartan treatment versus olmesartan in assessing the superiority at the Week 12 endpoint.

Statistical analysis

The primary assessment (change from baseline in CASP at Week 12 endpoint), was analysed using a two-way analysis of covariance (ANCOVA) model with treatment and region as factors and the baseline as a covariate in the full analysis set (FAS), which included all patients randomized for the study. Missing endpoints were imputed using last observation carried forward (LOCF).

Other secondary assessments, excluding 24-hour ambulatory assessments, were analyzed using an ANCOVA model similar to the model used for the primary variable, with corresponding baseline assessments as a covariate. For 24-hour ambulatory assessments, a two-way repeated-measures analysis of covariance model was used. The model included treatment, region, and post-dosing hours (1 through 24 hours) as factors, corresponding baseline assessment as

covariate, and treatment by post-dosing-hour interaction term. All analyses were conducted using FAS. Multiplicity adjustment for the secondary endpoints was not considered, thus all statistical tests were made at a two-sided significant level of 0.05.

The *post-hoc* descriptive statistics were provided for PWV and clinic SBP. The PWV data at 12 and 52 weeks for each quartile (using baseline PWV quartile as cut-off point) were analyzed using the similar ANCOVA model with treatment, region, and baseline assessment included. Only completers were included in the analyses and missing PWV data at Week 12 or 52 were not imputed.

Mean (±standard error) changes from baseline are presented for brachial and central clinic pressures (msSBP, msDBP, msPP, msMAP, and CMAP) and ambulatory brachial and central pressures (maMAP, maCADP, maCAPP, and maCMAP) at Weeks 12 and 52. Nighttime (10pm to 6am) and daytime (6 am to 10pm) means for ambulatory SBP and aortic SBP were calculated. Mean values are presented for quartile changes in PWV, with particular focus on PWV, CASP, and msSBP in the upper PWV quartile at Weeks 12 and 52. Percentage reduction in geometric mean (95% confidence interval [CI]) is presented for biomarkers. The last observation was carried forward and not imputed for missing endpoint. Safety is presented as counts and frequency. SAS 9.4 was used for the analysis (SAS Institute Inc., Cary, NC).

RESULTS

Patient demographics

A total of 454 patients were randomized to receive sacubitril/valsartan (n=229) or olmesartan (n=225). Of these, a total of 403 (88.8%) patients completed 12 weeks and 367 (80.8%) patients

completed 52 weeks, with the major reason for study discontinuation being patient/guardian decision followed by AEs (Figure 1). The demographics and baseline characteristics of the randomised patients were well balanced between the two treatment regimens (Table 1). Overall, 52% were males and the mean age was 67.7 years, 13% patients aged ≥75 years, 64.3% White Caucasian, 13.5% Asian, and 8.5% Black African, 35.5% had body mass index (BMI) ≥35 kg/m^2, 99% were previously treated for hypertension with a mean duration of hypertension of 11.9 years, and only 4 patients were hypertension-treatment-naïve, and 28.5% had type 2 diabetes. The most common antihypertensive medications used by the patients prior to the study were; angiotensin receptor blockers (27.8%), ACE inhibitors (27.5%), beta blockers (11.0%), dihydropyridine calcium channel blockers (24.2%) and thiazides diuretics (17.6%). The other medications used by more than 10% of the total study population included HMG CoA reductase inhibitors (38.8%), biguanides (i.e. metformin) (22.0%) and acetylsalicylic acid (aspirin) (23.1%). 67.0%, were never smokers, 11.9% were current smokers and 21.1% were former smokers. The mean eGFR was 80 ml/min/1.73m^2. The baseline brachial BP was 158.6/88.9 mmHg, with a PP of 69.7 mmHg, with a corresponding baseline CASP of 144.4 mmHg and CAPP of 54.4 mmHg. The baseline PWV was 10.2 m/second.

Clinic central and brachial pressures

The mean reductions in CASP after 12 weeks of treatment from baseline, the primary assessment, was −12.6 mmHg (95% CI: −14, −10.1) with sacubitril/valsartan and −8.9 mmHg (95% CI: −11.1, −6.7) with olmesartan. The least squares mean (LSM) reductions in CASP (primary endpoint) were superior with sacubitril/valsartan versus olmesartan with a between-treatment difference of −3.7 mmHg (95% CI: −6.4, −0.9 mmHg, *P*=0.01; Figure 2).

After 12 weeks of treatment the LSM reductions in CAPP (key secondary outcome) were superior with sacubitril/valsartan versus olmesartan with a between-treatment difference of −2.4 mmHg (*P*=0.01; Figure 2). Similarly, sacubitril/valsartan lowered mean msSBP, and msPP to a greater extent than olmesartan at Week 12 endpoint (Table 2). In contrast, no difference was observed between treatments with regard to the change in CADP or msDBP from baseline to Week 12.

Ambulatory central and brachial pressures

The LSM reductions in mean 24-hour ambulatory brachial and central aortic systolic pressures were significantly greater with sacubitril/valsartan versus olmesartan after 12 weeks of treatment with a between-treatment difference of −4.1 mmHg (P<0.001) for maSBP and −3.4 mmHg (P<0.001) for maCASP (Table 2). The hourly brachial and central systolic pressures over 24 hours at Week 12 are presented in Figure 3. It is notable that the between treatment differences in mean 24-hour CASP and SBP are predominantly due to more effective reductions in both pressures during the nocturnal period, presumably during sleep. Nighttime (10 pm to 6 am) reductions in maCASP (-5.2 mmHg) and maSBP (-5.9 mmHg) were significantly (*P*<0.001) greater with sacubitril/valsartan compared with olmesartan with the greatest differences in the early morning hours (2 am to 6 am) in maCASP (-6.3 mmHg) and maSBP (-6.9 mmHg). Similarly, greater LSM reductions in maDBP, maPP, maMAP, maCADP, maCAPP and maCMAP (p<0.001) were observed with sacubitril/valsartan than with olmesartan at Week 12 endpoint (Table 2). BP control rates were also greater with sacubitril/valsartan (54.0%) compared with olmesartan (34.7%) at Week 12 (*P*<0.001).

Add-on therapy from Week 12 to 52

The requirement of an add-on antihypertensive therapy was significantly lower in patients treated with sacubitril/valsartan versus olmesartan (P<0.002) from Weeks 12 to 52. In the sacubitril/valsartan group, greater proportion of patients remained on monotherapy compared with that of the olmesartan group (68% versus 53%). Add-on amlodipine (+/− HCTZ) was required in 74 (32%) patients in the sacubitril/valsartan group and in 105 (47%) patients in the olmesartan group.

