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CLINICAL RESEARCH
Hypertension

The effect of sacubitril/valsartan compared to olmesartan on cardiovascular remodelling in subjects with essential hypertension: the results of a randomized, double-blind, active-controlled study

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Aims Progressive aortic stiffening eventually leads to left ventricular (LV) hypertrophy and heart failure if left untreated. Anti-hypertensive agents have been shown to reverse this to some extent. The effects of sacubitril/valsartan (LCZ696), a dual-action angiotensin receptor blocker (ARB), and neprilysin inhibitor, on arterial stiffness and LV remodelling have not been investigated.

Methods and results This was a randomized, multi-centre, double-blind, double-dummy, active-controlled, parallel group, study to compare the effects on cardiovascular remodelling of sacubitril/valsartan with those of olmesartan in patients with hypertension and elevated pulse pressure. Magnetic resonance imaging scans were used to assess LV mass and local aortic distensibility, at baseline and at 12 and 52 weeks after initiation of treatment. Central pulse and systolic pressure were determined using a SphymoCor® XCEL device at each time point. A total of 114 patients were included, with 57 in each treatment group. The mean age was 59.8 years, and 67.5% were male. Demographic characteristics did not vary between the two sets of patients. Left ventricular mass index decreased to a greater extent in the sacubitril/valsartan group compared to the olmesartan group from baseline to 12 weeks (-6.36 vs. -2.32 g/m^2; $P = 0.039$) and from baseline to 52 weeks (-6.83 vs. -3.55 g/m^2; $P = 0.029$). These differences remained significant after adjustment for systolic blood pressure (SBP) at follow-up ($P = 0.036$ and 0.019 at 12 and 52 weeks, respectively) and similar signals (though formally non-significant) were observed after adjusting for changes in SBP ($P = 0.0612$ and $P = 0.0529$, respectively). There were no significant differences in local distensibility changes from baseline to 12 or 52 weeks between the two groups; however, there was a larger reduction in central pulse pressure for the sacubitril/valsartan group compared to the olmesartan group ($P = 0.010$).

Conclusion Since LV mass change correlates with cardiovascular prognosis, the greater reductions in LV mass indicate valuable advantages of sacubitril/valsartan compared to olmesartan. The finding that LV mass index decrease might be to some extent independent of SBP suggests that the effect of the dual-acting agent may go beyond those due to its BP-lowering ability.

Keywords Hypertension • Arterial stiffness • Heart failure • Left ventricular hypertrophy • Angiotensin • Neprilysin

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Introduction

Cardiovascular (CV) remodelling is a gradual process that progresses with age and is accelerated in the presence of hypertension.[1] There are a number of contributory factors, including decreasing elastin content of the artery wall, increased collagen deposition, endothelial dysfunction, and alterations in smooth muscle tone.[2] The loss of artery elasticity results in increased systolic blood pressure (SBP) with little change in diastolic blood pressure (DBP), leading to increased pulse pressure (PP). This process results in increased cardiac afterload, leading to left ventricular (LV) remodelling followed by LV hypertrophy. Both arterial stiffening and increased LV mass have been associated with increased CV risk in community-based cohorts[3–7] and patients with essential hypertension,[8–10] and are therefore important treatment targets.

Treatment-induced decreases in BP have been shown to indirectly reduce arterial stiffness and LV mass by lowering stress applied to the blood vessel wall and the heart, respectively, diminishing the extent of CV remodelling.[11] On the other hand, certain antihypertensive agents have demonstrated efficacy that goes beyond BP reduction.[12–14] Drugs that inhibit the renin–angiotensin system (RAS) have been shown to be particularly effective.[14] Such agents disrupt angiotensin-II-mediated signalling pathways, decreasing extracellular matrix remodelling, endothelial dysfunction, and inflammation.[11,15] In addition, similar changes to the more peripheral arteries result in decreased pulse wave reflection, leading to a lesser augmentation of central PP at the aorta.[11] Both angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been shown to reduce vascular and LV remodelling, and cause reduction of LV hypertrophy, in patients with hypertension or CV disease.[13,14,16–19]

A further target for BP reduction is the endopeptidase, neprilysin. Inhibition of this species increases bioavailability of natriuretic peptides, promoting vasodilation and reducing ventricular remodelling.[20] However, agents that inhibit neprilysin also increase the formation of vasoconstrictory species, such as angiotensin II and endothelin.[21,22] Evaluation of the neprilysin inhibitor, candoxatril, demonstrated disappointing antihypertensive effects, leading to discontinuation of its development.[23] Dual inhibition of neprilysin and ACE with the agent omapatrilat provided SBP and PP lowering along with decreased stiffness, which was superior to that achieved with the ACE-inhibitor, enalapril, alone.[24] However, the unacceptable rate of angioedema thwarted its approval. Sacubitril/valsartan, a more recently developed drug, disrupts angiotensin II signalling through blockade of the AT1 receptor, and inhibits neprilysin through the non-peptidic AHU377 moiety.[20,25] In patients with heart failure with a reduced ejection fraction, the agent was found to significantly reduce the risk of the composite end point of CV death or heart failure hospitalization, CV death and death from any cause in comparison to enalapril.[26] Sacubitril/valsartan is presently approved in more than 60 countries worldwide and is indicated to reduce the risk of CV death and hospitalization for patients with chronic heart failure with a reduced ejection fraction. To further understand the effects of sacubitril/valsartan on the LV and large arteries the present study evaluated the effects of sacubitril/valsartan compared to the ARB, olmesartan, on CV remodelling in patients with hypertension.

Methods

Study design

This was a multi-centre randomized, multi-centre, double-blind, double-dummy, active-controlled, parallel group study to compare the effects on CV remodelling of sacubitril/valsartan with those of olmesartan in patients with hypertension and elevated PP (Clinicaltrials.gov, NCT01870739). The study comprised a screening period followed by a 4-week washout period, where eligible patients stopped using any antihypertensive medication (*Figure 1*). During these 4 weeks, patients received both a placebo to sacubitril/valsartan and a placebo to olmesartan in order to evaluate treatment compliance. The patients subsequently underwent a cardiac and aortic magnetic resonance imaging (MRI) scan (3.0 Tesla), had SphygmoCor® XCEL measurements taken, and provided blood samples. The CV-MRI images were sent to an academic imaging core laboratory for quality control. Upon verification that the scans were evaluable, patients were randomized 1: 1 to sacubitril/valsartan or olmesartan by using consecutive ascending randomization numbers in the treatment blocks allocated to each study site. The randomization was stratified by the presence or absence of statin and oral antidiabetic therapy. The randomization list was produced using an automated random number generator.

During the first 2 weeks of the drug treatment period, patients received sacubitril/valsartan 200 mg q.d. (tablet) plus a placebo to olmesartan (capsule), or olmesartan 20 mg q.d. (capsule) plus a placebo to sacubitril/valsartan (tablet). The dosages were then force-titrated to maintenance doses of sacubitril/valsartan 400 mg q.d. or olmesartan 40 mg q.d., which were taken for the subsequent 10 weeks. After this time, amlodipine could be added to the therapy (add-on period) if deemed necessary for achieving adequate BP control. No dose adjustments of sacubitril/valsartan or olmesartan, or interruptions, were permitted.