Brachial and central aortic pressures at Week 52

No significant differences were observed in any BP parameters (seated, ambulatory, brachial, or central) between the treatments at Week 52, although greater proportion of patients received add-on antihypertensive therapy in the olmesartan group (Table 2 and Figure 2). As a result BP control rates were not different at the end of the study between sacubitril/valsartan (58.8%) and olmesartan (57.0%).

Plasma and urinary biomarkers

Plasma NT-proBNP was elevated at baseline (overall geometric mean was 90 pg/mL). The reduction in the geometric mean plasma NT-proBNP from baseline to Week 12 (online supplement Figure S2A) was greater in patients treated with sacubitril/valsartan (34%) compared with olmesartan (20%), the difference of which was attenuated by Week 52. An increase in the geometric mean urine cGMP/creatinine ratio from baseline to Week 12 was observed, which persisted at Week 52, in the sacubitril/valsartan treated patients, consistent with its mechanism of action. No change in urinary cGMP was observed in patients treated with olmesartan at Week 12 or Week 52 (online supplement Figure S2B).

Post hoc analysis of PWV and msSBP at Weeks 12 and 52

The LSM reductions in PWV observed with both sacubitril/valsartan and olmesartan from baseline at Weeks 12 and 52 were similar for each treatment (on-line supplement Figure S3A). The changes in PWV for each treatment stratified by quartiles of baseline PWV are shown in the on-line supplement Figure S4. A possible trend of greater reduction in PWV with sacubitril/valsartan prompted a *post hoc* analysis of the impact of both treatments on PWV in the subgroup of patients at the upper quartile of baseline PWV (mean 12.9 m/second), indicating stiffest arteries. This *post hoc* analysis (on-line supplement Figure S3B) showed a non-significant trend of greater LSM reductions in PWV in the sacubitril/valsartan group versus olmesartan group at Week 12 endpoint (between-treatment difference, −0.61 m/sec), which was increased by Week 52 (between-treatment difference, −0.99 m/sec).

A *post hoc* analysis of SBP in the subgroup of patients in the upper quartile of PWV showed 2-fold greater reductions in CASP and msSBP with sacubitril/valsartan versus olmesartan than that was observed in the overall treatment groups (Table 2), with a between-treatment difference of −6.0 and −7.7 mmHg and −-2.3 and −2.4 mmHg, at Weeks 12 and 52, respectively, versus −3.7 and −3.6 mmHg and −1.5 and −1.2 mmHg in the overall treatment groups (on-line supplement Figure S3C-D).

Clinic and ambulatory heart rate

Treatment with both sacubitril/valsartan and olmesartan showed no changes from baseline mean sitting (~71 bpm) or ambulatory heart rate (~71 bpm) both at Week 12 and 52 endpoints. The 24-hour ambulatory heart rate followed a similar circadian pattern as BP with no differential

treatment effect at daytime or nighttime and with similar reductions in heart rate during the nighttime period (~8 bpm).

Safety assessments

Treatments with both sacubitril/valsartan and olmesartan were generally well tolerated. The incidence of AEs was slightly higher in the sacubitril/valsartan-based regimen (57.6%) compared with the olmesartan-based regimen (53.8%), with nasopharyngitis being the most common AE. The overall incidence of serious AEs (SAEs) was low and similar between the sacubitril/valsartan (7%) and olmesartan-based regimen (5.8%; Table 3). AEs, SAEs, and drug-related AEs leading to the study discontinuations were similar in both treatment groups. Mild angioedema (mild tongue swelling) was reported in one patient in the sacubitril/valsartan group during Week 48, which did not require study drug interruption or hospitalization and resolved by the end of the study. Two deaths (one due to cardiorespiratory arrest and other due to respiratory failure) were reported in the olmesartan group and one death due to myocardial infarction was reported in the sacubitril/valsartan group.

DISCUSSION

The PARAMETER study, for the first time, shows the effect of sacubitril/valsartan on central aortic pressures and demonstrates the superiority of sacubitril/valsartan in lowering CASP and CAPP compared with conventional RAS blockade with the ARB olmesartan, after 12 weeks of treatment. Sacubitril/valsartan also lowered brachial SBP and PP more effectively than olmesartan (online supplement Figure S5), which is consistent with previously published studies

comparing the effect of sacubitril/valsartan with an ARB on brachial BP and PP.[31, 32] This study also utilized new technology to measure 24-hour ambulatory central aortic pressures non-invasively alongside conventional 24-hour ambulatory brachial BP.[35] Sacubitril/valsartan was superior to olmesartan at lowering 24-hour ambulatory CASP and brachial SBP, with the differences predominantly accounted by more effective lowering of nocturnal CASP and SBP with sacubitril/valsartan. To our knowledge, this is the first time a drug treatment has been shown to be especially effective at reducing nocturnal blood pressure. This is important because nocturnal pressure is most strongly associated with CV risk, and CASP has been shown to exhibit less of a nocturnal reduction relative to brachial pressure.[12, 14, 15, 36] This effect of sacubitril/valsartan on nocturnal pressure might have particular relevance in reducing the risk in people with stiffened arteries, such as elderly patients, those with diabetes and patients with CKD, all of whom tend to have a blunted nocturnal pressure dip.[37] A characteristic of these patients is sodium retention and it is conceivable that the greater reduction in nocturnal BP with sacubitril/valsartan may be due to the diuretic action of NEP inhibition. A pharmacokinetic explanation is unlikely because the patients consumed their medication in the morning and the effect on nocturnal BP was towards the end of the dosing interval and when the patients were at steady state after 12 weeks treatment.

The study particularly focused on elderly patients with stiffened arteries as indicated by their elevated brachial PP (mean at baseline ~70 mmHg) and PWV (mean at baseline 10.2 m/second) in addition to a high SBP relative to DBP and often isolated systolic hypertension. Such patients are at highest risk of CV events, stroke and HF and have disproportionate increases in their central aortic pressures relative to brachial pressure. Sacubitril/valsartan had a greater BP

lowering effect on central and brachial SBP and PP, relative to DBP or CADP (Table 2). This is important for a number of reasons: (i) it mitigates against frequently quoted concerns about excessive lowering of DBP when treating isolated systolic hypertension, that could lead to compromised myocardial perfusion,[2, 37]; (ii) this may also be important in treating patients with HFpEF who frequently have existing or antecedent systolic hypertension, stiff arteries, and a wide PP.[17, 19] The impact of sacubitril/valsartan on clinical outcomes in patients with HFpEF is currently being investigated in the PARAGON-HF study (https://clinicaltrials.gov/ct2/show/NCT01920711); (iii) this finding also suggests an arterial 'de-stiffening' effect associated with BP-lowering in patients with systolic hypertension and an improvement in ventricular:vascular coupling and a reduction in characteristic impedance, such that aortic flow is maintained at a lower aortic PP and with less left ventricular work. Prior studies with dual RAS/NEP inhibition with omapatrilat support this interpretation.[16] A greater improvement in ventricular:vascular coupling with sacubitril/valsartan is supported by the greater reduction in NT-pro BNP (i.e. BNP release in response to cardiac wall stress) than olmesartan at Week 12 of the study (figure 4). Similar superior reductions in NT-pro BNP with sacubitril/valsartan versus RAS blockade alone (enalapril) have also been observed in the studies in patients with HF.[38, 39]

We also demonstrated a significant increase in urinary cGMP levels with sacubitril/valsartan treatment (+45% at Week 12), which persisted throughout the study (+36% at Week 52), the change which was not observed with olmesartan. This increase in cGMP is consistent with the mechanism of action of the NEP inhibition component of sacubitril/valsartan, which decreases

the breakdown of potentially beneficial vasoactive peptides such as atrial natriuretic peptide, BNP and bradykinin, which activate guanlyate cyclase to produce cGMP.[30]

We measured cf-PWV at baseline and Week 12 and 52, to establish whether there were differences in aortic stiffness with treatment and between treatments. Cf-PWV is strongly influenced by BP,[40] and as expected cf-PWV was reduced by both treatments after 12 weeks of treatment and further reduced by Week 52, when the BP difference between treatment arms was more closely matched. We found considerably more within-patient variance than expected in cf-PWV measurements with the technology used in this study (Sphygmocor X-CELl, AtCor, Australia), thereby reducing statistical power to compare the effects of sacubitril/valsartan versus olmesartan on aortic stiffness.

Beyond the initial 12 weeks of the study, add-on antihypertensive therapy was allowed until the study end at 52 weeks for those patients not achieving BP target (clinic BP <140/90 mmHg). By Week 52, the differences in brachial and central aortic pressures between treatments had diminished, in large part due to the significantly greater use of add-on therapy to achieve the BP goal in the patients treated with olmesartan. This data reinforces the superior BP-lowering efficacy of sacubitril/valsartan compared with RAS blockade alone.

Both treatments were similarly well tolerated throughout the 52 weeks of the study with a low rate of AEs (~7%) and SAEs (~2.6%), consistent with previously reported data for sacubitril/valsartan in patients with HFrEF.[33] Moreover, unlike prior concerns of angioedema with dual RAS/NEP inhibition with omapatrilat (which included ACE-inhibition), excess cough

was not reported, and mild angioedema (mild tongue swelling) was reported in only one patient (African American patient from the U.S.) in the sacubitril/valsartan group during Week 48 of the study. No complications or hospitalisation were reported with sacubitril/valsartan in our study. With regard to changes in plasma potassium levels, at week 12 the change in potassium with LCZ696 or olmesartan was +0.1 mmol/L and +0.7 mmol/L respectively. At week 52 the change in potassium with LCZ696 or olmesartan was +0.3 mmol/L and +0.8 mmol/L respectively. More patients experienced serum potassium >5.5 mmol/L during with LCZ696 group (8.0%) compared with the olmesartan group (5.9%), with more severe cases (serum potassium ≥6.0 mmol/L) in the olmesartan group (2.7%) versus the LCZ696 group (0.9%).

The PARAMETER study has a number of strengths; (i) the first 12 weeks of the study allowed direct comparison of sacubitril/valsartan with the ARB olmesartan, uncontaminated by add-on therapies and showed superiority of sacubitril/valsartan with regard to central aortic and brachial BP reduction; (ii) BP was comprehensively evaluated with 24-hour ambulatory BP monitoring and 24-hour ambulatory CASP, which confirmed superior BP lowering of sacubitril/valsartan on both parameters and demonstrated novel BP lowering effects of sacubitril/valsartan on nocturnal BP; (iii) olmesartan is an ARB with a long duration of action which has previously been shown to reduce arterial stiffness and central aortic pressure [41, 42] and was administered at the maximal recommended dose to ensure an optimal comparator[43]; (iv) the extension of the study to 52 weeks allowed the evaluation of effects of add-on therapies recommended by all international hypertension guidelines including a calcium channel blocker and/or a thiazide-type diuretic.[44] This phase of the study confirmed that less add-on therapy was required to improve BP control with sacubitril/valsartan versus olmesartan; and (v) finally, the study included different ethnic

groups and people with diabetes and no heterogeneity of effect was noted on the primary outcome across groups.

The study also has some limitations; (i) the study was not designed to, and was too short to evaluate the effects of sacubitril/valsartan on clinical outcomes. Nevertheless, the magnitude of BP reduction achieved, has previously been shown to have a major beneficial impact of CV outcomes, stroke and HF in patients with systolic hypertension.[21-23] In this regard, based on a recent comprehensive analysis of BP lowering on clinical outcomes,[45] the magnitude of systolic BP fall with sacubitril/valsartan in the first 12 weeks, if maintained over the long-term, could result in a reduced risk of major CV disease events and coronary heart disease by ~25%, HF by ~30%, and all-cause mortality by almost 20%; (ii) although we set out to examine the effects of both treatments on ameliorating aortic stiffness (cf-PWV), the methodology we used was not as robust as expected, and further studies, ideally using magnetic resonance imaging (MRI) are required to determine if sacubitril/valsartan has any specific BP-independent beneficial effects on ventricular:vascular coupling, aortic characteristic impedance, and distensibility. However, the greater reduction in NT-proBNP and pulse pressure observed with sacubitril/valsartan versus olmesartan indicates a 'de-stiffening' effect of sacubitril/valsartan and a reduction in cardiac wall stress.

PERSPECTIVE

The PARAMETER is the first randomized controlled trial demonstrating the ability of dual ARB/NEP inhibition with sacubitril/valsartan to reduce central aortic pressures (especially CASP and CAPP) more effectively than an ARB, in high-risk elderly patients with systolic hypertension and an increased PP, indicative of arterial stiffness. These results suggest that

sacubitril/valsartan provides beneficial effects on central aortic hemodynamics and function that could provide a therapeutic advantage beyond those observed with RAS blockade alone.

Acknowledgments:

The authors acknowledge support of Dr Sreedevi Boggarapu (Novartis Healthcare Pvt. Ltd, Hyderabad, India) for editorial support. They also thank all the clinical investigators and study coordinators at the participating centers and all the patients who participated in the study. Bryan Williams is a National Institute for Health Research (NIHR) Senior Investigator and his research is supported by the NIHR University College London Hospitals Biomedical Research Centre.