Patient compliance was evaluated by the counting of pills by a physician at selected time-points. In addition, patients were provided with individual diary cards to record administration of the study medication on a daily basis. These cards were checked regularly by site staff.

The study was approved by the local ethics committee at each trial centre, and was conducted in accordance with the Declaration of Helsinki and its amendments. All included patients provided written informed consent.

Patients

Included individuals were ≥18 years of age and had essential hypertension Stage 1 and 2 [mean seated [ms] SBP ≥140 mmHg and <180 mmHg)[8] and elevated brachial PP (≥50 mmHg).[27] Patients were excluded if they had any contraindications to MRI; had any contraindications to olmesartan or amlodipine; had severe hypertension (msSBP ≥180 mmHg, msDBP ≥110 mmHg); were pregnant; had a history of angioedema; had a history or evidence of a secondary form of hypertension; had experienced a transient ischaemic attack, stroke, myocardial infarction (MI), or peripheral artery disease requiring intervention in the 12 months prior to screening; had undergone percutaneous coronary intervention; had type 1 diabetes mellitus; or had type 2 diabetes mellitus that was not well controlled with oral medication, or was being treated with insulin. Certain concomitant medications were prohibited, including any antihypertensive agents (ARBs, ACE-inhibitors, β-blockers, diuretics) or antiarrhythmic drugs. Patients who were being treated with a statin were required to have been taking the same statin at the same dose for at least 4 weeks prior to screening.

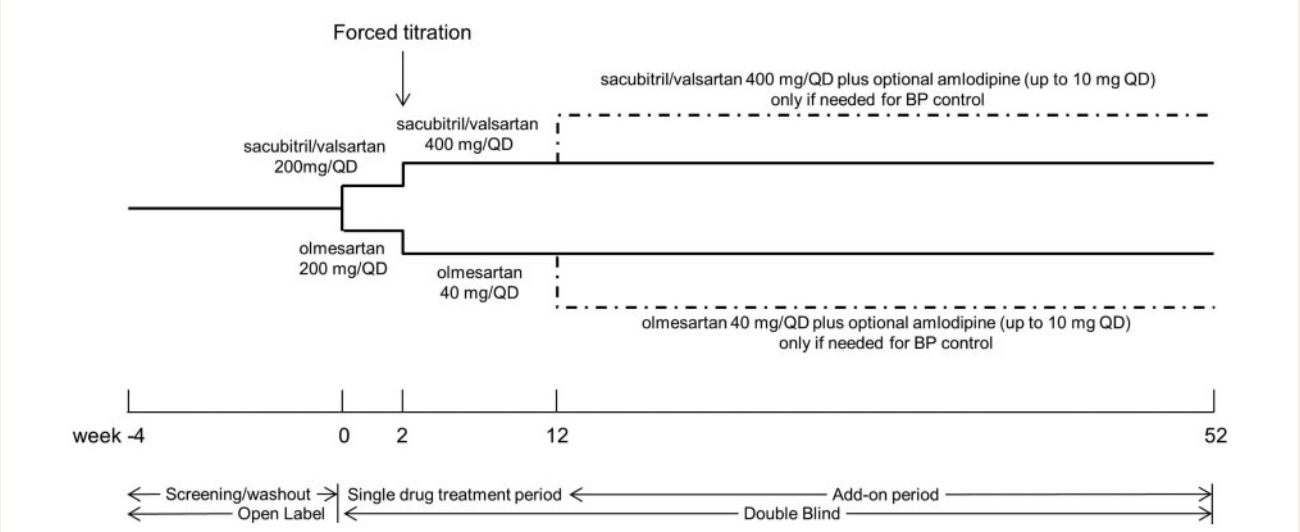

Figure 1 Trial design.

Measurements

Data were entered into an electronic case report form. All patients had their office BP and heart rate measured in standard fashion[8] and underwent a 12-lead electrocardiogram (ECG) at rest. At the visit immediately prior to initiation of the study drug, a CV-MRI scan was performed in order to determine aortic distensibility and LV mass. In addition the Sphygmocor device was used to perform pulse wave analysis and pulse wave velocity (PWV). The pulse wave assessments and MRI scans were performed at baseline and after 12 and 52 weeks of treatment.

Magnetic resonance imaging acquisition

Electrocardiogram-gated MRI was performed at each site on a 3.0 Tesla whole body scanner equipped with cardiac phased array coils (Magnetom Trio, Magnetom Skyra, Magnetom Prisma; Siemens Healthineers, Germany). After scout imaging and acquisition of a stack of axial Single Shot Turbo Spin Echo (HASTE) images of the whole chest cine balanced steady state free precession images were acquired in the short axis (contiuguous gapless, whole heart), as well as in vertical and horizontal long axes views (3 midventricular slices in each orientation) with the following sequence parameters: Slice thickness 8 mm, FOV 340 × 273 mm; In plane resolution 1.5 × 1.5 mm^2; Flip angle 50°; Lines per phase 13; retrospective ECG gating, 25 calculated phases; bandwith 970 Hz per pixel; repetition time 3 ms; echo time 1.5 ms. Subsequently retrospectively ECG gated axial spoiled gradient recalled echo were acquired at the level of the right pulmonary artery and 10 cm below with the following sequence parameters: Slice thickness 6 mm; matrix 256 × 256; FOV 340 × 292 mm^2; Spatial resolution 1.1 × 1.1 mm^2; Calculated phases 50; temporal resolution 20 ms; Lines per phase 7; bandwith 401 Hz per pixel; repetition time 7 ms; echo time 4 ms.

Magnetic resonance imaging analysis

Cine MRI was transferred to a post-processing server (SyngoVia; Siemens Healthineers, Germany) for evaluation of LV mass. Inner and outer contours of the LV myocardium were segmented on short axis images, position of aortic and mitral valves on horizonatal and vertical long axes. Mass and mass index were calculated as reported previously.[28] For aortic distensibility, the cross-sectional lumen area of the aorta was segmented in systole (Amax) and diastole (Amin) at three different locations: in the ascending (ascending aorta) and descending (proximal descending aorta) aorta at the level of the right pulmonary artery and 10 cm lower (distal descending aorta). Distensibility was calculated as follows:

$$\text{Distensibility } [10\text{-}3 \times \text{mmHg-}1] = \frac{\text{Amax-Amin}}{\text{Amin} \times (\text{pulse pressure})} \times 1000.$$

Pulse wave analysis and velocity

The SphygmoCor® XCEL device (AtCor Medical, Sydney Australia) was used to provide a central arterial pressure waveform from which central PP, augmentation pressure (AP; added pressure due to wave reflection), and augmentation pressure index (AI; % of central PP due to wave reflection) were derived. The carotid–femoral PWV, was also measured. Measurements were taken in supine position and BP measurements for calibration of the Sphygmocor were taken immediately prior to the pulse wave recording.

Statistics

The study primary end point was that change from baseline in local distensibility as measured by MRI in ascending, proximal descending, and distal descending aorta after 52 weeks of treatment. Secondary and exploratory end points included but not limited to: vascular parameters such as local aortic strain, aortic PWV, central blood pressure, augmentation index, as well as LV mass and LV mass index.