Source of funding:

This study was an investigator-designed and investigator-led study, funded by Novartis Pharmaceuticals Corporation.

Conflicts of Interest / Disclosures:

BW has received honoraria for conference lectures from Novartis and Daiichi Sankyo, JRC and KK have received fees for consultancy from Novartis, DHC, PCB, QW and WG are employees of Novartis Pharmaceuticals, Inc.

References

1. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, White IR, Caulfield MJ, Deanfield JE, Smeeth L, Williams B, Hingorani A, Hemingway H. Blood pressure and incidence of twelve cardiovascular diseases: Lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet*. 2014;383:1899-1911

2. Williams B, Lindholm LH, Sever P. Systolic pressure is all that matters. *Lancet*. 2008;371:2219-2221

3. Franklin SS. Pulse pressure as a risk factor. *Clinical and Experimental Hypertension (New York, N.Y. : 1993)*. 2004;26:645-652

4. Bangalore S, Messerli FH, Franklin SS, Mancia G, Champion A, Pepine CJ. Pulse pressure and risk of cardiovascular outcomes in patients with hypertension and coronary artery disease: An international verapamil sr-trandolapril study (invest) analysis. *European Heart Journal*. 2009;30:1395-1401

5. Franklin SS, Lopez VA, Wong ND, Mitchell GF, Larson MG, Vasan RS, Levy D. Single versus combined blood pressure components and risk for cardiovascular disease: The framingham heart study. *Circulation*. 2009;119:243-250

6. Haider AW, Larson MG, Franklin SS, Levy D. Systolic blood pressure, diastolic blood pressure, and pulse pressure as predictors of risk for congestive heart failure in the framingham heart study. *Annals of Internal Medicine*. 2003;138:10-16

7. Domanski M, Mitchell G, Pfeffer M, Neaton JD, Norman J, Svendsen K, Grimm R, Cohen J, Stamler J, Group MR. Pulse pressure and cardiovascular disease-related mortality: Follow-up study of the multiple risk factor intervention trial (mrfit). *JAMA*. 2002;287:2677-2683

8. Chirinos JA, Khan A, Bansal N, Dries DL, Feldman HI, Ford V, Anderson AH, Kallem R, Lash JP, Ojo A, Schreiber M, Sheridan A, Strelsin J, Teal V, Roy J, Pan Q, Go AS, Townsend RR. Arterial stiffness, central pressures, and incident hospitalized heart failure in the chronic renal insufficiency cohort study. *Circulation Heart Failure*. 2014;7:709-716

9. Kannel WB, Wolf PA, McGee DL, Dawber TR, McNamara P, Castelli WP. Systolic blood pressure, arterial rigidity, and risk of stroke. The Framingham study. *JAMA*. 1981;245:1225-1229

10. Townsend RR. Arterial stiffness and chronic kidney disease: Lessons from the chronic renal insufficiency cohort study. *Current Opinion in Nephrology and Hypertension*. 2015;24:47-53

11. Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic hypertension in europe trial investigators. *JAMA*. 1999;282:539-546

12. Hansen TW, Li Y, Boggia J, Thijs L, Richart T, Staessen JA. Predictive role of the nighttime blood pressure. *Hypertension*. 2011;57:3-10

13. Fan HQ, Li Y, Thijs L, Hansen TW, Boggia J, Kikuya M, Bjorklund-Bodegard K, Richart T, Ohkubo T, Jeppesen J, Torp-Pedersen C, Dolan E, Kuznetsova T, Stolarz-Skrzypek K, Tikhonoff V, Malyutina S, Casiglia E, Nikitin Y, Lind L, Sandoya E, Kawecka-Jaszcz K, Imai Y, Ibsen H, O'Brien E, Wang J, Staessen JA. Prognostic value of isolated nocturnal hypertension on ambulatory measurement in 8711 individuals from 10 populations. *Journal of Hypertension*. 2010;28:2036-2045

14. Fagard RH, Celis H, Thijs L, Staessen JA, Clement DL, De Buyzere ML, De Bacquer DA. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. *Hypertension*. 2008;51:55-61

15. Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, Den Hond E, McCormack P, Staessen JA, O'Brien E. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: The dublin outcome study. *Hypertension*. 2005;46:156-161

16. Mitchell GF, Izzo JL, Jr., Lacourciere Y, Ouellet JP, Neutel J, Qian C, Kerwin LJ, Block AJ, Pfeffer MA. Omapatrilat reduces pulse pressure and proximal aortic stiffness in patients with systolic hypertension: Results of the conduit hemodynamics of omapatrilat international research study. *Circulation*. 2002;105:2955-2961

17. Desai AS, Mitchell GF, Fang JC, Creager MA. Central aortic stiffness is increased in patients with heart failure and preserved ejection fraction. *Journal of Cardiac Failure*. 2009;15:658-664

18. Lam CS, Gona P, Larson MG, Aragam J, Lee DS, Mitchell GF, Levy D, Cheng S, Benjamin EJ, Vasan RS. Aortic root remodeling and risk of heart failure in the framingham heart study. *JACC. Heart Failure*. 2013;1:79-83

19. Pepine CJ, Nichols WW, Conti CR. Aortic input impedance in heart failure. *Circulation*. 1978;58:460-465

20. O'Rourke MF, Avolio A, Safar M, Nichols W. Changes in the central arterial pressure pulse with aging. *Journal of the American College of Cardiology*. 2010;55:2183; author reply 2184

21. Dahlof B, Lindholm LH, Hansson L, Schersten B, Ekbom T, Wester PO. Morbidity and mortality in the swedish trial in old patients with hypertension (stop-hypertension). *Lancet*. 1991;338:1281-1285

22. Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, Bulpitt CJ, de Leeuw PW, Dollery CT, Fletcher AE, Forette F, Leonetti G, Nachev C, O'Brien ET, Rosenfeld J, Rodicio JL, Tuomilehto J, Zanchetti A. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (SYST-EUR) trial investigators. *Lancet*. 1997;350:757-764

23. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ. Treatment of hypertension in patients 80 years of age or older. *The New England Journal of Medicine*. 2008;358:1887-1898

24. Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC, Jr., Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT. A randomized trial of intensive versus standard blood-pressure control. *The New England Journal of Medicine*. 2015;373:2103-2116

25. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: A systematic review and meta-analysis. *European Heart Journal*. 2010;31:1865-1871