Sample size estimation was based on an observed standard deviation (SD) for change from baseline to 52 weeks using MRI of 1.08793, 5.63031, and 1.51536 × 10^{-3} $mmHg^{-1}$ in ascending, proximal descending, and distal descending aorta in an internal study (unpublished data). A 50 patients per arm was considered sufficient to allow detecting a treatment difference of 0. 6785 × 10^{-3} $mmHg^{-1}$ between the two study groups in proximal descending aorta (approximately half of the observed SD). This difference was considered as clinically relevant. The number of randomized patients was believed appropriate to ensure that 100 patients complete 52 weeks of treatment.

For baseline characteristics, the continuous variables were provided as means with SD, while categorical data were presented as absolute values

and percentages. Statistically significant differences between baseline characteristics were determined using a student's *t*-test or a χ^2 test, as appropriate. The primary and secondary end points were analysed using a linear model, with treatment as the fixed effect and the corresponding baseline as a covariate. Least squares regression analysis was used to estimate the mean and 95% confidence interval (CI) for change from baseline of each variable between the sacubitril/valsartan and olmesartan patients. All analysis was performed using the SAS software.

Results

Study patients

A total of 115 patients were enrolled in the study, one of whom was discontinued after randomization. This left 114 patients who received the study medication to which they were assigned. The mean age of the population was 59.8 ± 10.7 years and 67.5% were male, with no significant differences between the two drug groups (*Table 1*). The mean SBP was 155.1 ± 9.0 mmHg, and the mean DBP was 92.2 ± 8.7 mmHg, with highly similar values in the two groups. Heart rate (mean: 70.2 ± 10.3 bpm) and PP (mean: 62.9 ± 9.3 mmHg) also did not differ between the sets of patients. Left ventricular mass at baseline was not different between the two drug groups (148 ± 46 vs. 145 ± 33 g and 72.1 ± 18 vs. 72.1 ± 12 g/m^2, respectively). Similar proportions of patients in each group were being treated with antidiabetic drugs and/or statins.

Office SBP decreased in the sacubitril/valsartan group by -25.7 and in the olmesartan group by -22.8 mmHg; treatment difference was not statistically significant [-2.58 (95% CI -7.53, 2.38), $P = 0.31$] following 12 weeks of treatment. The corresponding SBP decreases after 52 weeks were 26.1 mmHg in the sacubitril/valsartan group and 20.8 mmHg in the olmesartan group, with a significantly greater decrease in the sacubitril/valsartan group [-4.99 (95% CI -9.46; -0.53), $P = 0.028$]. After 12 weeks of treatment, office DBP decreased in the sacubitril/valsartan group by 11.9 mmHg and in the olmesartan group by 12.1 mmHg, with no significant difference between the groups [0.17 (95% CI -1.8, +3.2) mmHg, $P = 0.91$]. The corresponding values after 52 weeks are -13.5 mmHg and -12.2 mmHg for the sacubitril/valsartan group and olmesartan group, respectively, without any significant difference between the two groups [-1.29 (95% CI -4.2, 1, 6) mmHg, $P = 0.38$] (*Figure 2*). During the 40-week add-on period, 17.5% (10 patients) of the sacubitril/valsartan group and 29.8% (17 patients) of the olmesartan group received amlodipine ($P = 0.12$).

Changes in aortic distensibility

In the group of patients that were treated with sacubitril/valsartan, the distensibility of the ascending aorta increased by 0.22 (95% CI -0.17; 0.61), $P = 0.26$) $\times 10^{-3}$ mmHg^{-1} from baseline to 52 weeks, and by 0.30 [(95% CI -0.31; 0.92), $P = 0.33$] $\times 10^{-3}$ mmHg^{-1}. The treatment difference was 0.12 [(95% CI -0.35, 0.60), $P = 0.60$] (*Figure 3*). When considering the period from baseline to 12 weeks, the corresponding values were [0.66 $\times 10^{-3}$ (95% CI 0.28; 1.04), $P < 0.001$] mmHg^{-1} for the sacubitril/valsartan group and 0.56 (95% CI -0.06; 1.18) $P = 0.07 \times 10^{-3}$ mmHg^{-1} for the olmesartan group ($P = 0.60$). The treatment difference was -0.53 [(95% CI -1.18; 0.12), $P = 0.11$].

Table 1 Patient characteristics of the two groups

	Sacubitril/valsartan $N = 57$	Olmesartan $N = 57$	*P*-value
At baseline			
Age (years, mean ± SD)	60.5 ± 7.8	59.2 ± 13.1	0.53
Gender (male *N*(%))	37 (64.9)	40 (70.2)	0.55
BMI (kg/m^2, mean ± SD)	28.1 ± 4.5	28.6 ± 3.9	0.52
SBP (mmHg, mean ± SD)	155.3 ± 9.0	155.0 ± 9.1	0.88
Median (mmHg)	154	156	
Min–max (mmHg)	136–179	139–178	
DBP (mmHg, mean ± SD)	92.7 ± 8.8	91.7 ± 8.7	0.54
Median (mmHg)	93	92	
Min–max (mmHg)	68–107	69–110	
Heart rate (bpm, mean ± SD)	69.9 ± 9.4	70.5 ± 11.2	0.75
Median (bpm)	70	70	
Min–max (bpm)	49–92	46–100	
Pulse pressure (mmHg, mean ± SD)	62.6 ± 8.9	63.3 ± 9.7	0.82
Median (mmHg)	62	63	
Min–max (mmHg)	50–87	44–89	
Antidiabetic drug use (*N*(%))	4 (7.0)	5 (8.8)	0.72
Statin use (*N*(%))	7 (12.3)	7 (12.3)	1.0
At 12 weeks			
SBP (mmHg, mean ± SD)	129.9 ± 12.5	132.2 ± 14.2	0.31
Median (mmHg)	128.5	132	
Min–max (mmHg)	106–155	104–162	
DBP (mmHg, mean ± SD)	81.1 ± 8.8	80.2 ± 9.0	0.91
Median (mmHg)	80	80	
Min–max (mmHg)	58–105	64–103	
HR (bpm, mean±SD)	69.0 ± 9.58	68.8 ± 12.1	0.80
Median (bpm)	69.0	68.0	
Min–max (bpm)	50–99	50–97	
At 52 weeks			
SBP (mmHg, mean ± SD)	129.4 ± 11.3	134 ± 12.8	0.03
Median (mmHg)	129.4	134.0	
Min–max (mmHg)	105–162	107–168	
DBP (mmHg, mean ± SD)	79.1 ± 7.8	79.9 ± 9.2	0.38
Median (mmHg)	79.0	79.0	
Min–max (mmHg)	59–93	63–115	
HR (bpm, mean ± SD)	69.8 ± 9.0	68.9 ± 11.4	0.38
Median (bpm)	70	69	
Min–max (bpm)	50–96	49–95	

Safety analysis set. All comparisons from baseline to week 12 and to week 52 were significant (all $P < 0.001$). Differences between treatment groups were not statistically significant.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation.

In the proximal descending aorta, changes from baseline to 52 weeks were of 0.54 [(95% CI 0.09; 1.01), $P = 0.025$] $\times 10^{-3}$ mmHg^{-1} and 0.55 [(95% CI -0.10; 1.19), $P = 0.10$] $\times 10^{-3}$ mmHg^{-1} for sacubitril/valsartan and olmesartan, respectively; the treatment difference was -0.08 [(95% CI -0.70; 0.534) $P = 0.79$]. For the period from baseline to 12 weeks, the values for change from baseline were

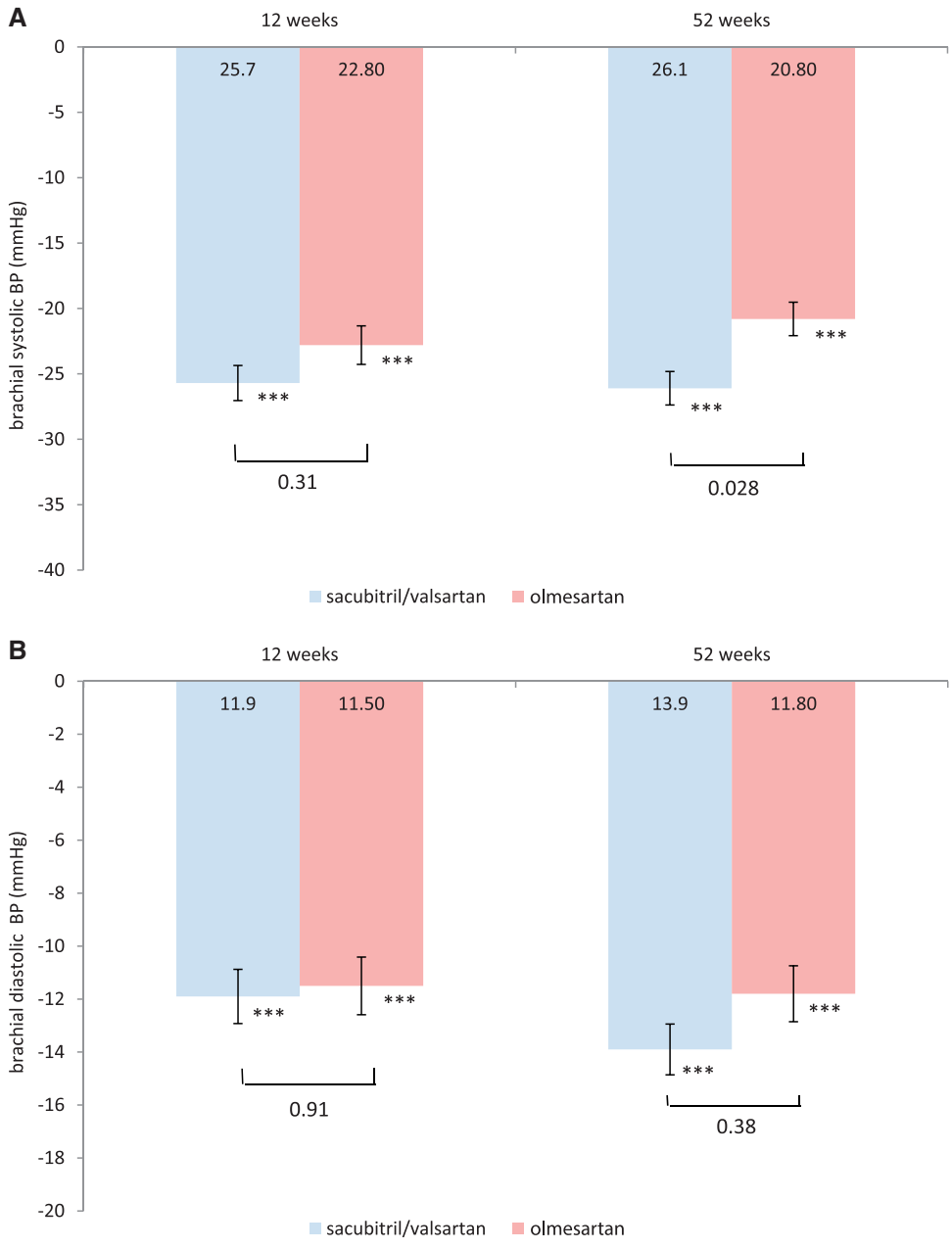

Figure 2 Changes in systolic and diastolic BP from baseline. (*A*) Changes in systolic BP from baseline. (*B*) Changes in diastolic BP from baseline. [Please note that after 12 weeks amlodipine treatment was added in 10 patients of the sacubitril/valsartan group vs. 17 patients in the olmesartan group ($P = 0.12$)]. Precise *P*-values are given for the comparison between the two groups; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.01$ vs. baseline. Mean ± standard error of the mean are given.

0.58 [(95% CI 0.12, 1.03), $P = 0.014$] $\times 10^{-3}$ mmHg^{-1} and 1.03 [(95% CI 0.38, 1.68), $P = 0.002$] $\times 10^{-3}$ mmHg^{-1}, for sacubitril/valsartan and olmesartan respectively; treatment difference -0.53 [(95% CI -1.18, 0.12), $P = 0.11$].

In the distal descending aorta changes from baseline were 0.37 ([95% CI -0.38; 1.13], $P = 0.33$) $\times 10^{-3}$ mmHg^{-1} and 0.57 ([95% CI -0.16, 1.30], $P = 0.13$) $\times 10^{-3}$ mmHg^{-1} at 52 and 12 weeks of treatment in the sacubitril/valsartan and were 0.57 ([95% CI -0.16, 1.30], $P = 0.13$) $\times 10^{-3}$ mmHg^{-1} and 0.90 ([95% CI 0.17; 1.63] $P = 0.016$) $\times 10^{-3}$ mmHg^{-1} and 52 and 12 weeks of treatment in the olmesartan group. No-significant differences were observed in the change from baseline in local distal descending distensibility between sacubitril/valsartan and olmesartan groups at 52 weeks, (treatment difference - 0.08 [95% -0.70, 0.54], $P = 0.79$) $\times 10^{-3}$ mmHg^{-1}) and at 12 weeks (treatment difference -0.25 [95% CI -0.92, 0.42], $P = 0.49$] $\times 10^{-3}$ mmHg^{-1}) (*Figure 2*).