26. McEniery CM, Cockcroft JR, Roman MJ, Franklin SS, Wilkinson IB. Central blood pressure: Current evidence and clinical importance. *European Heart Journal*. 2014;35:1719-1725

27. Williams B, Lacy PS. Central aortic pressure and clinical outcomes. *Journal of Hypertension*. 2009;27:1123-1125

28. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, Hughes AD, Thurston H, O'Rourke M. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: Principal results of the conduit artery function evaluation (cafe) study. *Circulation*. 2006;113:1213-1225

29. Boutouyrie P, Achouba A, Trunet P, Laurent S. Amlodipine-valsartan combination decreases central systolic blood pressure more effectively than the amlodipine-atenolol combination: The explor study. *Hypertension*. 2010;55:1314-1322

30. Gu J, Noe A, Chandra P, Al-Fayoumi S, Ligueros-Saylan M, Sarangapani R, Maahs S, Ksander G, Rigel DF, Jeng AY, Lin TH, Zheng W, Dole WP. Pharmacokinetics and pharmacodynamics of lcz696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (arni). *Journal of Clinical Pharmacology*. 2010;50:401-414

31. Kario K, Sun N, Chiang FT, Supasyndh O, Baek SH, Inubushi-Molessa A, Zhang Y, Gotou H, Lefkowitz M, Zhang J. Efficacy and safety of lcz696, a first-in-class angiotensin receptor neprilysin inhibitor, in asian patients with hypertension: A randomized, double-blind, placebo-controlled study. *Hypertension*. 2014;63:698-705

32. Ruilope LM, Dukat A, Bohm M, Lacourciere Y, Gong J, Lefkowitz MP. Blood-pressure reduction with lcz696, a novel dual-acting inhibitor of the angiotensin ii receptor and neprilysin: A randomised, double-blind, placebo-controlled, active comparator study. *Lancet*. 2010;375:1255-1266

33. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, Investigators P-H, Committees. Angiotensin-neprilysin

inhibition versus enalapril in heart failure. *The New England Journal of Medicine*. 2014;371:993-1004

34. Williams B, Cockcroft JR, Kario K, Zappe DH, Cardenas P, Hester A, Brunel P, Zhang J. Rationale and study design of the prospective comparison of angiotensin receptor neprilysin inhibitor with angiotensin receptor blocker measuring arterial stiffness in the elderly (parameter) study. *BMJ open*. 2014;4:e004254

35. Butlin M, Qasem A, Avolio AP. Estimation of central aortic pressure waveform features derived from the brachial cuff volume displacement waveform. *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual Conference*. 2012;2012:2591-2594

36. Williams B, Lacy PS, Baschiera F, Brunel P, Dusing R. Novel description of the 24-hour circadian rhythms of brachial versus central aortic blood pressure and the impact of blood pressure treatment in a randomized controlled clinical trial: The ambulatory central aortic pressure (amcap) study. *Hypertension*. 2013;61:1168-1176

37. Williams B. Hypertension and the "j-curve". *Journal of the American College of Cardiology*. 2009;54:1835-1836

38. Packer M, McMurray JJ, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile M, Andersen K, Arango JL, Arnold JM, Belohlavek J, Bohm M, Boytsov S, Burgess LJ, Cabrera W, Calvo C, Chen CH, Dukat A, Duarte YC, Erglis A, Fu M, Gomez E, Gonzalez-Medina A, Hagege AA, Huang J, Katova T, Kiatchoosakun S, Kim KS, Kozan O, Llamas EB, Martinez F, Merkely B, Mendoza I, Mosterd A, Negrusz-Kawecka M, Peuhkurinen K, Ramires FJ, Refsgaard J, Rosenthal A, Senni M, Sibulo AS, Jr., Silva-Cardoso J, Squire IB, Starling RC, Teerlink JR, Vanhaecke J, Vinereanu D, Wong RC. Angiotensin receptor

neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation*. 2015;131:54-61

39. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJ, Prospective comparison of AwARBoMOhfwpefI. The angiotensin receptor neprilysin inhibitor lcz696 in heart failure with preserved ejection fraction: A phase 2 double-blind randomised controlled trial. *Lancet*. 2012;380:1387-1395

40. The Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'Establishing normal and reference values'. *European Heart Journal*. 2010;31:2338-2350

41. Laurent S, Boutouyrie P. Dose-dependent arterial destiffening and inward remodeling after olmesartan in hypertensives with metabolic syndrome. *Hypertension*. 2014;64:709-716

42. Ruilope LM. Fixed-combination olmesartan/amlodipine was superior to perindopril + amlodipine in reducing central systolic blood pressure in hypertensive patients with diabetes. *Journal of Clinical Hypertension (Greenwich, Conn.)*. 2015, 18: 528-535.

43. Giles TD, Oparil S, Silfani TN, Wang A, Walker JF. Comparison of increasing doses of olmesartan medoxomil, losartan potassium, and valsartan in patients with essential hypertension. *J Clin Hypertens (Greenwich)*. 2007;9:187-95.

44. Kjeldsen S, Feldman RD, Lisheng L, Mourad JJ, Chiang CE, Zhang W, Wu Z, Li W, Williams B. Updated national and international hypertension guidelines: a review of current recommendations. Drugs. 2014;74:2033-5.

45 . Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387:957-67.

Novelty and Significance:

What is New: This is the first randomized controlled trial comparing an Angiotensin Rceceptor Blocker /Neutral Endopeptidase inhibitor (ARB/NEPi) (Sacubitril/valsartan) versus a conventional an ARB (Olmesartan) on central aortic pressures and hemodynamics in elderly patients with stiff arteries and systolic hypertension.

What is relevant: Controlling systolic hypertension is an unmet need in elderly patients and central aortic systolic and pulse pressures are disproportionately elevated in these patients.

Summary: The ARB/NEPi was significantly more effective at lowering brachial and central aortic systolic and pulse pressures than conventional renin angiotensin system blockade with an ARB.