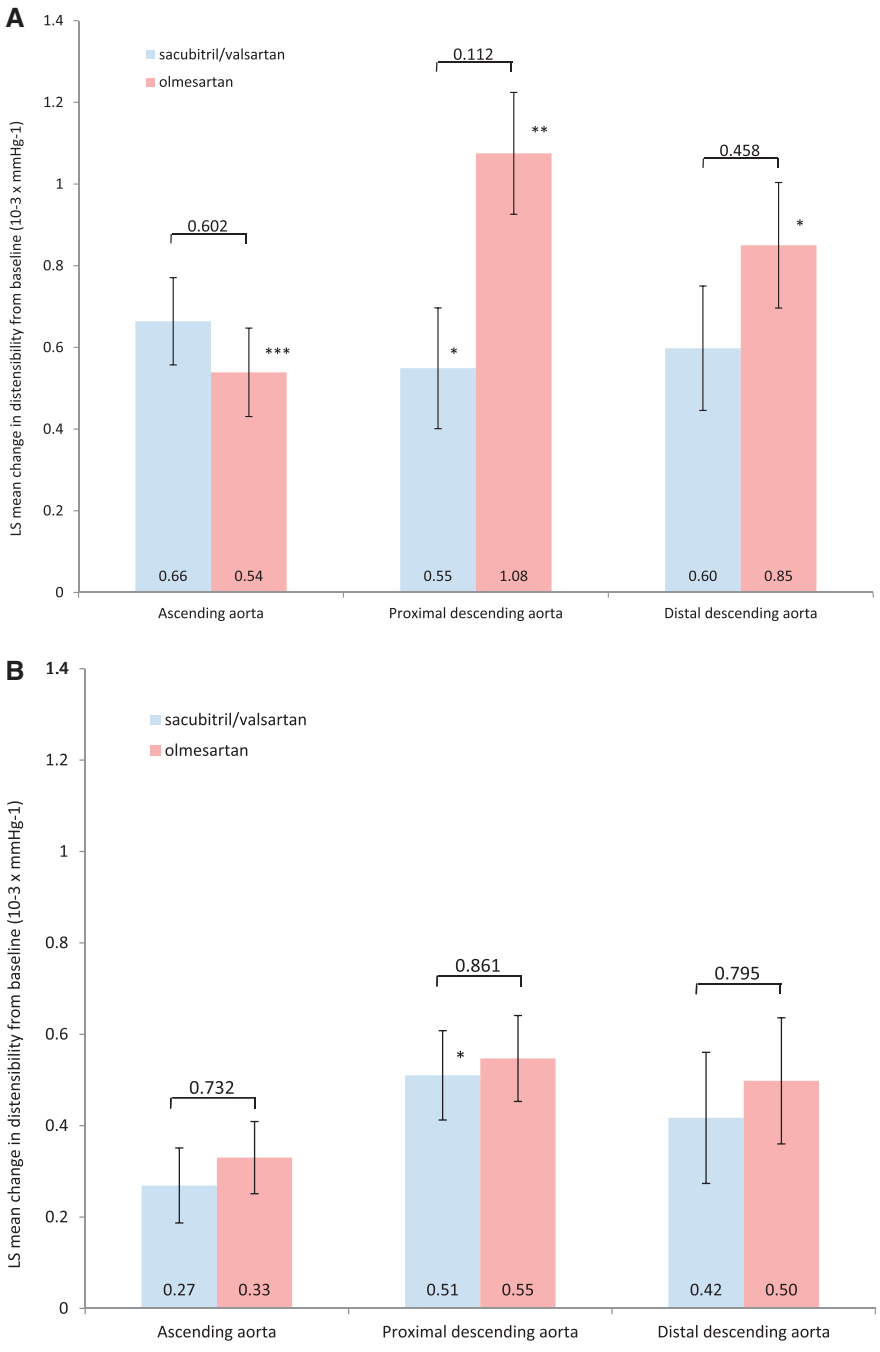

Figure 3 Changes in local aortic distensibility from baseline. (*A*) Changes from baseline to 12 weeks; (*B*) Changes from baseline to 52 weeks. Precise *P*-values are given for the comparison between the two groups; **P* < 0.05, ***P* < 0.01, ****P* < 0.01 vs. baseline. Mean ± standard error of the mean are given.

Changes in left ventricular mass

LV mass decreased for both groups from baseline to 12 weeks (-11.19 [95% CI -16.66; -5.72] in the sacubitril/valsartan patients vs. -3.28 [95% CI -8.81; 2.04] g) in the olmesartan patients, treatment difference was -8.0966 [95% CI -15.9848; -0.2084] g, *P* = 0.049 (*Figure 4A*). At 52 weeks, reduction LV mass reduction were -11.19 [95% CI -15.05; -7.33] g in the sacubitril/valsartan patients compared to vs. -5.60 [95% CI -9.30; -1.90] g in the olmesartan patients, treatment difference was -5.1942 [95% CI -10.65, 0.26] g, *P* = 0.062) (*Figure 4A*). The mean change from baseline to 52 weeks for the sacubitril/valsartan group was similar to the mean change between baseline and 12 weeks, while that for the olmesartan group was numerically higher for the longer time period. This resulted in the difference between the two groups being borderline statistically significant when comparing the 52-week data.

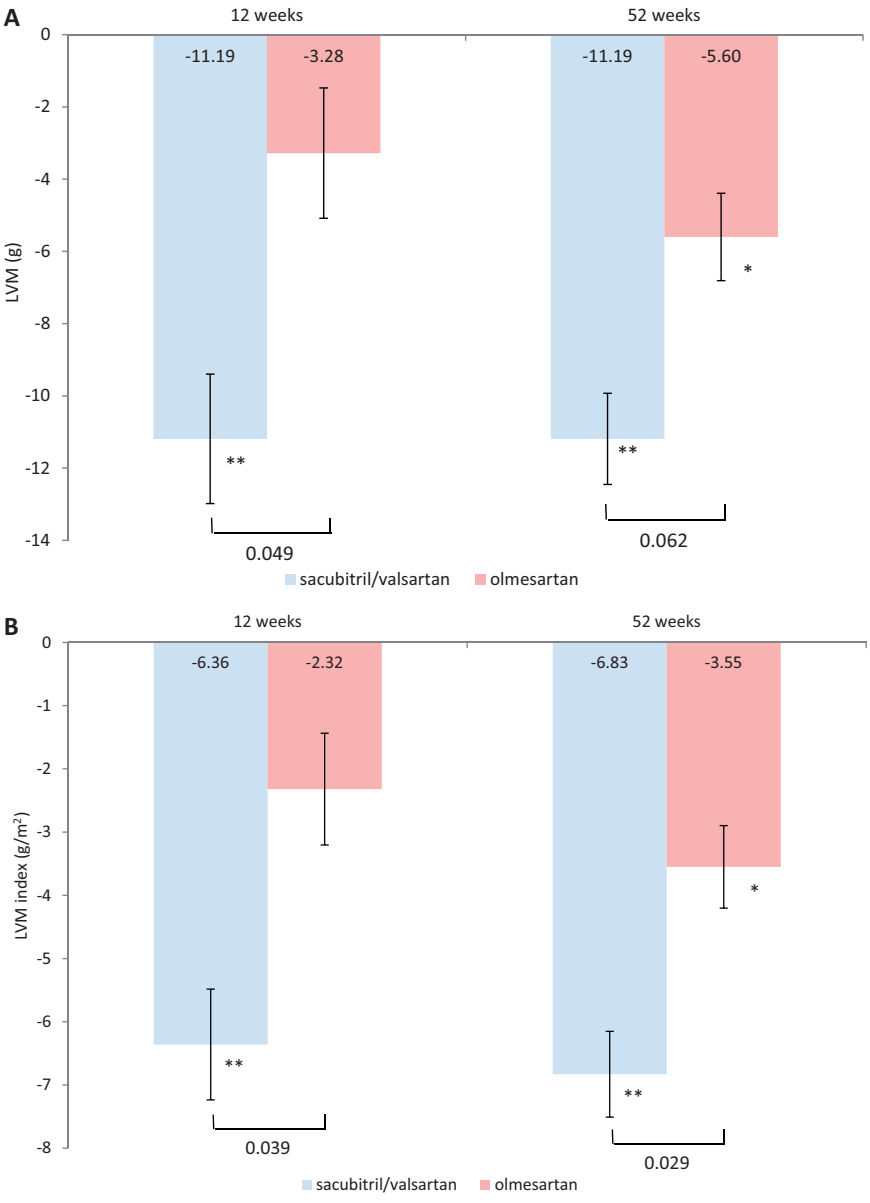

Figure 4 Changes in left ventricular mass from baseline. (*A*) Changes in least squares mean left ventricle mass from baseline; (*B*) changes in least squares mean left ventricle mass index from baseline. Error bars represent Mean ± standard error of the mean. Precise *P*-values are given for the comparison between the two groups; **P* < 0.05, ***P* < 0.01, ****P* < 0.01 vs. baseline.