Legends

Figure 1. Patient disposition

*All randomized patients

AE, adverse event

Figure 2. Reduction in CASP and pulse pressure from baseline at week 12 and 52

‡CASP was the primary efficacy

CASP, central aortic systolic pressure; CAPP, central aortic pulse pressure

Figure 3. Peripheral and central 24-hourly mean ambulatory SBP: at Week 12 (A) and Week 52 (B) endpoints

SBP, systolic blood pressure

Table 1. Demographics and baseline characteristics of the study participants

Characteristic	**LCZ696 regimen** (N=229)	**Olmesartan regimen** (N=225)	P value
Age, years	68.2 (5.73)	67.2 (5.97)	0.068
Age group, n (%)			
>60 and <65 years	68 (29.7)	91 (40.4)	0.056
≥65 and <75 years	129 (56.3)	107 (47.6)	
≥75 years	32 (14.0)	27 (12.0)	
Men, n (%)	119 (52.0)	118 (52.4)	0.919
Race, n (%)			
Caucasian	148 (64.6)	144 (64.0)	1.000
Black	20 (8.7)	19 (8.4)	
Asian	31 (13.5)	31 (13.8)	
Body mass index, kg/m^2	28.6 (4.47)	29.1 (4.9[†])	0.128
Diabetes, n (%)	65 (28.4)	65 (28.9)	0.905
Duration of hypertension, years[*]	11.4 (8.93)	12.3 (9.98)	0.321

Proportion of patients with prior history of hypertension (%)	99.6	98.7	0.307
BP and PP, mmHg			
CASP‡	144.0 (12.65)	144.9 (12.63)	0.444
CADP‡	89.0 (9.58)	91.1 (10.24)	0.025
CAPP‡	55.0 (11.86)	53.8 (12.95)	0.311
CMAP‡	109.9 (10.25)	111.5 (9.89)	0.095
msSBP‡	158.4 (13.41)	158.8 (13.48)	0.788
msDBP‡	87.8 (9.72)	89.9 (10.38)	0.027
msPP‡	70.6 (13.00)	68.8 (14.17)	0.171
msMAP‡	111.4 (9.24)	112.9 (9.37)	0.085
maCASP§	133.0 (13.63)	132.9 (12.11)	0.935
maCADP§	87.6 (10.14)	88.2 (9.44)	0.596
maCAPP§	45.3 (9.79)	44.6 (9.80)	0.523
maCMAP§	102.8 (10.45)	103.1 (9.33)	0.753
maSBP‖	145.3 (14.01)	144.6 (12.83)	0.656
maDBP‖	85.7 (10.11)	86.6 (9.42)	0.431

maPP[‖]	59.6 (11.19)	58.0 (11.29)	0.224
maMAP[‖]	113.0 (10.69)	113.2 (9.59)	0.895
PWV[¶]	10.3 (2.11)	10.2 (1.91)	0.507
msHR	70.4 (11.7)	71.2 (11.1)	0.413
maHR	71.1 (10.2)	71.9 (9.4)	0.451
eGFR (<60 ml/min//1.73 m^2)	78.9 (19.87)	81.5 (31.91)	0.306

Data are mean ± SD unless until specified; [*]n=224 for LCZ696, n=215 for olmesartan; [†]n=224; [‡]n=226 for LCZ696, n=220 for olmesartan; [§]n=159 for LCZ696, n=158 for olmesartan; [‖]n=164 for LCZ696, n=162 for olmesartan; [¶]n=214 for both treatments

BP, blood pressure; PP, pulse pressure; CASP, central aortic systolic pressure; CADP, central aortic diastolic pressure; CAPP, central aortic pulse pressure; CMAP, central mean arterial pressure; ms, mean sitting; SBP, systolic BP; DBP, diastolic BP; ma, mean ambulatory, PWV, pulse wave velocity; HR, heart rate; eGFR, estimated glomerular filtration rate; SD, standard deviation

Table 2. Hemodynamic changes from baseline at Weeks 12 Endpoint and 52 Endpoint

Parameter	Change from baseline to Week 12			Change from baseline to Week 52		
	LCZ696-regimen	Olmesartan-regimen	P value	LCZ696-regimen	Olmesartan-regimen	P value
BP and PP, mmHg						
	N=207	N=206		N=209	N=208	
CASP	−12.6 (−14.6, −10.6)	−8.9 (−10.9, −6.9)	0.01	−16.2 (−18.1, −14.3)	−14.7 (−16.6, −12.8)	0.271
CADP	−6.1 (−7.4, −4.8)	−5.0 (−6.2, −3.7)	0.212	−8.8 (−10.1, −7.6)	−8.1 (−9.3, −6.9)	0.408
CAPP	−6.4 (−7.7, −5.1)	−4.0 (−5.3, −2.6)	0.012	−7.2 (−8.5, −5.8)	−6.6 (−8.0, −5.3)	0.598
CMAP	−8.5 (−10.0, −7.1)	−6.5 (−8.0, −5.0)	0.054	−10.1 (−11.7, −8.6)	−8.6 (−10.2, −7.1)	0.117
msSBP	−13.7 (−15.9, −11.5)	−9.9 (−12.1, −7.6)	0.016	−17.7 (−19.8, −15.6)	−16.1 (−18.2, −14.0)	0.285
msDBP	−5.9 (−7.1, −4.7)	−4.9 (−6.2, −3.7)	0.282	−8.7 (−9.9, −7.5)	−8.1 (−9.3, −6.9)	0.465
msPP	−7.7 (−9.3, −6.2)	−4.9 (−6.5, −3.3)	0.013	−8.8 (−10.4, −7.2)	−8.0 (−9.6, −6.4)	0.479

msMAP	−8.5 (−10.0, −7.1)	−6.6 (−8.0, −5.1)	0.059	−11.8 (−13.2, −10.4)	−10.7 (−12.0, −9.3)	0.248
	N=159	N=158		N=169	N=173	
maCASP	−12.1 (−13.2, −10.9)	−8.7 (−9.9, −7.5)	<0.001	−13.0 (−14.2, −11.9)	−13.7 (−14.7, −12.6)	0.434
maCADP	−7.7 (−8.4, −6.9)	−5.7 (−6.5, −5.0)	<0.001	−9.0 (−9.7, −8.2)	−8.9 (−9.6, −8.2)	0.900
maCAPP	−4.4 (−5.0, −3.7)	−3.0 (−3.6, −2.4)	0.003	−4.0 (−4.7, −3.3)	−4.8 (−5.5, −4.1)	0.078
maCMAP	−9.1 (−10.0, −8.2)	−6.7 (−7.6, −5.8)	<0.001	−10.3 (−11.2, −9.5)	−10.5 (−11.3, −9.7)	0.817
	N=164	N=162		N=174	N=176	
maSBP	−13.3 (−14.5, −12.0)	−9.1 (−10.4, −7.9)	<0.001	−14.2 (−15.3, −13.0)	−14.3 (−15.5, −13.2)	0.831
maDBP	−7.4 (−8.2, −6.7)	−5.5 (−6.2, −4.8)	<0.001	−8.8 (−9.5, −8.2)	−8.4 (−9.1, −7.8)	0.396
maPP	−5.8 (−6.5, −5.1)	−3.7 (−4.4, −3.0)	<0.001	−5.3 (−6.0, −4.6)	−5.9 (−6.6, −5.2)	0.193
maMAP	−10.1 (−11.1, −9.2)	−7.1 (−8.0, −6.2)	<0.001	−11.3 (−12.2, −10.4)	−11.1 (−12.0, −10.2)	0.737
PWV*	−0.7 (−0.9, −0.4)	−0.6 (−0.8, −0.3)	0.522	−0.8 (−1.1, −0.6)	−0.8 (−1.0, −0.5)	0.731