When the LV mass was adjusted for body surface area (LV mass index), there was, again, a greater decrease for the sacubitril/valsartan patients than the olmesartan patients from baseline to 12 weeks [treatment difference -4.05 (95% CI -7.90, -0.20 g/m^2); *P* = 0.039] (*Figure 4B*). When comparing the changes from baseline to 52 weeks, a superior decrease in the sacubitril/valsartan patients was also observed compared to the olmesartan patients [treatment difference -3.27 (95% CI -6.21; -0.34) g/m^2; *P* = 0.029].

Importantly, the higher reductions in LV mass and LV mass index with sacubitril/valsartan compared to olmesartan were apparent following 12 weeks of treatment when there were no meaningful differences in brachial systolic and diastolic as well as central SBP. However, since systolic (not diastolic) office BP decreased to a greater extent with sacubitril/valsartan following 52 week of treatment, adjustment for attained office SBP at follow-up were made. Nevertheless, the differences between the effects of the two drugs on LV mass index remained significant (*P* = 0.036 and 0.019 at 12 and 52 weeks, respectively), with sacubitril/valsartan having superior efficacy on LV mass reduction. When adjusting for the change in office SBP at 12 and 52 weeks follow-up, the differences between two drugs on LV mass index were -3.57 (95% CI: -7.32, 0.18) g/m^2 (*P* = 0.0619) and -2.80 (95% CI: -5.63, 0.04) g/m^2, (*P* = 0.0529), respectively. Taking all the information together, our data point to some extent to a blood pressure independent effect of sacubitril/valsartan on LV mass reduction.

Table 2 Change in central haemodynamic parameters

	Baseline to 12 weeks			Baseline to 52 weeks		
	Sacubitril/valsartan (*N* = 53)	Olmesartan (*N* = 53)		Sacubitril/valsartan (*N* = 50)	Olmesartan (*N* = 50)	
	Adjusted LS mean ± SE		Difference (95% CI)	Adjusted LS mean ± SE		Difference (95% CI)
Central SBP (mmHg)	-17.99 ± 1.47	-17.14 ± 1.47	-0.84 (-4.97, 3.28)	-16.66 ± 1.50***	-13.63 ± 1.50***	-3.03 (-7.23, 1.17)
Central DBP (mmHg)	-11.44 ± 1.05	-11.08 ± 1.05	-0.37 (-3.31, 2.57)	-10.32 ± 1.06***	-10.43 ± 1.06***	0.11 (-2.85, 3.08)
Central pulse pressure (mmHg)	-6.70 ± 0.88	-5.89 ± 0.88	-0.81 (-3.29, 1.66)	-6.54 ± 0.94***	-3.04 ± 0.94*	-3.50 (-6.15, -0.85)****
Central AP (mmHg)	-2.46 ± 0.53	-2.93 ± 0.53	0.47 (-1.04, 1.98)	-2.44 ± 0.60***	-1.44 ± 0.60	-1.01 (-2.69, 0.67)
Central AI (%)	-1.94 ± 1.13	-4.53 ± 1.13	2.60 (-0.64, 5.83)	-2.39 ± 1.18*	-1.52 ± 1.18	-0.87 (-4.22, 2.48)
HR-corrected central AI (%)	-2.41 ± 1.03	-4.09 ± 1.03	1.69 (-1.24, 4.61)	-2.17 ± 1.13*	-1.63 ± 1.13	-0.55 (-3.75, 265)
Carotid–femoral PWV (m/s)	-0.98 ± 0.13	-0.82 ± 0.13	-0.17 (-0.53, 0.20)	-0.43 ± 0.17*	-0.43 ± 0.17*	0.01 (-0.46, 0.47)

LS, least squares; SE, standard error; SBP, systolic blood pressure; DBP, diastolic blood pressure; AP, augmentation pressure; AI, augmentation index; HR, heart rate; PWV, pulse wave velocity.
*$P < 0.05$,
**$P < 0.01$,
***$P < 0.01$ vs. baseline,
****$P = 0.010$ vs. olmesartan; all other comparisons were not statistically significant ($P > 0.05$).

Changes in central pulse wave parameters

Central SBP and DBP both decreased from baseline to 52 weeks, with no-significant differences between the sacubitril/valsartan and olmesartan patients (mean difference: SBP: -3.03 mmHg; 95% CI: -7.23, 1.17; $P = 0.156$; DBP: 0.11 mmHg; 95% CI: -2.85, 3.08; $P = 0.939$) (*Table 2*). The decrease in central PP was significantly greater in the sacubitril/valsartan group (-6.54 mmHg, 95% CI: -8.4, -4.67) compared to the olmesartan group (-3.04 mmHg, 95% CI: -4.91, -1.17) after 52 weeks (mean difference: -3.50 mmHg; 95% CI: -6.15, -0.85; $P = 0.010$). Other vascular parameters disclosed not any significant difference between the two groups (*Table 2*).

Discussion

The principal finding of our double-blind, randomized study is that in patients with hypertension treatment with sacubitril/valsartan resulted in superior reductions in LV mass and central PP at 52 weeks compared to treatment with olmesartan. Reductions in LV hypertrophy has been shown to be associated with an improvement in outcome and to reduce the risk of CV morbidity and mortality[8,9] significantly decreased CV risk and represents a therapeutic target of antihypertensive therapy.[8] Thus, these data indicate clinical benefits of the dual-acting ARB and neprilysin inhibitor, sacubitril/valsartan.