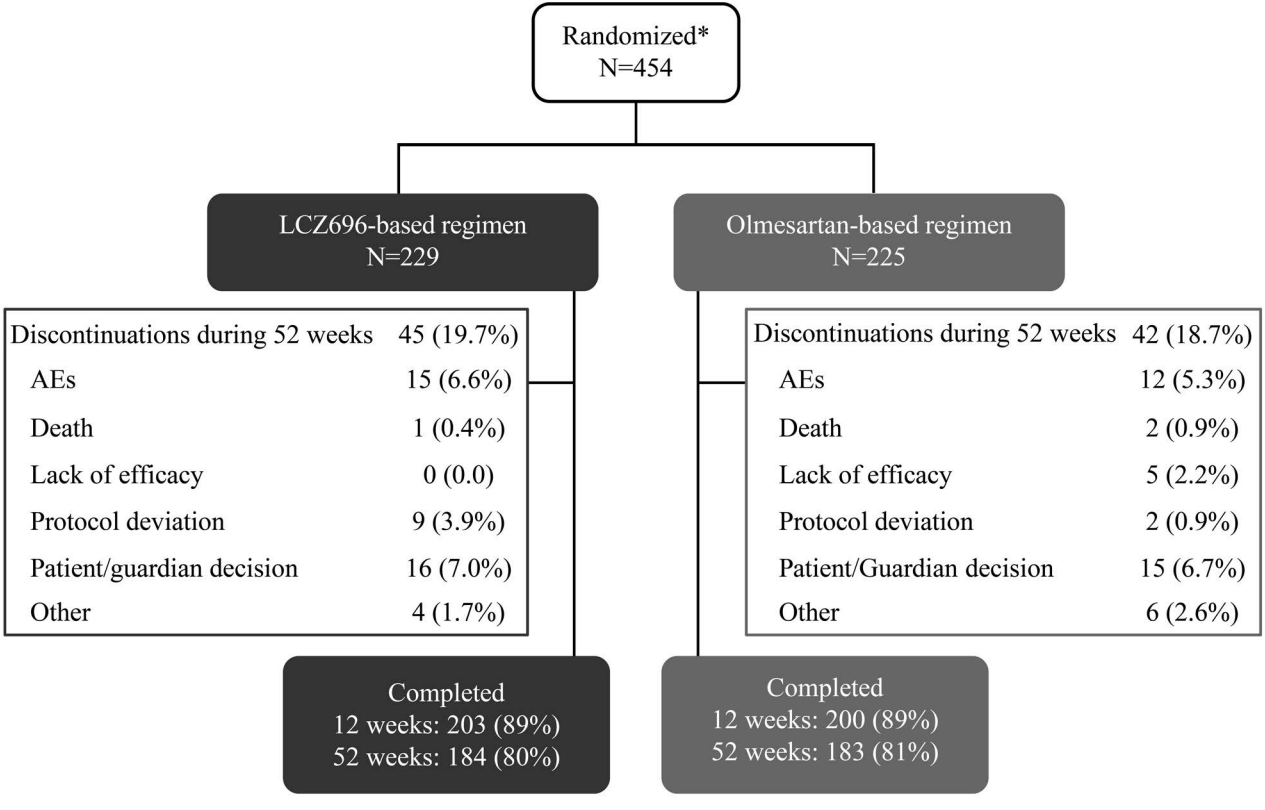
Data are mean with 95% CI; * n=192 for LCZ696, n=196 for olmesartan at Week 12 endpoint; n=199 for both the treatments at Week 52 endpoint; BP, blood pressure; PP, pulse pressure; CASP, central aortic systolic pressure; CADP, central aortic diastolic pressure; CAPP, central aortic pulse pressure; CMAP, central mean arterial pressure; ms, mean sitting; SBP, systolic BP; DBP, diastolic BP; ma, mean ambulatory; PWV, pulse wave velocity.

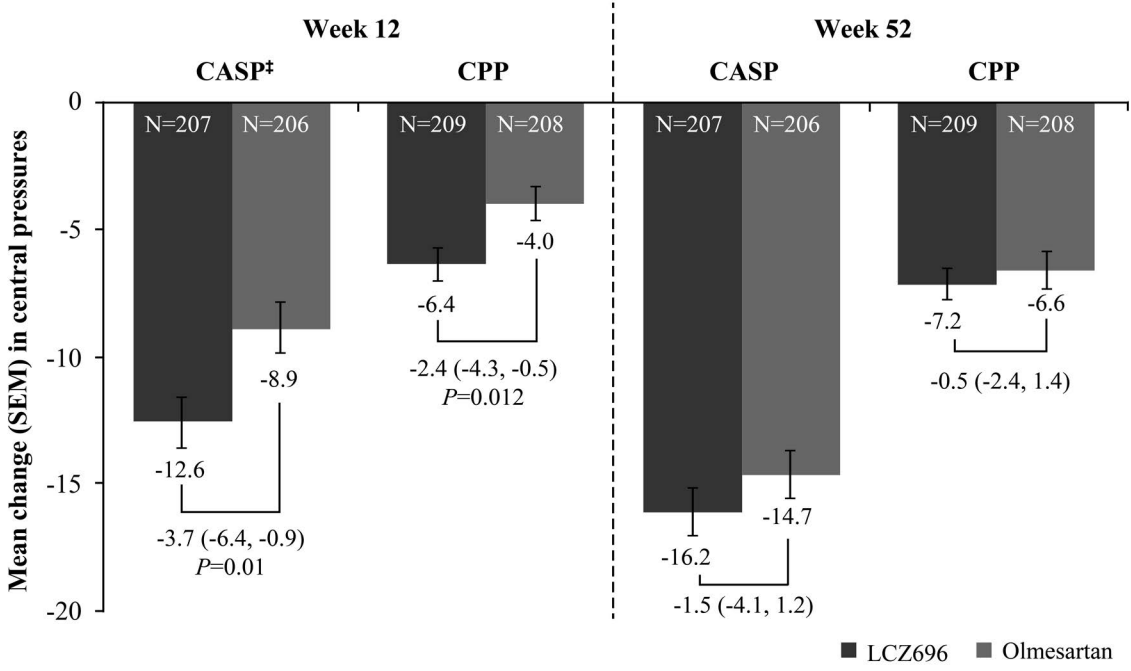
Table 3. Number of patients with adverse events (≥2% in any treatment group) in the double-blind period