The importance of LV mass as a treatment target in patients with hypertension has been demonstrated in a number of studies. Koren *et al.*[9] reported higher rates of CV events, CV death, and all-cause mortality for hypertensive patients with a high compared to a low LV mass. Similarly, Muiesan *et al.*[10] found that the proportion of patients that experienced a CV event increased with increased LV mass index, and that persistence of LV hypertrophy during antihypertensive treatment was an independent predictor of CV events. In the LIFE study, independent of treatment modality and BP control, LV mass index reduction was associated with a lower risk of the combined end point of CV death, stroke, and MI.[29] In another study, Mathew *et al.*[30] linked LVH regression during treatment with an ACE-inhibitor to decreased risk of CV death, MI, and heart failure. Finally, in a meta-analysis reduction of LV mass was associated with improved CV prognosis.[30]

Office SBP was reduced to a greater extent on treatment with sacubitril/valsartan compared to olmesartan. This is in agreement with previous studies, which have shown sacubitril/valsartan to be superior to valsartan for BP lowering in patients with hypertension.[31,32] In the present study, the greater reduction in LV mass index for the sacubitril/valsartan group compared to the olmesartan group was already observed after 12 weeks of treatment, at similar changes in brachial SBP and DBP. It remained significant at 12 and 52 weeks of treatment when adjusted for office SBP during follow-up, with a similar signal when adjusted for the difference in change of SBP. These analyses indicate that the difference in LV mass reduction cannot be attributed to differences in BP alone thereby suggesting that the dual inhibitor may exert beneficial effects beyond those attributable to decreases in BP. In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial, a larger decrease in LV mass was found for the patients being treated with losartan in comparison to those being treated with the beta-blocker, atenolol, while BP control did not differ greatly between the two groups.[13] The RAS has been previously linked to LV hypertrophy in patients with hypertension, with higher levels of angiotensin II associated with greater LV mass the independent of 24 h ambulatory BP.[33] Furthermore, in a meta-analysis evaluating the effects of different antihypertensive drugs, treatment with ACE-inhibitors and ARBs, resulted in greater decreases in LV mass than did diuretics and beta-blockers.[14] Now, we observed that beyond BP reduction and RAS inhibition the dual inhibitor sacubitril/valsartan exerts additional effects on LV mass reduction.

It has been hypothesized that the vasodilatory and antiproliferative effects of the neprilysin-inhibitor moiety of sacubitril/valsartan may provide additional benefits to those of the RAS-inhibitor component, further reducing the risks associated with LV remodelling. In the PARADIGM-HF trial, larger reductions in the composite

end point of CV death and heart failure hospitalization, CV death and death from any cause were observed for sacubitril/valsartan treatment compared to enalapril treatment in heart failure patients with a reduced ejection fraction.[26] The study did not provide further insight which pathogenetic mechanisms caused the improved CV outcome. Our data in a different population, namely hypertensive patients, support the hypothesis that reduction in LV mass may be one of the predominant mechanisms by which the lower incidence of CV events was caused in the PARADIGM-HF Study.[26] Nevertheless, a prospective double blind prospective study is needed to allow conclusive evidence on the cardioprotective effects of sacubitril/valsartan in a hypertensive population, with repeated measurements of LV mass.

In the present analysis, local distensibility was not found to differ between the two treatment groups. Numerically an increase of local distensibility was observed, but the effect seen was too small to reach statistical significance. Nevertheless, the larger decrease in central PP in the sacubitril/valsartan (compared to the olmesartan) patients indicates that global distensibility was improved. Amlodipine having preventing effects on the progression of arterial stiffness[34] was added in both treatments, but numerically more frequently in the olmesartan group thereby if any minimizing the difference of central PP between the two groups. Our data are supported by the PARAMETER study that was conducted in parallel to our study.[35] In this elderly hypertensive population treatment with sacubitril/valsartan demonstrated superiority in reducing central aortic pressure (primary objective) vs. treatment with olmesartan.[35] In accordance, treatment with omapatrilat vasopeptase inhibitor reduced PP and aortic stiffness to greater extent in patients with systolic hypertension than the comparator enalapril.[24] Thus, improved aortic stiffness that leads to unloading of the LV may have contributed to the greater decrease in LV mass observed for the sacubitril/valsartan group compared to the olmesartan group.

It is interesting to note that the effects of the two drugs on LV mass did not increase over time. Data collected 12 weeks after treatment initiation, prior to the add-on period, generally showed already significant decreases in LV mass when compared to the period from baseline to 52 weeks. The reductions in central SBP and DBP were almost the same for the period from baseline to 12 weeks and from baseline to 52 weeks, indicating that the initial antihypertensive effect was sustained, but did not increase over time.

Limitations

One limitation to this study is that MRI scans were only taken at three time points. This prevented us from analysing changes in vascular and ventricular modelling over time. A further drawback was the absence of peripheral biomarker analysis. This may have helped to elucidate the mechanisms by which the improvements in LV mass and distensibility were achieved. As adverse events were grouped according to treatment period rather than time, it is not possible to determine how the changes in therapy affected their frequency.

Conclusions

The hypertensive patients treated with sacubitril/valsartan displayed greater reductions in LV mass compared with those treated with olmesartan after 12 and 52 weeks of treatment. The observed difference in the change of LV mass cannot be attributed to minor differences in BP response. This suggests that the drug may exert beneficial effects on CV remodelling that go beyond that caused by BP reduction.

Conflict of interest: R.E.S. reports grants and personal fees from Novartis Pharma GmbH, during the conduct of the study. C.D. reports grants from Novartis, during the conduct of the study; grants from European Commission, grants from British Heart Foundation, outside the submitted work. T.H. reports grants from Novartis, during the conduct of the study. Y.K. is a Novartis employee at the time the study was conducted and holds or eligible to receive Novartis stocks. D.Y. is an employee of Novartis at the time the study was conducted and restricted stock shareholder. D.A. is a Novartis employee at the time the study was conducted and holds or eligible to receive Novartis stocks. T.L. is a Novartis employee at the time the study was conducted and holds or eligible to receive Novartis stocks. R.J. reports personal fees from Bracco Imaging, personal fees from Siemens Healthcare, outside the submitted work. All the other authors has nothing to disclose.

References

1. Cavalcante JL, Lima JA, Redheuil A, Al-Mallah MH. Aortic stiffness: current understanding and future directions. *J Am Coll Cardiol* 2011;**57**:1511–1522.
2. Steppan J, Barodka V, Berkowitz DE, Nyhan D. Vascular stiffness and increased pulse pressure in the aging cardiovascular system. *Cardiol Res Pract* 2011;**2011**:263585.
3. Bluemke DA, Kronmal RA, Lima JA, Liu K, Olson J, Burke GL, Folsom AR. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) study. *J Am Coll Cardiol* 2008;**52**:2148–2155.
4. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, Simonsick EM, Havlik R, Lakatta EG, Spurgeon H, Kritchevsky S, Pahor M, Bauer D, Newman A; Health ABC Study. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. *Circulation* 2005;**111**:3384–3390.
5. Redheuil A, Wu CO, Kachenoura N, Ohyama Y, Yan RT, Bertoni AG, Hundley GW, Duprez DA, Jacobs DR Jr, Daniels LB, Darwin C, Sibley C, Bluemke DA, Lima JA. Proximal aortic distensibility is an independent predictor of all-cause mortality and incident CV events. the MESA study. *J Am Coll Cardiol* 2014;**64**:2619–2629.
6. Tsao CW, Gona PN, Salton CJ, Chuang ML, Levy D, Manning WJ, O'Donnell CJ. Left ventricular structure and risk of cardiovascular events: a Framingham Heart Study cardiac magnetic resonance study. *J Am Heart Assoc* 2015;**4**:e002188.
7. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation* 2010;**121**:505–511.
8. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Redon J, Dominiczak A, Narkiewicz K, Nilsson PM, Burnier M, Viigimaa M, Ambrosioni E, Caufield M, Coca A, Olsen MH, Schmieder RE, Tsioufis C, van de BP, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Clement DL, Coca A, Gillebert TC, Tendera M, Rosei EA, Ambrosioni E, Anker SD, Bauersachs J, Hitij JB, Caulfield M, De Buyzere M, De Geest S, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano G, Gielen S, Haller H, Hoes AW, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Olsen MH, Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Ryden L, Sirenko Y, Stanton A, Struijker-Boudier H, Tsioufis C, van de BP, Vlachopoulos C, Volpe M, Wood DA. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;**34**:2159–2219.
9. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 1991;**114**:345–352.