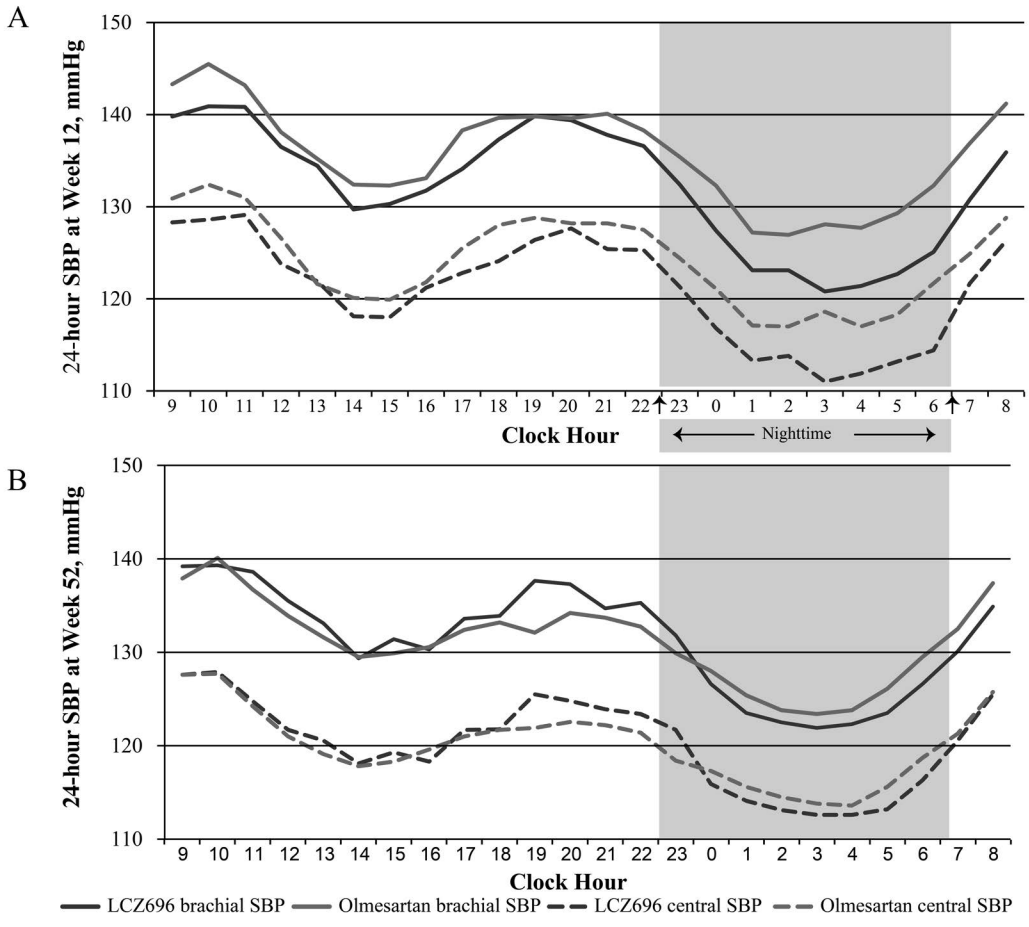
Variable	**LCZ696-regimen** (N=229)	**Olmesartan- regimen** (N=225)
Deaths	1 (0.4)	2 (0.9)
SAEs	16 (7.0)	13 (5.8)
Discontinuations due to AEs	16 (7.0)	14 (6.2)
Drug-related AE discontinuations	6 (2.6)	5 (2.2)
SAE discontinuations	6 (2.6)	6 (2.7)
Any adverse event	132 (57.6)	121 (53.8)
Any adverse event reported by ≥2%		
Nasopharyngitis	16 (7.0)	12 (5.3)
Headache	14 (6.1)	10 (4.4)
Dizziness	12 (5.2)	12 (5.3)
Cough	10 (4.4)	2 (0.9)
Influenza	7 (3.1)	5 (2.2)
Diarrhea	6 (2.6)	5 (2.2)

edema peripheral	6 (2.6)	2 (0.9)
Upper respiratory tract infection	6 (2.6)	6 (2.7)
Abdominal pain	5 (2.2)	1 (0.4)
Arthralgia	5 (2.2)	7 (3.1)
Nausea	5 (2.2)	2 (0.9)
Back pain	3 (1.3)	10 (4.4)
Hypotension	2 (0.9)	5 (2.2)

Data are number of patients (%).


Randomized*
N=454
LCZ696-based regimen
N=229
Olmesartan-based regimen
N=225
Discontinuations during 52 weeks 45 (19.7%)
AEs 15 (6.6%)
Death 1 (0.4%)
Lack of efficacy 0 (0.0)
Protocol deviation 9 (3.9%)
Patient/guardian decision 16 (7.0%)
Other 4 (1.7%)
Discontinuations during 52 weeks 42 (18.7%)
AEs 12 (5.3%)
Death 2 (0.9%)
Lack of efficacy 5 (2.2%)
Protocol deviation 2 (0.9%)
Patient/Guardian decision 15 (6.7%)
Other 6 (2.6%)
Completed
12 weeks: 203 (89%)
52 weeks: 184 (80%)
Completed
12 weeks: 200 (89%)
52 weeks: 183 (81%)


Week 12
Week 52
CASP‡
CPP
CASP
CPP
Mean change (SEM) in central pressures
0
-5
-10
-15
-20
N=207
N=206
N=209
N=208
N=207
N=206
N=209
N=208
-12.6
-8.9
-3.7 (-6.4, -0.9)
P=0.01
-6.4
-4.0
-2.4 (-4.3, -0.5)
P=0.012
-16.2
-14.7
-1.5 (-4.1, 1.2)
-7.2
-6.6
-0.5 (-2.4, 1.4)
LCZ696
Olmesartan


A
24-hour SBP at Week 12, mmHg
150
140
130
120
110
9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 0 1 2 3 4 5 6 7 8
Clock Hour
Nighttime
B
24-hour SBP at Week 52, mmHg
150
140
130
120
110
9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 0 1 2 3 4 5 6 7 8
Clock Hour
LCZ696 brachial SBP
Olmesartan brachial SBP
LCZ696 central SBP
Olmesartan central SBP