10. Muiesan ML, Salvetti M, Monteduro C, Bonzi B, Paini A, Viola S, Poisa P, Rizzoni D, Castellano M, Agabiti-Rosei E. Left ventricular concentric geometry during treatment adversely affects cardiovascular prognosis in hypertensive patients. *Hypertension* 2004;**43**:731–738.
11. Schiffrin EL. Circulatory therapeutics: use of antihypertensive agents and their effects on the vasculature. *J Cell Mol Med* 2010;**14**:1018–1029.
12. Ong KT, Delerme S, Pannier B, Safar ME, Benetos A, Laurent S, Boutouyrie P. Investigators. Aortic stiffness is reduced beyond blood pressure lowering by short-term and long-term antihypertensive treatment: a meta-analysis of individual data in 294 patients. *J Hypertens* 2011;**29**:1034–1042.
13. Devereux RB, Dahlof B, Gerdts E, Boman K, Nieminen MS, Papademetriou V, Rokkedal J, Harris KE, Edelman JM, Wachtell K. Regression of hypertensive left ventricular hypertrophy by losartan compared with atenolol: the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial. *Circulation* 2004;**110**:1456–1462.
14. Klingbeil AU, Schneider M, Martus P, Messerli FH, Schmieder RE. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. *Am J Med* 2003;**115**:41–46.
15. Heeneman S, Sluimer JC, Daemen MJ. Angiotensin-converting enzyme and vascular remodeling. *Circ Res* 2007;**101**:441–454.
16. Benetos A, Gautier S, Lafleche A, Topouchian J, Frangin G, Girerd X, Sissmann J, Safar ME. Blockade of angiotensin II type 1 receptors: effect on carotid and radial artery structure and function in hypertensive humans. *J Vasc Res* 2000;**37**:8–15; discussion 68–70.
17. Petrovic I, Petrovic D, Vukovic N, Zivanovic B, Dragicevic J, Vasiljevic Z, Babic R. Ventricular and vascular remodelling effects of the angiotensin II receptor blocker telmisartan and/or the angiotensin-converting enzyme inhibitor ramipril in hypertensive patients. *J Int Med Res* 2005;**33**(Suppl. 1):39A–49A.
18. Verdecchia P, Sleight P, Mancia G, Fagard R, Trimarco B, Schmieder RE, Kim JH, Jennings G, Jansky P, Chen JH, Liu L, Gao P, Probstfield J, Teo K, Yusuf S; Investigators OT. Effects of telmisartan, ramipril, and their combination on left ventricular hypertrophy in individuals at high vascular risk in the ongoing Telmisartan alone and in combination with Ramipril Global End Point Trial and the Telmisartan Randomized Assessment Study in ACE intolerant subjects with cardiovascular disease. *Circulation* 2009;**120**:1380–1389.
19. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force M. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–2200.
20. Bavishi C, Messerli FH, Kadosh B, Ruilope LM, Kario K. Role of neprilysin inhibitor combinations in hypertension: insights from hypertension and heart failure trials. *Eur Heart J* 2015;**36**:1967–1973.
21. Richards AM, Wittert GA, Crozier IG, Espiner EA, Yandle TG, Ikram H, Frampton C. Chronic inhibition of endopeptidase 24.11 in essential hypertension: evidence for enhanced atrial natriuretic peptide and angiotensin II. *J Hypertens* 1993;**11**:407–416.
22. McDowell G, Coutie W, Shaw C, Buchanan KD, Struthers AD, Nicholls DP. The effect of the neutral endopeptidase inhibitor drug, candoxatril, on circulating levels of two of the most potent vasoactive peptides. *Br J Clin Pharmacol* 2003;**43**:329–332.
23. Bevan EG, Connell JM, Doyle J, Carmichael HA, Davies DL, Lorimer AR, McInnes GT. Candoxatril, a neutral endopeptidase inhibitor: efficacy and tolerability in essential hypertension. *J Hypertens* 1992;**10**:607–613.
24. 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.
25. Minguet J, Sutton G, Ferrero C, Gomez T, Bramlage P. LCZ696: a new paradigm for the treatment of heart failure? *Expert Opin Pharmacother* 2015;**16**:435–446.
26. 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. *N Engl J Med* 2014;**371**:993–1004.
27. Asmar R, Vol S, Brisac AM, Tichet J, Topouchian J. Reference values for clinic pulse pressure in a nonselected population. *Am J Hypertens* 2001;**14**:415–418.
28. Sakuma H, Fujita N, Foo TK, Caputo GR, Nelson SJ, Hartiala J, Shimakawa A, Higgins CB. Evaluation of left ventricular volume and mass with breath-hold cine MR imaging. *Radiology* 1993;**188**:377–380.
29. Devereux RB, Wachtell K, Gerdts E, Boman K, Nieminen MS, Papademetriou V, Rokkedal J, Harris K, Aurup P, Dahlof B. Prognostic significance of left ventricular mass change during treatment of hypertension. *JAMA* 2004;**292**:2350–2356.
30. Mathew J, Sleight P, Lonn E, Johnstone D, Pogue J, Yi Q, Bosch J, Sussex B, Probstfield J, Yusuf S; Heart Outcomes Prevention Evaluation I. Reduction of cardiovascular risk by regression of electrocardiographic markers of left ventricular hypertrophy by the angiotensin-converting enzyme inhibitor ramipril. *Circulation* 2001;**104**:1615–1621.
31. 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.
32. Jhund PS, Claggett B, Packer M, Zile MR, Voors AA, Pieske B, Lefkowitz M, Shi V, Bransford T, McMurray JJ, Solomon SD. Independence of the blood pressure lowering effect and efficacy of the angiotensin receptor neprilysin inhibitor, LCZ696, in patients with heart failure with preserved ejection fraction: an analysis of the PARAMOUNT trial. *Eur J Heart Fail* 2014;**16**:671–677.
33. Schmieder RE, Hilgers KF, Schlaich MP, Schmidt BM. Renin-angiotensin system and cardiovascular risk. *Lancet* 2007;**369**:1208–1219.
34. Ichihara A, Kaneshiro Y, Sakoda M, Takemitsu T, Itoh H. Add-on amlodipine improves arterial function and structure in hypertensive patients treated with an angiotensin receptor blocker. *J Cardiovasc Pharmacol* 2007;**49**:161–166.
35. Williams B, Cockcroft JR, Kario K, Zappe DH, Brunel PC, Wang Q, Guo W. Effects of sacubitril/valsartan versus Olmesartan on central hemodynamics in the elderly with systolic hypertension: the PARAMETER study. *Hypertension* 2017;**69**:411–420.